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Functional & Reconstructive Oculoplastics

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Harrison Eds.

Functional & Reconstructive Oculoplastics

Functional & Reconstructive Oculoplastics is a practical and authoritative guide to the diagnosis and surgical management of functional and reconstructive periocular disorders. This volume provides a structured framework for understanding periocular anatomy, clinical evaluation, and operative planning, with an emphasis on restoring function, stability, and patient quality of life.

Covering core areas such as eyelid and lacrimal surgery, orbital pathology, facial nerve dysfunction, trauma, and reconstructive techniques, the book combines clinical insight with reproducible surgical strategies. Designed for both training and reference, this text serves as a valuable resource for surgeons seeking a clear, clinically grounded approach to functional oculoplastic surgery.

序言

眼周区域不仅是视觉功能的核心枢纽，更是面部表达与社会互动中最具辨识度的解剖单元。它承载着极为精细而复杂的解剖结构，任何微小的形态或功能异常，都会显著影响患者的生活质量、社会交流乃至心理健康。因此，眼整形外科不仅是一门精密的外科技术，更是一门融合解剖学、功能修复、组织重建与审美平衡的综合学科。

功能性与重建性眼整形外科，始终立足于“恢复”二字之上 — 恢复视野、恢复眼睑保护功能、恢复泪液动力学、恢复眼眶结构稳定性，以及恢复患者对自身形象与尊严的认同。这不仅要求术者具备极高的解剖理解能力与手术控制力，更要求我们在临床决策中始终以科学证据与长期功能结局为导向。

本论文集系统汇集了我在眼睑、泪道、眼眶及眶周重建领域的临床经验与研究成果，内容涵盖：
基础研究：围绕眼睑支持结构、眶隔系统、生物力学特性与瘢痕修复机制的深入探讨；
非手术治疗：针对神经肌肉调控、炎症控制及功能恢复的精准干预；
手术治疗：聚焦眼睑下垂、内外翻、泪道阻塞、甲状腺相关眼病及复杂眼眶病变的系统性矫正策略；
重建外科：涵盖外伤修复、肿瘤切除后结构重建、眼球缺失后的综合修复，以及复杂眼眶畸形的整体解决方案。
这些研究与实践反复印证一个核心理念：真正卓越的眼整形外科，不是单纯改变形态，而是以精准重建，恢复功能；以结构修复，重塑尊严。
在葆洛丽，我们始终坚持以循证医学为核心，以解剖逻辑为基础，将复杂问题拆解为可量化、可验证、可复制的临床路径。这种方法不仅提升了手术安全性，也为长期疗效提供了稳定保障。

谨以此论文集，献给所有致力于眼整形外科发展的同行—
愿我们在不断追求技术进步的同时，始终保持对基础科学的敬畏、对患者需求的敏感、以及对医学初心的坚守。

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Preface

The periocular region represents the anatomical and functional epicenter of vision, facial expression, and social interaction. Even subtle disturbances in eyelid position, tear dynamics, or orbital structure can profoundly impact visual performance, psychological well-being, and overall quality of life. As such, functional and reconstructive oculoplastic surgery stands at the intersection of anatomy, physiology, microsurgical precision, and compassionate care.

The primary mission of functional and reconstructive oculoplastics is restoration — restoration of vision, protection, comfort, structural stability, and ultimately, patient dignity. Achieving these goals requires not only refined surgical technique, but also a deep understanding of periocular anatomy, tissue biomechanics, and disease pathophysiology.

This volume compiles clinical experience and academic investigation across the full spectrum of oculoplastic practice, including foundational research, non-surgical therapies, advanced surgical correction, and complex periocular reconstruction. Particular emphasis is placed on ptosis repair, eyelid malposition, lacrimal disorders, thyroid eye disease, orbital trauma, oncologic reconstruction, and post-enucleation rehabilitation.

Through these studies, one central principle emerges: true excellence in oculoplastic surgery is defined not by cosmetic change, but by functional restoration, structural precision, and durable outcomes.

At Beauluxe, our clinical philosophy integrates evidence-based medicine with meticulous anatomical analysis, transforming complex reconstructive challenges into systematic and reproducible surgical solutions.

It is my hope that this collection will serve as both a scientific reference and a clinical guide for surgeons dedicated to advancing the art and science of oculoplastic surgery.

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ORIGINAL RESEARCH

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Practice Patterns and Opening Pressure Measurements Using Fluoroscopically Guided Lumbar Puncture

BACKGROUND AND PURPOSE: Evidenced-based protocols for fluoroscopically guided LP do not exist. This study analyzed the fluoroscopically guided LP techniques currently used by practicing neuroradiologists.

MATERIALS AND METHODS: An anonymous Web-based survey was e-mailed to members of ASNR. The results were compiled and tabulated on a spreadsheet.

RESULTS: A total of 577 neuroradiologists completed the survey. Most neuroradiologists perform fluoroscopically guided LPs with the patient in the prone position by using a 22-ga needle at the L2-L3 or L3-L4 intervertebral space. The OP measurement technique is quite variable. Only a minority of patients are rotated to the left LD position for OP measurement. Most neuroradiologists observe patients for 1–2 hours after the procedure and require strict bed rest.

CONCLUSIONS: Most neuroradiologists have similar protocols for thecal sac puncture. Normative adult OP data exist only for the LD position, and the accuracy of prone OP measurements is not known. We found that the OP measurement technique is not consistent and a standard protocol is warranted.

ABBREVIATIONS: ASNR = American Society of Neuroradiology; GI = gastrointestinal; IIH = idiopathic intracranial hypertension; LD = lateral decubitus; LP = lumbar puncture; OP = opening pressure

While LPs are historically performed at the bedside, fluoroscopically guided LPs have become a routine procedure for neuroradiologists. In 2008, the American College of Radiology and the ASNR published "Practice Guidelines for the Performance of Myelography and Cisternography,"[1] which included a description of the lumbar approach for accessing the subarachnoid space but did not outline a comprehensive LP protocol with OP measurement. To our knowledge, there are no published guidelines describing fluoroscopically guided LP. The accuracy of OP measurement is crucial to diagnosing those with intracranial hypertension or hypotension. This study aimed to identify practice patterns among neuroradiologists regarding the fluoroscopically guided LP technique and OP measurement.

Materials and Methods

Members of the ASNR were invited to complete an anonymous 16-question multiple-choice Web-based survey. Survey results were tabulated by Survey Monkey (http://iry.surveymonkey.com/?gclid=CKyK1PnXuasCFQhN4AodRktRgQ) and analyzed by using Excel (Microsoft, Redmond, Washington). The University of Minnesota institutional review board approved the exemption status for this study.

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Results

A total of 577 members of the ASNR completed the survey. Not all respondents answered every survey question. Ninety-five percent of survey respondents had >5 years of experience performing fluoroscopically guided LPs, with most (54%) performing fewer than 25 LPs annually (Table). Eighty-four percent of surveyed neuroradiologists measure OP, while 14% do not. Of those who measure OP, most (83%) measure it only when requested by the referring physician, 14% measure OP routinely, and 3% measure OP only when abnormally brisk CSF flow is noted on removal of the stylet from the spinal needle (Fig 1). Three respondents (0.6%) reported never measuring OP (Fig 1).

The overwhelming majority of fluoroscopically guided LPs are performed by using a 22- (68%) or 20- (24%) ga needle. The preferred spinal entry level varies, but the L2-L3 (42%) and L3-L4 (30%) levels are the most common. Eighty-eight percent of respondents perform the thecal sac puncture prone, while 12% puncture the sac with the patient in the LD position (Fig 1).

Of the 497 neuroradiologists who typically perform thecal sac puncture with the patient in the prone position, 356 (72%) measure OP in the prone position, while 141 (28%) rotate the patient to measure OP in the LD position (Fig 1). When measuring OP in the LD position, 73 (21%) use fluoroscopy to determine the level of the spinal canal (and thus the 0-cm mark on the manometer), 105 (31%) palpate the spinous processes, and 164 (48%) use "guesstimation" (Fig 1). When OP is measured with the patient in the LD position following prone thecal sac puncture, leg position varies among bent (37%), straight (24%), and ad lib (39%) (Fig 2). Of the survey respondents who typically measure OP with the patient in the prone position, 280 (79%) add the needle length to the OP measure-

Experience level of surveyed neuroradiologists	
Survey Respondent Characteristics	No. Respondents
LP experience (yr)	
0–5	29 (5%)
5–10	106 (18%)
10–15	85 (15%)
15–20	112 (19%)
>20	244 (42%)
LPs per year	
0–25	313 (54%)
26–50	120 (21%)
51–75	52 (9%)
76–100	37 (6%)
>100	54 (9%)

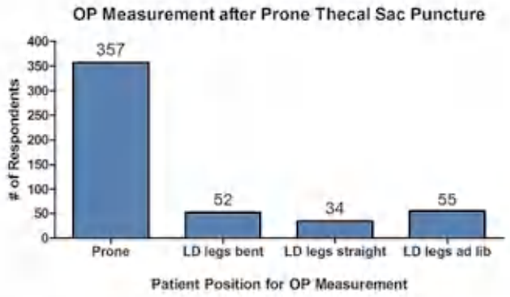

Fig 2. Patient position following prone LP.

ment (the tip of the needle in the thecal sac therefore serves as the 0-cm mark), while 72 (21%) do not. When assessing the equilibration point between the CSF pressure and the manometer in any position, 365 (64%) measure when the meniscus stops rising and 205 (36%) measure the OP when systolic-diastolic fluctuation/respiratory fluctuation begins.

Most survey respondents (71%) perform fluoroscopically guided LP on a GI fluoroscopy table. Alternatively, 21% use fixed-base single/dual plane fluoroscopy, and 8% use a portable C-arm. Of the 400 neuroradiologists who routinely use the GI fluoroscopy table, 68% perform the entire procedure with the patient prone, while 32% perform prone thecal sac puncture followed by a transfer to the LD position for OP measurement (Fig 1). Radiation protection of the radiologist during the procedure was not investigated.

Following fluoroscopically guided LP, most neuroradiologists (82%) regularly observe their patients for some time; 86% of whom observe their patients for 1–2 hours postprocedure (Fig 1). When patients are observed postprocedure, 95% of survey respondents restrict activity to bed rest, 57% further restrict body position to supine, and 38% allow ad lib positioning during bed rest (Fig 1). Five percent observe without any position or activity restrictions (Fig 1). In the event that an epidural blood patch is needed to treat post-LP headache, most surveyed neuroradiologists (61%) do not perform their own blood patches, while 39% do perform this procedure themselves.

Discussion

Despite the absence of practice guidelines for fluoroscopically guided LP, neuroradiologists generally appear to perform these in a similar fashion. Most perform thecal sac puncture and OP measurement on a GI fluoroscopy table with the patient prone throughout the entire procedure. A 22-ga needle is typically used to puncture at L2-L3 or L3-L4. Almost two-thirds (64%) record the OP when the CSF meniscus stops rising as opposed to the traditional, and likely more accurate, teaching of OP measurement when systolic-diastolic or respiratory fluctuation begins.[2] This may result in falsely high or low opening pressure measurements.

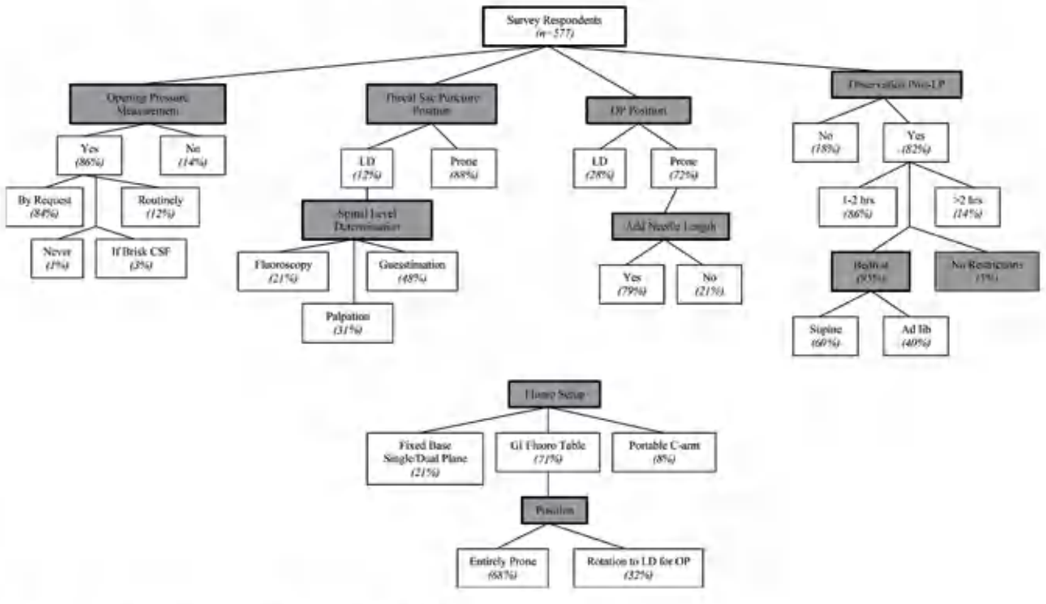

Fig 1. Practice patterns for fluoroscopically guided LP and OP measurement.

Most (80%) neuroradiologists who typically perform OP measurement with the patient prone add the needle length to the manometer reading to determine the final CSF OP. The OP is based on the CSF height within the manometer, where zero is the level of the left atrium of the heart. In the LD position, zero level corresponds to the position of the spinal canal and is determined clinically with various techniques. In the prone position, however, needle length must be added to the meniscus height or the recorded pressure will be falsely low. According to the survey data, 1 in 5 neuroradiologists does not add the needle length when measuring OP in the prone position. Underestimation of CSF pressure by omitting needle length from the final OP measurement may have clinical implications. For example, IIH is a diagnosis of exclusion that depends on an accurate OP measurement to prevent potentially irreversible vision loss. Conceivably, the respondents who do not add needle length to the manometer reading after prone OP measurement could be using flexible extension tubing, which theoretically allows prone OP measurement with zero at the level of the left atrium. This survey did not specifically address the use of flexible tubing, so prevalence of this technique remains unclear.

Most interesting, normative OP data exist only for the LD position, not for prone measurements. Clinical decisions based on these pressures deserve careful consideration, especially when the OP is borderline. We are currently studying the relationship of prone-versus-LD OP.

The lower extremity position likely affects the OP measurement. While some studies have demonstrated that the lower extremity position does not affect CSF pressure, others have shown a significant difference between OP in the flexed- and extended-leg positions.[5,6] In this survey, extended lower extremity position was not consistently maintained during OP measurement in the LD position. The clinical significance of this difference is debated, but lower extremity position could affect clinical decision-making in borderline cases. While this is more applicable to LPs performed at the bedside and only applies to the small percentage (28%) of OPs measured in the LD position during fluoroscopically guided LP, it illustrates a deficiency in practice guidelines that may affect opening pressures.

As obesity increases in the US population, it is likely that the incidence of IIH will also rise. The diagnosis of IIH depends on an accurate OP of ≥25-cm water measured in the LD position. In the absence of practice guidelines for OP measurement, patients may receive a false-positive IIH diagnosis or go undiagnosed if the neuroradiologist fails to add the needle length to prone OP measurements.

Conclusions

We recognize that the limitations of this study include accurate self-report by the survey respondents as well as a common understanding of the questions asked. Despite these limitations, it appears that neuroradiologists generally perform fluoroscopically guided LPs in a similar fashion. Practice guidelines for standardizing the fluoroscopically guided LP technique would improve the accuracy of OP measurement. Therefore, we propose the following suggestions regarding OP measurements for fluoroscopically guided LP:

1) Ideally, OP is measured in the left LD position because normative data exist for this position only. At the time of OP measurement, the neck and lower extremities should be completely extended.

2) If OP is measured in the prone position, the needle length must be added to the meniscus height. If flexible extension tubing is used, it should be positioned with zero at the level of the spinal canal. Procedure notes should reflect the manner of OP measurement.

3) Meniscus height should be assessed when systolic-diastolic fluctuation/respiratory fluctuation begins.

4) Patients should be coached to relax because use of the Valsalva maneuver to maintain body position can falsely elevate OP.[7] This is especially important in patients with excessive abdominal or thoracic girth who may struggle to maintain position.

5) Normative data for prone OP measurements are needed because most fluoroscopically guided LPs are performed with patients entirely in the prone position.

Disclosures: Andrew Harrison—*UNRELATED: Consultancy:* Merz Pharmaceuticals.

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Modulating Neuromuscular Junction Density Changes in Botulinum Toxin–Treated Orbicularis Oculi Muscle

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Purpose. Botulinum toxin A is the most commonly used treatment for blepharospasm, hemifacial spasm, and other focal dystonias. Its main drawback is its relatively short duration of effect. The goal of this study was to examine the ability of corticotropin releasing factor (CRF) or antibody to insulin growth factor I-receptor (anti-IGFIR) to reduce the up-regulation of neuromuscular junctions that are associated with return of muscle function after botulinum toxin treatment.

Methods. Eyelids of adult rabbits were locally injected with either botulinum toxin alone or botulinum toxin treatment followed by injection of either CRF or anti-IGFIR. After one, two, or four weeks, the orbicularis oculi muscles within the treated eyelids were examined for density of neuromuscular junctions histologically.

Results. Injection of botulinum toxin into rabbit eyelids resulted in a significant increase in the density of neuromuscular junctions at one and two weeks, and an even greater increase in neuromuscular junction density by four weeks after treatment. Treatment with either CRF or anti-IGFIR completely prevented this increase in neuromuscular junction density.

Conclusions. The return of function after botulinum toxin–induced muscle paralysis is due to terminal sprouting and formation of new neuromuscular junctions within the paralyzed muscles. Injection with CRF or anti-IGFIR after botulinum toxin treatment prevents this sprouting, which in turn should increase the duration of effectiveness of single botulinum toxin treatments. Future physiology studies will address this. Prolonging botulinum toxin's clinical efficacy should decrease the number of injections needed for patient muscle spasm relief, decreasing the risk of negative side effects and changes in drug effectiveness that often occurs over a lifetime of botulinum toxin exposure. (*Invest Ophthalmol Vis Sci.* 2011;52:982–986) DOI:10.1167/iovs.10-6127

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Botulinum toxin is the most common medical treatment for blepharospasm and hemifacial spasm. Developed in the 1970s,[1] it produces a chemodenervation by binding to and paralyzing the neuromuscular junction specifically by blocking neurotransmitter release. This is an excellent treatment; however, its main limitation is the relatively short duration of its action. The average reinjection interval for blepharospasm in the published literature is between two and three months.[2] In addition, many patients desire more frequent injections, partly to remain spasm-free and partly from decreasing sensitivity to the drug's effects.[3] Additionally, some patients develop antibodies to botulinum toxin, requiring increased dosing to achieve paralysis or rendering them unresponsive to treatment.[4]

The return of muscle function after botulinum toxin injection is caused by sprouting of axonal collaterals from the presynaptic nerve endings at the neuromuscular junctions of the paralyzed muscles.[5,6] Nerve sprouting after botulinum toxin treatment results in a significant increase in new acetylcholine receptors on the treated muscle compared to normal. These newly formed acetylcholine receptors are in locations distinct from those of the original, paralyzed neuromuscular junctions.[7] Peripheral nerve sprouting can be measured as early as three days after botulinum injection.[8] Compound action potentials demonstrate the return of 20% of normal activity in patients as soon as seven days after botulinum toxin injection.[9] This rapid and early sprouting results in some muscle function returning as quickly as the sixth day.[10] Quantification of neuromuscular junction number in rabbit extraocular muscle at various times after botulinum toxin injection showed doubling of neuromuscular junctions within the first month after treatment.[11] This is one of the major limitations of botulinum toxin use in patients with focal dystonias: the duration of effectiveness is too short to allow permanent alteration of innervation and muscle force. Increasing the duration of effectiveness of botulinum toxin would reduce both the need for frequent repeat injections and the lifetime exposure of patients to the drug. This in turn should reduce the chance for the decreased sensitivity to the treatment. This is an important concern, because there are few other widely accepted choices for medical management of blepharospasm and hemifacial spasm, and none that rival botulinum toxin in clinical efficacy.

Since the first use of botulinum toxin for treating blepharospasm patients,[12] there has been very little research focused on improving its duration of effect or developing new therapeutic agents to selectively weaken a single or small group of skeletal muscles.[13] Some animal studies examining co-treatment strategies have been performed, including studies from our laboratory. These include co-treatment with the immunotoxin ricin-mAb35,[14] insulin growth factor binding proteins,[15] and bupivacaine.[16] The goal of our research is to test agents that have the potential to enhance the duration of paralysis, which would potentially decrease the number of "lifetime" injections of botulinum toxin needed by patients.

The hormone corticotropin releasing factor (CRF) has potent anti-inflammatory effects when applied locally in tissues for treatment of pain.[17] We recently demonstrated that, when injected into an inflamed eyelid, CRF significantly reduces inflammatory cell infiltrate and nerve fibers at the site of injection.[18] The reduction in sensory nerve outgrowth caused by local CRF administration in the injured eyelids suggested that this agent might also have an effect on reducing the motor nerve sprouting and neuromuscular junction formation that occurs after botulinum toxin treatment of the orbicularis oculi muscle.

Insulin growth factor (IGF) is a neurotrophic and muscle growth factor that increases in muscles after nerve injury.[19] Previous studies demonstrate that co-injection of inhibitory binding proteins specific for IGF, such as IGF binding protein-4, reduces botulinum-induced sprouting in the levator ani muscle.[20] Local injection of antibodies to soluble neurotrophic factors and their receptors, such as IGF and IGF-R, have been shown to reduce collateral axonal branching after nerve injury.[21] Using either antibodies to IGF or antibodies to insulin growth factor receptor, proteins with known inhibitory effects on IGF effects in tissue, has the potential to reduce effectively the botulinum toxin–induced nerve sprouting and de novo increases in neuromuscular junction density locally within treated orbicularis oculi muscle.

These experiments test the ability of local injections of CRF or IGF-receptor antibody into the eyelid muscles to reduce axonal sprouting and the de novo neuromuscular junction formation induced by botulinum toxin injection. Clinically, the long-term goal is to increase the duration of effect of botulinum toxin treatment to reduce the need for repeat injections and the overall lifetime exposure to the drug in patients with chronic focal dystonias.

Materials and Methods

Adult male New Zealand White rabbits were obtained from Bakkom Rabbitry (Viroqua, WI) and housed in the AALAC-approved animal facility at the University of Minnesota. All animal studies were approved by the Institutional Animal Care and Use Committee at the University of Minnesota, as well as complied with the guidelines for the Use of Animals in Research published by the Association for Research in Vision and Ophthalmology as well as the guidelines of the National Institutes of Health.

Rabbits were anesthetized via an intramuscular injection of ketamine/xylazine (1:1) at a dose of 10 mg/kg-2 mg/kg, respectively. The cornea was anesthetized by placement of a drop of proparacaine-HCl in the conjunctival cul-de-sac. Three groups of animals were prepared. Group one received a single injection of 5 units of botulinum toxin A (Botox, Allergan, Los Angeles, CA) in 1 cc of sterile isotonic saline in one randomly selected upper eyelid and examined after one, two, or four weeks post-botulinum toxin treatment. All injections were made by inserting the needle into the central region of the eyelid with the needle tip pointing toward the medial canthus, with half the volume being dispensed and the needle slowly pulled toward the needle entry point. With the needle in place, the syringe was rotated and the needle directed toward the lateral canthus. The same slow injection procedure was performed with slow withdrawal of the needle. After dispensing the full volume, the needle was left in place for 30 seconds to prevent leakage. This method minimizes leakage, as only one needle stick is performed. Previous studies demonstrated that single injections of this volume spread into all regions of the treated eyelids.[22] Group two received a single injection of 5 units of botulinum toxin, followed on post-treatment days three and five with injection of corticotropin releasing factor (CRF; Peninsula Laboratories, Belmont, CA) (150 μg in 1 mL sterile saline).[18,23] Eyelids were examined two weeks after the final treatment. Group 3 received botulinum toxin injections similar to groups 1 and 2, followed on post-treatment days three and five with injections of an antibody to insulin growth factor-I receptor (anti-IGFIR; R&D Systems, Minneapolis, MN) at a dose of 30 μg/mL sterile saline.[24] Again, eyelids were examined two weeks after the final treatment. The contralateral upper eyelids were injected with sterile saline only in comparable volumes.

At the appropriate post-injection intervals, the rabbits were anesthetized deeply with ketamine and xylazine, followed by an overdose of barbiturate anesthesia. Both eyelids were trimmed to remove the fur and dissected completely to include the muscle at both the medial and lateral canthi. They were pinned to their in situ length in embedding molds, surrounded by tragacanth gum, frozen in methylbutane chilled to a slurry on liquid nitrogen, and stored at −80°C until sectioned and processed. The muscles were sectioned completely in the longitudinal plane at 12 μm, and the sections were mounted on gelatin-subbed microslides. Every tenth section was immunostained for the presence of neuromuscular junctions using α-bungarotoxin conjugated to Alexa Fluor 488 (Molecular Probes) at a concentration of 1:100 overnight at 4°C. The slides were coverslipped with mounting medium (Vectashield; Vector Laboratories, Burlingame, CA) and analyzed the same day they were immunostained.

The muscle sections were examined for neuromuscular junction position and number using a microscope (Leica DMR; Leica, Wetzlar, Germany). Using image analysis software (Topographer program of NovaPrime; Bioquant, Nashville, TN), the area of the entire orbicularis oculi muscle in longitudinal section was measured at 1.6×. Every neuromuscular junction was located at 20× and marked with *X* and *Y* coordinates recorded in the Topographer program. This analysis was repeated for every tenth section through the entire eyelid. The image analysis program (Bioquant Topographer) was used to reconstruct the entire muscle, including the area outlines and locations of each neuromuscular junction. This allowed for a three-dimensional reconstruction of all the neuromuscular junctions in their actual *X*, *Y*, and *Z* planes within the entire muscle. Four orbicularis oculi muscles were examined for each of the experimental paradigms.

Density of neuromuscular junctions was calculated as the number of neuromuscular junctions per mm^2. Statistical significance was determined between the densities of neuromuscular junctions in the saline-treated control muscles, the botulinum toxin A–only treated orbicularis oculi, and the co-treated eyelid muscles. Statistics were performed using an unpaired *t*-test aided by statistical software (Prism and Statmate software; Graphpad, San Diego, CA). An *F*-test was used to verify that the variances were not significantly different. Data were considered significantly different if $P < 0.05$.

Results

The effect of botulinum toxin A injections on neuromuscular density in orbicularis oculi of adult rabbits was determined (Figs. 1, 2, 3). The neuromuscular junction density was twofold greater in the pretarsal region of normal orbicularis oculi muscle compared to the preseptal region. The density of neuromuscular junctions was 3.3 ± 0.14/mm^2 and 1.55 ± 0.09/mm^2 in the pretarsal and preseptal regions, respectively. At one and two weeks after botulinum toxin injection, the density increased significantly, particularly in the preseptal region. In the pretarsal region, neuromuscular junction density was 4.0 ± 0.21/mm^2 after one or two weeks. In the preseptal region, neuromuscular junction densities were two- to threefold greater than control at one and two weeks post-treatment, with densities of 4.4 ± 0.1/mm^2 and 2.9 ± 0.1/mm^2, respectively. At four weeks post-botulinum toxin treatment, the up-regulation of neuromuscular junctions was even greater when compared to control levels, and was also significantly greater than the density at two weeks. Densities in the pretarsal and preseptal regions at four weeks post-treatment were 5.7 ± 0.8/mm^2 and 5.23 ± 0.7/mm^2, respectively.

Injection of CRF into the botulinum toxin–treated eyelids resulted in neuromuscular junction densities that were not

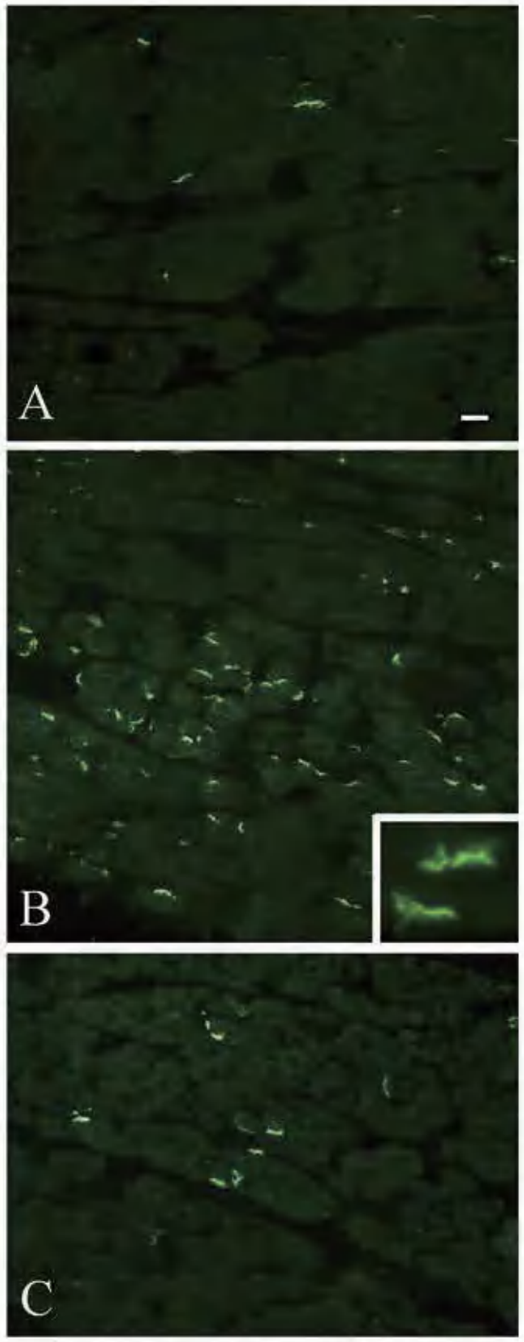

FIGURE 1. Photomicrographs of neuromuscular junctions stained with fluorescently labeled α-bungarotoxin. (**A**) Normal control rabbit orbicularis oculi muscle. (**B**) Two weeks after an injection of 5 units of botulinum toxin. (**C**) Two weeks after an injection of 5 units of botulinum toxin A followed by two injections of corticotrophin releasing factor. Scale bar, 20 μm. Inset magnification, 40×.

significantly different from the density in the control orbicularis oculi muscles (Figs. 1, 2, 4), with the CRF-treated neuromuscular junction density at 2.39 ± 0.23/mm^2 compared to 2.42 ± 0.19/mm^2 in the control orbicularis oculi muscles. As

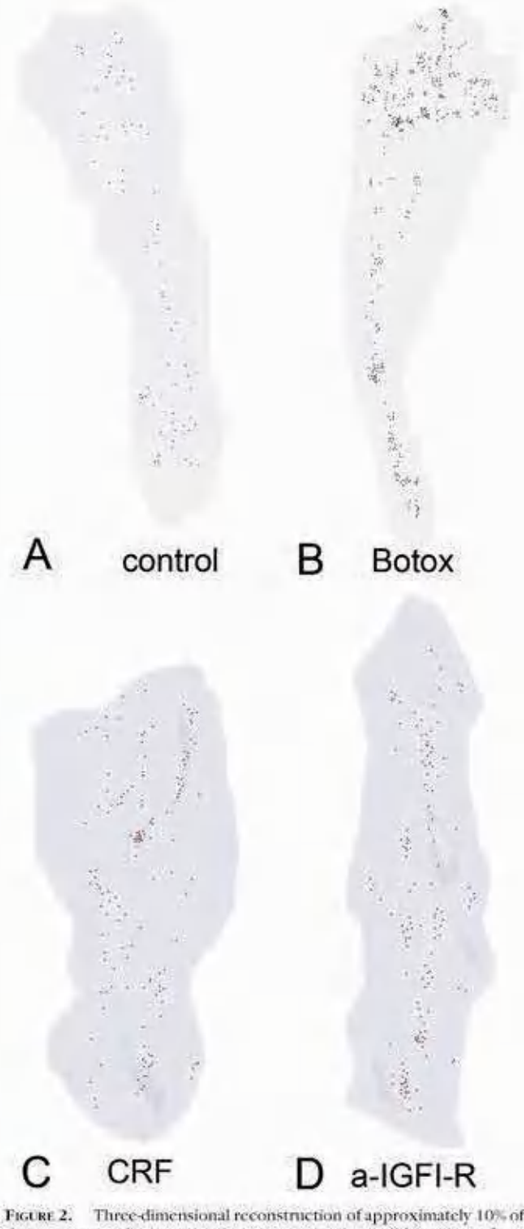

FIGURE 2. Three-dimensional reconstruction of approximately 10% of the neuromuscular junctions in a representative eyelid specimen from (**A**) normal control orbicularis oculi muscle, (**B**) an eyelid treated two weeks earlier with botulinum toxin A, (**C**) an eyelid treated two weeks earlier with botulinum toxin A followed by CRF, and (**D**) an eyelid treated two weeks earlier with botulinum toxin A followed by anti-IGFIR. Each *dot* represents a single neuromuscular junction.

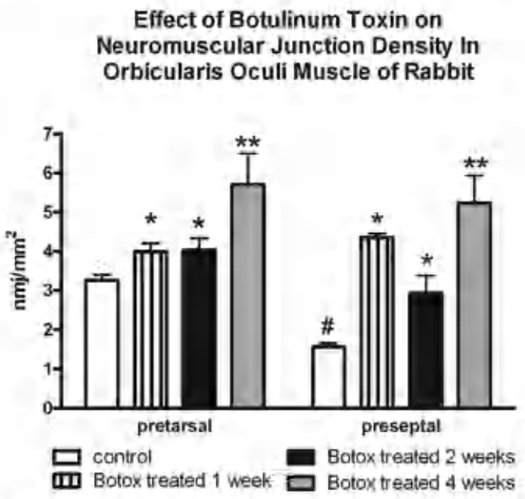

FIGURE 3. Quantification of neuromuscular junction density of control orbicularis oculi muscles (*white bar*) as well as one (*vertical hatched bar*), two (*black bar*), and four (*gray bar*) weeks after an injection of 5 units botulinum toxin A (Botox). *Significantly different from control; **significantly different from control and from 1 and 2 weeks; #significantly different from pretarsal control.

the combined total muscle neuromuscular junction density in the orbicularis oculi muscle increased almost threefold after the botulinum toxin A treatment to 5.9 ± 0.43/mm^2, it is quite interesting that the up-regulation of neuromuscular junctions was completely negated by the injection of CRF within days of the botulinum toxin.

Similarly, injection of anti-IGFIR within days of the botulinum toxin treatment resulted in no increase in neuromuscular junction density compared to control levels, with neuromuscular junction density in the anti-IGFIR-treated orbicularis oculi muscles at 2.88 ± 0.28/mm^2 compared to control levels at 2.4 ± 0.19/mm^2 (Figs. 1, 2, 4).

DISCUSSION

Botulinum toxin A injection resulted in a significant increase in neuromuscular junction density, as previously demonstrated.[11] Injection of the botulinum toxin–treated eyelids with either CRF or anti-IGFR negated the botulinum toxin–induced de novo formation of neuromuscular junctions on the paralyzed muscles.

Botulinum toxin A directly binds to the neuromuscular junction and prevents neurotransmitter release.[23] Botulinum toxin specifically cleaves SNAP-25, a protein needed for transmitter exocytosis,[24] but leaves the neuromuscular junction intact.[26] This botulinum toxin–induced paralysis leads to sprouting of the terminal nerves that project to the poisoned neuromuscular junctions.[27] These sprouts induce the formation of new neuromuscular junctions, and these new motor endplates are responsible for functional return at the onset of recovery.[5] Eventually, over the course of one to three months, there is a return of function at the original motor endplates, and the sprouts are eliminated.[28] We hypothesized that inhibition of nerve sprouting at the muscle level should extend the duration of effectiveness of botulinum toxin treatment.

The rationale for the use of CRF as an anti-sprouting treatment is based on studies that show its potent analgesic effects require the presence of peripheral nerve within injured tissue.[29] Our previous work demonstrated that localized injection of CRF decreased PGP 9.5-positive nerve density in inflamed eyelid tissue.[18,43] This reduction in nerve fiber density correlated with a reduction in tissue hypersensitivity to touch. In the present study, CRF prevented the formation of new motor endplates.[5] CRF also can act directly by reducing synaptic transmission.[30,31] This mechanism could also potentially alter muscle contractile properties. Future studies will address these complex issues. As CRF is an FDA-approved medication, local injection of CRF is a particularly attractive approach for extending the duration of botulinum toxin's paralyzing effects in the treatment of blepharospasm and related focal dystonias.

Muscle paresis and paralysis induce the expression of a number of neurotrophic molecules that play a role in peripheral nerve regeneration.[5,7] IGF1 and IGFII are particularly potent in increasing the rate of peripheral nerve regeneration, with IGFI playing a role in initial sprouting and subsequent elongation of the regenerating axons.[5,7] It is particularly interesting to note that IGFI levels significantly increase as early as three days after a single injection of botulinum toxin and remain elevated for up to one month.[18,34] Just as increased levels of IGFI can increase terminal sprouting,[35] precedence exists for decreasing terminal sprouting by reduction or inactivating IGFI-related molecules. Local treatment at the site of paralyzed muscles with either IGF-binding protein-4 or -5 results in suppression of terminal sprouting.[36,37] Antibodies to IGFI, when focally applied, result in reduction of terminal axon branching of injured facial nerve.[21,36] In the present study, injection of antibody to IGFIR proved to be just as effective as CRF in preventing new neuromuscular junction formation caused by botulinum toxin locally within the paralyzed orbicularis oculi muscle. Future studies of longer duration as well as muscle function studies will address whether preventing new neuromuscular junctions results in functional extension of botulinum toxin–induced muscle paresis, as predicted by the present results.

In summary, local injection of either CRF or anti-IGFIR prevented the up-regulation of neuromuscular junctions that occurs after botulinum toxin A injection. There is increased evidence that long-term treatment of muscle dystonias with botulinum toxin A results in reduced duration of effect over time, as well as the development of antibodies to botulinum toxin A that reduce the drug's effectiveness.[3–7] The ultimate

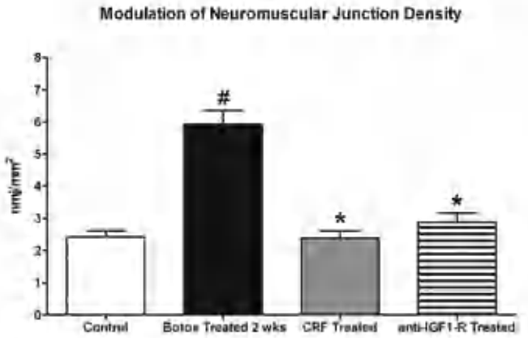

FIGURE 4. Quantification of neuromuscular junction density of control orbicularis oculi muscles (*white bar*) compared to two weeks after an injection of 5 units of botulinum toxin A only (Botox; *black bar*), and two weeks after botulinum toxin followed by corticotrophin releasing factor (*gray bar*) or an antibody to insulin growth factor-I receptor (*hatched bar*). *Significantly different from control; #significantly different from botox treated 2 weeks.

goal is to develop a co-treatment strategy to increase the duration of effect of single botulinum toxin A treatments. Decreasing frequency of patient injections for treatment of blepharospasm or other focal dystonias would, in turn, decrease the life-time exposure of these patients to the toxin, with concomitant reduction in potential side-effects.[98]

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Myofiber Length and Three-Dimensional Localization of NMJs in Normal and Botulinum Toxin–Treated Adult Extraocular Muscles

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Purpose. The density and three-dimensional localization of neuromuscular junctions (NMJs) of normal and botulinum toxin–treated normal adult rabbit and monkey extraocular muscles (EOMs) were analyzed. To demonstrate average myofiber length, randomly selected individual myofibers were reconstructed and compared with total muscle length.

Methods. Normal adult rabbit and monkey EOM and normal adult rabbit tibialis anterior were dissected in their entirety, frozen, sectioned longitudinally, and immunostained for NMJ localization. In addition, adult rabbit EOMs were injected with 5 U botulinum toxin, and NMJ density was determined after 2 weeks. NMJ locations for the three groups of EOM were reconstructed, and density of NMJ was determined. Individual myofibers were reconstructed from the orbital and global layers to determine mean fiber length.

Results. NMJs were dispersed throughout the entire length of all EOMs examined from adult rabbits and monkeys and were visualized by alpha-bungarotoxin staining and three-dimensional reconstruction of serial sections. In leg muscle, two relatively tight bands of NMJs were seen. Botulinum toxin significantly increased total NMJ density. Mean fiber lengths were 1.9 and 4.83 mm in the orbital and global layers, respectively, approximately 10% and 24% of the total origin-to-insertion muscle lengths. In addition, individual myofibers continuously changed their intrafascicular relationships over their lengths.

Conclusions. The density and distribution of NMJs in normal EOMs are more extensive than previously described. Individual myofibers are significantly shorter than the tendon-to-tendon muscle length in both muscle layers. Botulinum toxin results in a doubling of NMJ density. NMJ localization in normal EOMs has ramifications for understanding eye movement control, but it is also important when surgical or pharmacologic intervention is used for the treatment of strabismus, nystagmus, or other eye muscle disorders. (*Invest Ophthalmol Vis Sci.* 2007; 48:3594–3601) DOI:10.1167/iovs.06-1239

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The distribution of neuromuscular junctions (NMJs) in limb skeletal muscles of vertebrates has been described for many muscles. In general, most limb skeletal muscles have discrete, narrow motor endplate zones. Most NMJs in adult skeletal muscles are generally found in the approximate middle third of the tendon-to-tendon length of the muscle. Most craniofacial muscles diverge from this generalized plan of single motor endplate zones. In a study of 10 facial muscles, three major patterns of motor endplate zone localization were described[1]: one predominant motor endplate zone with two or three small zones evenly spread across the muscle, as in the zygomaticus major; two to four motor endplate zones located in eccentric positions, as in the levator labii superioris; multiple clusters of motor endplates distributed across the entire muscle, as in the orbicularis oculi.[1–3] This last pattern has also been described in laryngeal muscles.[4] Thus, motor endplate distribution is distinctly different between craniofacial muscles and limb skeletal muscles.

In general, studies of NMJ distribution in extraocular muscles (EOMs) have focused on visualizing and quantifying the en plaque and en grappe endings through the use of cholinesterase histochemistry[4,5] or autoradiography,[6] with a focus on the pattern of innervation on single myofibers. The distribution of NMJs is complicated by the presence of multiple innervated fibers in the orbital and global layers of adult EOM. However, it should be emphasized that multiple innervated fibers are in fact a minority, constituting only 7% to 20% of the myofibers in the orbital layer and 10% to 20% of the myofibers in the global layer.[7–9] Whole muscle analyses of NMJ distribution within EOM used cholinesterase histochemical procedures to visualize the junctions but did not examine complete three-dimensional reconstructions.[10,11] In the present analysis, the three-dimensional locations of all α-bungarotoxin–positive NMJs were mapped along the complete origin-to-insertional length of superior rectus muscles from normal adult rabbits and monkeys in every 10th section through the entire muscle. The extensive characterization in the present study is critical because the location of NMJs within normal EOM is important for understanding motor control of eye movements and for understanding when surgical or pharmacologic intervention is required for the treatment of strabismus, nystagmus, or other eye muscle disorders.

Botulinum toxin paralyzes NMJs and is routinely used as a treatment for strabismus and other muscle contractile disorders.[12] Studies have shown that muscle activity returns in part because of terminal nerve sprouting in the paralyzed muscle.[5,13] The extent of this change in terms of NMJ density within botulinum toxin–treated EOM is unknown. Thus, we examined alterations in the normal three-dimensional patterning of NMJs 2 weeks after a single injection of botulinum toxin in adult rabbit EOM.

Analyses of the length of individual myofibers relative to the whole muscle tendon-to-tendon length have described the orbital layer as containing fibers that run the entire length of the muscle and global fibers as being shorter than full muscle length.[10] However, individual myofibers have not been specif-

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ically examined and reconstructed. With the use of serially sectioned cross-sections, individual myofibers can be observed and reconstructed unequivocally. We reconstructed a number of randomly selected myofibers in normal adult rabbit EOM to determine their lengths proportionate to total muscle length.

Materials and Methods

Adult New Zealand White rabbits were obtained from Bakkom Rabbitry and housed in Association for Assessment of Laboratory Animal Care–approved animal facilities at the University of Minnesota. Monkey EOMs were obtained as waste tissue from macaque monkeys with Institutional Animal Care and Use Committee approval. All eye muscles came from normal monkeys used as controls. All procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the guidelines of the National Institutes of Health on the use of animals in research and were approved by the Institutional Animal Care and Use Committee at the University of Minnesota.

Normal adult rabbits were anesthetized with ketamine and xylazine (10 mg/kg, 2 mg/kg), and proparacaine drops were placed in the conjunctival cul-de-sac. One randomly selected superior rectus muscle received an injection of 5 U botulinum toxin in 100 μL sterile isotonic saline. After 2 weeks, all animals were anesthetized deeply with ketamine and xylazine, followed by barbiturate anesthesia overdose or thoracotomy and exsanguination. The orbit was opened superiorly, and the superior rectus muscles were removed completely from their scleral insertion to their origin in the orbital apex. Additionally, the tibialis anterior muscles were removed from four normal adult rabbits from origin to insertion. The muscles were pinned to their in situ length in embedding molds and were surrounded by tragacanth gum, frozen in methylbutane, chilled to a slurry on liquid nitrogen, and stored at −80°C until sectioned and processed. Muscles were sectioned completely in the longitudinal plane at 12 μm, and sections were mounted on gelatin-subbed microslides. Every 10th section for the EOM and every 20th section for the tibialis anterior were immunostained for the presence of NMJs using α-bungarotoxin conjugated to Alexa Fluor 488 (Molecular Probes, Eugene, OR) at a concentration of 1:100. Slides were coverslipped with mounting medium (Vectashield; Vector Laboratories, Burlingame, CA) and were analyzed the same day they were immunostained. Monkey muscles were obtained after the monkeys were humanely killed by our collaborators. Monkey muscles were treated exactly as were rabbit muscles. Four muscles were analyzed for each species and for each experimental time point: four rabbit control extraocular muscles, four rabbit control tibialis anterior muscles, four monkey control extraocular muscles, and four rabbit muscles injected with botulinum toxin 2 weeks before examination.

NMJs in the muscle sections were visualized under a microscope (DMR; Leica Microsystems, Wetzlar, Germany). With the use of image analysis software (Topographer program, NovaPrime; Bioquant, Nashville, TN), the area of the entire muscle in longitudinal section was measured at 1.5×. Every NMJ was located at 20× and marked with X and Y coordinates recorded in the software program. This analysis was repeated for every 10th section through the entire superior rectus. The program (Topographer program, NovaPrime; Bioquant) was used to reconstruct the entire muscle, including the area outlines and locations of each NMJ. This allows for a three-dimensional reconstruction of all the NMJs in their actual X, Y, and Z locations within the entire muscle. Four normal rabbits, four normal monkeys, and four botulinum toxin–treated superior rectus muscles were reconstructed.

Density of the NMJs was calculated by determining the number of NMJs per cubic millimeter. Statistical significance between the density of NMJs in the normal and botulinum-toxin treated muscles was calculated using an unpaired *t*-test aided by statistical software (Prism and StatMate; GraphPad, San Diego, CA). An F test was used to verify that the variances were not significantly different. Data were considered significantly different if $P \leq 0.05$.

Individual myofibers from the control superior rectus muscles were reconstructed using the image analysis software (Topographer program, NovaPrime; Bioquant). Individual myofibers were chosen randomly from one of three positions within the muscle cross-section: the orbital layer, the boundary of the orbital and global layers, and the global layer. In general, they were selected from the middle one third of the width of the muscle cross-section rather than the lateral edges. If the myofiber chosen could not be traced definitively throughout its length because of section folding or tearing or other histologic artifact, another fiber was chosen. Fiber areas were manually traced, and serially sectioned muscles were used to follow the myofibers proximally and distally to their terminations. At least 10 myofibers were reconstructed from each layer, allowing for three-dimensional reconstruction of single myofibers and determination of their total length by multiplying the number of sections that contained the myofiber by the thickness of the cryostat sections. Mean fiber length was determined, and statistical significance was determined using an unpaired *t*-test as described.

Results

In all normal superior rectus muscles examined from rabbit and monkey, NMJs were found along the entire length of each muscle, from the scleral insertion to the muscle origin in the apex (Figs. 1A, 2, 3). There was no obvious endplate zone in any of the reconstructed muscles. No obvious pattern of NMJ distribution could be discerned, in contrast to tibialis anterior muscles (Fig. 4). In normal adult tibialis anterior muscles, two narrow endplate zones were clearly apparent in these whole-muscle reconstructions (Fig. 4).

After botulinum toxin injections in the rabbit superior rectus muscles, the density of the NMJ increased (Figs. 1B, 5). In addition, the individual NMJs appeared smaller than the uninjected control muscles, but individual NMJ lengths and areas were not determined (Fig. 5).

The density of NMJs was calculated based on numbers of NMJs counted and section thickness for the superior rectus muscles from the normal rabbits and monkeys and from the botulinum toxin–treated muscles from rabbits. Average density of the NMJs in rabbit superior rectus was 277 ± 179 /mm^3, which was similar to that seen in monkey superior rectus muscles (2593 ± 106 /mm^3). In distinct contrast to the extraocular muscles, the average density of NMJs in adult rabbit tibialis anterior was 18.9 ± 0.54/mm^3 (Fig. 6), a 100-fold difference from the densities seen in normal extraocular muscle. Botulinum toxin treatment caused a significant change in NMJ density. Two weeks after injection of 5 U botulinum toxin in the rabbit superior rectus, the density of NMJs doubled to 6557 ± 700/mm^3 (Fig. 6).

Individual myofibers were reconstructed from the orbital layer, from fibers at the border of the orbital and global layers, and from the global layer (Fig. 7). All reconstructed fibers were significantly shorter than the complete tendon-to-tendon muscle length (Fig. 8). In addition, individual myofibers did not stay in the same fascicle from beginning to end (Fig. 9). When fibers were observed serially, it was clear that nearest neighbors continually changed. It was also clear that individual myofibers began (e.g., fibers 9 and 10, indicated by the horizontal arrows) and ended (e.g., fiber 9, indicated by the vertical arrow) continuously (Fig. 9). Thus, for individual myofibers, fascicular organization and neighboring myofibers changed throughout their course within the muscle.

Discussion

In contrast to most adult limb skeletal muscles, NMJs in the EOMs of adult rabbits and monkeys are extensively dispersed along the entire length of the muscles, from origin to insertion. No obvious pattern of NMJ localization could be discerned in

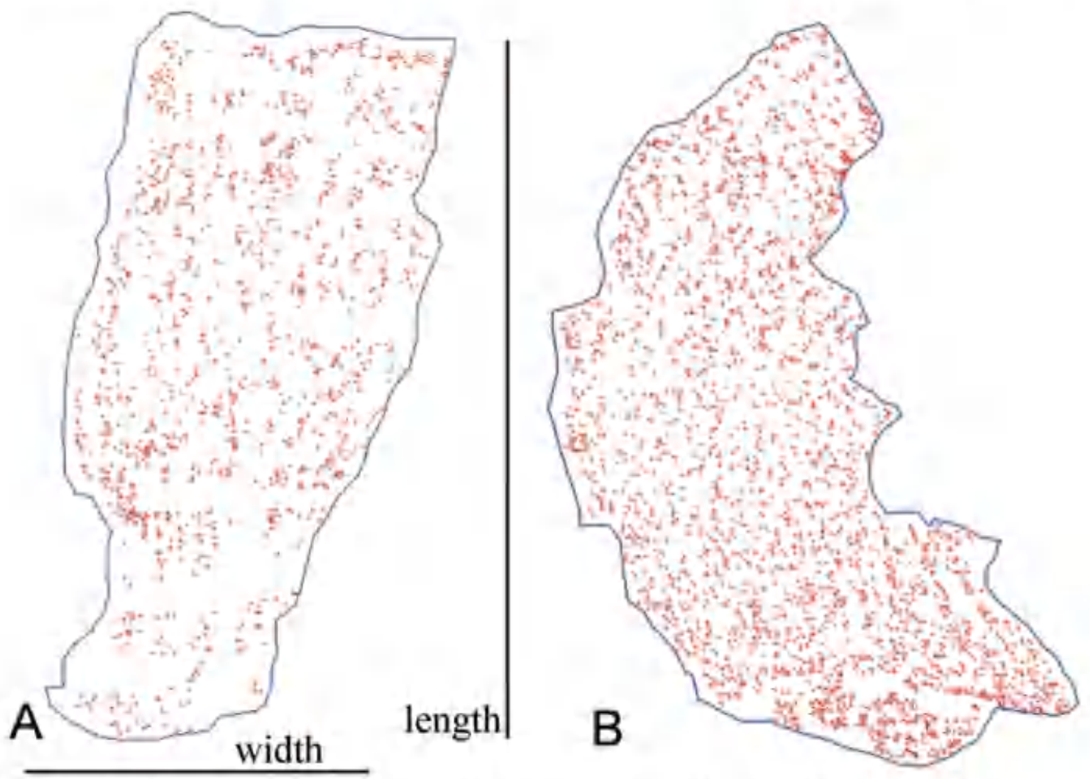

FIGURE 1. (**A**) Single longitudinal section taken from the middle of the muscle thickness, and thus the global layer, of a control superior rectus muscle from a normal adult rabbit. All the NMJs marked in *red* are oriented with the origin and insertion at the *top* and *bottom* of the reconstruction. (**B**) Single longitudinal section taken from the middle of the thickness, and thus the global layer, of a superior rectus muscle from an adult rabbit 2 weeks after a single injection of 5 U botulinum toxin. All the NMJs marked in *red* are oriented with the origin and insertion at the *top* and *bottom* of the reconstruction.

these three-dimensional reconstructions, in direct contrast to the reconstructions of the tibialis anterior muscles, where two narrow endplate zones were clearly evident. This difference is further supported by NMJ density calculations because the density of NMJs, calculated as NMJ/mm^3 in the EOM, is 100-fold higher than in the tibialis anterior muscle. A single injection of botulinum toxin results in a significant increase in the overall density of the NMJs compared with normal adult EOM, indicating that a large amount of nerve sprouting occurs within the first few weeks after botulinum toxin injection.

Most adult limb skeletal muscles, which are derived from somites in development, develop single motor endplate zones. Muscles that are bipennate, such as the gastrocnemius, can develop two or three motor endplate zones, but they are consistently located within a single motor endplate zone for each division of the muscle.[14] Very long muscles, such as sternocleidomastoid, develop an "in-series" structure with multiple endplate zones, but again these bands are tightly localized within the segmental subdivisions within these muscles.[15,16] Interestingly, a number of parallel-fibered muscles develop more complex patterns related to short, interdigitated fibers that taper to an end within the muscle mass.[17,18] However, these muscles still develop clearly observable banding patterns of NMJs. Many of the craniofacial muscles have a more complex pattern of NMJ distribution. These patterns vary even within a similar group of muscles, such as the facial musculature,[1] where muscles innervated by the same motor nerve develop distinct patterns of NMJ localization. Some of the facial muscles have one main endplate zone, such as the zygomaticus major, whereas others have more dispersed patterns of NMJs, such as the orbicularis oculi.[1,2] These patterns vary between humans and other vertebrates for the cricoarytenoid and thyroarytenoid muscles of the larynx, which have focal bands in rabbits and rats and dispersed distribution within these muscles in humans.[19] EOMs appear to be at the far end of this continuum relative to NMJ localization.

Several reports in the literature have investigated patterns of NMJ localization in the EOM of various species. With the use of cholinesterase histochemistry in mouse EOM, a central zone of NMJs of the en plaque type and a more widespread distribution of en grappe endings were observed throughout the muscle.[13] Other studies in rat and mouse demonstrate similar localization, suggesting species differences between these small rodents and larger mammals; however, three-dimensional reconstructions were not performed.[20–22] In human EOM, more complex patterns of innervation of individual myofibers were described; 34% of the fibers had multiple endplates on individual fibers, 29% of which were not en grappe–type endings.[6] Although earlier studies of EOM using cholinesterase incubation methods described a concentration of motor endplates in the middle third of the orbital layer and five to six zones in the global layer of cat EOM, three-dimensional reconstruction of all

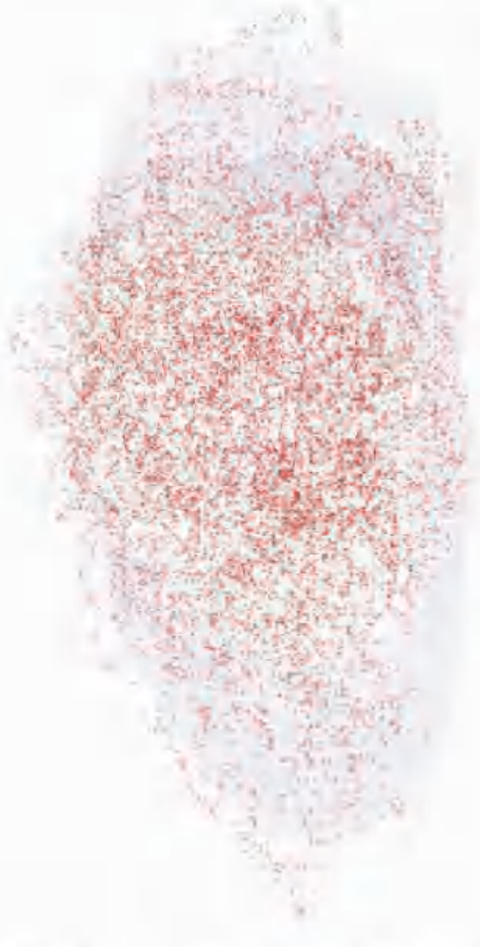

FIGURE 2. Three-dimensional reconstruction of all the α-bungarotoxin–positive NMJs in every 10th section through the entire thickness of a single control superior rectus muscle from an adult rabbit. All NMJs are indicated in *red*, and the specimen is oriented with the origin and insertion at the *top* and *bottom* of the reconstruction.

the NMJs was not performed.[10] However, a scattered distribution of endplates was described, particularly in the global layer. In other muscles NMJ disbursement is thought to be caused by the presence of many short myofibers and the localization of NMJs in eccentric positions along the length of single myofibers.[2,6] The dispersed nature of NMJ localization is not just a function of short individual myofibers that do not run the full tendon-to-tendon length of the muscle. Sartorius, tenuissimus, and semitendinosus muscles, which all contain short fibers, still develop discrete motor endplate zones spaced at fairly regular intervals from origin to insertion.[17]

The dispersed nature of the NMJs and their density in the adult rabbit and monkey EOM provide a good visual demonstration of how short the average myofibers are within the adult EOM. This is true in orbital and global layers of the rabbit and monkey. One report indicates that orbital layers span the full tendon-to-tendon length in cats[10]; however, this was based not on fiber reconstructions but on whole muscle acetylcholinesterase staining. The presence of short, overlapping myofibers in the EOM has been described.[10,23,24] In addition, the fact

FIGURE 3. Three-dimensional reconstruction of all the α-bungarotoxin–positive NMJs in every 10th section through the entire thickness of a single control superior rectus muscle from an adult monkey. All the NMJs are indicated in *red*, and the specimen is oriented with the origin and insertion at the *top* and *bottom* of the reconstruction.

FIGURE 4. Three-dimensional reconstruction of all the α-bungarotoxin–positive NMJs in every 20th section through the entire thickness of a single control tibialis anterior muscle from an adult rabbit. All the NMJs are indicated in *red*, and the specimen is oriented with the origin and insertion at the *top* and *bottom* of the reconstruction. *Inset* is an example of an α-bungarotoxin–labeled NMJ. Total length of rabbit tibialis muscle is approximately 5.5 cm.

that individual myofibers in the EOM are generally shorter than the full muscle length is supported by significant differences in the patterns of myosin heavy chain isoform expression along the length of individual EOMs,[25] the reconstruction of individual myofibers in this and other studies,[26,27] and the demonstration that myomyous junctions, representing overlapping nonspanning myofibers that terminate intrafascicularly, exist within the EOM.[10] It is particularly interesting that during development, production of secondary myotubes is linked to sites of innervation of the primary myotubes.[28,29] Widespread innervation may result in the formation of small myofibers dispersed based on this pattern of innervation. In addition, the EOM retains a population of activated satellite cells that fuse into existing myofibers in apparently random locations along the muscle length.[26,27] The localization of sites for this process may be related to this dispersed nature of the sites of innervation in adult EOM, either by direct induction of myoblast fusion or by providing an environment that secondarily results in fusion of these activated satellite cells into mature myofibers.

This architectural arrangement has important implications for an understanding of length-tension relationships, shortening velocities, and the development of force within the EOM. In studies of ocular convergence, muscle force was found to be paradoxically less than would be predicted based on firing rates.[30] In another series of experiments examining extraocular motor units and whole muscle contractile properties in cats and monkeys, individual motor units lost an average of 45% to 50% of their force output when they fired in concert with additional motor units.[31–33] The presence of many short fibers

FIGURE 5. Three-dimensional reconstruction of all the α-bungarotoxin–positive NMJs in every 10th section through the entire thickness of a single superior rectus muscle from a rabbit 2 weeks after a single injection of 5 U botulinum toxin. All the NMJs are indicated in *red*, and the specimen is oriented with the origin and insertion at the *top* and *bottom* of the reconstruction.

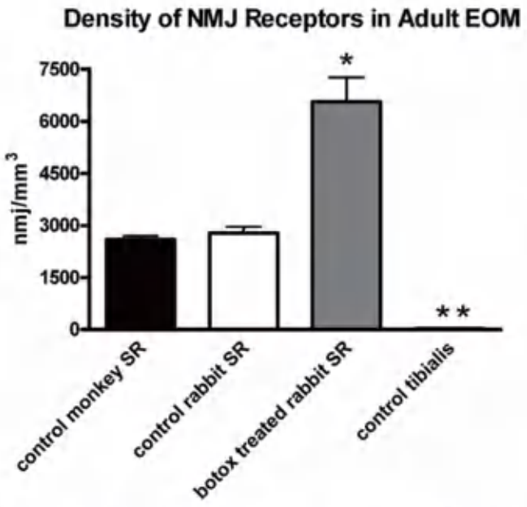

FIGURE 6. Graph of the mean NMJ density in cubic millimeters in control monkey (*black*), control rabbit (*white*), and botulinum toxin–treated (*gray*) superior rectus (SR) muscles. *Significant difference from control at $P < 0.005$. **Density is low (18.9 ± 0.54/mm^3) and thus is not clearly visible when graphed compared with NMJ density within the normal EOM of rabbit and monkey.

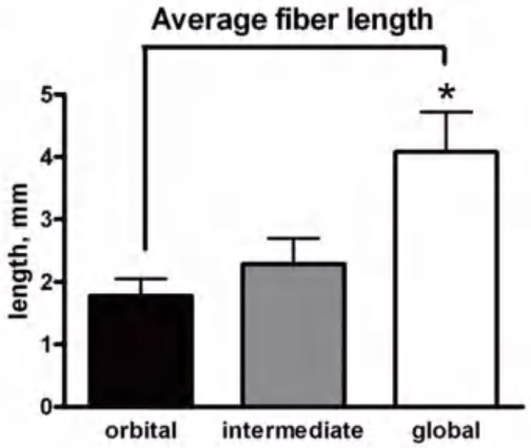

FIGURE 8. Mean myofiber length, in millimeters, of individual myofibers reconstructed from the orbital layer (*black*), global layer directly contiguous with the orbital layer (*gray*), and middle of the global layer (*white*). *Significant difference from orbital and intermediate layer fibers compared with fibers from the middle of the global layer ($P < 0.005$).

also may explain why force is relatively normal in the EOM after injury.[32] In addition, it suggests that motor units may be bigger than would be predicted by counting muscle fibers in a given muscle cross-section because this would be an underrepresentation of the total number of muscle fibers in each EOM.

Botulinum toxin is commonly used in strabismus to weaken the EOM,[12] and the nature of its effect on the three-dimensional localization of NMJs has not been examined. The method of action of botulinum toxin is to cleave SNAP25, which prevents the docking of synaptic vesicles containing acetylcholine, effectively paralyzing the NMJs.[34] After injection, force gradually decreases over an 18-hour period.[35] Nerve sprouting is seen as early as 2 days after botulinum toxin

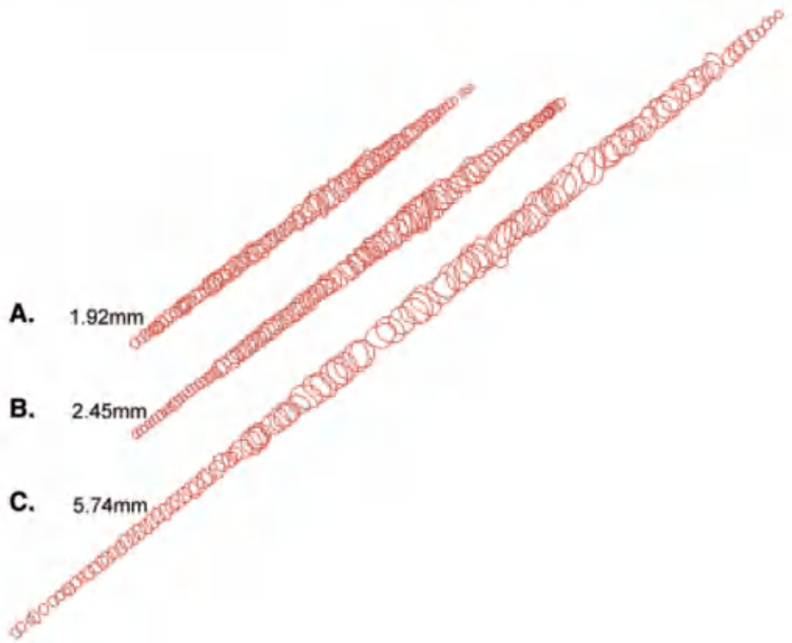

FIGURE 7. Representative examples of individual myofibers reconstructed from the (**A**) orbital layer, (**B**) global layer directly contiguous with the orbital layer, and (**C**) middle of the global layer. These represent the complete lengths of these three fibers followed in serial sections.

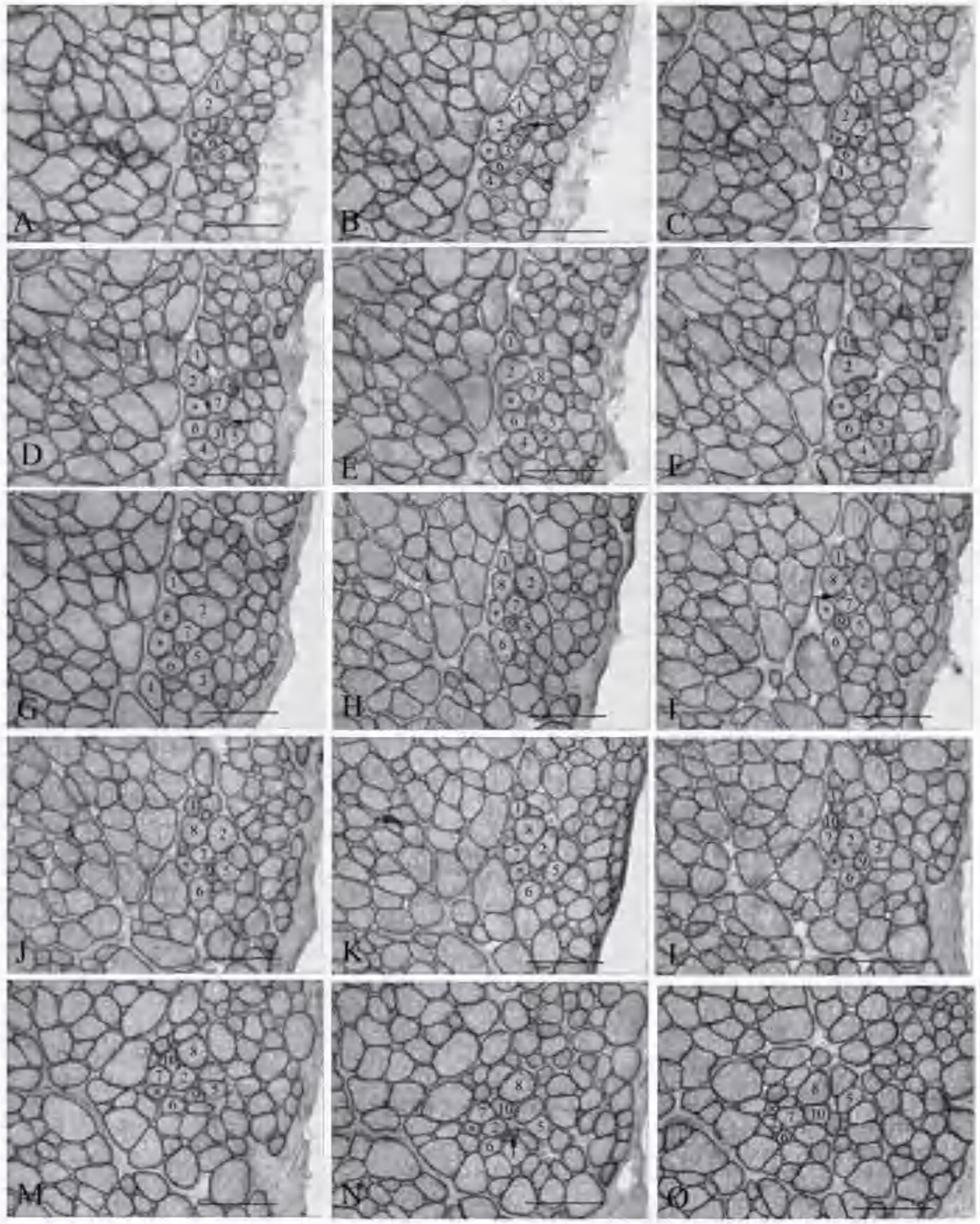

FIGURE 9. (A–O) Representative photomicrographs of a single fiber from an adult normal superior rectus muscle (4.622 mm long) from rabbit, demonstrating changes in its fascicular relationship with its neighboring fibers relatively often in the course of its fiber length. *Individual myofiber that was reconstructed. Numbered fibers allow observation of the changes in the neighboring muscle fibers over the course of 2.9 mm represented by these selected sections. *Horizontal arrows* indicate fibers that newly appear in the cross-sections within 2.9 mm of the reconstruction (numbers 9 and 10). *Vertical arrow* indicates a fiber that ends within 2.9 mm.

treatment and slowly increases over time.[36,37] This results in a supersensitivity of the muscle in the regenerative phase[38] and correlates well with our observation that a significant increase occurs in NMJ density and that the sprouted nerves appear to maintain NMJs smaller than normal. Functional return of muscle force is related to the return of original nerves to their NMJs, though in human patients who have received multiple injections of botulinum toxin, these sprouts can persist long after functional recovery has occurred.[39] These observations suggest that it may be possible to prolong the effectiveness of a single botulinum toxin injection if nerve sprouting or NMJ assembly is inhibited or delayed, which would improve the treatment of patients with focal dystonias and related motor disorders.

It is unclear what controls EOM tone and how strabismus surgery alters muscle structure and function.[40] Understanding the normal density and localization patterns of NMJs and understanding the variation in individual myofiber lengths will facilitate future studies examining whether and how these characteristics are altered in the muscles of patients with strabismus, nystagmus, and other eye muscle motor disorders.

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REVIEW

Perioperative visual loss in ocular and nonocular surgery

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Abstract: Incidence estimates for perioperative vision loss (POVL) after nonocular surgery range from 0.013% for all surgeries up to 0.2% following spine surgery. The most common neuro-ophthalmologic causes of POVL are the ischemic optic neuropathies (ION), either anterior (AION) or posterior (PION). We identified 111 case reports of AION following nonocular surgery in the literature, with most occurring after cardiac surgery, and 165 case reports of PION following nonocular surgery, with most occurring after spine surgery or radical neck dissection. There were an additional 526 cases of ION that did not specify if the diagnosis was AION or PION. We also identified 933 case reports of central retinal artery occlusion (CRAO), 33 cases of pituitary apoplexy, and 245 cases of cortical blindness following nonocular surgery. The incidence of POVL following ocular surgery appears to be much lower than that seen following nonocular surgery. We identified five cases in the literature of direct optic nerve trauma, 47 cases of AION, and five cases of PION following ocular surgery. The specific pathogenesis and risk factors underlying these neuro-ophthalmic complications remain unknown, and physicians should be alert to the potential for loss of vision in the postoperative period.

Keywords: perioperative, postoperative, vision loss, ocular surgery, nonocular surgery

Introduction

Vision loss is a rare, and devastating, complication that can be seen following both ocular and nonocular surgeries. The specific pathogenesis of perioperative vision loss (POVL) remains elusive in most cases, with much controversy surrounding patient and surgical risk factors. Many publications have speculated on causation. Unfortunately, given the rarity of POVL, these are based solely on retrospective data. We present a detailed review of the literature on the subject of vision loss following ocular and nonocular surgical procedures.

Method of literature review

We searched the National Library of Medicine's PubMed database with a subsequent review of the accompanying references (last accessed February 8, 2010). The major search words and word combinations included: posterior ischemic optic neuropathy; anterior ischemic optic neuropathy; central retinal artery occlusion; pituitary apoplexy; cortical blindness; optic nerve trauma; postoperative vision loss; postoperative blindness; perioperative vision loss; perioperative blindness; and ocular surgery. In addition, the citations from the above searches were also included. Cases from the non-English literature and cases prior to 1970 were not included. Cases with documented direct surgical trauma to orbital structures other than the optic nerve were not included.

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Cases attributed to steroid injection into orbital structures were also not included.

Neuro-ophthalmologic causes of vision loss after nonocular surgery

Incidence and prevalence of POVL

Vision loss occurring after nonocular surgery with general anesthesia typically results from: anterior ischemic optic neuropathy (AION); posterior ischemic optic neuropathy (PION); central retinal artery occlusion (CRAO); pituitary apoplexy; or cortical blindness. While studies of 400,000[1] and 61,000[2] patients undergoing general anesthesia have demonstrated a low incidence of POVL in noncardiac, nonspinal fusion procedures, the actual incidence, overall, remains unknown. However, the risk of POVL is believed to be highest following cardiac or spine surgeries. A recent review of 5.6 million patients from the National Inpatient Sample (NIS) found that the incidence of POVL to be 8.64/10,000 after cardiac procedures and 3.09/10,000 after spinal fusion, while the incidence was only 0.66/10,000 after cholecystectomy, and just 0.12/10,000 after appendectomy.[3] In a retrospective study of 501,342 noncardiac surgeries carried out at one institution, only four patients (0.0008%) developed persistent vision loss not attributed to direct surgical trauma to optic or cerebral tissues.[4] In a separate study at the same institution, 17 patients were found to have perioperative ION out of a total of 27,915 coronary artery bypass graft (CABG) procedures (0.06%).[4] Similar studies of POVL following cardiac surgery have shown comparable findings, with the incidence rates ranging from 0.09%[5] to 0.113%.[6] Other studies suggest that the rate of POVL may be even higher after spine surgery. A study of over 225,000 surgeries at a single institution over a 15-year period found three cases of POVL out of 3,351 spine surgeries (0.09%), a 50-fold higher rate compared with other surgeries in the study.[7] Additional large-scale studies of POVL after spine surgery have demonstrated incidence rates varying from 0.094%[8] to 0.2%,[9] though the higher incidence seen in the latter study may be because it was carried out at three tertiary care specialty hospitals, which may have attracted more complex cases.

Ischemic optic neuropathies

The two most common types of POVL are AION and PION.[10,11] In a recent study of 126,666 surgeries from a single institution, there were 17 cases of ischemic optic neuropathy (ION) (0.013%): 8 AION and 9 PION.[12] The type of ION varies depending on the type of surgery performed, with AION occurring most often after cardiac surgery[13] and PION occurring most often after prone-positioned spine surgery or radical neck dissection.[10,13]

In a recent analysis of 4,728,815 spine surgeries from the NIS registry, the overall incidence of postoperative ION was found to be 0.006%.[3] Other incidence estimates for ION following spine surgery range from 0.028%[13] to 0.12%.[9]

A review of 27,915 cardiac surgeries found the overall incidence of ION to be 0.06%, with 12 cases of AION and five cases of PION,[4] while another study of 9,701 CABG procedures found an ION incidence of 0.11%, with eight cases of AION and three cases of PION.[6] A review of 602 CABG procedures found the incidence of AION to be 1.3%,[15] while a similar study of 7,685 CABG procedures found an ION incidence of 0.09%.[5]

When the incidence values from these large-scale reviews are compiled, the overall incidence of AION is 0.00079% (1/126,666) after spine surgery and 0.024% (42/172,569) following cardiac surgery. There were no cases of AION following noncardiac, nonspine surgery in any of the large-scale reviews. When the incidence values for PION are compiled, the overall incidence is 0.005% (7/140,768) after spine surgery, 0.0061% (10/164,282) following cardiac surgery, and 0.0032% (4/126,666) after nonspinal, noncardiac surgery.

Diagnosis

AION is likely caused by occlusion or relative hypoperfusion of the anterior optic nerve head by the posterior ciliary arteries.[16] Typical presentation includes sudden painless vision loss and a visual field defect, most commonly inferior altitudinal in nature. Diffuse or segmental disc edema is observed on funduscopy at symptom onset, with the development of optic nerve atrophy after 4–8 weeks (Figure 1).[17] Three forms of AION are recognized: perioperative, arteritic, and nonarteritic.[16] The arteritic form of AION, associated with giant cell arteritis (GCA), often presents in the elderly with an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and systemic symptoms such as weight loss and jaw claudication. It is important to note that inflammatory markers are often extremely elevated after general surgery. Because of this, in the absence of other features of GCA such as systemic symptoms or abnormal temporal arteries, it is not advisable to check ESR and CRP in a patient who awakes from surgery with visual loss. If these are checked, an elevated ESR alone is not enough to diagnose arteritic AION in the postoperative period.[18] The

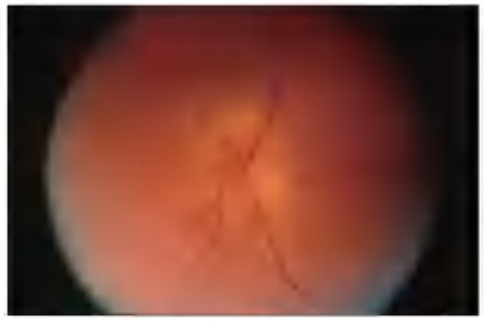

Figure 1 Optic disc edema observed in all cases of acute anterior ischemic optic neuropathy.

gold standard for diagnosing arteritic AION is the temporal artery biopsy. Giant cell arteritis is considered an ophthalmic emergency, requiring the urgent administration of systemic corticosteroids to prevent the development of permanent, bilateral blindness.[18]

PION is believed to result from infarction to the intraorbital optic nerve, supplied by pial blood vessels. PION is much less common than AION. There are three recognized types of PION: perioperative, arteritic, and nonarteritic; the perioperative type is the most common.[20] PION presents with similar signs and symptoms as AION, and is differentiated from AION based on the presence of a normal optic disc and fundoscopic examination at the onset of visual symptoms (Figure 2).[17] Gadolinium enhancement[21] and/or restricted diffusion[22] may be seen on orbital magnetic resonance imaging (MRI), while the MRI is typically unremarkable in AION.

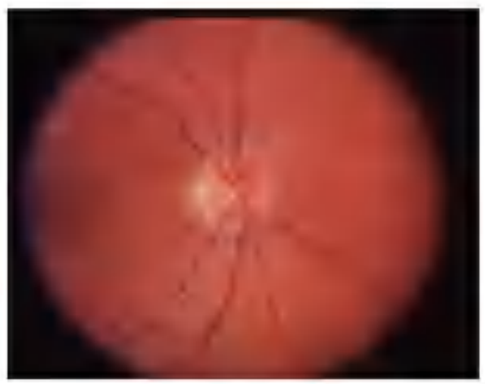

Figure 2 Normal appearing optic disc is seen in all cases of acute posterior ischemic optic neuropathy.

Pathogenesis, risk factors, and outcomes

The pathogenesis of postoperative ION remains undefined. AION may occur in the setting of substantial blood loss or hypotension, such as that seen following gastrointestinal bleeding or hemodialysis. It is for this reason that some have suggested that intraoperative hypotension and anemia underlie the development of ION.[23] Of 83 cases of ION following spine surgery listed in the American Society of Anesthesiologists (ASA) Postoperative Visual Loss Registry, 96% had 1 L or more of blood loss or 6 hours or more of total anesthesia time, (with a mean anesthetic time of 9.6 hours).[10] Blood loss, with or without arterial hypotension, has been shown to cause the release of endogenous vasoconstrictors due to the activation of the sympathetic nervous system, which can produce choroidal and optic nerve ischemia.[24] The use of vasoconstricting agents to correct intraoperative hypotension has also been suggested to promote optic nerve ischemia.[5,11,24] Analysis of the NIS registry found that patients who developed ION were more likely to have hypotension, peripheral vascular disease, or anemia.[8] However, there have been cases of ION development in patients with blood pressure readings >90 mmHg[25] and in those with minimal (less than 500 mL) blood loss.[10,25,26]

Postoperative AION occurs most often after cardiac surgery, especially CABG. The mild to moderate hypothermia used during bypass could cause increased blood viscosity, which may lead to watershed infarction of the optic nerve.[5] Indeed, it has been shown that cerebral blood flow decreases by 6%–7% for every degree Centigrade drop in body temperature.[27] Cardiopulmonary bypass has also been shown to promote complement activation, causing a five-fold increase in C3a levels, a known smooth muscle spasminogen.[28] A recent time-matched, case-control study found that patients who developed AION after CABG had lower postoperative hemoglobin values, a higher rate of atherosclerotic disease, and were more likely to have had a coronary angiogram within 48 hours of surgery when compared with control CABG patients.[4] A similar study found that CABG patients who developed postoperative AION had prolonged bypass times, lower hematocrit levels, marked perioperative weight gain from large fluid infusions required to support intraoperative blood pressure, and lower cardiac outputs requiring higher doses of inotropic medications.[15]

CABG could also contribute to the development of AION through elevations in intraocular pressure (IOP). It has been noted that AION has occurred with elevations in IOP,[29,30] and there is experimental evidence that elevated IOP can cause optic nerve ischemia by reducing blood flow to the eye.[31]

10 patients from pre-existing case reports and the rest were cases from the authors' institution or data received from a solicitation to a spine society. The controls were taken from the authors' institution rather than matched to where the surgery took place. Finally, all of the hemodynamic variables were not available for all of the cases.[36] Meanwhile, Holy and colleagues identified 17 patients with ION from a single institution. Each case was assigned two control patients, matched for age and gender, who underwent similar surgeries at the same institution with a similar date of surgery. All preoperative, intraoperative, and postoperative hemodynamic variables were available for cases and controls. There was no significant difference between cases and controls in any single hemodynamic variable, suggesting that the cause of ION following nonocular surgery is multifactorial. Almost all patients who develop postoperative ION experience some degree of blood loss, anemia, and hypotension, though not to a greater degree than that seen in control patients who did not suffer ION after surgery.[12]

There have been many documented cases of PION following radical neck dissection. Distension of ophthalmic veins, with accompanying facial edema, due to internal jugular vein ligation has been proposed as a potential mechanism for PION development. The venous distention could cause compression of the orbital apex, resulting in reduced perfusion and further anoxia of the posterior aspect of the optic nerve.[23,43]

While there is no established treatment for postoperative AION or PION, some have documented an improvement in visual acuity after the correction of anemia with blood transfusion,[9,44] the correction of hypotension with vasopressors,[45] or the use of high-dose corticosteroids.[9] However, some patients recover full acuity without any treatment,[46] suggesting that the improvements seen following the proposed interventions may be merely coincidental.

Anterior ischemic optic neuropathy literature review

Through our review of the literature, we encountered 111 reports of AION following nonocular surgery, as well as an additional 526 reports defined only as "ischemic optic neuropathy" (Table 1).[5,10,47,48] While AION was most commonly seen after: cardiac procedures;[4–6,12,15,18,47,49–57] it also occurred after spine surgery;[9,10,12,36,58–63] shoulder surgery;[64,65] radical neck dissection;[66–70] total parathyroidectomy;[55] peripheral vascular surgery;[71] emergent Cesarian section;[44] transurethral prostatectomy;[72] radical prostatectomy;[73] hip replacement;[74] osteosynthesis;[74] bilateral knee replacement;[74]

Table 1 Ischemic optic neuropathy cases following nonocular surgery

Number of patients, reference	Age; gender	Surgery performed	Diagnosis
*271[9]	NA; 51% male	Spine surgery	ION, not further specified
*245[5]	NA	Spinal, orthopedic, Cardiac, and general Surgery	ION, not further specified
8[10]	36–64; 72% male	Spine surgery	ION, not further specified
2[47]	NA	CABG	ION, not further specified
19[10]	36–64; 72% male	Spine surgery	AION
*8[36]	12–68; gender NA	Spine surgery	AION
1[61]	65 F	Spine surgery	AION
1[62]	60 F	Spine surgery	AION
1[63]	41 M	Spine surgery	AION
1[58]	57 M	Spine surgery	AION
1[59]	50 F	Spine surgery	AION
1[60]	16 F	Spine surgery	AION
1[61]	44 M	Spine surgery	AION
1[9]	56 F	Spine surgery	AION
1[12]	71 M	Spine surgery	AION
12[4]	57–73; 71% male	CABG	AION
8[15]	58–70; 63% male	CABG	AION
8[6]	39–81; 82% male	CABG	AION
7[5]	44–61; all male	CABG	AION
3[47]	NA	CABG	AION
1[13]	60 M	CABG	AION
1[52]	54 M	CABG	AION
1[12]	64 M	CABG	AION
1[53]	55 M	CABG	AION
1[12]	72 M	CABG	AION
1[12]	60 M	CABG	AION
1[13]	54 M	CABG	AION
1[19]	54 M	CABG	AION
1[19]	54 M	CABG	AION
1[18]	63 M	CABG	AION
1[11]	46 M	CABG	AION
1[51]	63 M	CABG	AION
1[50]	55 M	CABG	AION
1[16]	68 M	CABG	AION
1[17]	68 M	CABG	AION
1[71]	74 M	CABG	AION
1[58]	56 M	CABG	AION
1[55]	44 M	CABG	AION
1[54]	71 F	CABG	AION
1[56]	58 M	CABG	AION
1[57]	63 M	CABG	AION
1[51]	71 F	CABG	AION
1[52]	70 M	CABG[43]	AION
1[54]	63 M	CABG	AION
1[67]	47 M	Neck dissection	AION
1[69]	48 M	Neck dissection	AION

(Continued)

Table 1 *(Continued)*

Number of patients, reference	Age; gender	Surgery performed	Diagnosis
1[70]	60 M	Neck dissection	AION
1[66]	16 F	Total parathyroidectomy	AION
1[69]	40 M	Dynamic cardiomyoplasty	AION
1[52]	64 F	Coronary catheterization	AION
1[71]	62 F	Peripheral vascular surgery	AION
1[64]	45 M	Shoulder surgery	AION
1[65]	55 M	Shoulder surgery	AION
1[74]	52 M	Hip replacement	AION
1[74]	75 M	Hip replacement	AION
1[74]	80 F	Hip replacement	AION
1[74]	55 M	Osteosynthesis	AION
1[74]	66 M	Bilateral knee replacement	AION
1[44]	29 F	Cesarian section	AION
1[73]	66 M	Transurethral prostatectomy	AION
1[73]	50 M	Radical prostatectomy	AION
1[75]	47 F	Liposuction	AION
56[10]	36–64; 72% male	Spine surgery	PION
14[20]	mean age 43.3; gender NA	Spine surgery	PION
*14[36]	12–68; gender NA	Spine surgery	PION
1[37]	66 M	Spine surgery	PION
1[37]	43 M	Spine surgery	PION
1[37]	12 M	Spine surgery	PION
1[37]	57 M	Spine surgery	PION
1[37]	44 M	Spine surgery	PION
1[14]	13; gender NA	Spine surgery	PION
1[14]	13; gender NA	Spine surgery	PION
1[14]	43; gender NA	Spine surgery	PION
1[14]	29; gender NA	Spine surgery	PION
1[12]	63 M	Spine surgery	PION
1[13]	77 M	Spine surgery	PION
1[12]	66 M	Spine surgery	PION
1[62]	49 F	Spine surgery	PION
1[9]	79 F	Spine surgery	PION
1[9]	27 F	Spine surgery	PION
1[9]	37 M	Spine surgery	PION
1[77]	24 M	Spine surgery	PION
1[77]	44 M	Spine surgery	PION
1[78]	33 F	Spine surgery	PION
1[79]	24 M	Spine surgery	PION
1[11]	13 M	Spine surgery	PION
1[80]	51 M	Spine surgery	PION
1[43]	59 M	Spine surgery	PION
1[81]	48 M	Spine surgery	PION
1[46]	58 M	Spine surgery	PION
1[82]	68 F	Spine surgery	PION
1[69]	10 M	Spine surgery	PION
1[83]	60 M	Spine surgery	PION

(Continued)

Table 1 *(Continued)*

Number of patients, reference	Age, gender	Surgery performed	Diagnosis
1[9,10]	67 M	Neck dissection	PION
1[84]	71 M	Neck dissection	PION
1[85]	48 M	Neck dissection	PION
1[86]	49 M	Neck dissection	PION
1[68]	64 M	Neck dissection	PION
1[102]	73 M	Neck dissection	PION
1[87]	37 M	Neck dissection	PION
1[1]	77 M	Neck dissection	PION
1[1]	67 F	Neck dissection	PION
5[4]	57–73; 71% male	CABG	PION
3[6]	39–81; 82% male	CABG	PION
1[12]	61 M	CABG	PION
1[13]	68 F	CABG	PION
1[21]	57 F	CABG	PION
1[88]	46 F	CABG	PION
1[71]	81 F	CABG	PION
3[91]	59 M	Rhinoplasty	PION
1[91]	40 M	Rhinoplasty	PION
1[91]	23 F	Rhinoplasty	PION
1[89]	62 M	Drainage of infected hip prosthesis	PION
1[90]	64 M	Shoulder surgery	PION
1[97]	65 F	Knee surgery	PION
1[12]	66 M	Knee surgery	PION
1[12]	62 M	Osteosynthesis	PION
1[74]	51 M	Osteosynthesis	PION
1[83]	59 F	Gastroduodenotomy	PION
1[71]	51 F	Abdominal exploration	PION
1[1]	52 M	Thoracotomy	PION
1[12]	88 M	Thoracotomy and segmentectomy	PION
1[33]	43 F	Breast augmentation and abdominal liposuction	PION
1[40]	41 M	Axillary vein grafting	PION
1[28]	42 M	Laparoscopic nephrectomy	PION
1[12]	70 M	Femoral aneurysm repair	PION
14[20]	mean age 58.3; gender NA	NA	PION

Notes: *Study contains information compiled from data submitted to a registry, or compiled case reports, which may be redundant with that seen in the other papers listed.

Abbreviations: ION, ischemic optic neuropathy; AION, anterior ischemic optic neuropathy; PION, posterior ischemic optic neuropathy; NA, information not available; M, male; F, female; CABG, cardiopulmonary bypass grafting.

and liposuction.[75,76] Patients ranged in age from 16[55,60] to 80 years.[74] Of the 75 cases that provided individual patient information, 43 cases were bilateral (57%). Of the 32 cases in which the information was provided for individual patients, 27 (84%) reported perioperative "anemia", which we defined as a hemoglobin of less than 10 gm/dL and/or a hematocrit less than 30%. Of the 38 cases that provided

perioperative blood pressure measurements for individual patients, 18 (48%) reported perioperative systolic blood pressure (SBP) measurements of less than 90 mmHg and/or MAP measurements less than 70.

Posterior ischemic optic neuropathy literature review

We are aware of 165 cases of postoperative PION in the literature, as well as an additional 526 reports defined only as "ischemic optic neuropathy" (Table 1).[5,10,47,48] The most common procedure that resulted in PION was spine surgery.[9,10,12,14,20,30,33,42,46,60,62,71,77,85] PION has also been documented following: radical neck dissection;[3,43,68,84,87] CABG;[8,9,21,71,98] knee surgery;[12,37] osteosynthesis;[12,74] drainage of an infected hip prosthesis;[89] shoulder surgery;[89] gastroduodenotomy;[23] abdominal exploration;[71] thoracotomy;[1,42] axillary vein grafting;[90] femoral aneurysm repair;[12] laparoscopic nephrectomy;[20] rhinoplasty;[91] and breast augmentation with abdominal liposuction.[25] Patients ranged in age from 10[60] to 81.[71] Of the 80 cases that provided individual patient data, 47 (59%) were bilateral. Of the 42 cases in which the information was provided for individual patients, 28 (67%) reported perioperative "anemia", which we defined as hemoglobin of less than 10 gm/dL and/or hematocrit less than 30%. Of the 42 cases that provided blood pressure measurements, 28 (67%) reported perioperative SBP readings of less than 90 mmHg and/or MAP measurements less than 70.

Central retinal artery occlusion

Central retinal artery occlusion (CRAO) has been well-documented in children and adults following trauma,[92] and embolic,[93] thrombotic, or vasospastic episodes.[94] Of the 93 spine surgery cases submitted to the ASA Postoperative Visual Loss Registry, there were 10 cases of CRAO, 7 of which resulted in acuity readings of no light perception.[10] In a recent analysis of 4,728,815 spine surgeries from the NIS registry, the overall incidence of postoperative CRAO was found to be 0.001%.[5]

Diagnosis

CRAO presents with a cherry-red spot on the macula, a white ground-glass appearance of the retina, attenuated arterioles with preserved choriocapillaries, and an afferent pupillary defect (Figure 5).[10]

Pathogenesis, risk factors, and outcomes

CRAO occurring after general surgery is typically observed following external ocular compression. When compared with cases of ION after spine surgery, patients who developed CRAO were found to have significantly lower mean anesthetic durations and median estimated blood losses. Periocular trauma was documented in the majority (70%) of cases, evidenced by ipsilateral decreased supraorbital sensation, ophthalmoplegia, corneal abrasion, ptosis, or unilateral erythema.[10] The ophthalmic artery gives rise to the central retinal artery, as well as the posterior ciliary artery, which supplies the choroid. Extensive pressure on the globe may raise IOP above the SBP leading to retinal ischemia.[95] Experiments in rhesus monkeys have shown that the retina can tolerate pressure-induced ischemia for approximately 95 minutes and still recover, although it suffers permanent ischemic damage after 105 minutes.[96] The majority of postoperative CRAO cases occur in prone-positioned patients, or in those positioned supine with excessive ocular pressure secondary to an anesthetic mask.[95]

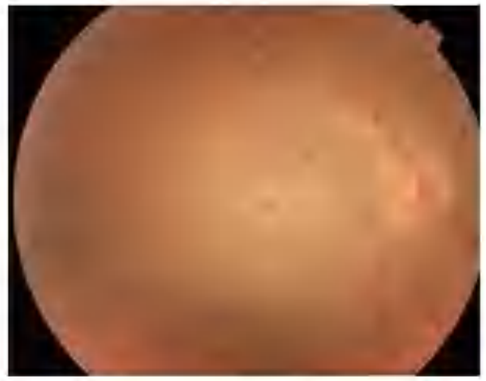

Figure 5 Funduscopic appearance of central retinal artery occlusion demonstrates a cherry-red spot on the macula, attenuated arterioles, and retinal whitening from edema.

No Class I data on the effective treatment for CRAO exists, and the accompanying blindness is often permanent. It has been suggested that the use of a foam headrest with orbital cutouts may prevent postoperative CRAO development.[95]

CRAO literature review

We are aware of 933 documented cases of postoperative CRAO (Table 2), with the overwhelming majority seen following spinal surgery.[8,10,40,48,95,97–104] Cases were also documented after hip/femur treatment,[33] knee replacement,[1] cholecystectomy,[1] appendectomy,[1] colorectal resection,[1] and cardiac surgery.[1] There was also one case following hip replacement in the lateral decubitus position without direct pressure on the orbit. The authors speculate that the CRAO

Table 2 Central retinal artery occlusion case reports

Number of patients, reference	Age, gender	Surgery performed
[a]86[48]	NA	Spinal, orthopedic, cardiac, and general surgery
[b]47[8]	NA	Spine surgery
[b]10[10]	33–59; gender NA	Spine surgery
1[97]	12 F	Spine surgery
1[98]	28 F	Spine surgery
1[99]	30 M	Spine surgery
1[99]	23 M	Spine surgery
1[100]	NA	Spine surgery
1[101]	29 M	Spine surgery
1[102]	12 F	Spine surgery
1[103]	73 M	Spine surgery
1[104]	38 M	Spine surgery
1[99]	12 F	Spine surgery
1[103]	58 M	Hip replacement

Notes: [a]Study results include all causes of retinal vascular occlusion, not exclusively CRAO; [b]Study contains information compiled from data submitted to registry, or compiled case reports, which may be redundant with that seen in other papers listed.
Abbreviations: NA, information not available; M, male; F, female.

in this case may have been due to venous hypertension from a chest strap, which could have resulted in IOP elevation.[105] All cases were unilateral, and most authors reported postoperative periocular swelling and/or erythema. Patients ranged in age from 12[95,97,102] to 73 years.[103]

Pituitary apoplexy

Diagnosis

Pituitary apoplexy is a rare clinical syndrome caused by infarction or hemorrhage of an existing pituitary adenoma. There is typically rapid enlargement of the adenoma, leading to compression of parasellar structures and the abrupt onset of signs and symptoms such as headache, meningismus, vomiting, visual field defects, unilateral or bilateral vision loss, ophthalmoplegia, and/or stupor.[106] MRI is the imaging modality of choice in the diagnosis of pituitary apoplexy, with a sensitivity of 88% (Figure 6).[107]

Pathogenesis, risk factors, and outcomes

Autopsy studies have suggested that the overall incidence of pituitary adenomas in adults is 1.4%, with the vast majority being completely asymptomatic.[108] There are many factors implicated in the development of pituitary apoplexy, including major surgery.[109] During surgery, fluctuations in blood pressure, hypotension, blood dilution with crystalloid, anticoagulation, excessive steroid secretion, and transient increases in intracranial pressure may all play a role in pituitary apoplexy pathogenesis.[110] Postoperative pituitary apoplexy occurs most often after cardiac surgery,[110] especially CABG.[111] In fact, an autopsy study of patients who died within 10 days of CABG found that 15% had evidence of pituitary necrosis, suggesting that pituitary apoplexy following CABG may be even more common than its clinical recognition.[108] Factors specifically associated with bypass that may lead to pituitary apoplexy include reduced tissue oxygenation, embolism, anticoagulation, edema, and/or positive pressure ventilation.[111]

The recommended management for pituitary apoplexy is urgent transsphenoidal decompression surgery and high-dose corticosteroid administration.[112] However, a more

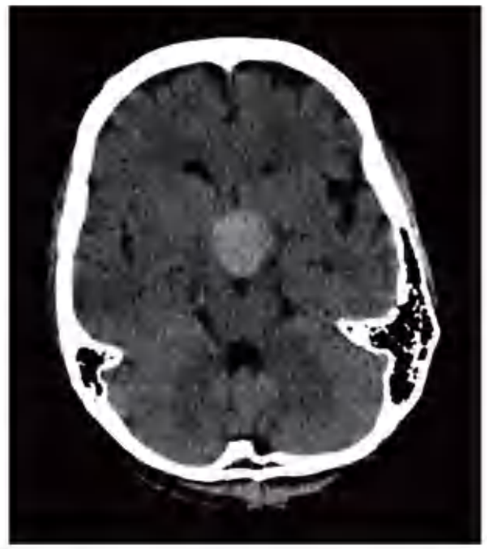

Figure 6 Head computed tomography of a patient with pituitary apoplexy. The hyperdense region represents hemorrhage within a pre-existing pituitary adenoma.

conservative medical approach can be considered when vision is unaffected, or when the visual deficit is stable or improving, because spontaneous recovery may ensue.[113]

Pituitary apoplexy literature review

We are aware of 33 cases in the literature of postoperative pituitary apoplexy (Table 3). The majority of cases occurred following cardiac surgery, especially CABG,[113,114,124] as well as mitral valve repair,[127] and aortic valve replacement.[126] Pituitary apoplexy was also seen following: abdominal aortic aneurysm repair;[122] liposuction;[128] knee arthroplasty;[129,130] hip arthroplasty;[116,150] spine surgery;[151] cholecystectomy;[132] orchiectomy;[114] and endoscopic sinus surgery.[116] Patients ranged in age from 45[151] to 79 years.[123]

Table 3 Pituitary apoplexy case reports

Number of patients, reference	Age, gender	Surgery performed
1[124]	69 F	CABG
1[124]	65 M	CABG
1[114]	57 M	CABG
1[114]	55 M	CABG
1[116]	58 M	CABG
1[116]	65 M	CABG
1[116]	68 M	CABG
1[122]	72 M	CABG
1[132]	64 M	CABG
1[123]	79 M	CABG
1[124]	64 M	CABG
1[148]	77 M	CABG
1[149]	59 M	CABG
1[127]	70 M	CABG
1[131]	60 F	CABG
1[119]	61 M	CABG
1[150]	71 M	CABG
1[151]	60 M	CABG
1[145]	63 M	CABG
1[116]	62 M	CABG
1[115]	55 M	CABG
1[129]	56 M	Mitral valve replacement
1[144]	68; gender NA	Aortic valve replacement
1[122]	73 M	Abdominal aortic aneurysm repair
1[125]	65 F	Knee arthroplasty
1[130]	61 M	Knee arthroplasty
1[116]	72 M	Hip arthroplasty
1[150]	76 M	Hip arthroplasty
1[151]	45 M	Spine surgery
1[128]	50 F	Liposuction
1[114]	52 M	Orchiectomy
1[132]	47 M	Cholecystectomy
1[116]	67 M	Endoscopic sinus surgery

Abbreviations: NA, information not available; M, male; F, female; CABG, cardiopulmonary bypass grafting.

Cortical blindness

Diagnosis

Cortical blindness results from the destruction or denervation of the primary visual cortex. The parieto-occipital region of the brain is a watershed zone for the middle cerebral and posterior cerebral arteries, and may undergo infarction during periods of systemic hypotension. Stroke after general surgery is very rare, although the risk appears to be increased after cardiac or vascular surgery, especially CABG. The majority of postoperative strokes are ischemic or embolic in nature.[133] Bilateral lesions cause a syndrome with signs and symptoms ranging from bilateral lower visual field defects, difficulty in the visual judgment of size, distance, and movement, disrupted smooth oculomotor pursuit, restricted visual attention, and optic ataxia.[134] Patients have reduced vision with normal pupil reaction, intact corneal reflexes, and normal eye movement. Bilateral complete vision loss is rare, and is usually seen in association with other neurologic symptoms associated with vertebrobasilar strokes, such as ataxia, hemisyndrome, diplopia, and nausea.[135] Patient evaluation should include a detailed neurologic examination and brain computed tomography (CT) or MRI to evaluate the lesion.[133]

Pathogenesis, risk factors, and outcomes

Postoperative cortical blindness results from embolism, generalized cerebral underperfusion, or both.[133] Symptoms may be immediate, identified in the first postoperative day, or delayed, presenting from the second postoperative day onward.[136] Early embolism leading to stroke in CABG is thought to result from manipulations of the heart and aorta, or from the release of particulate matter from the bypass pump. Delayed embolism is generally due to postoperative atrial fibrillation, myocardial infarction, and hypercoagulability due to surgical trauma and associated tissue injury. Most strokes due to hypoperfusion are diagnosed in the first postoperative day; delayed hypoperfusion strokes are usually due to postoperative dehydration or blood loss.[133] It has been suggested that repeated short episodes of extreme hypotension are more likely to result in cortical blindness than a longer episode of moderate hypotension.[137] Risk factors for developing postoperative stroke include: hypertension, diabetes mellitus, renal insufficiency, smoking history, COPD, peripheral vascular disease, cardiac disease, and/or systolic dysfunction. Patients with symptomatic carotid stenosis may be at increased risk of postoperative stroke, including cortical

blindness, and may benefit from carotid revascularization prior to undergoing surgery.[133]

The prognosis of postoperative parieto-occipital stroke ranges from total permanent blindness to brief periods of transient ischemic attacks with full recovery of visual acuity.[136] Cortical blindness is generally seen as permanent after the window for spontaneous recovery has passed, which is thought to be several months post-lesion.[138]

Cortical blindness literature review

We are aware of 245 cases of postoperative cortical blindness in the literature (Table 4). Most cases were seen following CABG.[3,51,134,136,139,139,140] Cases were also seen following: aortic arch repair;[139] aortic valve replacement;[134] radical neck dissection;[1] total hip arthroplasty;[1,3,141] knee replacement;[2] cholecystectomy;[1] appendectomy;[3] colorectal resection;[3] and spine surgery.[3,9,56,135] Patients ranged in age from 31[139] to 77 years.[1]

Table 4 Cortical blindness case reports

Number of patients, reference	Age, gender	Surgery performed
~215[48]	NA	Spinal, orthopedic, cardiac, and general surgery
1[124]	51 M	CABG
1[136]	63 F	CABG
1[136]	50 M	CABG
1[136]	58 F	CABG
1[136]	46 M	CABG
1[136]	62 M	CABG
1[136]	53 M	CABG
1[136]	49 M	CABG
1[136]	46M	CABG
1[136]	58 M	CABG
1[137]	35 M	CABG
1[133]	51 M	CABG
1[137]	66 M	CABG
1[137]	48 M	CABG
1[51]	67 M	CABG
1[56]	67 M	CABG
1[140]	56 M	CABG
1[135]	35 M	CABG
1[135]	52 M	CABG
1[134]	51 F	Aortic valve replacement
1[139]	31 M	Aortic arch repair
~3[56]	12–68; gender NA	Spine surgery
1[135]	66 F	Spine surgery
1[9]	58 F	Spine surgery
1[9]	57 M	Spine surgery
1[141]	51 F	Hip arthroplasty
1[1]	73 F	Hip arthroplasty
1[1]	77 M	Neck dissection

Notes: [a]Study contains information compiled from data submitted to registry, or compiled case reports, which may be redundant with that seen in other papers listed.
Abbreviations: NA, information not available; M, male; F, female; CABG, cardiopulmonary bypass grafting.

Neuro-ophthalmologic causes of vision loss after ocular surgery

Neuro-ophthalmologic complications of ocular surgery include optic neuropathies such as AION, PION, and direct trauma to the optic nerve. Vision loss following ocular surgery due to CRAO, central retinal vein occlusion (CRVO), globe rupture, retinal detachment, and retrobulbar hemorrhage occur much more commonly and will not be discussed here. The majority of large-scale incidence data for vision loss is for orbital surgery, such as lateral decompressions and cavernous hemangioma removal, rather than for ocular surgery. The incidence of POVL appears to be much lower following ocular surgery when compared to orbital surgery. In a review of 67 lateral decompression surgeries, there were seven cases of unilateral POVL (2.99%).[142] Another review found 14 cases of POVL out of 2500 orbital surgeries (0.56%), with all 14 occurring during 1150 orbital exploration surgeries (1.22%).[143] We are not aware of any large-scale reviews providing incidence measurements for POVL following ocular surgery.

Traumatic optic neuropathy

Diagnosis

Periocular injection of anesthetic can result in direct trauma to the optic nerve, especially following retrobulbar injection, though they may also occur following peribulbar or sub-Tenon's injection. Other potential complications of retrobulbar injection include retrobulbar hemorrhage, central retinal artery or vein occlusion, brain stem anesthesia,[144] or globe rupture with retinal detachment,[145] and will not be discussed here.

Postoperative vision loss from trauma to the optic nerve occurs immediately. An orbital MRI is important for the proper diagnosis in patients presenting with symptoms of optic neuropathy in the first 24 hours following periocular injection. Orbital MRI may show focal enlargement of the optic nerve or enhancement of the optic nerve sheath with gadolinium. The bright ring of signal from cerebrospinal fluid may be absent around the damaged optic nerve on T_2-weighted images.[146] The MRI may also demonstrate normal results.

Prevention, treatment, and outcomes

The sub-Tenon's "blind" insertion technique has been shown to be safer than either retrobulbar or peribulbar injections,

while still providing equally effective anesthesia and akinesia. This is believed to be due to the cannula's relatively short length and blunt tip, which limits damage to the optic nerve.[47–49] There have been rare reports of optic nerve trauma following sub-Tenon's injection; therefore changing the mode of injection alone is not enough to prevent the occurrence of optic nerve trauma.[50] Corticosteroid administration may relieve optic nerve swelling and restore visual acuity, and a trial of corticosteroids should be considered in patients presenting with evidence of direct needle trauma postoperatively.[50]

Direct optic nerve trauma literature review

We are aware of five reported cases of optic nerve trauma following ocular surgery. Most cases were following retrobulbar injection,[51–54] although cases were also seen following peribulbar[55] and sub-Tenon's injection.[50] One patient showed partial recovery of visual acuity after receiving corticosteroid therapy.[53] Three other patients showed no improvement despite receiving corticosteroids[52–54] (follow-up information is unknown for one patient).[50]

Ischemic optic neuropathies

While rare, there have been a number of documented cases of AION or PION developing after ocular surgery with the use of periocular or general anesthesia. A retrospective review of 5787 cataract extractions found two cases of AION within six weeks of surgery. However, one patient had a history of spontaneous AION in the contralateral eye 21 months prior.[156]

Pathogenesis, risk factors, and outcomes

The pathogenesis of AION after ocular surgery remains controversial. It has been postulated that elevated intraocular pressure, in eyes with vulnerable optic nerve circulation, may promote ischemia of the optic nerve head following cataract extraction.[157] However, there have been many cases of ION development in eyes with normal IOP.[158–160] Elevated IOP has also been postulated to play a role in the development of AION following laser *in-situ* keratomileusis (LASIK).[161] In order to create a lamellar flap during LASIK, the IOP must be raised to >65 mmHg by a suction ring on the anterior segment of the eye.[162] However, AION has also been documented following the use of a femtosecond laser flap with low suction ring, a technique that maintains the IOP at or below 30–40 mmHg,[163] and in another patient whose IOP was maintained at 25 mmHg through the administration of glaucoma medication.[164] It is worth noting that both of these patients had small cup-to-disc ratios in the fellow eye, a proposed risk factor for AION development.[165] Some have suggested that AION occurring after ocular surgery is coincidental in nature. However, one study compared the likelihood of developing AION 0–6 months or 6–12 months after cataract extraction found that all 18 cases of AION were within the first 6 postoperative months, which differed significantly ($P < 0.001$) from the uniform distribution expected if there were no temporal relationship to surgery.[166] Approximately 50% of patients who develop AION following cataract extraction who undergo contralateral extraction at a later date developed AION in the fellow eye, compared to 19% in a control group who did not have cataract surgery.[167] This suggests that some patients may be predisposed to developing AION after ocular surgery.

No treatment has been proven effective in the management of postoperative ischemic optic neuropathies. Many patients report spontaneous improvement in visual acuity, although none enjoy complete improvement.[140] Improvements in microkeratome design with shorter suction times and faster cutting have caused a decrease in the incidence of optic nerve damage after LASIK.[168] Contralateral cataract extraction should be approached with caution in patients who develop ION postoperatively, as these patients are at increased risk of developing ION in the fellow eye.

Anterior ischemic optic neuropathy literature review

We are aware of 43 cases in the literature of AION occurring after ocular surgery. The most common surgery was cataract extraction,[156,157,169–171] followed by LASIK.[164,172,173] Cases were also seen following vitrectomy,[173] scleral buckle,[174] pneumoplethysmography,[175] and strabismus surgery.[176] Patients ranged in age from 26[177] to 94 years old.[174]

Posterior ischemic optic neuropathy literature review

We are aware of five cases in the literature of PION occurring after ocular surgery. The most common surgery was LASIK.[162–164] There was also one case following blepharoplasty[178] and one case following cataract extraction.[179] Patients ranged in age from 29[164] to 78 years.[179]

Conclusions

Potential neuro-ophthalmologic complications following nonocular surgery include anterior ischemic optic neuropathy, posterior ischemic optic neuropathy, central retinal artery occlusion, pituitary apoplexy, and cortical blindness. Reports have attempted to connect anemia, hypotension, blood loss, and other hemodynamic variables to the pathophysiology of AION and PION. These variables occur in nearly all cases of cardiac and spine surgery and yet, AION and PION occur rarely. There may be an individual predisposition of certain patients, or multiple factors that lead to a "perfect storm" of events resulting in AION or PION. Meanwhile CRAO almost always occurs following spinal surgery in the prone position, where ocular compression by the headrest prevents ocular perfusion.

Cortical blindness occurs most frequently after cardiac or vascular surgery, and may be due to embolism or general cerebral underperfusion. Pituitary apoplexy is seen most often following cardiac surgery in patients with pre-existing pituitary adenomas. Causes likely include fluctuations in blood pressure, hypotension, blood dilution with crystalloid, anticoagulation, excessive steroid secretion, and transient increases in intracranial pressure. While there are currently no established treatments available for AION, PION, CRAO, or cortical blindness, patients with pituitary apoplexy may benefit from urgent transsphenoidal decompression surgery and corticosteroid administration.

Potential neuro-ophthalmologic complications following ocular surgery include traumatic optic neuropathy, anterior ischemic optic neuropathy, and posterior ischemic optic neuropathy. Traumatic optic neuropathy is seen most frequently following retrobulbar injection, although it may also occur after peribulbar, or even sub-Tenon's, injection. Diagnosis can often be confirmed with orbital MRI, and visual acuity may improve with corticosteroid administration. AION is seen most often after cataract extraction or laser in-situ keratomileusis, and may be linked to elevated intraocular pressure during surgery. PION is seen most often following LASIK. There is no established treatment available for AION or PION. Contralateral cataract extraction requires careful consideration and patient counseling in patients who develop AION after unilateral extraction, because of the increased risk of developing of AION in the fellow eye.

Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL ARTICLE

Floppy eyelids: sleeping patterns of spouses as indicators of laterality

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Abstract
Floppy eyelids are usually asymmetrical, and more severe on the side the patient sleeps on. This has been related to the mechanical basis of this entity's pathophysiology. Patients who exhibit floppy eyelid syndrome (FES) tend to suffer from obstructive sleep apnea and other sleeping disorder such as snoring; therefore, their spouses are likely to be found sleeping facing away from them. In this study, we aim to assess this correlation between FES laterality and the spouse's sleeping side. 185 patients with floppy eyelid were assessed. Upper lids were pulled cephalad towards the orbital rim to assess which side everted and was more floppy. Based on the upper lid distraction test, a prediction was made to which side of the bed the spouse slept on. 185 patients with floppy eyelid syndrome were assessed, 160 male patients and 25 females, at an average age of 68. All 25 female patients, and 117 of the male patients, had spouses that slept in the same bed. Their side of sleep was predicted correctly in 87% of cases. The physician extrapolated the spouse slept on the opposite side facing away from the snoring spouse and was correct in 91% of cases. There is a high correlation between FES laterality and the patient's spouse's sleeping side. These data strengthen the mechanical etiology, and can also be used to confirm the worse-affected side in FES patients.

Keywords Floppy eyelid syndrome · Sleep apnea

Introduction

Floppy eyelid syndrome (FES) is a condition characterized by excess upper eyelid laxity, papillary conjunctivitis, and was initially described in obese, middle-aged men [1]. Since its description by Culbertson and Osler in 1981, this entity's association with sleep disturbances and specifically, obstructive sleep apnea (OSA) has been described in a number of studies [2–4].

Frequent episodes of waking up, gasping for air, wheezing and snoring have been recognized both by FES patients and by their spouses [2, 5], as they interfere with both partners' sleep. Most FES patients have a preferred side on which they sleep and this [1, 3] corresponds to the more affected side of the eyelid condition. This in turn would determine the direction of their snoring. A person who shares a bed with a FES partner would want to avoid these sleeping disturbances, being directly in the line of snoring by choosing to sleep on the contralateral side.

Based on this assumption, the physician can guess the sleeping side of the patient's spouse by physical examination alone—the eyelid which is floppier upon digital eversion is likely the side that the FES patient sleeps on. The spouse would, therefore, sleep on the opposite side. This link strengthens the observation that FES patients sleep prone, the laterality of the condition, and also provides another tool to evaluate and indicate the worse-affected side.

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Methods

This is a prospective, cross-sectional, multi-central study, conducted between 2014 and 2018. The study was approved by an Institutional Review Board and adheres to the tenets of the Declaration of Helsinki. All information was obtained in a Health Insurance Portability and Accountability Act compliant manner.

The participants were patients sent for oculoplastics consultation either for upper eyelid evaluation, or for ocular irritation of unknown etiology. The diagnosis of floppy eyelid syndrome was based on upper eyelid distraction and tarsal eversion, papillary conjunctivitis and lacrimal gland exposure. The extent of the upper lid distraction was correlated with floppy lid severity. The examiner then concluded the patient's and his/her partner's side of sleep, based on the assumption that the patient was sleeping on the worse-affected side, and the partner was sleeping on the opposite side. Without revealing the examiner's findings and deductions, the patients were then questioned about their sleeping side and their spouses'. The examiner's extrapolations and the patient's answer were documented.

Only patients with floppy eyelids were included in the study. Patients without partners and patients who sleep in separate beds from their partners were excluded (Fig. 1).

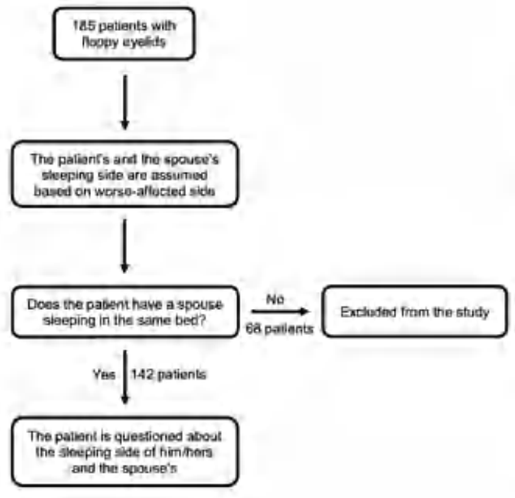

Fig. 1 Study design

Results

A total of 185 patients diagnosed with floppy eyelid syndrome were included in the study, 160 male patients and 25 females, at an average age of 68. There were no patients that refused to answer the study questions. Most patients were referred for chronic papillary conjunctivitis or upper blepharoplasty and were found to have FES. Over half of the patients did not carry a prior diagnosis of floppy lid or sleep apnea. 45% of the patients already carried a diagnosis of sleep apnea and some of them were on CPAP. The floppy eyelid was found to be worse on the right side in 58% of cases, and on the left in 42%.

All 25 female patients, and 117 of the male patients, had spouses that slept in the same bed. The side of the bed on which they slept, based on the worse floppy eyelid, was predicted correctly in 87% (123 patients) of cases. The physician extrapolated that the spouse slept on the opposite side facing away from the snoring spouse and was correct 91% (129 patients) of cases.

Discussion

Floppy eyelid syndrome was first described by Culbertson and Ostler [1], as a distinct condition apparent in high body mass index (BMI), middle-aged men, and characterized by easily everted upper eyelids with papillary conjunctivitis. Since their report, FES has been shown to appear also in patients who are normal-weight, female, younger or older than the original group described [3, 4] in up to 30% of cases [6]. A broader definition of "lax eyelid syndrome" has been proposed to incorporate all patients with the typical physical features, including those who do not fit the characteristics of the group initially described [7–9]. However, the term has failed to achieve consensus so far [10].

The diagnosis of FES is largely clinical, based on a distinctive appearance, susceptibility to eyelid eversion, papillary conjunctivitis, and typical complaints of ocular irritation, tearing and discharge. A few grading systems based on measurements of the extent of eyelid laxity have been introduced, such as the distance between the cornea and the distracted eyelid, the extent of lateral excursion of the lower punctum during lower eyelid traction, the amount of tarsus exposed upon digital eversion, and vertical distensibility measurements using a "laxometer" device [6, 11]. Some have demonstrated a correlation with disease severity and the need for surgical intervention [4]; however, none has yet become a standard evaluation tool [6]. Due to the inconsistency in diagnostic criteria and

study methodology, the prevalence of FES in the general population is difficult to estimate but appears to range between 2.3% and 3.8% [12].

The exact pathogenesis of FES is still unclear; however, current data suggest that both physiological alterations and external, mechanical elements play a role. The authors speculate that the upper lid becomes lax or floppy due to repetitive mechanical sheer and stretch of the distracted, everted upper lid against the pillow. Culbertson and Osler noted that the tarsal plates of the affected eyelids lost their intrinsic rigidity and became "rubbery". This allowed the floppy eyelids to be easily everted during sleep, causing nocturnal exposure, keratinization of the conjunctiva, and inflammation [1, 5]. Increased laxity of the eyelids was thought to interfere with the interface between the palpebral conjunctiva and the ocular surface, leading to poor tear distribution and irritation [4]. Impairment in eyelid function can also potentially damage the nasolacrimal pump mechanism [5], which in turn may enhance tearing, irritation and inflammation.

The mechanical explanations are supported by the finding that most cases of FES are asymmetric, with the worse-affected side corresponding to the side that the patient usually sleeps on [3–5] (Fig. 2). Nevertheless, substantial physiological modifications were investigated as a causative factor. Primarily, the excess laxity of the eyelid was found to be associated with depletion and disorganization of elastin in both the tarsus and eyelid skin in FES patients [5, 13, 14]. This has been attributed to upregulation of elastolytic enzymes, particularly metalloproteinase (MMP)-7 and MMP-9, which may be related either to mechanical stress, or to ischemia–reperfusion injury [2]. Leptin, a hormone produced by adipocytes, was speculated to contribute to elastin degradation by increasing MMP-9 [6]; however, obesity comprises a confounding factor for its levels. Recently, elevated levels of MMP-9 were demonstrated in tears of patients with floppy eyelids compared to control group [11], thus further supporting the systemic etiology for this condition.

The common complaints of FES patients usually relate to the constant ocular irritation caused by persistent conjunctivitis [4], accompanied by tearing, discharge and visual disturbances, usually worse upon waking [1, 2]. The affected eyelid commonly exhibits dermatochalasis, blepharoptosis along with eyelash ptosis and loss of eyelash parallelism [3, 15], with occasional corresponding lower eyelid laxity [4] (Fig. 3). Alterations in meibomian gland function such as posterior blepharitis, as well as Demodex brevis infestation have been implicated in tear film abnormalities in FES patients [4, 5, 16]. Elevated skin temperature and increased tear evaporation have also been linked to this process [16].

The facial skin around the affected eye can be found saggy and wrinkled, due to loss of skin elasticity [2]. Ocular signs include papillary conjunctivitis with keratinization of the conjunctiva, corneal changes, ranging from widespread punctate keratopathy to ulceration, vascularization, and rarely corneal perforation [1, 2]. Keratoconus or corneal ectasia are strongly related to FES, apparent in up to 60% of patients and usually associated with the more affected side [3, 6]. This may be related to the mechanical friction, but can also result from reduced corneal hysteresis, both linked to the pathogenesis of FES [6]. Systemically, FES patients have

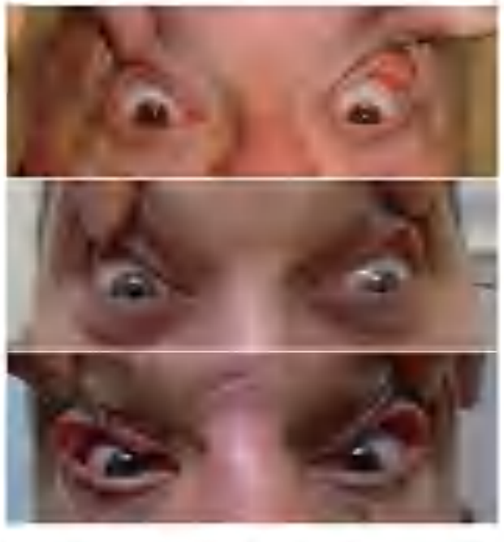

Fig. 2 Upper eyelid distraction test of three FES patients. Top- left floppy eyelid. Center-bilateral floppy eyelids, worse on the left. Bottom- bilateral severe floppy eyelids, worse on the right

Fig. 3 Top-FES patient, exhibiting dermatochalasis, bilateral ptosis worse on the left, eyelash ptosis, and retraction-ectropion related to lower lid laxity. Bottom-upper eyelid distraction test demonstrating bilateral floppy eyelids, worse on the right

demonstrated a high prevalence of systemic hypertension [2, 3], along with hyperglycemia or diabetes. Nonetheless, these can be related to obesity as a confounding factor [3].

Sleep disturbances have been shown to affect the vast majority of FES patients. Even without frank signs of OSA, up to 92% of FES patients admitted to snoring [4]. In other studies, symptoms suggestive of OSA such as apnea during sleep and daytime somnolence were present in up to 96% of FES patients [2].

Anecdotal reports [3, 17], followed by larger scale studies conducted by McNab [2, 14] and later by Ezra et al. [3] demonstrated an association between FES and OSA. The incidence of OSA in FES patients was found to be up to 96% in McNab's studies, whereas Ezra et al. found a rate, albeit probably underestimated due to methodology, of 31%, translated into an odds ratio of 12.5. Muniesa et al. found this incidence to be 85% [18]. Nonetheless, the consensus among oculoplastic surgeons is that FES is strongly associated with OSA [19], with some studies claiming that "virtually all patients with FES have OSA" [6].

The opposite association, that is of OSA patients having FES, is less well established, as studies aiming to evaluate this relationship have produced a range of results. The incidence of FES among OSA patients has been shown to range from 0.5 to 64.5% [2, 3, 10–12, 14, 15, 20, 21]. Some reports suggest that eyelid laxity may be an indicator of severe OSA, with increasing odds values according to the severity of OSA [20–22].

Anecdotal reports observed that FES symptoms may improve or even disappear following treatment of OSA [23, 24], while lack of treatment was related to recurrence after surgical treatment [2]. Hence, treatment of FES includes addressing underlying OSA, if it exists, and prevention of the constant damage caused by eyelid stretching, along with surgical measures to repair eyelid laxity. Conservative measures such as lubricating agents, topical steroids, lid taping, eye shields or custom-made silicone masks can provide relief in mild to moderate disease, while eyelid tightening procedures such as full-thickness wedge resection and re-enforcing the lateral canthal tendon or both tendons have been proved efficient in reducing ocular signs and symptoms of FES [2, 4, 6, 19].

FES assessment usually reveals a worse-affected side. This study is the first to demonstrate a correlation between this laterality and the patient's spouse's sleeping habits. Our presumption that FES patients snore is based on previous data, in which snoring was noted by both patient and their spouses in 92% of cases [4]. Taking this finding one step further, we assumed that the spouses would be found sleeping on the side contralateral to the patient's sleeping side, and this was proven correct, with 91% of couples exhibiting such sleeping pattern. This finding strengthens the association between FES, snoring and a breathing disorder during sleep. It also reinforces the mechanical aspect of FES pathophysiology theory. FES has been shown to be more pronounced on the side facing the pillow, in up to 86% of cases in previous reports [4]. Our study exhibits very similar data, with 87% of patients stating that they sleep on the side which was noted to be worse clinically.

This study exhibits some limitations. Its results derive from the patients' answers in a matter which some may find intimate and, therefore, the data may be biased. Severity of the physical findings was not documented, and stratification of the information gathered was not possible. In addition, there may be a few confounders such as obesity and other concurrent medical conditions that may have affected the study results. The OSA rate among FES patients in our study was found to be 45%; however, it is unclear whether the remaining 55% were evaluated for sleep disturbances or OSA, so the actual incidence of OSA may be higher.

This study was performed by oculoplastic surgeons who usually address ocular alterations and pathologies, whereas sleep studies and systemic evaluations are managed by either the family physician or internal disease specialist. Therefore, this study lacks the information gathered through polysomnography. Future studies may incorporate these data to support ocular findings and conclusions.

Nevertheless, this is a large-scale study which supports the data collected thus far regarding both the mechanical basis for FES and its laterality. Our data suggest that predicting the spouse's sleeping side confirms the recognition of the worse-affected eyelid. It may also be useful in bilateral cases, when in doubt, to identify which eyelid is more prone to further deterioration, thereby assisting in clinical and surgical planning. Furthermore, our findings may also influence matters of physician–patient communication and relationships. By correcting predicting which side of the bed the spouse sleeps on, the physician can demonstrate greater empathy and understanding, and may boost patients' trust and cooperation for future management.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Effects of Elevated Thyroid Hormone on Adult Rabbit Extraocular Muscles

Andrew R. Harrison,[1] *Michael S. Lee,*[1] *and Linda K. McLoon*[1,2]

Purpose. Human extraocular muscles (EOM) are preferentially susceptible to thyroid eye disease. Although the specific cause of this autoimmune disorder is unknown, it is often associated with elevated thyroid hormone levels. Thus, the effect of elevated thyroid hormone levels on cross-sectional area, myofiber size, satellite cells, and myosin heavy chain (MyHC) isoform expression was examined in adult rabbit EOMs, to determine how elevated thyroid hormone alters EOM biology.

Methods. After 1 month of elevated thyroid hormone levels, the EOMs were removed and prepared for histologic examination. Total muscle mass, myofiber size, patterns of MyHC isoform expression, and the number of satellite cells were determined.

Results. Elevated thyroid hormone levels significantly decreased muscle mass, total number of myofibers, and mean cross-sectional area of the myofibers. Alterations in MyHC isoform expression were extremely complex, but several basic patterns emerged. The percentages of neonatal- and developmental-positive myofibers decreased in almost all EOM regions examined, and the percentages of slow-positive myofibers significantly increased. In contrast to normal EOMs, which retain a population of activated satellite cells throughout life, elevated thyroid hormone levels resulted in the virtual disappearance of MyoD-positive cells and a decrease in Pax7-positive cells.

Conclusions. The reductions in EOM size, number of fibers expressing developmental and neonatal MyHC, and number of MyoD- and Pax7-positive satellite cells suggest that elevated thyroid hormone levels decrease the ongoing myofiber remodeling normally seen in the EOM. These catabolic changes have important implications for maintenance of function in the EOMs. (*Invest Ophthalmol Vis Sci.* 2010;51:183–191) DOI: 10.1167/iovs.09-3681

Extraocular muscles (EOM) differ from other skeletal muscles in their anatomy, physiology, and even more important, in their propensity for involvement or sparing in skeletal muscle diseases.[1] In particular, the EOM are unique in their exclusive involvement in thyroid eye disease (TED), an autoimmune disease of the eye muscles that results in their enlargement in the acute phase and, in the chronic phase, muscle fiber replacement and contraction or tightening of the muscles. TED in humans is often associated with thyroid hormone endocrinopathy, and this inflammatory orbitopathy results in proptosis, strabismus, and eyelid retraction.[2,3] Unfortunately, there is no satisfactory animal model for the autoimmune process that leads to TED, in part because the pathophysiology is complex and not well understood. TED does not always occur in cases of elevated thyroid hormone, but its frequent association—eye signs in 50% of patients with Graves' disease—lends credibility and relevance to the study of the specific effects of hyperthyroidism on the EOMs. Although elucidation of the effects of elevated thyroid hormone cannot explain the mechanism of this complex autoimmune disease, characterization of the changes in the EOM muscle as a result of altered thyroid hormones may suggest important directions for future research.

Thyroid hormone has well-described catabolic effects on adult skeletal muscle, and sustained elevations in blood thyroid hormone levels result in muscle weakness and wasting.[4] The direct effects of elevated thyroid hormone are complex. Increased rates of protein degradation occur,[5] specifically reducing myosin heavy chain isoform content, but oxidative modifications that impact the ability of the contractile proteins to generate force also are seen.[6] Significant decreases occur in mitochondrial uncoupling proteins 2 and 3 as well.[7] Elevated thyroid hormone levels affect muscle proliferative cells, increasing both the rate of myoblast withdrawal from the cell cycle[8] and their rate of terminal differentiation.[9,10] In the adult, the EOMs retain a population of activated satellite cells,[11] with resultant continuous myofiber remodeling that involves both myonuclear addition and removal.[12] As elevated thyroid hormones significantly alter these properties in development, the effects of increased thyroid hormone on satellite cell content, MyHC isoform, and muscle size in adult EOMs were examined.

In limb skeletal muscle, four MHC isoforms are commonly expressed: three produce fast contractile properties, type IIA, -IIB, and -IIX, and one produces slow contractile properties, type I. Thyroid hormone status has a significant impact on differential expression of MyHC isoforms in adult mammalian limb skeletal muscle.[13,14] In fact, thyroid hormone status appears to predominate over other potential regulators of MyHC expression, such as electrical stimulation. For example, in muscles composed of mostly type I or slow MyHC isoform myofibers, high levels of thyroid hormone upregulate the expression of type II MyHC mRNA, whereas chronically low levels of thyroid hormone upregulate type I MyHC expression,[15,16] which in turn results in alterations in contraction velocity (V_{max}).[17,18] Elevated thyroid hormone levels also result in increased percentages of hybrid fibers, which coexpress multiple MyHC isoforms in single fibers.[19]

Compared with limb skeletal muscle, EOMs have a more complex composition with regard to MyHC isoform expression, expressing nine distinct isoforms, including two normally found only in developing or regenerating muscle, neonatal, and developmental MyHC.[20,21] The neonatal and developmental

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MyHC isoforms normally are downregulated in limb skeletal muscles during late stages of development. Adding to this complexity is the fact that many of these individual MyHC isoforms are coexpressed in single myofibers.[22–26] EOMs normally express an increased number of thyroid hormone receptors compared with nonocular skeletal muscles.[27] Elevated thyroid hormone accelerates the MyHC transition from neonatal to adult isoforms.[28] Thus, elevation of thyroid hormone levels could result in significantly more complex MyHC expression changes than in normal limb muscle. To our knowledge, the effects of elevated thyroid hormones on EOM myosin composition, satellite cell activity, and muscle size in populations of myofibers from mature eye muscles have not been studied. In this study, we evaluated the effects of elevated thyroid hormone levels on the size and number of EOM fibers, the overall size of EOM muscles, and the percentage of myofibers expressing fast, slow, neonatal, and/or developmental MyHC in adult rabbits, as well as the effect on the Pax7- and MyoD-positive populations of satellite cells. These effects were compared to the properties of normal adult EOMs.

Materials and Methods

New Zealand White rabbits were purchased from Birchwood Valley Farms and housed in University of Minnesota animal facilities. All experiments complied with the published guidelines of the National Institutes of Health and the ARVO Statement for Use of Animals in Ophthalmic and Vision Research and were approved by the University Animal Care and Use Committee at the University of Minnesota. Hyperthyroidism was induced in six rabbits by IP injection of 3,5',3-triiodothyronine (T3) at a dose of 0.2 μg/kg body weight every other day for 1 month.[29–31] Serum thyroid hormone levels were determined at 1 week, 2 weeks, and 1 month. Blood samples were analyzed for blood thyroid hormone levels by the clinical laboratory in the Department of Veterinary Medicine at the University of Minnesota Veterinary School. All animals were considered to have hyperthyroidism if their blood T3 levels increased by 50%. All animals met this criterion with significantly elevated levels of T3 and T4 compared with baseline and control rabbits. The rabbits were given access to food ad libitum and were monitored daily for signs of hyperthyroidism including weight, food intake, water intake, diarrhea, and irritability. Weight loss occurred within the first 2 weeks and then stabilized, dropping from an average initial weight of 2.23 to 1.37 kg, as previously published.[32]

The rabbits were killed after 1 month by an overdose of barbiturates given via the ear vein. The extraocular muscles were dissected from the orbits, frozen, and processed for histologic examination. In accordance with other studies,[33] the four rectus muscles were chosen for quantitative analysis: the superior rectus (SR), medial rectus (MR), inferior rectus (IR), and lateral rectus (LR). Immunohistochemistry was performed on serial frozen sections of EOMs to visualize pan fast, slow, neonatal, and developmental MyHC isoforms (Vector Laboratories, Burlingame, CA). After incubation in blocking serum, the sections were incubated in the primary antibody for 1 hour at a dilution of 1:40 for the antibodies to fast and slow MyHC isoforms and 1:20 for the antibodies to neonatal and developmental MyHC isoforms. The sections were rinsed and incubated using the reagents of an ABC kit (Vectastain Elite, Vector Laboratories) containing biotin-avidin-peroxidase complexes. The reacted tissue sections were processed by using the heavy metal–intensified diaminobenzidine procedure. Sections were also immunostained for the presence of satellite cells positive for either Pax7 or MyoD, one of the myogenic regulatory factors, using the procedure described earlier with the following modifications. For Pax7, the sections were fixed in cold acetone, rinsed in PBS, and incubated in a primary antibody to Pax7 at a concentration of 1:500 (Hybridoma Bank, University of Iowa, Iowa City, IA). For MyoD, the cross sections were fixed in 4% paraformaldehyde, rinsed in PBS, and incubated with a primary antibody to MyoD at a concentration of 1:50 (Vector Laboratories). For the control muscles, both primary antibody incubation times were 1 hour. For the hyperthyroid muscles, sections were incubated overnight to maximize the possibility of staining even cells that contained small amounts of MyoD or Pax7. This method allowed the visualization of a few Pax7-positive cells that were not seen with a 1-hour primary incubation period. Muscle sections from six age-matched control rabbits were similarly processed and analyzed to assess whether the muscle from the thyroid hormone–treated rabbits were significantly different.

Because of the complexity of MyHC isoform expression in different regions and layers of individual EOM,[33–35] and the complex coexpression patterns of MyHC isoforms within single myofibers,[22–25,36] we chose to study populations of myofibers, rather than changes in a small number of single, identified myofibers. This method would elucidate trends in MyHC isoform expression within the muscles as a whole. At least three cross sections from the midbelly region and the distal EOM near the tendon from each of the four rectus muscles were analyzed for individual myofiber cross-sectional area, total muscle cross-sectional area, percentages of myofibers positive for each of the specific MyHC isoforms examined in this study, and the number of MyoD-positive satellite cells. A minimum of four fields, or between 200 and 400 myofibers, were analyzed on each cross section from each of the six experimental and six control rabbits studied. Fiber cross-sectional areas, total muscle cross-sectional areas, and counts of myofibers positive for each of the four MyHC isoforms in control and hyperthyroid EOMs were determined with the aid of a morphometry program (Nova Prime; Bioquant, Nashville, TN). Because of the known changes in MyHC isoform composition along the muscle length in rabbits,[34] care was taken to quantify muscle sections from areas the same distance from the tendon end of each muscle. The percentage positive for each of the four isoforms examined was determined based on the total number of myofibers analyzed for each specimen, and these were compared with the percentage positive for each of the four antibodies in mature rabbit EOMs from untreated controls. All data were analyzed for statistical significance with an unpaired Student's *t*-test (Prism and Statmate software; Graphpad, San Diego, CA). An *F*-test was used to verify that the variances of the control and experimental groups were not significantly different. Data were considered significantly different if $P < 0.05$. Error bars represent SE of the means.

Results

Grossly, the EOM from the rabbits with elevated thyroid hormone were thinner compared with normal control rabbit EOM. Both total muscle cross-sectional area and total number of myofibers in the EOMs from rabbits with elevated thyroid hormone levels were significantly smaller than those of euthyroid rabbits (Fig. 1). There was a significant difference in mean individual myofiber cross-sectional areas of myofibers positive for fast and developmental MyHC isoforms, whereas slow myofibers actually increased in mean cross sectional area compared with the control muscles (Fig. 2). No significant change was seen in the cross-sectional areas of neonatal MyHC-positive myofibers. When the distal ends of the EOM from the rabbits with elevated thyroid hormone levels were examined, the inner orbital layer (intermediate layer) was either substantially thinned or not visible in the sections analyzed (data not shown). This finding was consistent and particularly pronounced in the lateral and superior rectus muscles. It is unclear whether it was due to changes in patterns of MyHC isoform expression or to the decreased number of myofibers. It should be noted that there was no evidence of inflammatory cell infiltrate or fiber necrosis in any of the muscle sections examined.

Elevated thyroid hormone levels resulted in complex changes in MyHC composition in the four rectus muscles examined compared with age-matched control subjects (Figs. 3–7). Specifically, there was a decrease in the percentage of

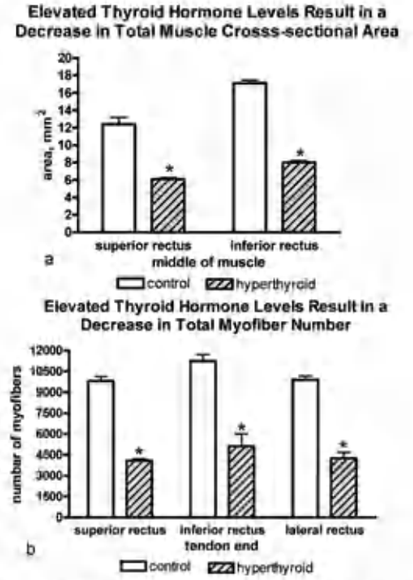


FIGURE 1. (**a**) There was a significant decrease in overall muscle mass as indicated by midbelly cross-sectional areas in the hyperthyroid EOMs in all rectus muscles studied (SR and IR shown here) compared with control EOMs. Individual myofiber cross-sectional areas were unchanged. (**b**) There was a decrease in the total number of myofibers in all three muscles compared with control EOMs. *Significant difference from controls. Data are the mean ± SEM.

myofibers positive for the fast MyHC isoform in the orbital layer of all muscles examined and a large decrease in percentage of fast myofibers in the global layer of only the superior rectus muscle (Fig. 4). Several of the muscles showed a decreased number of fast MyHC-positive myofibers in the tendon region, most pronounced in the superior and lateral rectus muscles. Elevated thyroid hormone levels resulted in an increase in the percentage of myofibers positive for slow myosin in both the orbital and global regions from each of the four EOMs examined (Figs. 4–7), although the difference was not always statistically significant. Note that percentages of fast and slow myofibers do not add up to 100%; it appears that elevated thyroid hormone levels resulted in an increased number of hybrid myofibers.

The changes in expression patterns of the immature MyHC isoforms were relatively similar for the four rectus muscles (Figs. 3–7). Each showed a significant decrease in the percentage of myofibers positive for the neonatal MyHC isoform in all layers in both regions of the muscle. The percentage of myofibers positive for the developmental MyHC isoform decreased in the global layers of all muscles examined. Whereas the superior rectus muscles showed a significant reduction in the percentage of developmental positive myofibers in the orbital layer, the other three rectus muscles demonstrated only a trend toward a decreased number in the orbital layer.

Elevated thyroid hormone levels resulted in a significant reduction in the number of pax7-positive cells, even after substantially increasing antibody incubation times (Figs. 8, 9). In addition, the virtual disappearance of MyoD-positive cells in the EOM cross-sections in both layers of all regions of the hyperthyroid muscles was seen (Fig. 8).

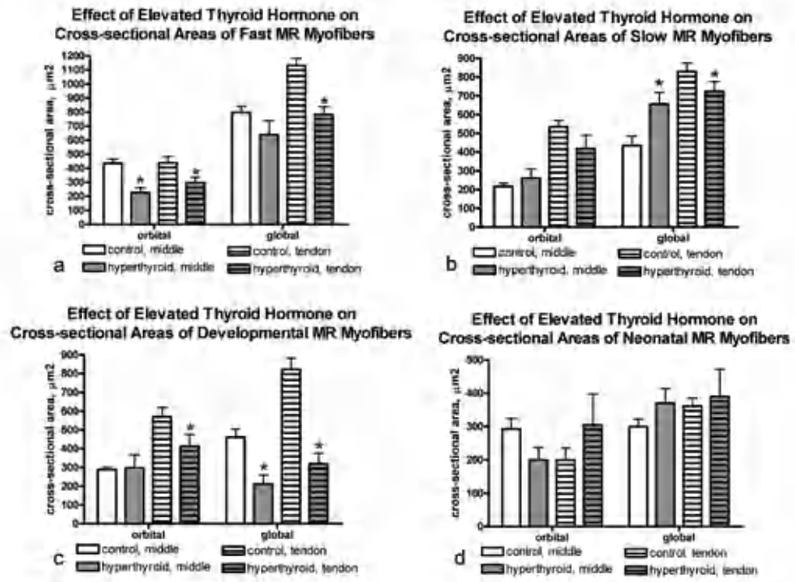


FIGURE 2. Mean cross-sectional areas for (**a**) fast, (**b**) slow, (**c**) developmental, and (**d**) neonatal MyHC-positive myofibers from medial rectus muscles of rabbits exposed to elevated blood thyroid hormone levels compared with age-matched controls. *Significant difference from control sections. Data are the mean ± SEM.

Discussion

Elevated thyroid hormone levels resulted in significant decreases in single myofiber and total muscle cross-sectional areas and a decrease number of myofibers in the EOM in rabbits, a phenomenon observed in orbicularis oculi muscle from rabbits with hyperthyroidism.[32] It is particularly important to point out that no alterations in connective tissue were seen in the thyroid hormone–treated EOMs, similar to what we saw in the eyelid muscles. Loss of satellite cells positive for both Pax7, the general satellite cell marker, and MyoD, a

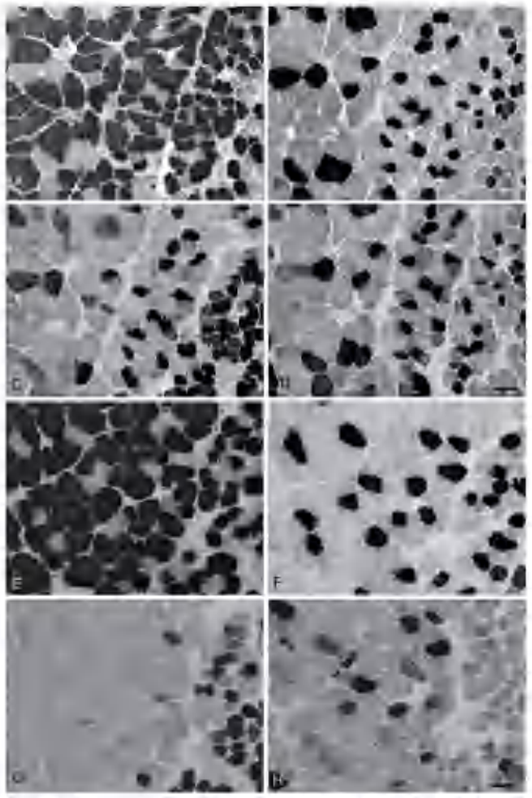


FIGURE 3. Extraocular lateral rectus muscle sections: (A–D) control; (E–H) hyperthyroid rabbits immunostained for the presence of (A, E) fast, (B, F) slow, (C, G) developmental, and (D, H) neonatal MyHC isoforms. Positive myofibers appear *black*. Note that the global layer is to the *left* in all images and a portion of the orbital layer can be seen at *right*. These sections are intermediate between the midbelly and tendon ends. Note the decrease in myofibers positive for developmental and neonatal MyHC isoforms in the muscles from the hyperthyroid rabbit. Bar, 20 μm.

marker of activated satellite cells, was seen. A complex pattern of changes in the four MyHC isoforms examined emerged. Generally, increases in the percentage of slow MyHC isoforms fibers were seen, and decreases were seen in the percentages of fast, developmental, and neonatal MyHC isoform expressing fibers. It appears that as little as 1 month of elevated thyroid hormone levels can result in a complex set of MyHC isoform alterations in the EOM myofiber populations, in both the orbital and global layers along the length of the muscle from insertion toward the midbelly region. Further studies should address changes in the more EOM-specific MyHC isoforms, as this type of detailed analysis was beyond the scope of the present study. These changes are summarized and graphically depicted in Figure 10. In the hyperthyroid extraocular muscle, the total muscle cross-sectional area and individual myofiber cross-sectional areas are reduced, there is a reduction in expression of immature MyHC isoforms, in this case neonatal MyHC is depicted, and a decrease in cells positive for the MyoD and Pax7 markers.

Although measurements of muscle force were not determined in the present study, alteration in myofiber size, number of myofibers, and MyHC isoform composition would have a significant impact on force development. In animal studies, elevated thyroid hormone levels cause significant reduction in force production in both diaphragm and soleus muscles, fast and slow muscles, respectively.[5,52] When the effect of elevated thyroid hormone on EOM force was assessed in patients with both active and chronic, mild and severe TED, the muscles from all patients showed abnormal tension, even those with no clinical signs of eye movement disorders.[34] The authors hypothesize that this abnormality had to be due to direct EOM changes in these patients, and this hypothesis is supported by our current analysis. Although magnetic resonance imaging studies demonstrate significant enlargement of one or more of the EOM in patients with TED, these patients have already developed eye signs. Enlargement of the muscles is due to inflammatory processes within the muscle, and to our knowledge, the muscle itself in these patients has not been studied. This problem will be difficult to solve, as hyperthyroid humans could not reasonably have biopsies of eye muscles taken, nor is EOM surgery a part of normal treatment for patients in whom TED develops. Ongoing experiments in the laboratory are focused on whether and when the EOMs return to normal size after the rabbits return to control levels of thyroid hormone. Our prediction, based on studies of hyperthyroid patients in whom muscle strength eventually returns to normal levels after they are maintained for 6 months in the normal euthyroid state, is that the same will occur in rabbit EOMs.[35]

Decreases in the number of myofibers, mean myofiber cross-sectional area, and total muscle cross-sectional area are not surprising, given the well-known catabolic effects of thyroid hormone on skeletal muscle in general. In the EOM, we propose that the catabolic effects of increased myofibrillar protein degradation caused by elevation in thyroid hormone are exacerbated by the normal process of myofiber remodeling that occurs throughout life, which is not present in normal adult limb skeletal muscle.[11,12] Elevating thyroid hormone levels in animals during normal limb skeletal muscle development results in an accelerated process of differentiation.[9–11,36] As would be predicted by the premature withdrawal from the cell cycle, premature myoblast fusion, and accelerated differentiation in developing limb skeletal muscle exposed to elevated thyroid hormone levels,[8] increased thyroid hormone levels in EOMs resulted in smaller muscles presumably because of the same effects of thyroid hormone on the satellite cell populations within the EOM. Based on immunostaining alone, it is unclear whether there is an overall reduction in the total number of satellite cells in these muscles, as indicated by the decrease in Pax7-positive cells, or there is a decrease in the expression of Pax7 within individual cells (Fig. 10). The net result, however, of either scenario is that less muscle regeneration/repair would be possible, and thus a smaller muscle would be predicted.

The decrease in the percentage of EOM myofibers expressing the neonatal and developmental MyHC isoforms in most of the rectus muscles examined mirrors the accelerated loss of these immature isoforms in developing skeletal muscle under conditions of elevated thyroid hormone.[29] Thus, the overall decrease in the percentage of EOM myofibers expressing these immature MyHC isoforms is compatible with current knowledge about the effects of elevated thyroid hormone on nonocular skeletal muscle differentiation processes and rates of differentiation.

Elevated levels of thyroid hormones are known to hinder muscle repair and cause skeletal muscle atrophy in adult nonocular skeletal muscle.[37] These processes would explain the reduction in overall muscle cross-sectional area seen in the present study. There are three processes that can be proposed to explain the decreased myofiber size and overall myofiber

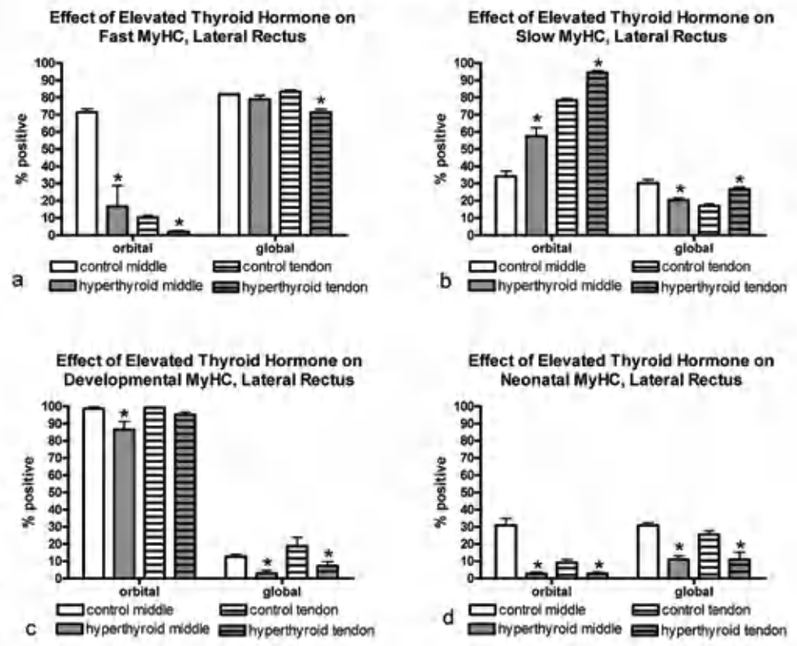


FIGURE 4. Quantification of the percentage of myofibers in the lateral rectus muscle from hyperthyroid and control sections positive for (**a**) fast, (**b**) slow, (**c**) developmental, and (**d**) neonatal MyHC isoforms. *Significant difference from control sections. Data are the mean ± SEM.

number. First, it is known that the EOMs continue to express various myogenic growth factors, including IGF, in the adult.[38] Previous studies demonstrated that the addition of exogenous IGF results in increased skeletal muscle mass.[39,40] Since IGF is regulated by thyroid hormone, reduction of this myogenic growth factor would result in reduced muscle mass.[41] This hypothesis is currently under investigation. Second, a significant reduction in the number of satellite cells positive for the

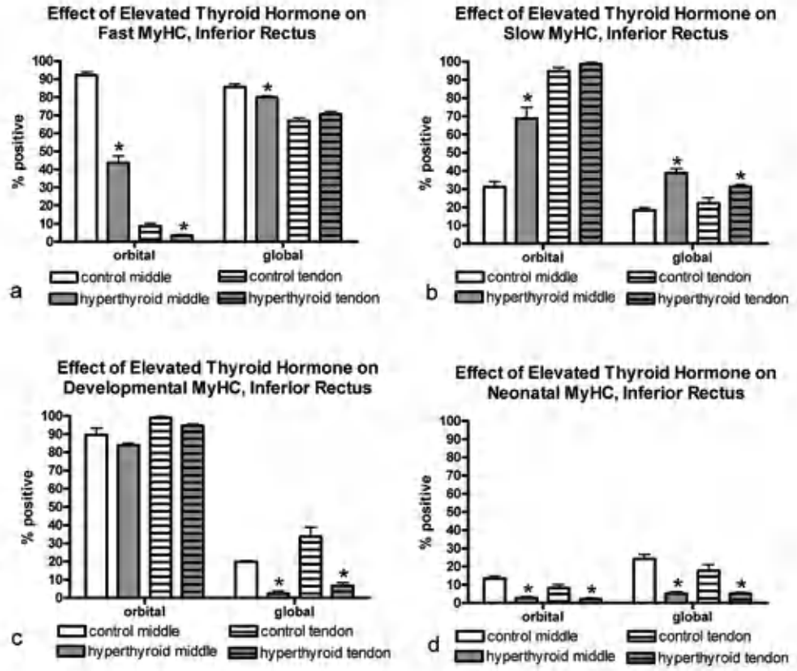


FIGURE 5. Quantification of the percentage of myofibers in the inferior rectus muscle from hyperthyroid and control sections positive for (**a**) fast, (**b**) slow, (**c**) developmental, and (**d**) neonatal MyHC isoforms. *Significant difference from control sections. Data are the mean ± SEM.

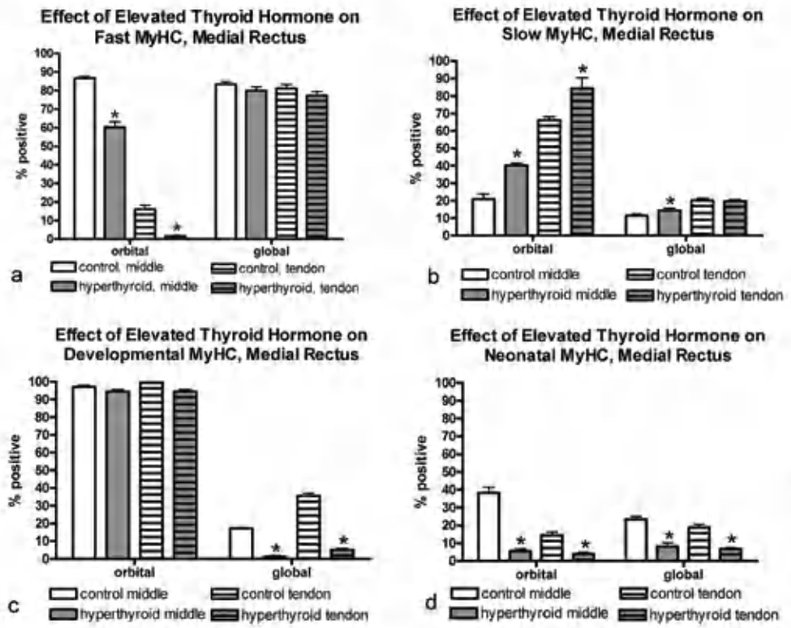


FIGURE 6. Quantification of the percentage of myofibers in the medial rectus muscle from hyperthyroid and control sections positive for (**a**) fast, (**b**) slow, (**c**) developmental, and (**d**) neonatal MyHC isoforms. *Significant difference from control sections. Data are the mean ± SEM.

myogenic regulatory factor MyoD, a marker of activated satellite cells,[42] was seen. This means that elevated thyroid hormone levels appear to decrease the process that controls myofiber remodeling in adult rabbit EOMs.[42,43] Inhibition of ongoing myofiber remodeling would be predicted to result in decreased muscle mass, as seen in the present study. Other laboratories have demonstrated that thyroid hormone specifically inhibits satellite cell proliferation in vitro,[8,44] which again supports the present results. Finally, elevated levels of thyroid hormone can stimulate apoptosis in muscle cells.[5,45,46] Of

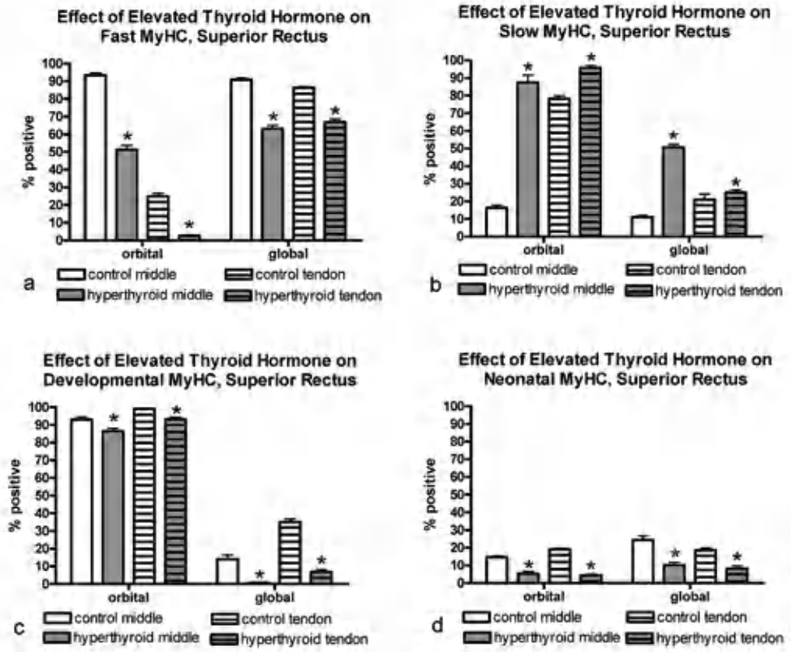


FIGURE 7. Quantification of the percentage of myofibers in the superior rectus muscle from hyperthyroid and control sections positive for (**a**) fast, (**b**) slow, (**c**) developmental, and (**d**) neonatal MyHC isoforms. *Significant difference from control sections. Data are the mean ± SEM.

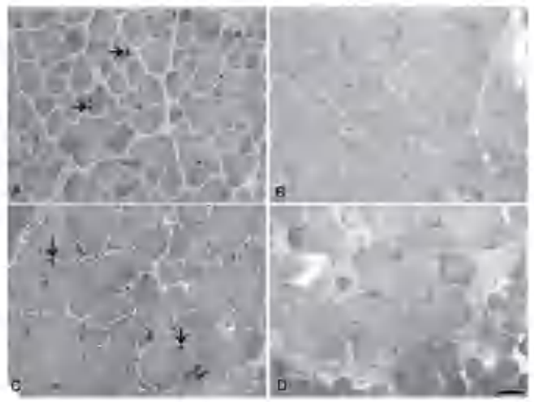


FIGURE 8. Extraocular inferior rectus muscle sections from (**A**, **B**) control and (**C**, **D**) hyperthyroid rabbits immunostained for the presence Pax7 (**A**, **B**) and MyoD (**C**, **D**). *Arrows*: positive nuclei. Note the complete absence of positive cells in the hyperthyroid muscle samples. Bar, 20 μm.

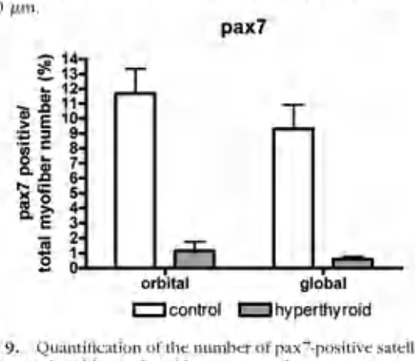
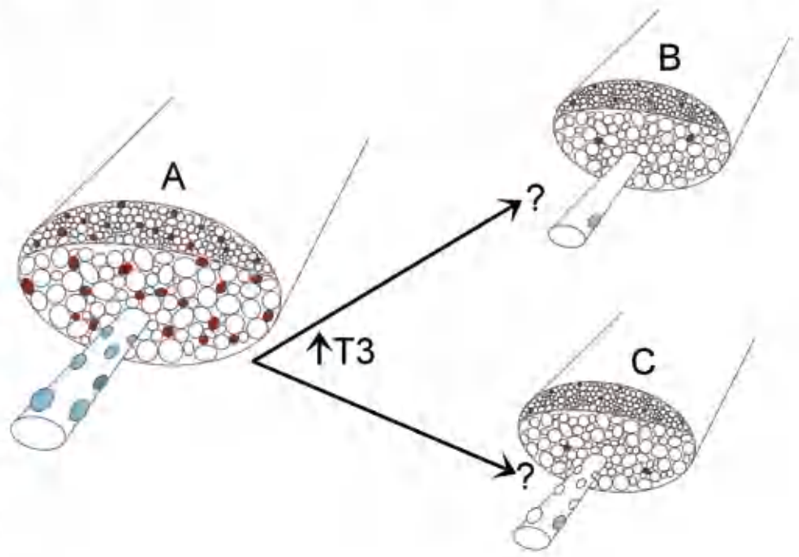


FIGURE 9. Quantification of the number of pax7-positive satellite cells in the control and hyperthyroid rectus muscles.

FIGURE 10. Depiction of the changes that occur in the extraocular muscles after exposure to elevated thyroid hormone. Relative to the normal muscle depicted on the left, the orbital and global layers, superiorly and inferiorly placed on the drawing, show decreased overall muscle cross-sectional area, decreased individual myofiber cross-sectional areas, and decreased number of fibers. In addition, immature MyHC isoform expression decreases, with neonatal MyHC isoform changes depicted here. There is a loss of cells expressing Pax7 and MyoD. Two alternative hypotheses for the disappearance of pax7-positive myogenic precursor cells (satellite cells) are proposed. Elevated thyroid hormone causes a decrease in the number of these cells, due to fusion into existing fibers or apoptosis or to a loss of Pax7 expression. *Left*: a normal extraocular muscle. (**A**) One fiber, with several satellite cells, is depicted: Pax7-positive (*blue*) and MyoD-positive (*green*). *Right*: two possible explanations for the loss of Pax7-positive cells. Either (**B**) all but a very few disappear, or (**C**) the cells remain but they no longer express Pax7.



interest, the basal level of cell turnover in normal thyroid glands is regulated by apoptosis, which in turn is altered in several thyroid diseases.[47] In light of these studies, similar changes in rates of cell turnover in the EOM are not surprising. Studies of the effect of thyroid hormone on apoptosis in the EOMs are ongoing. However, as the effects of both these processes would be to decrease muscle mass, the overall decrease in myofiber size and number would be expected. Elevated thyroid hormone levels cause many other changes in cells. In particular, it is known that the EOMs are particularly rich in mitochondria and that these mitochondria display metabolic differences compared with normal limb muscle.[48] As elevated thyroid hormones alter mitochondrial uncoupling proteins,[7] this and other aspects of the unique metabolism of EOMs would certainly play a role in alterations in these muscles under these conditions.[49] Based on the appearance of the muscles, as seen in Figure 3, no fibrosis was observed. Thus, the satellite cells did not change their differentiation pathway toward a fibroblast fate, nor is it likely that the myofibers themselves would have transdifferentiated into connective tissue.

The alterations of muscle size and myosin isoform expression were relatively uniform among the four rectus muscles despite their significant differential involvement in TED in humans.[50] Thus, it appears that these particular characteristics would not contribute to the differential susceptibility of individual EOM to TED, where the medial and inferior rectus muscles are affected more often.[51] However, as any type of increased cell loss can trigger release of inflammatory mediators,[52] it may be that the myofiber loss plays a role in initiation of the inflammatory cascade in this disease.

The effects of elevated thyroid hormone levels on fast and slow MyHC isoform composition have been studied in nonocular adult skeletal muscles. Most skeletal muscles, when subjected to elevated thyroid hormone, shift their overall MyHC composition in the opposite direction from their normal state; thus, in the soleus, a muscle predominantly containing slow MyHC-positive myofibers, elevated thyroid hormone levels result in a shift toward an increasing number of myofibers posi-

tive for fast myosin.[10,33] In the plantaris, a muscle normally containing predominantly fast MyHC–positive myofibers, elevated thyroid hormone results in a shift toward an increased number of slow myofibers.[34] In orbicularis oculi from hyperthyroid rabbits, which is also a muscle expressing predominantly fast-positive myofibers, similarly there is a significant increase in the percentage of myofibers expressing the slow MyHC.[9,2] It is unclear what controls these patterns of fast and slow MyHC transitions under hyperthyroid conditions. One factor may be the number of thyroid hormone receptors on the nuclei within each muscle type, as the EOMs express an increased number of thyroid hormone receptors compared with limb skeletal muscles[27]; however, it is unknown whether receptor expression varies between fiber types. Thus, the effects of thyroid hormone on metabolism and MyHC phenotype appear to be extremely complex and fiber specific.[5,6,34]

The rabbit model used in the present study addresses changes in the EOMs caused by increased systemic thyroid hormone levels. Human TED is a complex autoimmune inflammatory response in the EOM, and it must be stressed that it is not the same as simple hyperthyroidism. However, it is evident from our study that hyperthyroidism itself leads to significant changes in extraocular muscle metabolism, such that the muscles are reduced in size, have altered populations of satellite cells (the muscle regenerative cell), as well as altered expression of MHC isoforms in populations of myofibers in the EOMs. As clinically relevant eye signs are seen in at least 50% of patients with Graves' disease,[54] changes within the EOM with increased thyroid hormone levels may suggest new testable hypotheses. It may be that TED is a result of a set of predisposing factors in patients, but it only develops if some type of precipitating factor is added as occurs with blepharospasm.[55] Additionally, muscle catabolism may expose nuclear antigens to the immune system, suggesting new directions for future studies. It is hoped that a greater understanding of the changes in the EOM as a result of increased thyroid hormone may suggest alternative strategies for manipulating the muscles in the acute phase of patients who develop this potentially blinding disease.

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ORIGINAL INVESTIGATION

Normal Exophthalmometry Measurements in a United States Pediatric Population

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Purpose: The normal distribution of exophthalmometry measurements in a U.S. pediatric population was determined as a reference for clinical practice.

Methods: This was a cross-sectional study, in which 673 normal subjects, between 1 and 17 years of age, randomly selected from patients presenting to our institution, were measured with an exophthalmometer. Normal volunteers also participated at a booth at the annual state fair. Subjects were excluded for a prior history of orbital tumor, craniofacial anomaly, thyroid disease, orbital trauma, or inability to tolerate the measurement.

Results: A total of 673 subjects (52% female) with a mean age of 9.6 years were studied. There was no difference in exophthalmometric measurements between male and female subjects. Mean exophthalmometric measurements increased with age: less than 4 years old (13.2 mm), 5–8 years old (14.4 mm), 9–12 years old (15.2 mm), and 13–17 years old (16.2 mm). Asymmetric measurements occurred in 100 (14.9%) subjects, with a 2-mm maximal difference in 2 subjects.

Conclusion: Exophthalmometric measurements vary with age among the pediatric population. Reference data are presented for each age group in a U.S. cohort.

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Exophthalmometric measurements represent clinically important data for children and adults and require normative values for all ages. Exophthalmometric measurements quantify the spatial interaction between the size of the bony orbital cavity and its contents. The bony orbital cavity surrounds the orbital soft tissues in all directions except anteriorly, making exophthalmos a sign of orbital disease. In children, 50% of exophthalmos results from an orbital tumor.[1] Trauma, hyperthyroidism, systemic diseases, and high myopia can also cause exophthalmos.[2] Normal exophthalmometric measurements vary in association with gender, age, and ethnicity.[3] Previous pediatric studies on the normal distribution of exophthalmometric measurements provide some data but remain limited to a minority or ethnic group outside of North America.[4,5] These studies have shown substantial variability and may not apply to a U.S. cohort. Additionally, measurements for children younger than 5 years of age have limited data.[6] The purpose of this study is to produce the normal distribution of exophthalmometric measurements in a U.S. pediatric population as a reference for clinical practice.

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METHODS

This was an institutional, cross-sectional study conducted with a Hertel exophthalmometer (Hertel, Jacksonville, FL) to measure the position of the globe. The Hertel exophthalmometer, the most widely used method of measuring globe position, simultaneously measures the distance from the plane of the lateral orbital rims to the apex of the cornea to the nearest millimeter in both eyes while also measuring the outer orbital margin distance.[7,8] Three observers individually collected the exophthalmometry measurements. These observers, at the same institution, collaborated before the study in an effort to ensure consistent technique to reduce interobserver variation. Subjects in this study were randomly selected from pediatric patients at the University of Minnesota Ophthalmology Clinic. Additionally, a booth was established at the Minnesota State Fair, in which participants were asked to volunteer for the study. We only included subjects between 1 and 17 years of age. Any subject was excluded for history of an orbital tumor, craniofacial anomaly, thyroid disease, orbital trauma, or inability to tolerate the measurement. We also recorded gender and self-designated race. Statistical analysis was performed to determine mean exophthalmometry and base readings with standard deviation.

RESULTS

A total of 673 subjects were measured with the Hertel exophthalmometer. Of these subjects, 351 (52%) were female, and the mean age for all subjects was 9.6 years of age. For all subjects, exophthalmometric measurement ranged from 9 to 21 mm, with a mean of 15.0 ± 1.9 mm. Overall, there was no difference in measurements between male and female subjects (15.1 ± 1.8 and 15.0 ± 2.0 mm, respectively ($p = 0.64$)). Asymmetric measurements occurred in 100 (14.9%) subjects: 98 subjects showed 1 mm of difference, and 2 subjects showed 2 mm of difference. Of the asymmetric subjects, 35 had left exophthalmometric measurements greater than right, and 65 had right exophthalmometric measurements greater than left. The distance between the lateral rims of the orbits, or base, ranged between 77 and 110 mm. The mean for all subjects was 92.0 ± 5.5 mm. There was a statistical difference in base between males and females (92.5 ± 5.9 and 91.5 ± 5.1 mm, respectively ($p = 0.02$)).

TABLE 1. Caucasian subgroup analysis

Sex	N	Mean age (years)	Mean exophthalmometry measurements ± SD (mm)	Mean base ± SD (mm)
All	595	10.1	15.0 ± 1.9	92.0 ± 5.5
M	279	10.0	15.1 ± 1.8	92.4 ± 5.8
F	316	10.2	14.9 ± 2.0	91.7 ± 5.1

N, number; M, male; F, female.

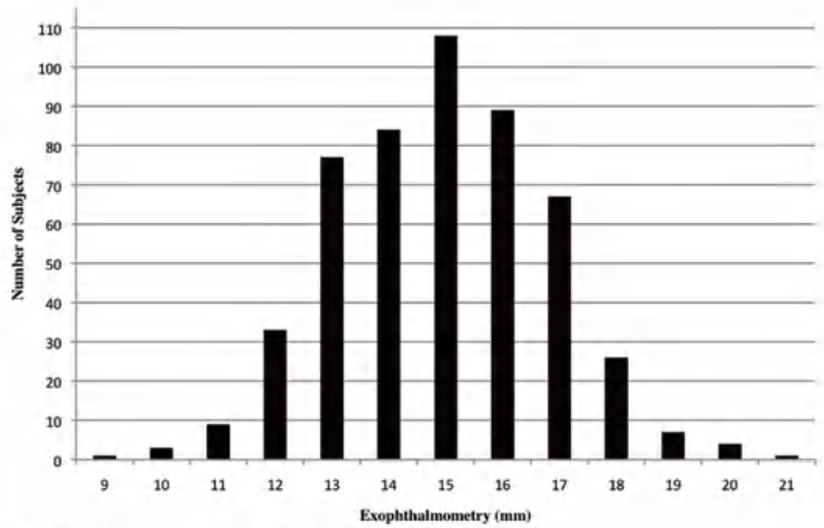

FIG. 1. Distribution of mean exophthalmometry measurements in all Caucasians.

Race was self-assigned by each participant. There were 595 (89%) Caucasian, 27 (4.0%) Asian, and 16 (2.4%) African-American subjects. Of the Caucasian subjects, 31 (4.6%) and 4 (0.6%) described themselves as Hispanic or Middle Eastern, respectively. There was a slight female preponderance (n =316, 53%) among Caucasian volunteers (Table 1). The range of exophthalmometric measurements for the Caucasian subjects was 9–21 mm with mean exophthalmometry measurement of 15.0 ± 1.9 mm (Fig. 1). The mean exophthalmometry measurements for male and female Caucasians were similar (14.9 ± 1.9 and 15.1 ± 1.8, respectively ($p = 0.27$) (Fig. 1). The range of base measurements in the Caucasian population was 77–108 mm with a mean base of 92.0 ± 5.5 mm (Fig. 2). There was no statistical difference in base between males and females (92.4 ± 5.4 and 91.7 ± 5.1, respectively ($p = 0.11$)). The Caucasian population was further divided in 4 subgroups by age. These data are summarized in Table 2. The Asian, Hispanic, and African-American groups were too small to analyze.

For all subjects, increasing exophthalmometric measurements were significantly correlated with increasing age with $y = 0.2358x + 12.792$, $r^2 = 0.25836$, $p < 0.001$ (Fig. 2). Similarly, there was a statistically significant increase in base measurements with increasing

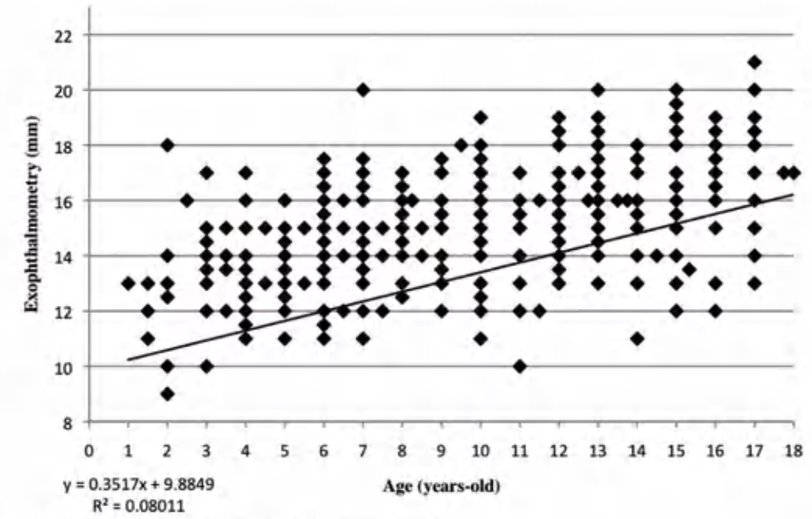

FIG. 2. Mean exophthalmometry measurements of Caucasians by age.

TABLE 2. Caucasian age subgroup analysis

Age (years)	N	Mean exophthalmometry measurements (95% CI) mm	Mean base (95% CI) in mm
1–4	79	13.2 (10.1–16.4)	84.9 (77.0–92.9)
5–8	171	14.4 (11.3–17.4)	89.7 (81.0–98.5)
9–12	164	15.2 (11.9–18.6)	93.7 (85.8–101.6)
13–17	181	16.2 (12.8–19.5)	95.7 (87.8–103.7)

N, number.

age: $y = 0.88x + 83.536$, $r^2 = 0.42988$, $p < 0.001$. Finally, as base measurements increased, a statistically significant increase was seen in mean exophthalmometric measurements: $y = 0.1918x - 2.585$, $r^2 = 0.3077$, $p < 0.001$. Significance was determined by a Student's t test resulting in a p value less than 0.001.

DISCUSSION

The normal distribution of exophthalmometric measurements is clinically important to accurately assess exophthalmos in the pediatric population. While unilateral exophthalmos is easily appreciated, a normal distribution of exophthalmometric measurement is particularly important in diagnosing bilateral exophthalmos. The changes in a patient's exophthalmometric measurement over time could also provide insight into the progression or onset of orbital disease.[1,6] This study and others have shown that exophthalmometric measurement increases with normal growth and development.[1,2,4–6] A normal distribution for various age groups allows physicians following children with conditions such as pediatric thyroid eye disease to distinguish normal growth and development from orbitopathy.

Our study contained 673 subjects, of which 89% were self-designated Caucasian subjects. Gender, race, and age have been shown to influence exophthalmometric measurement.[2] In addition, we performed a subgroup analysis for the Caucasian population. Normative data for exophthalmometric measurement in the Caucasian population has been limited to the Italian population, ages 3–10 years of age, and the Danish population, ages 5–19 years of age.[1,6] The mean exophthalmometric measurements in these studies varied substantially from each other and from the current study for approximately the same ages (Table 3). For example, Fledelius et al.[6] found mean Hertel exophthalmometric measurements in Danish males and females 8–10 years of age to be 13.7 and 14.1 mm, respectively. Also, using a Hertel exophthalmometer, Nucci et al.[1] found much smaller mean measurements for similar age groups with 11.3 mm for 7-year-old males and females and 11.7 for 10-year-old males and females. Our study found 14.4 mm for children 5–8 years of age and 15.2 mm for children 9–12 years of age. Limited data exist regarding the normal mean exophthalmometric measurements in children under 5 years of age. Nucci et al.[1] found a subgroup of children 3 years old to have a mean exophthalmometric measurement of 9.1 mm.

TABLE 3. Comparison of Caucasian mean exophthalmometry measurements

Author	Age group (years)	All subjects (mm)	Male (mm)	Female (mm)
Dijkstal	0–4	13.2	12.9	13.6
	5–8	14.4	14.4	14.3
	9–12	15.2	15.2	15.2
	13–17	16.2	16.1	16.3
Nucci	3	9.1	—	—
	5	9.9	—	—
	7	11.3	—	—
	10	11.7	—	—
Fledelius	5–7		13.7	12.6
	8–10		13.6	14.1
	11–13	—	14.5	14.4
	14–16	—	14.9	15.7

—, no data.

In our study, children between 1 and 4 years of age had substantially higher mean exophthalmometric measurements of 13.2 mm and a normal range of 10.1–16.4 mm. The mean exophthalmometric measurements found in Nucci et al.[1] were not even within our study's normal range, showing dramatically different findings. This variability likely reflects the wide variety of ethnicities that contribute to the American Caucasian population when compared with a more homogeneous Italian or Danish population or the techniques used to measure their subjects.

In summary, we have provided the normal distribution of Hertel exophthalmometric measurements for the pediatric population in the United States. These measurements include normative data for children at various ages including those under the age of 5 years (Table 2). We have also included data for pediatric patients of Caucasian descent (Table 1). The number of minority subjects measured is less than the number of Caucasian subjects measured, limiting our ability to draw comparisons between each ethnic group and creating an area for future study. In addition, because 3 observers collected the data, we recognize that interobserver variation of these measurements is possible; however, studies have shown interobserver variation in Hertel exophthalmometry readings to be negligible.[9,10]

These reference values are particularly useful for determining bilateral exophthalmos in a child. In adults, asymmetric exophthalmometric measurements of more than 2 mm deserve further investigation to rule out orbital disease.[3] In this study, only 2 children out of 673 had asymmetric exophthalmometry of 2 mm, suggesting a lower threshold in children for investigation of asymmetric exophthalmometric measurements.[6]

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Clinical Ophthalmology

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REVIEW

Update on thyroid eye disease and management

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Abstract: Thyroid eye disease is a heterogeneous autoimmune orbital reaction typically manifesting in middle age. The inflammation may parallel or remain isolated from a related inflammatory cascade in the thyroid called Graves' disease. The orbital manifestations can lead to severe proptosis, dry eyes, strabismus, and optic neuropathy. In this article, we will discuss this unique condition including the ophthalmic findings and management.

Keywords: Graves' disease, thyroid eye disease, proptosis, orbital decompression, enlarged extraocular muscles

Pathogenesis and epidemiology

The overwhelming majority (90%) of thyroid eye disease (TED) cases are associated with hyperthyroidism, while the rest are either euthyroid or hypothyroid.[1] Cross-reactivity against shared antigen(s) in thyroid and orbital tissue is most likely responsible for the autoimmune ophthalmologic reaction. Antibodies involving the thyroid-stimulating hormone (TSH) receptor may drive the pathogenesis of this inflammation.[2] Autoreactive T lymphocytes migrate into the orbital soft tissue, fat and musculature reacting with the shared thyroid and orbital antigen(s). The inflammation results in anatomical changes including eyelid retraction (NOSPECS class I) and redness and swelling of periorbital tissues (class II) including the eyelids, conjunctiva, and caruncle.[3,4] Secretion of a cytokine cascade stimulates fibroblast proliferation and secretion of glycosaminoglycans resulting in proptosis (class III) from retro-orbital fat expansion and extraocular muscle swelling. The expansion of orbital tissues may lead to the severe motility disorders (class IV), corneal exposure (class V) and optic nerve damage (class VI). Eventually this process results in fibrosis of the extraocular musculature and permanent restriction of eye and lid movements.

Both endogenous (genetic factors, increased age, male sex) and exogenous factors (smoking, thyroid dysfunction, and radioiodine treatment) likely contribute to the development or severity of TED.[5,6] Approximately half of Graves' disease patients experience ophthalmic manifestations, with sight-threatening disease in 3% to 5% of cases.[7] The heterogeneous manifestations and variable course of TED may greatly affect the quality of life in affected patients.

Although TED is a heterogeneous genetic disorder, finding a common genetic loci remains elusive. Candidate genes include human leukocyte antigen (HLA, 6p21–3), cytotoxic T-lymphocyte antigen-4 (CTLA-4, 2q33), tumor necrosis factor (TNF, 6p21–3), interferon-γ, 12q14), intercellular adhesion molecule-1 (ICAM-1, 19p13), and thyroid

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stimulating hormone receptor gene (TSH-R, 14q13).[1] TED exhibits a female to male ratio of 4:1; however, more severe disease occurs among affected elderly males.[5]

Course of disease

Thyroid eye disease typically has an inflammatory, active phase subsiding over one to two years (range 6 months to 5 years) into a fibrotic, inactive phase (Figure 1).[6] After the inflammation subsides, patients may suffer permanent structural changes around the eyes requiring treatment. Active inflammation recurs in about 1% of patients after months to years of inactivity. Unfortunately, no reliable test or sign exists to determine when the inactive phase has begun. These patients return for repeat evaluations to document changes in symptoms or clinical findings. Stable clinical findings for 6 months suggest that the patient has passed from the active to the inactive phase. It is important to recognize every patient's course of TED is different and unique. Some may have minimal signs while others have sudden onset of severe complications such as severe diplopia, proptosis and vision loss.

Smoking has a strong relationship with the course and severity of thyroid eye disease. The relationship is dose-responsive between cigarette use and probability of developing thyroid eye disease.[10] Smoking is associated with an increased risk of ophthalmic disease after radioiodine therapy and worse or delayed outcomes for treatment of thyroid eye disease.[11]

Clinical findings

Ophthalmic findings are generally bilateral, but may present unilaterally or asymmetrically.[1] The presence of pre-existing autoimmune thyroid disease increases suspicion for TED, but isolated eye findings may represent the presenting manifestations of thyroid disorders. The classic presentation in the setting of acute Graves' disease involves thyrotoxicosis, goiter and bilateral exophthalmos. In one cohort of 120 TED patients, clinical features included: eyelid retraction 91%, exophthalmos 62%, extraocular muscle dysfunction 43%, ocular pain 30%, lacrimation 23%, and optic nerve disease 6%.[12]

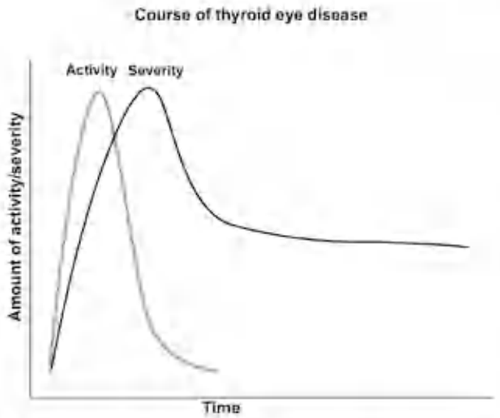


Figure 1 Rundle's curve mapping increase in disease activity or severity followed by a reduction over time.

The earliest findings in TED usually involve mild soft tissue inflammation. Early symptoms include foreign body sensation, excessive tearing from dry eye, conjunctival or eyelid redness and swelling, blurred vision, and retro-orbital pain. Dilated conjunctival vasculature, keratoconjunctivitis, and corneal staining may be seen on slit lamp examination.

As the orbital inflammation progresses in severity, swelling of the extraocular muscles (EOM) or orbital soft tissue often manifests as chemosis, lid edema and ocular proptosis.[13] The EOM may become visible as blood vessels over their anterior portion show prominence. Such vessel engorgement overlying the lateral rectus has been described as a sign of activity;[14] however this may persist during the inactive disease phase.[13] Poor venous drainage secondary to the congestive mass effect behind the eyes may contribute to redness and swelling of the eyelids, conjunctiva, and caruncle. Involvement of the levator palpebrae results in eyelid retraction and the characteristic "stare" of TED (Figure 2). This appearance is often exaggerated by the presence of exophthalmos. Progressive proptosis with eyelid retraction and meibomian gland inflammation may worsen corneal exposure and progress to corneal ulceration and perforation.[15,16] Inflammation and scarring of the EOM can cause strabismus and ophthalmoplegia. In mild cases, patients might feel a pulling sensation around the eyes. With more advanced disease, horizontal, vertical and torsional strabismus and double vision ensues (Figure 3). Asymmetric EOM restriction manifests as incomitant deviations with diplopia in eccentric gazes, ie, sidegaze esotropia or upgaze hypotropia with medial or inferior involvement respectively. In severe cases the restrictive, incomitant strabismus occurs in primary gaze and patients complain of constant double vision. In addition to vertical and torsional tropias, inferior rectus involvement may lead to a poor Bell's phenomenon with increased risk of corneal exposure. Diffuse orbital and EOM restriction may lead to intermittent spiking or chronic elevation of intraocular pressure. Intraocular pressures should regularly be tested in both primary and upgaze. Strabismus may develop at any stage in the disease or secondary to orbital changes after decompression surgery. In addition,

Figure 2 Severe inflammation and proptosis with classic "stare" of thyroid eye disease may be prominent in the active phase of disease.

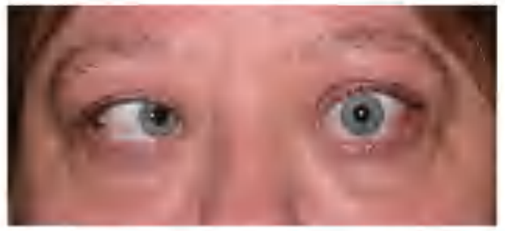


Figure 3 Esotropia strabismus is a common manifestation of medial rectus enlargement in thyroid eye disease.

vertical rectus strabismus surgery may cause iatrogenic eyelid retraction and worsen corneal exposure.

With severe inflammation, the expansion of soft tissues confined within the bony orbit and swelling of the muscles at the apex of the orbit may compress the optic nerve causing dysthyroid optic neuropathy (Figure 4).[17] Although early symptoms include progressive blurring of vision and fading of colors in one or both eyes, visual acuity may be preserved in a minority of patients with optic neuropathy.[18] Of note, when optic neuropathy occurs the degree of proptosis often does not correlate. Presumably, this occurs when the enlarged EOM expand to compress the optic nerve instead of producing exophthalmos. Signs of optic neuropathy include decrease in visual acuity, visual field, and color vision along with the development of an afferent pupillary defect. Bilateral, simultaneous optic neuropathy can occur which would eliminate a relative afferent pupillary defect. The optic disc may be normal or edematous. Without detection through serial screenings and subsequent prompt treatment, permanent optic atrophy and visual loss may occur.

Careful evaluation of TED patients presenting to an ophthalmologist allows for quantitative assessment disease activity and severity.[17] Activity of thyroid eye disease can be assessed with the Clinical Activity Score (Table 2).[19] The clinical features of inflammation are graded based upon comparison with photographs to improve objectivity.[17] Severity may be assessed using the NOSPECS classification; this mnemonic for evaluation assists in differentiation of mild, moderate, and severe disease (Table 1).[3,20] Impairment of quality of life can be elicited with the Graves'-ophthalmopathy specific QOL questionnaire (GO-QoL).[21] Initial laboratory studies include bloodwork for thyroid stimulating hormone (TSH), thyroid stimulating immunoglobulin (TSIG), thyroid peroxidase (TPO) antibody, and TSH receptor antibody.

Lastly, radiographic imaging using CT, MRI, or ultrasound may aid in the diagnosis of thyroid eye disease. CT scanning is the modality of choice to evaluate dysthyroid optic neuropathy and the planning of surgical intervention. Findings often include enlargement of orbital fat or musculature with sparing of insertions. The inferior and medial recti are most commonly affected. Other finding on imaging include intracranial prolapse of fat through the superior orbital fissure, straightening of the optic nerve or impingement of apical musculature on the optic nerve.

The differential diagnosis for the clinical features of thyroid eye disease includes infectious and inflammatory orbital conditions such as orbital myositis, idiopathic orbital inflammatory syndrome, and orbital cellulitis. Rarer conditions include orbital neoplasms and carotid artery – cavernous sinus fistulas. New onset diplopia may result from cranial nerve palsies, internuclear ophthalmoplegia, or myasthenia gravis.

Management

Patients with Graves' ophthalmopathy should be managed by a coordinated team of primary care physicians,

Figure 4 CT imaging of extraocular muscle enlargement at orbital apex.

Table 1 Clinical activity or severity may be assessed with either the Clinical Activity Score (CAS) or the NOSPECS severity assessment

Clinical Activity Score (CAS)		
Score determined by sum of the symptoms and signs in a patient with TED at a given visit		
Spontaneous retrobulbar pain		
Pain on attempted up-gaze or down-gaze		
Redness of the eyelids		
Redness of the conjunctiva		
Swelling of the eyelids		
Inflammation of the caruncle and/or plica		
Edema of the conjunctiva		
NOSPECS Severity Assessment		
Class 0	No signs or symptoms	
Class 1	Only signs, no symptoms	Lid aperture (mm)
Class 2	Soft tissue involvement	Swelling, redness
Class 3	Proptosis	Exophthalmos (mm)
Class 4	Extraocular muscle involvement	Ductions (degrees), diplopia score (0, no diplopia; 1, intermittent: diplopia in primary position of gaze when tired or awake; 2, inconstant: diplopia at extremes of gaze; 3, constant: diplopia always present)
Class 5	Corneal involvement	Punctate keratopathy, ulceration
Class 6	Sight loss	Optic nerve involvement: changes in visual acuity, color vision, visual fields, or optic disk

endocrinologists, and ophthalmologists with specialty experience in managing TED. This typically involves a neuro-ophthalmologist, an orbital surgeon, and a strabismus surgeon. The complicated nature of treatment often requires coordination of medical, surgical and radiation therapy.[22] Uncontrolled thyroid function is associated with more severe thyroid eye disease.[23,24] However, antithyroid drugs and surgical subtotal/near-total thyroidectomy therapies typically do not improve the ophthalmic disease course.[25,26] In fact, radioiodine therapy for Graves' disease can exacerbate ophthalmic disease; particularly in the context of smoking, active disease, or elevated TSH-receptor autoantibodies.[27,28] Administration of steroids during and following radioiodine therapy decreases the risk of exacerbation in patients with active TED.[29] When radioiodine is administered to patients with inactive TED, risk of eye disease exacerbation is minimal.[30]

Ophthalmologic treatment must be tailored to the patient's quality of life,psycho-social effects, and severity and stage of disease. Smoking cessation is mandatory in all phases because it worsens outcome and represents a modifiable risk factor.[31] Mild, early disease does not require surgical or immunomodulating therapy and clinicians may choose to wait and monitor signs. Management can be symptomatic with lubricating eye drops and ointments for corneal exposure and temporary prisms for diplopia.[32] Serial examinations are necessary to screen for progression of disease and determination of stability. Moderately severe or severe worsening of orbital congestion and/or severe proptosis can occur with concurrent dysthyroid disease or many years after well-controlled thyroid function from Graves' disease. When sight is threatened from optic neuropathy or corneal breakdown, urgent referral is necessary to initiate "rescue" therapy, often with glucocorticoid administration and/or orbital decompression. Once the chronic inflammation associated with TED becomes quiescent and a period of stability is noted, "rehabilitative" surgical therapies may be considered.

Rescue therapy

When moderate to severe TED is present, early "rescue" intervention may be indicated. Indications for "rescue" include evidence of optic neuropathy, signficant proptosis and extensive exposure keratopathy. Urgent "rescue" treatment, either alone or a combination, includes corticosteroids, surgical orbital decompression, and orbital radiation.

Severe thyroid eye disease is often treated initially with glucocorticoids. The efficacy and tolerability of intravenous administration (IV) is superior to oral or local injection. Oral glucocorticoids, typically prednisone 60 to 100 mg/day, must be taken over an extended period of time.[33,34] With oral glucocorticoids, bisphosphonates should be considered

Table 2 Proposed methylprednisolone dosing regimens

Author	Proposed methylprednisolone dosing regimen
Kahaly[46]	iv methylprednisolone once weekly: 0.5 g, then 0.25 g, 6 wk each (4.5 g total)
van Geest[51]	iv methylprednisolone 500 mg, over 3 consecutive days, in 4 cycles at 4 weekly intervals (6 g total)
Marcocci[49]	iv methylprednisolone; 15 mg/kg for 4 cycles and then 7.5 mg/kg for 4 cycles; each cycle consisted of 2 infusions on alternate days at 2-week intervals (9 to 12 g total)

for limitation of osteoporosis.[35] Intravenous glucocorticoids pulse therapy may be more effective and better tolerated than oral glucocorticoids.[20] Marcocci et al found optic neuropathy improved in 11 of 14 patients receiving IV steroids vs 3 of 9 taking glucocorticoids orally. Additionally, the final Clinical Activity Score convalesced IV as compared to the oral glucocorticoid treated group. Improvement in symptoms generally occurs after 1 to 2 weeks of high dose intravenous glucocorticoids.[17] Rarely adverse effects have included reports of acute liver damage and failure at high doses.[36] For this reason, it is recommended to confine the cumulative glucocorticoid dose to less than 8 g[20] (Table 2).[36,40,43]

Alternatively, some surgeons feel intraorbital injection of glucocorticoids provide relief of ophthalmologic symptoms with minimal systemic side effects.[20] A dose of 20 mg triamcinolone (Kenalog® 40 mg/mL) monthly is injected into the inferior lateral quadrant of the orbit. There is disagreement,[43] however, between data comparing injections to other forms of steroid administration.[43]

Orbital decompression has been a mainstay in historical treatment for TED. Medical therapies have come to replace surgical for the initial management of certain cases of dysthyroid optic neuropathy although both are efficacious.[43] When contraindications exist to medical management or disease is refractory to trial of glucocorticoids and radiation, urgent surgical decompression is necessary. Decompression for optic neuropathy traditionally involves removal of the medial and inferior walls.[45] Access to these structures is achieved through transconjunctival or transcaruncular incisions. Otolaryngology may also decompress the posterior medial orbit through a transphenoidal approach. Removal of sufficient posterior bone is important for decompressing optic neuropathy.

The use of botulinum toxin for dysmotility in TED was first described by Scott.[46] Early in the disease course, a botulinum extraocular muscle injection may temporarily improve motility. However as the disease progresses and the musculature becomes more fibrotic, lasting effects are often limited. Botulinum administration to the levator complex has been shown to temporarily improve lid retraction and corneal exposure.[47]

The data surrounding use of external ionizing orbital radiation is mixed. Clinical application of such therapy for dysthyroid optic neuropathy lacks conclusive support. Orbital radiation in the active disease phase showed no efficacy in one report.[48] Radiation is equally as effective as oral glucocorticoids,[49] yet the combination of treatments provide better results than either individual therapy.[50] In trials approximately 60% of patients respond to radiation.[51] A recent report reviewing orbital radiation found improvement in extraocular motility, however, no evidence of improvement in proptosis, eyelid retraction, or soft tissue swelling.[52] Lower doses of radiation, 1 Gy per week for 20 weeks, have been shown to be equally effective and better tolerated than higher doses, 20 Gy per orbit over 2 weeks.[53,54] Safety of orbital radiation is encouraging; new onset of definite radiation retinopathy is 1% to 2% over 10 years.[55] Absolute contraindications include diabetic retinopathy and severe hypertension, while young age represents a relative contraindication.[56] Fortunately, radiation therapy does not appear to compromise future surgical therapies.[57]

Rehabilitative surgical therapy, as described below, is best initiated after six months of stable, inactive thyroid eye disease.[58] If decompression surgery is performed in the active phase, additional decompression may be necessary due to inflammatory changes that persist post-operatively. Additionally, spontaneous remission of symptoms is possible with resolution of the active phase. Wise timing could, therefore, spare patients from unnecessary procedures.

Rehabilitative surgical therapy

Rehabilitative surgical therapies are implemented for stable, inactive TED. Such surgical therapy typically involves orbital decompression, strabismus surgery, eyelid repositioning and blepharoplasty. Patients with mild disease may only require one of these restorative procedures. Conversely, patients with severe disease may require all three types of surgery in succession as needed. The order of these procedures is important because decompression may alter or create strabismus, and strabismus surgery on vertical recti can alter eyelid positioning.

Orbital decompression surgery

Traditional indications for decompression involved predominantly optic neuropathy and severe exposure keratopathy. Currently medical therapy including external beam radiotherapy may be considered prior to decompression

Figures 5 (left) and 6 (right) Pre- and post-operative orbital decompression images document a marked decrease in proptosis.

for optic neuropathy. Proptosis has expanded as a surgical indication to include decompression for cosmesis; and decompression is often utilized to provide relief of congestion. Orbital decompression involves either removal of or thinning of any combination of orbital wall surfaces in addition to removal of orbital fat. In bony decompression, additional space is created for soft tissues to prolapse, often into the ethmoid or maxillary sinuses, temporal fossa, and/or cranial cavity. Removal of the inferior wall with the medial, inferomedial and lateral, balanced medial and lateral, and deep lateral wall decompression are common techniques. Alteration of the orbital vault structure can lead to new onset of diplopia.

In patients lacking diplopia before surgery a medial and lateral balanced decompression has been advocated. The objective of this technique is to decrease morbidity including hypoglobus and imbalanced motility. Endoscopic medial and external lateral technique has been shown to provide effective orbital decompression and compares favorably to 3-wall decompression.[59]

Deep lateral wall decompression has reportedly reduced proptosis as much as 6 mm. (Figures 5, 6) Lateral wall decompression alone has a low rate of new onset diplopia of approximately 7%, with reports as low as 2.6%.[59] Complications of deep lateral decompression include cerebrospinal fluid leaks. A volume expansion of 5.6 cc may be achieved with this procedure alone.[60] Deep lateral decompression may also be combined with removal of other walls as needed.

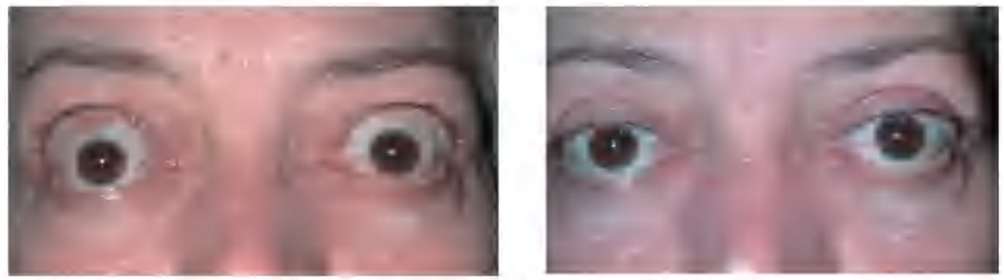
Fat decompression

Removal of intraconal fat reduces congestive orbitopathy, proptosis, and may improve preoperative diplopia. Selection of patients is important and CT or MRI is useful in assessing those with predominantly fatty or muscular soft tissue enlargement.[61] Patients with orbital fat expansion experience better outcomes from fat-only decompression than patients with predominantly extraocular muscle enlargement. Decompression typically involves the inferolateral and superomedial compartments with removal of 3–6 cc of intraconal fat. Safety has been verified with proper selection of patients with orbital fat volume expansion, and new onset diplopia is rare.[62] Intraconal fat debulking may be utilized alone or in combination with bony decompression.

Strabismus

Thyroid eye disease patients often develop diplopia and strabismus requiring surgical correction. The restrictions in motility are most commonly hypotropia or esotropia caused

Figures 7 (left) and 8 (right) Pre- and post-operative strabismus surgery images document improvement of motor alignment.



Figures 9 (left) and 10 (right) Pre- and post-operative eyelid retraction repair images document improvement of eyelid position.

by inferior and medial rectus involvement respectively. Strabismus may present with the onset of orbitopathy or as a direct result of decompression surgery. Patients with preoperative diplopia undergoing inferior and medial wall decompression may experience worsening.[63] Surgical correction of strabismus is, therefore, planned after decompression. The primary goal of strabismus surgery in TED is restoration of single binocular vision in primary gaze and reading position. (Figures 7, 8) Managing patient expectations is important and the surgeon should counsel that single binocular vision in all fields may not be possible. Resection of extraocular muscles is rarely recommended due to the fibrosis and restriction of musculature. Muscle recession on adjustable sutures are frequently utilized since results are more unpredictable compared to the pediatric population.[64] A single surgery functions sufficiently in 85% of cases with reoperation or prism use in the remainder.[65] Approximately 25% of all TED patients use prisms or adopt an abnormal head positioning after surgery.

Eyelid repositioning and blepharoplasty

Surgery for lengthening eyelids and reducing retraction is frequently performed for patients. Benefits include improvement in symptoms of corneal exposure and appearance. Eyelid repositioning should take place after orbital decompression and strabismus surgeries since vertical rectus surgery may alter eyelid position.[66] (Figures 9, 10) Patients with TED often develop significant fatty prolapse and dermatochalasis of the eyelids requiring blepharoplasty. This procedure may be performed in concert with eyelid repositioning, but often is performed later as a separate procedure.

Future therapies

Controversial therapies include a variety of other immunomodulatory agents. Cyclosporine has been shown to work synergistically when used with glucocorticoids.[67] Other research suggests that agents including rituximab and etanercept may be beneficial.[68,69] Agents with less proven value include azathioprine, ciamexone, iv immunoglobulin, and somatostatin analogs. There is hope for future use of therapies targeting the immune system and the pathophysiologic mechanism of thyroid eye disease; however, no conclusive data yet exists.

Summary

Patients with thyroid eye disease necessitate serial examinations and at times intensive specialty care for the ocular manifestations of this disfiguring and potentially blinding disorder. At the University of Minnesota such care is orchestrated by the Center for Thyroid Eye Disease where patients are cared for at each clinical visit by a neuro-ophthalmologist, orbital and oculoplastic surgeon, and strabismologist. Through this multispecialty approach, the patient's strategic management and outcome are maximized.

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Disclosures

The authors disclose no conflicts of interest.

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Hydroxychloroquine retinopathy screening

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Abstract

Aim—To compare current hydroxychloroquine retinopathy screening practices with the published 2002 American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPP).

Methods—A multiple-choice survey was distributed to 105 ophthalmologists to assess current screening practices and knowledge of patient risk factors. Results were compared with the PPP guidelines. A cost analysis of the PPP and survey paradigms was conducted.

Results—Sixty-seven (64%) of 105 surveys were completed. The majority (90%) of physicians screen for hydroxychloroquine retinopathy with either central automated threshold perimetry or Amsler grid as recommended by the PPP. Most survey respondents could not correctly identify the evidence-based risk factors. The majority screen more frequently than recommended: 87% screen high-risk patients and 94% screen low-risk patients more frequently than recommended in the PPP. The increased screening frequency of low-risk patients translates into an excess of $44 million in the first five years of therapy. If all patients were screened using exact PPP paradigm, savings could exceed $150 million every 10 years.

Conclusions—Ophthalmologists currently screen for hydroxychloroquine retinopathy correctly, however, their lack of familiarity with evidence-based guidelines may result in excessive follow up. Increasing awareness and implementation of the PPP could potentially reduce hydroxychloroquine retinopathy screening costs significantly.

Keywords

hydroxychloroquine; plaquenil; toxicity; screening; cost analysis

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INTRODUCTION

Since the 1950's, antimalarial drugs have been used to treat various autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. In the United States, hydroxychloroquine is the antimalarial drug of choice because of its low retinal toxicity.[1–4] Between 1960 and 2005, only 47 cases of hydroxychloroquine retinopathy have been reported in the peer-reviewed literature.[5] Despite the existence of unreported cases, hydroxychloroquine retinopathy is rare. The exact pathophysiology remains unknown, but daily dose, duration of therapy, renal function, liver function and patient age modify patient risk.[1–5]

The ophthalmology and rheumatology literature continually debate the most appropriate paradigm for hydroxychloroquine retinopathy screening.[2,4–7,12–14] In 2002, the American Academy of Ophthalmology (AAO) addressed this controversy by publishing preferred practice patterns (PPP) for hydroxychloroquine retinopathy screening. These evidence-based guidelines attempted to maximize practicality and optimize the cost/benefit ratio of hydroxychloroquine retinopathy screening. They were designed as guidelines that physicians might choose to modify based on their clinical judgment, patient preference, and medico-legal concerns.[7]

The PPP recommends baseline examination and risk assessment within the first year of therapy. There is no need for follow-up in the first five years for low-risk patients, however, the PPP recommend annual screening of high-risk patients. High-risk patients are those with: (1) daily hydroxychloroquine exceeding 6.5 mg/kg, (2) duration of therapy greater than five years, (3) age greater than 60, (4) obesity, (5) renal disease, (6) hepatic disease, or (7) concurrent retinal disease.[8]

The PPP hydroxychloroquine retinopathy screening exams include a comprehensive ophthalmologic evaluation with central visual field assessment by either Amsler grid or Humphrey Visual Field (HVF) 10-2 perimetry (Zeiss, Dublin, CA). Color vision testing, fundus photography, fluorescein angiography, and multifocal electroretinography (mfERG) are considered optional.[8]

This investigation compared the current hydroxychloroquine screening practices of community ophthalmologists to the guidelines outlined in the PPP. Knowledge of risk factors and recommended follow-up frequencies were assessed along with the financial implications of current screening methods.

MATERIALS AND METHODS

An anonymous, nine question, multiple-choice survey was distributed to 105 attendees of the 2007 Twin Cities Eye Meeting prior to a hydroxychloroquine presentation. The survey focused on physician's hydroxychloroquine screening practices and their knowledge of risk factors for developing hydroxychloroquine retinopathy. Following institutional review board approval, survey results were compared with the PPP guidelines.

Based on the survey results, we performed a conservative cost analysis comparing current screening costs to the hypothetical cost of screening all patients according to the PPP recommended protocol. Although the PPP only recommends one initial visit for low-risk patients in their first five years of therapy, we accounted for the cost of additional routine AAO-recommended ophthalmologic exams that may occur during this time for certain age groups (Table 1).[9]

Since hydroxychloroquine patient demographics are not known, we assumed that 150,000 patients are taking hydroxychloroquine at any time in the United States.[2] Age distribution of these patients was estimated from hydroxychloroquine patient ages published in two previous studies (25% under age 40, 31% ages 40–54, 12% ages 55–60, and 33% over age 60).[10–11] These ages were then projected onto our estimated population of 150,000 patients.

We arbitrarily assumed that 10–20% of patients under age 60 (7–15% of the total patient population) are high-risk for hydroxychloroquine retinopathy due to one or more of the following: daily dose greater than 6.5 mg/kg, duration of therapy greater than five years, obesity or underlying liver, kidney or retinal disease. Combining these patients with those over age 60 (33%) who are high-risk based solely on age, it follows that approximately 40–50% of the estimated 150,000 US hydroxychloroquine patients are at high risk for developing retinopathy. The remaining 50–60% of patients are considered low-risk.

Screening costs were estimated at $108 per exam based on Medicare reimbursement of a Level 3 eye exam ($35) and HVF testing ($73). The cost of optional screening exams was not included.

RESULTS

Sixty-seven (64%) of the 105 distributed surveys were completed. The majority of respondents (67%) were comprehensive ophthalmologists, but all ophthalmologic subspecialties were represented at least once. The majority (55%) of ophthalmologists screen between one and twenty-five hydroxychloroquine patients a year. Of the remainder, 31% screen 26–50, 12% screen 51–75, and 2% screen 76–100 patients annually.

Screening Techniques

The vast majority (90%) of the surveyed ophthalmologists screen hydroxychloroquine patient's visual fields as recommended in the PPP. Fifty-four (81%) use macular automated perimetry, 7 (10%) combine perimetry with Amsler grid, and 6 (9%) use Amsler grid alone. In addition, many physicians perform optional exams including color vision tests (73%) and fundus photography (28%). Less common exams were fluorescein angiography (3%) and electroretinography (ERG) (3%). None of the participants screen with the mfERG.

Knowledge of Risk Factors

Knowledge of the evidence-based quantitative risk factors (daily dose, duration of therapy, patient age) was poor. As shown in Table 2, the majority of survey respondents failed to identify the risk factors. Few correct responses were given and no respondent identified all

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three risk factors. Twenty-six (39%) responded "I don't know" to all three risk factor questions. On average, the number of "I don't know" responses was similar for all ophthalmologists, regardless of the annual hydroxychloroquine patients seen.

Follow-up

While all ophthalmologists appropriately screen high-risk patients more often than low-risk patients, most screen all of their patients more frequently than recommended in the PPP. Eighty percent screen high-risk patients every six months, which is twice as frequent as the PPP recommendation. Sixty-five percent screen low-risk patients annually. The PPP recommends only one initial visit for these patients in the first five years.

Cost Analysis

Cost analysis revealed significant potential savings if current screening were modified to fit the PPP paradigm. Using conservative cost estimates, screening all low-risk patients in the first five years of therapy currently costs approximately $56.8 million. In contrast, we estimated it would cost $12.9 million for the first five years of therapy if low-risk patients were screened strictly according to the PPP. These estimates suggest a potential savings of $44 million every five years if all physicians would screen their low-risk patients without deviating from the PPP.

Current high-risk patient screening was estimated to cost $68.9 million every five years, while the PPP paradigm would cost approximately $36.4 million. This translates into an additional $32.4 million five-year potential savings if high-risk patients were screened strictly using the PPP paradigm.

If we assume the hydroxychloroquine patient population size and demographics are constant over time, these estimates suggest a potential savings of $152.6 million every ten years if all patients were screened precisely according to the PPP recommendations.

DISCUSSION

We found that community ophthalmologists generally screen for hydroxychloroquine retinopathy as recommended in the PPP. In addition to comprehensive eye exams, 90% of entire group regularly test visual fields with Amsler grid or automated central threshold perimetry.

Although this overall screening competency is reassuring, the general lack of familiarity with evidence-based guidelines may affect patient care and healthcare costs.

We estimated a ten-year savings of over $150 million using the evidence-based guidelines for all patients. We acknowledge that high-risk patients may necessitate more frequent screening based on both physician and patient concern. However, it seems reasonable to follow the PPP for low-risk patients. Therefore, the most significant potential savings exists in low-risk hydroxychloroquine retinopathy screening.

Our estimated $44 million spending excess in the first five years of therapy for low-risk hydroxychloroquine patient screening in the United States does not include the cost of fundus photography, fluorescein angiography, or electrophysiology. It also does not include the economic impact of missed work, transportation, parking, co-payments, and childcare for patient visits. Therefore, the actual economic impact of current low-risk hydroxychloroquine retinopathy screening is likely much greater than our conservative estimate of $88 million over ten years.

While some of this cost excess is justified by more frequent follow-up with select patients, screening most low-risk patients more than recommended leads to inconvenience and excessive healthcare costs. Strict implementation of the evidence-based guidelines into clinical practice, with modification on an individual case basis when necessary, could potentially increase the cost effectiveness of care. Moreover, increased use of low-cost self-testing and education (Amsler Grid) could be better utilized.

The survey respondents' lack of knowledge regarding evidence-based follow-up intervals suggests physicians may not consciously deviate from the PPP guidelines, but instead are less familiar with current screening standards. Interestingly, we found that nearly half (49%) of the survey respondents follow-up at 6-months/12-months for high and low risk patients, respectively. This may represent a persistent screening protocol presumably acquired prior to the 2002 PPP publication. This suggests that the hydroxychloroquine screening cost/benefit ratio may be optimized simply by increasing awareness of the PPP recommendations and encouraging physicians to incorporate them into practice.

One major limitation of this study is that the opinions and practices of sixty-seven individuals are assumed to represent all U.S. ophthalmologists. This sample size is not ideal, however, substantial trends were seen that suggest a widespread, inadequate knowledge base among ophthalmologists. While a larger scale survey would give a better representation of U.S. screening practices, simply raising physician awareness of the hydroxychloroquine retinopathy PPP may obviate the need for further investigation. Another potential criticism is that the majority (55%) of survey respondents perform between one and twenty-five screening exams a year. Although no direct correlation was seen between familiarity with hydroxychloroquine retinopathy risk factors and increased patient load, knowledge may vary greatly between physicians at the extremes of each range. A more finite range may add insight to the lack of physician familiarity with the PPP.

An additional potential weakness of this study is that multiple assumptions were needed to estimate hydroxychloroquine patient demographics, especially the number of high-risk patients under sixty years old. However, our patient risk stratification is comparable to a recent study of 109 hydroxychloroquine patients that were screened at the San Francisco Veterans Affairs Medical Center. In this study, thirty-two (29%) of the patients under sixty years old were high-risk.[15] In our study, we assumed 10–20% of the patients under 60 were high-risk based on the same criteria. While our estimate is smaller, it accounts for a more diverse patient population that is not limited to a VA patient population.

Ultimately, the AAO will eventually reevaluate their hydroxychloroquine retinopathy screening recommendations in light of the evolving technology. Recent studies suggest that mfERG may represent the future of hydroxychloroquine retinopathy screening.[8,11–14] Its objective analysis of the parafoveal retina may prove to be the most effective means of detecting possibly reversible, early retinopathy. While this is an exciting development in ophthalmologic care, current mfERG use is not widespread and its future role in hydroxychloroquine retinopathy screening is not fully understood. It seems unlikely that mfERG will replace visual field testing, and adding mfERG to screening protocols may result in greater overall costs.

The incidence of hydroxychloroquine retinopathy is low, but its consequences can be devastating. Together, physicians and patients must decide if the benefits of hydroxychloroquine outweigh its risks. While the PPP were intended as patient care guidelines, they represent an evidence-based balance of the cost/benefit ratio and deserve consideration by all screening clinicians. Until new guidelines are developed, we must rely on the evidence-based screening practices outlined in the PPP to guide our minimum standard of care. While we await new recommendations, a national effort to increase awareness and implementation of the PPP would be simple, inexpensive and may significantly reduce the economic impact of hydroxychloroquine retinopathy screening.

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Table 1

AAO Routine Comprehensive Exam Recommendations

Age (yrs)	Exam Frequency (yrs)
<40	Q5–10
40–54	Q2–4
55–64	Q1–3
65+	Q1–2

*Adapted from the AAO Comprehensive Adult Medical Eye Evaluation Preferred Practice Pattern.[9]

Table 2

Knowledge of AAO Defined Risk Factors

	# responses
Dose > 6.5 mg/kg	
Correct	9 (13%)
Incorrect	58 (87%)
Overestimate	9 (16%)
Underestimate	11 (19%)
Unsure	38 (66%)
Duration > 5 years	
Correct	18 (27%)
Incorrect	49 (73%)
Overestimate	8 (16%)
Underestimate	9 (18%)
Unsure	32 (65%)
Age > 60 years	
Correct	7 (10%)
Incorrect	60 (90%)
Overestimate	1 (1%)
Underestimate	14 (23%)
Unsure	45 (75%)

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Outcomes of Patients With Thyroid Eye Disease Partially Treated With Teprotumumab

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Abstract

Purpose: In response to the coronavirus (COVID-19) pandemic, teprotumumab production was temporarily halted with resources diverted toward vaccine production. Many patients who initiated treatment with teprotumumab for thyroid eye disease were forced to deviate from the standard protocol. This study investigates the response of teprotumumab when patients receive fewer than the standard 8-dose regimen.

Methods: This observational cross-sectional cohort study included patients from 15 institutions with active or minimal to no clinical activity thyroid eye disease treated with the standard teprotumumab infusion protocol. Patients were included if they had completed at least 1 teprotumumab infusion and had not yet completed all 8 planned infusions. Data were collected before teprotumumab initiation, within 3 weeks of last dose before interruption, and at the visit before teprotumumab reinitiation. The primary outcome measure was reduction in proptosis more than 2 mm. Secondary outcome measures included change in clinical activity score (CAS), extraocular motility restriction, margin reflex distance-1 (MRD1), and reported adverse events.

Results: The study included 74 patients. Mean age was 57.8 years, and 77% were female. There were 62 active and 12 minimal to no clinical activity patients. Patients completed an average of 4.2 teprotumumab infusions before interruption. A significant mean reduction in proptosis (−2.9 mm in active and −2.8 mm in minimal to no clinical activity patients, $P < 0.01$) was noted and maintained during interruption. For active patients, a 3.4-point reduction in CAS ($P < 0.01$) and reduction in ocular motility restriction ($P < 0.01$) were maintained during interruption.

Conclusions: Patients partially treated with teprotumumab achieve significant reduction in proptosis, CAS, and extraocular muscle restriction and maintain these improvements through the period of interruption.

Thyroid eye disease (TED) is the most common orbital disorder in adults.[1] Based on the findings of 2 randomized placebo controlled clinical trials, teprotumumab became the first and only Food and Drug Administration (FDA) approved medication for TED.[2,3] These studies have shown significant improvement in proptosis, clinical activity score (CAS), subjective diplopia, and quality of life in patients with active, moderate to severe TED.

As a response to the coronavirus (COVID-19) pandemic, teprotumumab production was temporarily halted in December 2020 with resources diverted toward government mandated

COVID-19 vaccine production orders.[4] The FDA allowed manufacturing to resume in April 2021.[5] As a result of this disruption, teprotumumab was widely unavailable during the first quarter of 2021, resulting in a treatment protocol deviation for many patients who could not receive intravenous infusions every 3 weeks for a total of 8 doses.

Disease control and patient outcomes depend on medication adherence and drug availability. Although drug supply shortages have generally been linked to adverse patient outcomes in other areas,[6,7] the ramifications in the treatment of TED are unknown particularly since the optimal dosing regimen for teprotumumab had never been ascertained through a randomized control trial with the current regimen reflecting an empiric extrapolation of oncologic protocols. Therefore, this disruption presented a unique opportunity to evaluate the treatment response of teprotumumab when patients receive a shorter than 8-dose regimen.

MATERIALS AND METHODS

The study was approved by the institutional review boards at each participating site and coordinated through the institutional review board at the Washington University School of Medicine in St. Louis. This study is compliant with the Health Insurance Portability and Accountability Act and the Helsinki Declaration.

In this observational cross-sectional cohort study, data from 15 institutions were included. Participants were adult patients greater than 18 years old with active or minimal to no clinical activity TED treated with a standard teprotumumab infusion protocol that was interrupted by the national drug shortage. Standard protocol dosing was planned for each case. This consisted of initial infusion of 10 mg/kg followed by subsequent infusions of 20 mg/kg given every 3 weeks for a total of 8 doses.[2] Patients were included if they had completed at least 1 infusion of teprotumumab before treatment interruption and had not yet completed all 8 planned infusions. Exclusion criteria included patients who were interrupted for reasons other than national drug shortage and patients with insufficient follow-up data. In addition to assessing pre- and post-treatment characteristics, we further extended the study to potentially differentiate between active and minimal to no clinical activity TED at time of treatment initiation. Active TED was defined as a CAS of 4 or more on a 7-point scale regardless of duration of TED symptoms.[8] Minimal to no clinical activity TED was defined as CAS less than 4 and TED symptoms longer than 9 months.[9] These minimal to no clinical activity criteria were selected as patients in this group were excluded from the active TED teprotumumab clinical trials.

Patient data collection occurred at 3 time points. First, patients were evaluated before the teprotumumab initiation. Following this visit, patients received standard protocol dosing every 3 weeks. The second time point was the partial-treatment baseline examination and occurred within 3 weeks following the last dose of teprotumumab before interruption. The third time point was the latest visit before teprotumumab reinitiation (final follow-up visit) at least 4 weeks following the postinterruption baseline examination.

Clinical information was extracted from patient records. Patient demographics and clinical history were analyzed including age, gender, thyroid history, smoking status, and prior treatment modalities.

The primary outcome measure was reduction of more than 2 mm in proptosis. Analysis was performed on the more proptotic (study eye). In patients with equal exophthalmometry measurements, 1 eye was selected randomly to be the study eye. Maintained responders were those patients who continued to meet the response definition of more than 2 mm in proptosis reduction at the final follow-up visit. Secondary measures included CAS, diplopia, extraocular motility restriction, MRD1, and medication-related adverse events. Maintenance of secondary measures includes those patients who continued to have a statistically significant response at final follow-up visit compared with before teprotumumab initiation.

Proptosis measurements were made using a Hertel exophthalmometer. The 7-point CAS scale was used to quantify activity. CAS of 0 or 1 was indicative of disease inactivity.[8] Diplopia was assessed in primary gaze as present or absent. Ocular ductions were assessed using a standard 4-point scale with zero indicating full motility and −4 indicating no motility past midline.[10] Restriction was summated in the horizontal and vertical directions for each eye.[11] MRD1 measurements were obtained for each eye individually. Adverse events were documented at each patient visit.

For comparison of categorical variables between 2 cohorts, the 2-tailed paired t-test and Fisher's exact test were employed. Linear regression was performed to assess correlation between number of infusions and change in proptosis. Multivariate modeling was performed to assess effects of number of infusions and interruption time on the change in proptosis during the interruption period. A *P* value of less than 0.05 was considered statistically significant. All analysis was conducted using IBM IPSS (version 26, IBM Corporation, Armonk, NY).

RESULTS

The study population included 74 patients from 15 institutions. The mean age before initiation of teprotumumab was 57.8 years (median 58 years, range 21–92 years). There were 62 active and 12 minimal to no clinical activity patients. There were 57 females (77.0%) and 17 males (23.0%). All patients had Graves' disease, which was diagnosed an average of 5.3 years (median 2 years, range 2 months–38 years) before teprotumumab initiation. The average duration of TED symptoms was 23.4 months (median 12 months, range 3 weeks–360 months) at the first visit when teprotumumab was prescribed.

Prior treatments for Graves' disease include methimazole (41/74), levothyroxine (9/74), radioactive iodine (17/74), thyroidectomy (19/74), and combination of these treatments. Thirty-1 patients had previously received treatments for TED including oral steroids (17), intravenous steroids (11), surgery (7), orbital radiation (3), and rituximab (2). All patients with history of surgery were active patients. Six patients had prior orbital decompression, 2

patients had prior eyelid retraction repair, and 1 patient had strabismus surgeries. No patients had active TED-related optic neuropathy at the time of teprotumumab initiation.

Patients underwent a mean of 4.2 teprotumumab infusions before interruption (median 4, range 1–7). The average follow-up period was 13.2 weeks (median 11.7 weeks, range 7–23 weeks) after the postinterruption examination. Baseline characteristics are summarized in Table 1.

Primary Outcome.

The primary outcome of more than 2 mm proptosis reduction was achieved by 73% of patients (45 active and 9 minimal to no clinical activity) before interruption. Both active and minimal to no clinical activity patients showed a significant decrease in proptosis while on teprotumumab. Active patients demonstrated 2.9mm in mean proptosis reduction ($P < 0.01$) while the minimal to no clinical activity patients achieved an average 2.8 mm proptosis reduction ($P < 0.01$). Further statistical analysis revealed a weak but significant correlation between number of infusions and increasing amount of proptosis reduction ($r = 0.406$ and $P < 0.01$) (Figure 1).

During interruption, all proptosis responding patients (45 active and 9 minimal to no clinical activity) maintained the significant decrease, and 3 additional active patients met primary outcome for proptosis reduction (Table 2). Six active patients (8.1%) had additional more than 2 mm proptosis reduction during the interruption period. One active patient had 2.5 mm worsening in proptosis at final follow up but still met proptosis responder criteria. A multivariate regression revealed no significant correlation between number of infusions ($P = 0.78$) or time of interruption ($P = 0.98$) on change in proptosis measurement during interruption.

Secondary Outcomes.

In our cohort of 62 active patients, there was a significant 3.4-point reduction in CAS while on teprotumumab ($P < 0.01$), which was maintained during interruption (Table 2). In these patients, 48.3% (30/62) achieved CAS of 0 or 1, while on teprotumumab. By the last follow-up visit, 61.2% (38/62) had a CAS of 0 or 1. Four patients (6.5%) had an increase in CAS greater than 2 from the partial-treatment baseline examination to the final follow-up visit.

Sixty-two patients reported diplopia in primary gaze before initiation of teprotumumab. Subjective diplopia resolved in 11 patients (17.7%) while on teprotumumab. Two patients (3.2%) reported a return of diplopia during the interruption period. For active patients, there were a significant decrease in the total extraocular muscle restriction on teprotumumab ($P < 0.01$) that was maintained during interruption. For minimal to no clinical activity patients, there was no significant change in extraocular motility restriction while on teprotumumab or during the interruption period. There was no significant change in MRD1 for both active and minimal to no clinical activity patients while on teprotumumab or during interruption.

During the interruption period, no patients developed new TED-related optic neuropathy. One patient who was status-post left medial and lateral orbital decompression underwent

left floor decompression for symmetry and worsening exposure symptoms. No other patients required additional therapy such as pulsed intravenous or oral corticosteroids for worsening TED during the interruption period.

Adverse Events.

At the first postinterruption visit (second timepoint), 45 patients (66%) reported at least 1 or more adverse events (range 1–7 adverse events). The most commonly reported adverse event included muscle cramps 27% (20/74) followed by hair loss 17.5% (13/74), hyperglycemia 13.5% (10/74), hearing changes 10.8% (8/74), fatigue 9.4% (7/74), and gastrointestinal upset 8.1% (6/74).

At the postinterruption examination, 22 (29%) patients continued to report at least 1 adverse event. Of those who reported adverse events, the most common adverse events at the last visit were hyperglycemia 36% (8/22), muscle cramps 32% (7/22), and hearing changes 23% (5/22). Three patients (4%) who did not have a diabetes mellitus diagnosis before initiation of teprotumumab were started on oral hypoglycemic agents. One patient had persistently high blood glucose (>700) during the interruption, and the decision was made to discontinue future infusions. During postinterruption examination, no patient developed new safety concerns that were not present while receiving teprotumumab infusions.

DISCUSSION

Drug supply shortages are a growing global problem, but there is limited literature on their effects on patient safety.[6,7,12,13] Since noncompliance can be a factor for poor clinical outcomes, advisory panels have recommended strict adherence to standard treatment regimens including for teprotumumab.[14] Hence, when the disruption in teprotumumab production was first announced, there was substantial concern regarding the potential negative impact on disease progression, adverse event profile, and efficacy of teprotumumab therapy for TED.[15]

All randomized controlled trials utilizing teprotumumab have been conducted with a standard 8-dose regimen. Based on pharmacokinetic modeling, this regimen was selected to sustain greater than 20 μg/mL trough concentration to maintain greater than 90% saturation of insulin-like growth factor 1 receptor (IGF-1R) during the dosing intervals[16] and for total treatment duration of 6 months. Studies have yet to be conducted on the optimal dosing regimen for teprotumumab for different phases, phenotypes, and clinical presentations of TED. It is conceivable that shorter dose intervals are required for sustained improvement in some presentations and longer dosing intervals would be required in others. Additionally, requirements for an 8-dose protocol are not strictly based on specific clinical studies. Decreasing the total doses could be a useful strategy for some patients to optimize outcomes while reducing the incidence of dose dependent adverse events.

When examining the proptosis response curve over time from the phase 2 and 3 clinical trials, more than 75% of active patients met the benchmark of 2 mm proptosis reduction by 12 weeks (after 4 infusions), and the response rate plateaued at more than 80% after 16 weeks.[2,3] When pooling the clinical trials data set, Kahaly et al.[17] found that 65

(77%) of patients in the teprotumumab group achieved a proptosis reduction of more than 2 mm after completion of teprotumumab 8-dose treatment regimen. This current study identified proptosis reduction (>2 mm) in 72.5% active and 75% minimal to no clinical activity patients after an average of 4.2 teprotumumab infusions. Our findings support prior studies that the onset of significant clinical response occurs early in the treatment course. However, increasing teprotumumab doses correlates with increased proptosis reduction. This highlights the importance of dose-ranging studies to determine the optimal frequency, duration, and number of teprotumumab infusions for achieving optimal efficacy and safety outcomes. A randomized controlled trial evaluating the safety and efficacy of 4, 8, and 16 teprotumumab infusions is currently ongoing.

In this study, we evaluated the short-term ramifications of interrupted treatment regimens in a cohort of 74 patients partially treated with teprotumumab. At the final follow-up visit after an average of 13.2 weeks of teprotumumab interruption, 77% of patients met proptosis response criteria with 3 initial nonresponders achieving the primary outcome. These initial nonresponders received between 2 and 4 infusions before interruption. Given teprotumumab's long half-life of 19.9 days[16] and slow systemic clearance,[16] residual drug activity may contribute to additional proptosis improvement during drug cessation. These findings also concur with the OPTIC-X study in which 90% of proptosis responders at week 24 maintained their proptosis response 3 months after final teprotumumab dose.[18] At 27 weeks after final teprotumumab dose, the response remained high (89%). Long-term efficacy for treatment with teprotumumab is still an open question, and studies on the matter are ongoing.

Secondary outcomes in this study followed a similar pattern with significant reduction of CAS, proptosis, and motility restriction on teprotumumab. These changes were maintained during the interruption period. Similar to previously published clinical trials results at 12 weeks,[2,3,17] the observations of the present study included proptosis reduction (2.9 mm in active patients) and CAS reduction (3.4 points), with 49% of patients demonstrating a CAS of 0–1 points at the final study follow-up visit. Our study suggests that a delay of several weeks to months between teprotumumab infusions does not appear to have clinically deleterious effects with regard to most measured data points. Patients overwhelmingly maintained the gains achieved with prior teprotumumab doses and did not require adjunctive medical treatments for worsening disease in the short-term.

Although the clinical trials were conducted on patients with active TED, recent reports on the effectiveness of teprotumumab on minimal to no clinical activity TED patients have highlighted improvements in proptosis, diplopia, and orbital soft tissue volume.[9,19,20] Inclusion of patients with minimal to no clinical activity TED in this study may capture a subset of active patients with low CAS who have classically been described by Nunery as Type 1 patients.[21–23] These patients typically have proptosis, minimal diplopia, and low CAS and have been excluded from prior clinical trials. Given the significant improvement observed in the present study following a mean of 4.2 infusions, patients with minimal to no clinical activity TED may also demonstrate an early response to teprotumumab, similar to active patients. Additional studies investigating how TED patients with minimal to no clinical activity and whose disease process is later in its time course respond to

teprotumumab treatment will help elucidate the medication's efficacy and safety. A phase 4 randomized controlled trial investigating the treatment of TED patients with CAS < 1 and disease duration over 2 years with teprotumumab is currently in the recruitment process.[24,25]

In our study, there was no significant change in MRD1 for patients on teprotumumab. Prior studies have demonstrated similar results in active[11] and minimal to no clinical activity patients.[9] A variety of factors contribute to the etiology of upper eyelid retraction including Müller's muscle hyperactivity mediated by thyroid hormones and the cicatricial changes within Müller's and levator muscle.[26–28] Although teprotumumab targets the overexpression of IGF-1R on orbital fibroblasts,[29] this signaling pathway may not modify the fibrosis and inflammation contributing to upper eyelid retraction. Additional studies are needed to elucidate the role of IGF-1R on eyelid tissue and the long-term effects of teprotumumab on upper eyelid retraction.

Adverse events were common in this study with 60% of all patients experiencing at least 1 adverse event. Higher rates of adverse events were previously reported in a review analysis.[17] Although most adverse events were mild and resolved with drug cessation, serious adverse events such as hyperglycemia and hearing changes appear to persist during short-term interruption and after 72 weeks follow-up.[17] Further investigations are needed to analyze the duration of these adverse events.

This study has several limitations. The patient population included a heterogenous population including patients from several institutions who had received a range of medical and surgical treatments before the initiation of teprotumumab. However, this diverse patient population does appropriately reflect the different ways in which physicians incorporate teprotumumab in their clinical practice. Further limitations include the small number of minimal to no clinical activity TED patients. Finally, the patients in this cohort were not followed long enough to comment on the durability of teprotumumab treatment or determine the recurrence rate. Long-term follow up to review the outcomes of these patients impacted by interruption was not available and will be the subject of ongoing work.

In summary, this study found that patients partially treated with teprotumumab achieve significant reduction in proptosis, CAS, and extraocular muscle restriction and maintain these improvements during short-term interruption.

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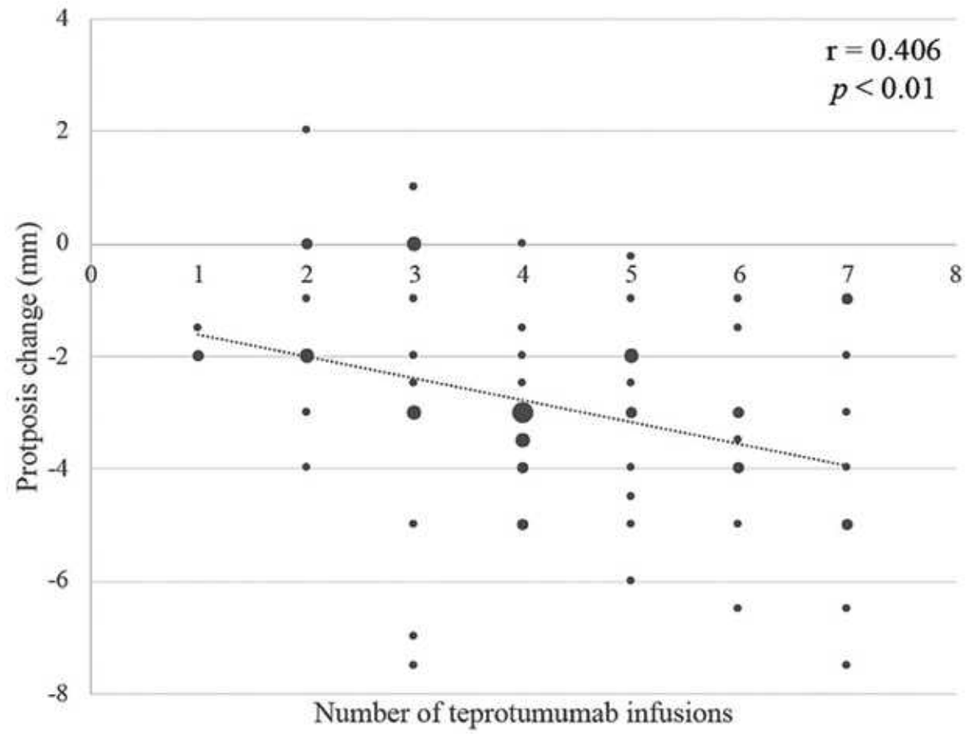

FIG. 1.
Scatterplot of number of teprotumumab infusions against proptosis change. Larger data points indicate more than 1 patient represented.

TABLE 1.

Baseline patient demographics, clinical history, and thyroid treatment characteristics

	Total patients	Active TED patients	Minimal to low activity TED patients
Age, mean (range)	58 (21–92)	58 (22–92)	51 (21–77)
Sex, n (%)			
Female	57 (77%)	48 (77%)	9 (75%)
Male	17 (23%)	14 (23%)	3 (25%)
Tobacco use history, n (%)			
Nonsmoker	55 (74%)	45 (73%)	10 (83%)
Smoker	19 (26%)	17 (27%)	2 (17%)
Years since diagnosis of Graves' Disease, Median (range)	2	2 (0.2–31)	4.5 (2–38)
Months since diagnosis of TED, Median (range)	12	10 (0.75–360)	22 (10–20)
History of radioactive iodine, n (%)	17 (23%)	14 (23%)	3 (25%)
History of thyroidectomy, n (%)	19 (26%)	17 (27%)	2 (17%)
Concomitant medications at baseline, n (%)			
Methimazole	41 (55%)	32 (52%)	9 (75%)
Levothyroxine	9 (12%)	7 (11%)	2 (17%)
Prior TED treatments, n (%)			
Oral steroids	17 (23%)	16 (26%)	1 (8%)
Intravenous steroids	11 (15%)	6 (10%)	5 (42%)
Orbital radiation	3 (4%)	3 (5%)	0
Rituximab	2 (3%)	2 (3%)	0
Surgery	7 (9)	7 (11%)	0

TED, thyroid eye disease.

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TABLE 2.

Clinical examination data for active and minimal to low activity TED patients at baseline, partial teprotumumab treatment course, and following treatment interruption

	Active TED patients					Minimal to low activity TED patients				
	Pretreatment exam	Partial-treatment exam	*P*	Final follow-up exam	*P*	Pretreatment exam	Partial-treatment exam	*P*	Final follow-up exam	*P*
Proptosis (mm)	23.4 ± 4.1	20.4 ± 3.0	<0.01	20.2 ± 3.0	<0.01	22.9 ± 1.7	20.3 ± 2.1	<0.01	20.1 ± 2.5	<0.01
CAS (points)	4.9 ± 1.2	1.5 ± 1.4	<0.01	1.6 ± 1.6	<0.01	1.7 ± 1.0	1.3 ± 1.5	0.14	1.0 ± 1.3	0.05
Total extraocular restriction	−2.6 ± 2.8	−1.5 ± 1.9	<0.01	−1.3 ± 1.8	<0.01	−0.3 ± 0.7	−0.1 ± 0.2	0.96	−0.2 ± 0.5	0.17
MRD1 (mm)	5.4 ± 1.9	5.4 ± 1.8	0.89	5.4 ± 1.9	0.87	4.9 ± 1.4	4.8 ± 1.2	0.25	4.7 ± 1.1	0.48

P compares partial-treatment exam and follow-up exam during interruption to pretreatment exam.

TED, thyroid eye disease.

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CME

Myotonic dystrophy type 2

Molecular, diagnostic and clinical spectrum

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Abstract—*Background:* Myotonic dystrophy types 1 (DM1) and 2 (DM2/proximal myotonic myopathy PROMM) are dominantly inherited disorders with unusual multisystemic clinical features. The authors have characterized the clinical and molecular features of DM2/PROMM, which is caused by a CCTG repeat expansion in intron 1 of the *zinc finger protein 9 (ZNF9)* gene. *Methods:* Three-hundred and seventy-nine individuals from 133 DM2/PROMM families were evaluated genetically, and in 234 individuals clinical and molecular features were compared. *Results:* Among affected individuals 90% had electrical myotonia, 82% weakness, 61% cataracts, 28% diabetes, and 19% cardiac involvement. Because of the repeat tract's unprecedented size (mean ~5,000 CCTGs) and somatic instability, expansions were detectable by Southern analysis in only 80% of known carriers. The authors developed a repeat assay that increased the molecular detection rate to 99%. Only 30% of the positive samples had single sizeable expansions by Southern analysis, and 70% showed multiple bands or smears. Among the 101 individuals with single expansions, repeat size did not correlate with age at disease onset. Affected offspring had markedly shorter expansions than their affected parents, with a mean size difference of −17 kb (−4,250 CCTGs). *Conclusions:* DM2 is present in a large number of families of northern European ancestry. Clinically, DM2 resembles adult-onset DM1, with myotonia, muscular dystrophy, cataracts, diabetes, testicular failure, hypogammaglobulinemia, and cardiac conduction defects. An important distinction is the lack of a congenital form of DM2. The clinical and molecular parallels between DM1 and DM2 indicate that the multisystemic features common to both diseases are caused by CUG or CCUG expansions expressed at the RNA level.

NEUROLOGY 2003;60:657–664

Myotonic dystrophy type 2 (DM2) is an autosomal-dominant, multisystemic disease. In 1998 we mapped the disease locus to 3q21[1] and recently demonstrated that DM2 is caused by the expansion of a CCTG repeat located in intron 1 of the *zinc finger protein 9* (*ZNF9*) gene.[2] In Europe, the disease in these families has been called proximal myotonic myopathy (PROMM)[3] or proximal myotonic dystrophy (PDM).[4] In the United States these families were described as having "myotonic dystrophy with no CTG repeat expansion".[5,6]

The discovery of the tetranucleotide CCTG expansion for the first time allows definitive molecular testing for DM2. We screened a large panel of European and American families that during the previous 8 years were suspected of having PROMM or DM2 based on clinical criteria. We describe an improved method for detecting the DM2 expansion and report the features of 379 individuals with genetically confirmed DM2. Defining the clinical features of DM2 in a large group of genetically confirmed patients should be helpful for future patient management. In addition, comparing the extent of the clinical similarities and distinctions between DM1 and DM2 has important implications for understanding the molecular pathogenesis of these diseases.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the February 25 issue to find the title link for this article.

Methods. *Family identification and clinical studies.* A large number of families and single patients have been seen in Germany and Minnesota with undiagnosed myopathies suspected of being DM2/PROMM. DNA samples from these patients have been stored with the patients' informed consent for possible future diagnostic research. Patients and additional family members who agreed to participate had blood drawn and underwent neurologic examinations. Many of the interviews and examinations took place in patient homes. Although not actively recruited, 12 DM2-positive family members younger than 21 years also participated. Clinical and genetic data are reported for 234 individuals, some of whom were summarized previously;[2] genetic information is included for an additional 145 individuals for whom detailed clinical information was not available. The study was done with the approval of the Institutional Review Boards/Ethics Committee at the Universities of Minnesota and Würzburg.

Electrophysiological assessment was done with portable equipment. Ophthalmologic examination of the American patients was performed in the field with direct ophthalmoscopy; a limited number of patients underwent slit lamp examination in ophthalmology clinics. Muscle biopsies were taken from 42 clinically affected patients. The specimens were quick-frozen, sectioned, and stained with hematoxylin and eosin for most results reported; fiber types were identified by ATPase staining at different pH values. Studies were performed over a period of 10 years with additional testing included as our understanding of the disease evolved. Clinical results are reported as percentages of individuals tested for each specific feature.

Age at onset was determined by either the patient's recollection of the age at which the first symptom of the disease occurred or the age of diagnosis for patients unaware of their disease. An extended discussion on the potential bias with using this estimate has been published in a previous report.[7] Ages at onset between parent–offspring pairs were compared using a paired two-tailed *t* test.

Genetic methods. PCR amplification across the DM2 CCTG repeat was performed as previously described.[2] Genomic Southern analysis was done using DNA digested with either *BssBI* or *EcoRI*. To improve detection of the DM2 expansion we developed a repeat assay (RA) based on previously published methods for DM1 and SCA-10.[8,9] The RA amplifies the genomic DM2 region containing the CCTG repeat expansion, using primers CL3N58-D R (5′-GGCCTTATAACCATGCAAATG-3′), JJP4CAGG(5′-TACGCATCCGAGTTTGAGACGCAGGCAGGCAGGCAGGCAGG-3′), and JJP3 (5′-TACGCATCCGAGTTTGAGACG-3′), followed by Southern analysis of the PCR products probed with an internal probe. Detailed methods for the RA are online (see the supplementary material on the *Neurology* Web site; go to www.neurology.org).

The monozygosity of the twins was confirmed by analysis of the genotypes of six short tandem repeat markers from different chromosomes, as previously described ($p < 0.001$).[7]

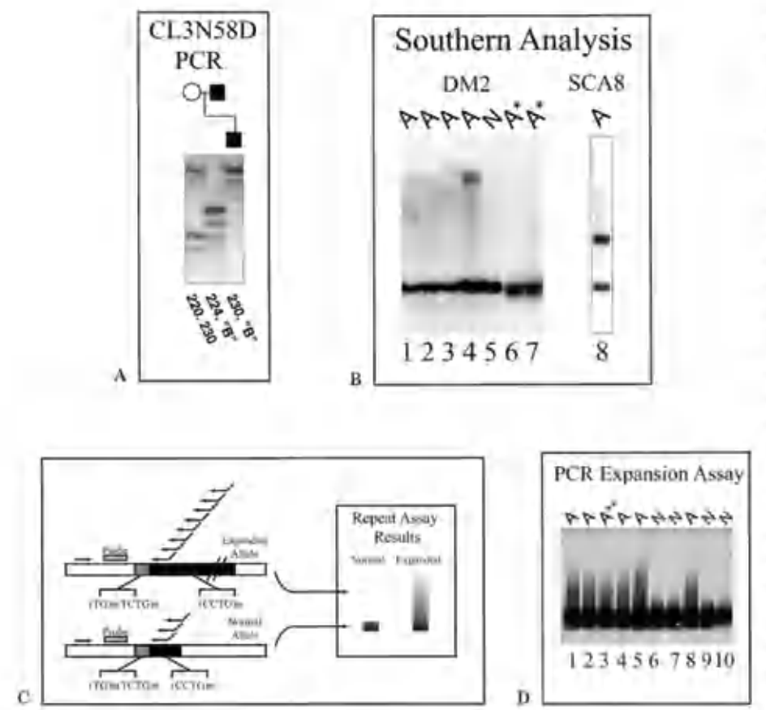

Figure 1. Molecular diagnosis of DM2. (A) PCR analysis of the CL3N58 marker. The genotype of each individual is shown in base pairs. Alleles too large to amplify by PCR, which are referred to as "blank alleles," are indicated by a "B" and make the segregation of the markers appear non-Mendelian. (B) Expansion detection by genomic Southern analysis. DM2 Southern analysis of genomic DNA from control (N), affected individuals with a detectable (A) and nondetectable (A) expanded allele is shown (Lanes 1–7). In contrast to DM2, an SCA8 Southern (Lane 8) shows equally intense signals for the normal and expanded alleles. (C) Schematic diagram of the PCR-based RA. The straight arrow represents the flanking primer CL3N58-D R. Tailed arrows represent the JJP4CAGG primer. A third primer (JJP3, not shown), used to make the PCR reaction more robust, has the same sequence as the hanging tail of JJP4CAGG. The primer used to probe Southern blots of the PCR products is CL3N58-E R. (D) Repeat assay results. RA results for affected individuals with expansions that were detected (A) or not detected (A*) by genomic Southern analysis and are shown in Lanes 1 to 5 and 8. Negative results from unaffected controls (N) are shown in Lanes 6,7,9, and 10.*

Results. *Molecular diagnostics.* The unprecedented size and somatic instability of the DM2 expansion complicate molecular testing and the interpretation of genetic test results (figure 1). Outlined below is a description of three steps involved in the molecular detection of the DM2 expansion and the types of data obtained by PCR, Southern analysis, and the RA (see Methods).

Step 1: PCR analysis. Because DM2 expansions are too large to amplify by PCR, all expansion-positive individuals appear to be homozygous and thus indistinguishable from the 15% of unaffected controls who are truly homozygous. Family studies can distinguish true homozygotes from expansion carriers (figure 1A) because affected children often do not appear to inherit an allele from their affected parent. We refer to this apparent non-Mendelian inheritance pattern, which is caused by the failure of the expandest allele to amplify, as the presence of a "blank allele." Demonstration of a blank allele provides strong evidence that a family carries a DM2 expansion but can also occur in cases of misattributed paternity.[10]

Step 2: Southern analysis. Because of the size (mean ~5,000, range 75 to >11,000 CCTG repeats) and somatic instability of the DM2 repeat, genomic Southern analyses fail to detect expansions in 20% of known carriers (table 1). Expanded alleles when detected can appear as single discrete bands, multiple bands, or smears (figure 1B). Compared to other expansion disorders, such as SCA8 (figure 1B, lane 8), in which the expanded and normal

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Table 1 *Molecular diagnostic sensitivity to DM2*

Total no. of independently confirmed DM2 subjects*†	No. with expansion detected by Southern	No. with expansion detected by repeat assay	No. with expansion detected by either Southern or repeat assay†
166	133 (80%)	165 (99%)	165 (99%)

* Individuals independently confirmed to have DM2 expansions by presence of "blank allele" or linkage analysis.
† The individual who did not test positive by Southern or the RA inherited a "blank" allele and the affected haplotype from his affected father. The patient's father and three other affected family members were positive by both the RA and Southern analysis, ruling out the possibility that the RA assay failed because of a polymorphism in the primer binding site that was present in the family. Although the presence of the normal alleles by Southern analysis demonstrated that the DNA was not degraded, it is possible that the RA failed because of other DNA quality issues.

alleles are equally intense, detectable DM2 expansions are almost always less intense than the normal alleles. This intensity difference indicates that even when a proportion of the expanded allele creates a discrete visible band, the rest of the expanded allele varies markedly in size within blood and migrates as a diffuse undetectable smear.

Step 3: Repeat assay. To detect the presence of DM2 expansions in individuals with inconclusive Southern blots, we used the RA (see Methods). By using a PCR primer that primes from multiple sites within the elongated CCTG repeat tract, our RA can be used to detect DM2 expansions by the presence of a smear of products with molecular weights higher than in control lanes (figure 1C and D). Although the RA reliably identifies the presence or absence of the DM2 expansion, it cannot be used to determine repeat size. To insure specificity, RA PCR products are transferred to a nylon membrane and probed with an internal oligonucleotide probe; there were no false-positives among 320 control chromosomes. Probing with an internal primer is critical for avoiding false-positives; there was a 21% false-positive rate when the RA PCR products were simply visualized by ultraviolet light after staining with ethidium bromide. False-positive, high molecular weight products were also detected when the RA PCR products were run on an ABI 3100 machine (Applied Biosystems, Inc., Foster City, CA). When performed as we describe (Methods), the RA is both sensitive and specific, increasing the detection rate of DM2 expansions from 80% by genomic Southern analysis alone to 99% for a panel of known expansion carriers (see table 1).

Pedigree examples of instability. The pedigree shown in figure 2 illustrates the diagnostic challenges and the types of repeat instability that are typical in a DM2 family. "Blank alleles" that failed to amplify due to a CCTG expansion are indicated by a "B." There is marked variation in intergenerational repeat sizes. For example individual III-7 has a smaller expansion than her affected parent, which is larger in one of her children (IV-1) and smaller in the other (IV-2). The extreme somatic instability is illustrated by monozygotic twins III-1 and III-2, with expansion sizes that differ in size by 11 kb (2,750 CCTGs). Some family members have single discrete expansions, but many others have multiple expansions or diffuse bands. An example of the utility of the RA is demonstrated by individual II-5, who was RA-positive but negative by Southern analysis.

DM2-positive patients and families. We have identified 379 DM2 positives from 133 families by using Southern and RA analyses. Most families could trace an affected ancestor to Germany or Poland, and all were of European descent. As expected for a dominantly inherited disease, approximately 50% of adults at first-degree risk for DM2 were affected. The higher number of affected women compared to men in our study (210 vs 169) is consistent with the higher rate of female participation (420 vs 332 males). The age of DM2-positive subjects when examined ranged from 8 to 85 with a mean of 47 years.

Clinical features. The clinical features of the DM2 expansion positive patients are described below for the 234 affected subjects whom we had examined.

Muscle symptoms and signs. Muscle symptoms (pain, stiffness, myotonia, and weakness) are the most common symptoms reported in adult DM2 subjects of all ages (table 2). Fluctuating or episodic muscle pain is frequent in DM2 (63% in those >50 years). The characteristic pattern of muscle weakness involves neck flexors, elbow extensors, thumb and deep finger flexors, and hip flexors and extensors. Facial and ankle dorsiflexor weakness is less common. Thirty percent of the subjects reported symptomatic hip muscle weakness that developed after age 50. In DM2/PROMM patients who come to medical attention because of muscle pain, stiffness, or myotonia prior to developing symptomatic weakness, manual strength testing is frequently abnormal in neck flexors and deep finger and thumb flexors, suggesting that these are the muscle groups affected the earliest. Though rarely severe, muscle atrophy was recorded in 9% of subjects.

Muscle biopsies. Muscle biopsies from 42 DM2 patients (18 to 73 years, mean 50 years) had many of the same histologic features that are found in DM1 biopsies, with a high percentage of fibers

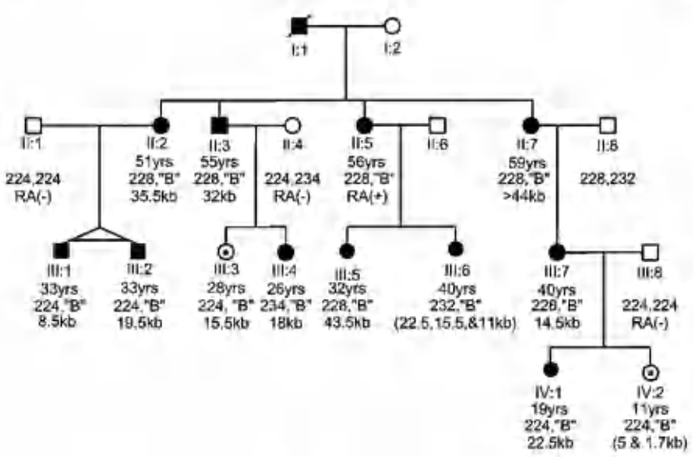

Figure 2. Abbreviated pedigree of a DM2 family: Solid symbols represent affected individuals. Although sex of the youngest generation shown for various branches of the family has been changed to insure confidentiality, the sex of transmitting parents was not changed so that information about how sex influences repeat size in subsequent generations is preserved. Information below each symbol includes age at blood draw; CL3N58 PCR allele sizes ("B" indicates a nonamplifying blank allele); and either the size of the expansion(s) detected by Southern (in kb) or repeat assay results (RA+ or RA−) for those with no expansion on Southern analysis. The RA was positive for all individuals with positive Southern results (not shown).

Table 2 *Clinical features of DM2 and DM1*

Feature	DM2 subjects by age, y: 21–34 (n = 45)	35–50 (n = 77)	>50 (n = 100)	DM2 all ages (n = 234)	DM1
Skeletal muscle features					
History of muscle pain, %	43	61	63	56	NA
Myotonia					
By history	39	39	34	36	+++
On physical exam	80	84	71	75	+++
On EMG	87	94	92	90	+++
Weakness					
By history	36	69	84	64	+++
Any weakness on exam	59	85	99	82	NA
Facial	18	9	13	12	++
Neck flexors	47	75	95	75	+++
Shoulder abductors	0	34	21	20	++
Elbow extension	8	16	52	31	++
Thumb or deep finger flexors	39	63	49	55	+++
Hip flexors	36	58	88	64	+
Ankle dorsiflexors	9	14	19	16	++
Deep knee bend	26	48	77	54	+
Elevated creatine kinase, %	88	91	93	90	++
History of multisystemic features					
Cardiac					
History arrhythmia/Palp.	7	27	27	19	+
History cardiomyopathy	0	0	7	3	+/−
Cataracts					
By history or exam	36	59	78	60	++
History of extraction	13	18	55	31	NA
Diabetes, by history	4	17	36	23	+

Additional laboratory findings	DM2: % affected	DM2: Median age when tested, y (range)	DM1
Serology (n)			
High GGT (152)	64	44 (13–78)	+
Low IgG (20)	65	43 (28–64)	++
Low IgM (20)	11	43 (28–64)	+/−
Low testosterone (22)	29	42 (27–64)	++
High FSH (26)	65	40 (16–64)	++
Insulin insensitivity (16)	75	49 (28–75)	++
EKG (n)			
AV block (44)	11	47 (16–73)	++
IV block (44)	11	47 (16–73)	+
Muscle biopsy (n)			
Internal nuclei (42)	95	49 (16–64)	++
Nuclear clumps (36)	89	49 (16–64)	++
Fibrosis (38)	71	49 (16–64)	+
Necrotic fibers (38)	47	49 (16–64)	+
Abnormal fiber type distribution (31)	16	49 (16–64)	+/−

The qualitative frequencies of DM1 features were abstracted from Dr. Peter Harper's monograph,[1] and they are reported as being almost universally present (+++), common and almost universally present late in the course of the disease (++), well recognized and common late in the course of the disease (+), recognized but not common (+/−), or NA if data were not available.

having centrally located nuclei sometimes occurring in chains, angulated atrophic fibers sometimes occurring in groups, severely atrophic fibers with pyknotic nuclear clumps ("nuclear clumps" in table 2), hypertrophic fibers, occasional necrotic fibers, fibrosis, and adipose deposition. There was no consistent abnormality of fiber type distribution, with two biopsies having mild type 1 predominance and two having mild type 2 predominance. Atrophic angulated fibers of both fiber types, as determined by ATPase

Table 3 *Identification of initial symptom and age at onset*

Initial symptom	No. of subjects reporting each initial symptom (%)	Age at onset median (range), y
Myotonia	83 (39.7)	30 (13–67)
Weakness	81 (38.7)	41 (18–66)
Stiffness/pain	33 (15.7)	36 (20–54)
Cataracts	17 (8.1)	45 (34–57)

The initial symptom and age at onset for that symptom for the 209 individuals who reported symptomatic onset of DM2 before their enrollment in this study (see Methods).

Overall n = 209, with some subjects reporting multiple initial symptoms.

staining, were evident in most biopsies. Most biopsies were of vastus lateralis and were abnormal despite manual strength testing being normal for that muscle; two biopsies were normal (biceps brachii, 18 and 26 years), and three had only increased central nuclei (biceps brachii 39 years, and vastus lateralis 30 and 36 years).

Cataracts. The posterior subcapsular iridescent cataracts are identical in DM1 and DM2 patients.[1] Cataracts needed to be extracted in 75 individuals at ages ranging from 28 to 74 years. Among 10 genetically positive subjects under 21 years, cataracts were present in 2 by slit lamp examination, indicating that this is a prominent and early feature of the disease. Cataracts detected by ophthalmoscopy typically develop in the third to fifth decades of life, with slit lamp demonstrating cataracts in 2 of 10 subjects in the second decade.

Cardiac features. Cardiac complaints include frequent palpitations, intermittent tachycardia, and episodic syncope, with syncopal spells reported in 18 (8% of the entire panel of 234 subjects). These symptoms increase in frequency with age (see table 2). Cardiac conduction abnormalities were seen in 20% of patients (9 of 44), either atrioventricular (11%) or intraventricular (11%) blocks. DM2 patients can develop unexpected fatal arrhythmias. A history of progressive cardiomyopathy, in the absence of overt myocardial ischemia or other obvious causes, was found as a potentially life-threatening condition in 7 of 100 DM2 patients over 50 years.

Serologic and other changes. Laboratory results from 150 patients showed elevated serum CK, typically less than five times the upper limits of normal, and elevated gamma-glutamyltransferase. Additional serologic testing on 20 patients showed low IgG and IgM but normal IgA, the same pattern that is seen in DM1.[1] Primary male hypogonadism was present in the majority (17 of 26) of the men serologically tested for testicular function, with elevated follicle-stimulating hormone (FSH), low or low-normal testosterone levels, and oligospermia. By history, diabetes was present in 23% (n = 79), with glucose tolerance testing showing insulin insensitivity (elevated basal insulin levels or prolonged insulin elevation, n = 16) in 75%. Age-independent hyperhydrosis is reported by 20% to 30% of patients, and early-onset male frontal balding is observed in approximately 20% of German and 50% of American men aged 21 to 34 years.

Age at onset and disease progression. Patients reported that they remembered first symptoms of disease to have occurred from ages 13 to 67 (median = 48 years, mean ± SD = 37 ± 15). Table 3 details the initial symptom and age at onset for the 209 individuals in whom symptomatic onset was reported to have occurred prior to enrollment in the study. Subjects younger than 21 years were not recruited and are not included in table 2, but 12 genetically confirmed family members in this age group participated voluntarily (range = 8 to 20 years, mean = 16); none had muscle weakness, cardiac symptoms, diabetes, or visual impairment from cataracts, but 3 reported muscle pain and symptoms of myotonia, and 1 had hyperhydrosis. Consistent with a previous study[2] there is strong statistical evidence ($p < 1 \times 10^{-14}$) for earlier ages at onset among offspring of affected individuals (−13 years, n = 79 parent-offspring pairs). Lack of congenital DM2 and aspects of disease severity. We did not observe any congenital DM2 patients among our large group of families, and there was no evident relationship between DM2 and mental retardation. Some affected women had recurrent spontaneous abortions, although it is not clear whether DM2 leads to higher than normal rates of spontaneous abortion, nor does it lead to higher than normal rates of hydramnios, or still birth, all of which occur at markedly increased frequency in DM1.[2] Some women experienced an increase of myotonic stiffness during pregnancy, but DM2 did not seem to cause any problems of delivery. We did not encounter DM2 patients who had experienced problems during general anesthesia.

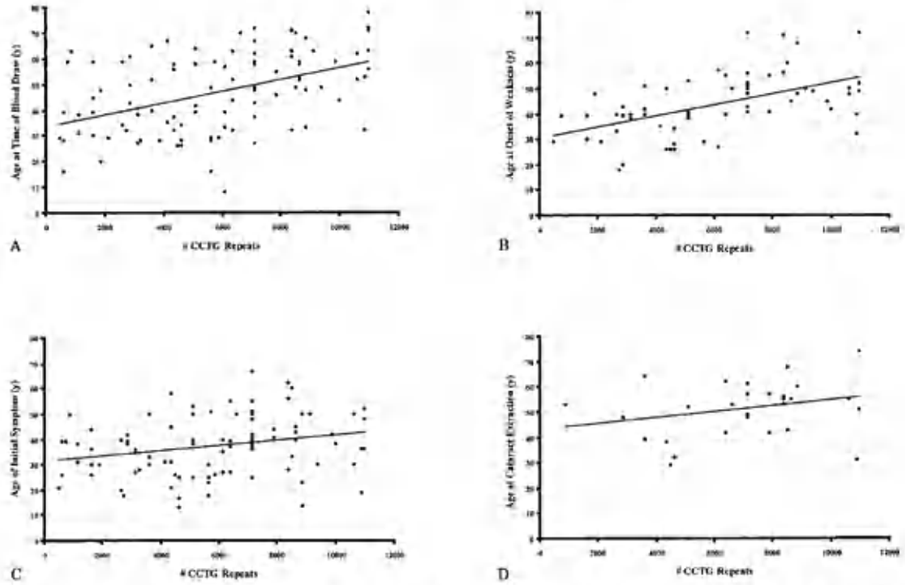

Figure 3. Correlation of repeat length with clinical severity. Among individuals with single sizable expansions correlations between the repeat size and (A) age at the time the blood sample was drawn; (B) age at onset of initial symptom; (C) age at onset of weakness; and (D) age at initial cataract extraction are shown. In contrast to DM1 and other microsatellite disorders, longer DM2 repeat tracts are not correlated with earlier onset of disease.

Clinical and molecular correlations. An unusual feature of the DM2 expansion is that repeat size is positively correlated with the age at which the blood is drawn (figure 3A, $r^2 = 0.19$, $p = 4.6 \times 10^{-9}$, n = 101). The fact that the repeat tracts expand as an individual gets older complicates any analysis of the effects of repeat length on age at onset. Correlations of repeat size with various measures of disease onset are shown in figure 3, B through D using the subset of individuals with single measurable bands on Southern analysis. Positive correlations (i.e., smaller repeats associated with earlier age at onset) were found for repeat size versus both age at onset of the initial symptom ($r^2 = 0.07$, $p = 1.3 \times 10^{-3}$, n = 93), and age at onset of weakness ($r^2 = 0.28$, $p = 8.8 \times 10^{-6}$, n = 63). No significant correlation was observed between repeat size and age at cataract extraction (n = 29). The apparent positive correlation between repeat length and age at onset was unexpected because in other microsatellite expansion disorders there is a negative correlation, with larger expansions associated with earlier ages at onset. To determine if the positive correlations we observed could simply reflect the fact that repeat length increases with age, multivariate analysis was performed. These results indicate that the effect of the age at which the blood sample was drawn explained nearly all (>99%) of the apparent correlation between repeat length and age at symptom onset.

Although complicated by both somatic instability and the increase in repeat length with age, we determined intergenerational differences in repeat for 25 parent–child pairs, the subset of affected individuals in which both the parent and child had single bands on Southern analysis (figure 3A). In 23 of 25 transmissions we observed smaller repeat lengths in the younger generation, with a mean change of −17 kb (−4,250 CCTG repeats). In one instance the repeat size was 38 kb smaller in the affected child (−9,500 CCTG repeats). There were apparent size increases in two transmissions (+3 and +8 kb). These apparent intergenerational changes in repeat length are much greater for DM2 than for any other microsatellite disorder (figure 4B). No differences in degree or direction of intergenerational changes were seen in male versus female transmissions.

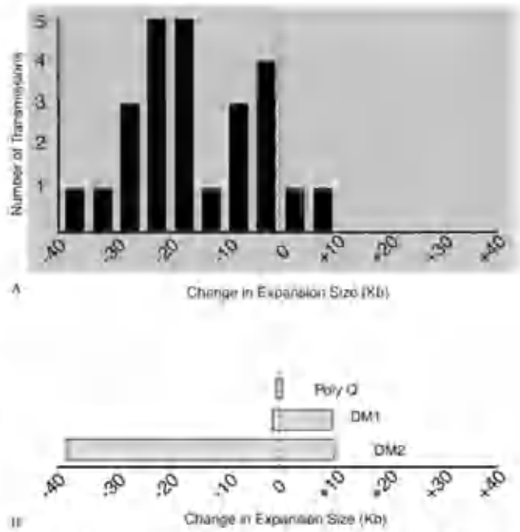

Figure 4. Intergenerational repeat instability. (A) Repeat lengths of 25 affected parent–child pairs from a subset of individuals in which both the parent and child had single bands on Southern analysis are shown. (B) The relative repeat size differences among parent–offspring pairs in DM2 patients is compared with those observed for the polyglutamine (poly Q) diseases and DM1.

Discussion. Defining the clinical features of DM2 has important implications for understanding the molecular mechanisms of DM pathogenesis. This study demonstrates that DM2 closely resembles adult-onset DM1, with common features including progressive weakness, myotonia, disease-specific muscle histology, cardiac arrhythmias, iridescent cataracts, male hypogonadism, insulin insensitivity, and hypogammaglobulinemia. These similarities are the main reason why DM2/PROMM had not been delineated before genetic testing became available.[2,3] Despite the striking similarities of DM2 and DM1 as multisystemic disorders, there are important differences. One clear distinction is the absence of a congenital form of DM2. In DM1, longer repeats are often associated with severe neonatal weakness, mental retardation, and skeletal abnormalities; to date, no comparable cases of DM2 have been reported despite the fact that DM2 expansions are typically much larger than the DM1 expansions associated with congenital cases. Other differences of DM2 include an apparent lack of mental retardation in juvenile cases; less evident central hypersomnia; less symptomatic distal, facial, and bulbar weakness; and less pronounced muscle atrophy.

DM1 individuals often come to medical attention because of the mental retardation or disabling distal weakness and myotonia, but DM2 patients typically first seek medical evaluation because of muscle pain, stiffness, fatigue, or when they develop proximal lower extremity weakness. Although some DM2 features are milder than in DM1 (clinical myotonia, distal and facial weakness), others are comparable in presentation (cataracts, hypogonadism, and insulin insensitivity). We have seen a progressive cardiomyopathy that appears to be a consequence of DM2, although specific investigation of this point is necessary. DM2 patients often seek medical attention for isolated symptoms of the disease, without being aware of their complex underlying disorder. A genetic diagnosis of DM2 will improve patient care by facilitating better monitoring of the diverse clinical features known to be part of the disease, including early onset cataracts, diabetes, testicular failure, and cardiac arrhythmias.

We have identified 379 DM2-positive individuals from 133 families, indicating that DM2 is not rare in populations of northern European ancestry. In Germany DM2 may be as common as DM1.[12] Because DM1 families often come to the attention of physicians when a child is severely affected, the lack of

congenital DM2 may explain its apparent underdiagnosis. All three of the original families described with PROMM[2] and 11 of the 14 subsequently described PROMM families have the DM2 expansion (families 7, 12 ,and 13 from Ricker et al.[12] had features of PROMM/DM2 that with additional investigation did not cosegregate in the individual families). In addition, other PROMM families initially reported to have been excluded from the DM2 locus by linkage analysis[13,14] have now been shown to be DM2 positive. These data indicate that families previously described with PROMM or DM2 have the same clinical disorder caused by the DM2 CCTG expansion on chromosome 3. Contrary to earlier views, analysis of our large collection of families has not revealed any convincing examples that would suggest the existence of a third mutation that causes a similar dominantly inherited multisystemic myotonic disorder, i.e., DM3.

The DM2 expansion has several novel molecular features including: (1) it is the first pathogenic tetranucleotide expansion; (2) expansions are larger than reported in any other disease (more than 44 kb in DM2 versus 12 kb in DM1); and (3) the degree of somatic heterogeneity of the repeat expansion is unprecedented. In other expansion disorders, Southern analysis (figure 1B) can reliably confirm the presence of expansions too large to amplify by PCR.[15,16] In contrast, for DM2 the heterogeneity of repeat sizes in blood is so extreme that approximately one of five of the expansions are not detectable by Southern analysis, which causes a diagnostic challenge not previously encountered, even among disorders with large expansions such as DM1, SCA8, and SCA-10. Although the somatic heterogeneity complicates the molecular diagnosis of DM2, the RA described here improved detection to 99%.

In other reported microsatellite expansion disorders larger repeat expansions are associated with earlier onset and increased disease severity.[21] Although anticipation has been reported in DM2/PROMM families based on clinical criteria,[2] and earlier ages at onset in offspring of affected parents was found in this study, the expected trend of longer repeat expansions in patients with earlier ages at onset was not observed, so the explanation of the observed intergenerational changes remains unclear. The somatic heterogeneity of the repeat, and the fact that the size of the repeat increases with age, complicate this analysis and may mask meaningful biologic effects of repeat size on disease onset and severity. However, it is also possible that expansions over a pathogenic size threshold exert similar effects regardless of how large they become, or even that smaller repeats are more pathogenic than larger repeats. In adult-onset DM1, the most significant correlations between repeat length and disease onset are for repeats less than 400 CTGs.[22] Another unusual molecular feature of DM2, the tendency of repeats to be shorter in offspring after both maternal and paternal transmission, may in part reflect increases in repeat size with age, but the overall cause and biologic significance of this observation are yet to be determined.

DM2 provides an opportunity to better understand the pathogenic mechanisms of DM. Our cloning and characterization of the DM2 mutation revealed that the DM2 mutation, like that of DM1, involves a similar microsatellite motif (CCTG and CTG, respectively). Both mutations are transcribed into RNA but not translated and accumulate as nuclear RNA foci. These molecular parallels, combined with the clinical parallels, indicate that the repeat expansions expressed at the RNA level cause the multisystemic features common to both diseases.[7] Intranuclear RNA foci in both DM1 and DM2 bind specific RNA binding proteins,[23,24] and the repeat expansions in both diseases alter splicing of the insulin receptor and chloride channel transcripts. Changes in the insulin receptor splicing lead to insulin insensitivity and a predisposition to diabetes,[26,27] and alterations in chloride channel splicing lead to a loss of chloride channel protein that results in electrical myotonia.[28,29] These changes in RNA binding proteins and the alteration in gene splicing provide a convincing model of how untranslated repeat expansions in RNA can cause the multisystemic features common to both forms of myotonic dystrophy.

Although DM2 has many of the clinical features found in adult-onset DM1 patients, DM2 does not involve some of the changes seen in the early onset or congenital forms of DM1. Defining the pathophysiological differences between DM1 and DM2, which could involve spatial and temporal expression differences between the two repeat-containing transcripts, the regulation of locus specific genes such as *DMPK*, *SIX5*, or *ZNF9* and/or downstream RNA effects of the CUG or CCUG expansions, will be important for understanding the clinical differences.[7] Fillipova et al. have suggested that methylation at the DM1 locus in congenital cases could increase expression of the CUG-containing transcripts.[30] Although the etiology of the congenital form of DM1 remains enigmatic, Occam's razor suggests that the simplest model of DM pathogenesis is that pathogenic effects of RNAs containing the CUG and CCUG expansions cause the multisystemic features common to DM1 and DM2.

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Myotoxic Effects of the Skeletal Muscle-Specific Immunotoxin, Ricin-mAb35, on Orbicularis Oculi Muscle After Eyelid Injections in Rabbits

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Purpose: The authors recently demonstrated that a single injection of the immunotoxin ricin-mAb35 has potent and long-lasting myotoxic effects in extraocular muscles. The myotoxicity of injected ricin-mAb35 was tested in the eyelids of rabbits to determine its potential for use in the treatment of benign essential blepharospasm and other dystonias.

Methods: The immunotoxin ricin-mAb35 was injected in one eyelid of adult rabbits. After 1 week, 1 month, or 6 months, the rabbits were euthanized, and the eyelids were prepared for histologic examination of inflammatory cell infiltrate with immunohistochemical localization of cd11b and myosin heavy chain isoform expression. Muscle loss was quantified by analysis of muscle fiber cross-sectional area and total myofiber number.

Results: Within the first week after a single injection of ricin-mAb35, some edema developed, which resolved by the second week. Otherwise, the eyelids were normal in appearance. A short-lived inflammatory response was seen at 1 week, but this resolved 1 month after treatment. One week after injection, there was a significant decrease in the total number of orbicularis oculi myofibers in the ricin-mAb35–treated eyelids. This myofiber loss remained significant 1 month later and was maintained 6 months after the initial injection.

Conclusions: Direct injection of the immunotoxin ricin-mAb35 resulted in significant, acute muscle loss in the orbicularis oculi of rabbits that was maintained for up to 6 months. Physiologic studies are needed to demonstrate concomitant loss of muscle strength, but these results suggest that ricin-mAb35 injection holds promise as a muscle-weakening agent in the eyelid.

Facial botulinum toxin injections have become the mainstay treatment for patients with muscle spasm diseases that involve the eyes and face, including benign essential blepharospasm and hemifacial spasm.[1,2] The overwhelming acceptance by patients and their physicians attests to the therapeutic effects of these treatments and their safety and ease of administration. Although effective, one of the concerns with the use of botulinum toxin injections is that injections often become less effective over time, and patients require decreasing time intervals between subsequent injections.[3,4] In some patients, antibodies to botulinum toxin develop, and this correlates with decreasing effectiveness of the treatments.[5] There also is a group of patients who are unresponsive to botulinum toxin.[6]

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Recent studies in extraocular muscle suggest that ricin-mAb35, an immunotoxin targeted to skeletal muscle, might have a longer treatment effect than botulinum toxin.[7,8] The ricin-mAb35 molecule is composed of the toxin ricin, which has been conjugated to an antibody to the nicotinic acetylcholine receptor, which targets the immunotoxin specifically to adult skeletal muscle fibers.[9] The mechanism of action for muscle weakening caused by the ricin-mAb35 is direct myotoxicity to muscle fibers. A single injection of ricin-mAb35 in rabbit extraocular muscles results in a significant long-term muscle fiber loss[8] and a significant reduction in muscle force compared with the contralateral control muscles for up to 24 weeks.[10] Thus, injection of this immunotoxin could add a potential therapeutic modality for treatment of patients with muscle spasm diseases of the eyelids and face, especially for those in whom a longer-term treatment effect is desired or for those who are or have become nonresponders to botulinum toxin treatment. The purpose of this study was to examine the histologic effects of ricin-mAb35 injection in the eyelids of rabbits to determine the potential usefulness of this agent for the treatment of muscle spasm diseases of the face and other dystonias.

METHODS

This study involved the injection of ricin-mAb35 in the upper eyelids of adult New Zealand White rabbits obtained from Bakkon Rabbitry (Viroqua, WI, U.S.A.) and housed with Research Animal Resources at the University of Minnesota. This study was approved by the Institutional Animal Care Committee at the University of Minnesota and adhered to the Guidelines of the National Institutes of Health for Use of Animals in Research. Rabbits were anesthetized with a 1:1 volume of ketamine (10 mg/kg) and xylazine (2 mg/kg). After a suitable level of anesthesia was achieved, proparacaine HCl was placed in the conjunctival cul-de-sac to reduce blinking. Ricin mAb35,[9] in a volume of 1 ml, was injected from the medial to lateral canthus of the upper eyelids with a 30-gauge needle. Based on our previous studies, ricin-mAb35 was injected in the upper eyelids of 4 rabbits at a dose of 1/5 and 8 rabbits at 1/10 maximum tolerated dose for mice.[7] An identical procedure was performed on the contralateral eyelids, substituting an equal volume of normal saline for the immunotoxin. The treatment and control eyelids were randomized. The rabbits were monitored daily for eyelid changes and any systemic reactions to the immunotoxin.

One week, 1 month, and 6 months after a single injection of the ricin-mAb35, the treated rabbits were euthanized with an overdose of barbiturate anesthesia. The eyelids were removed, embedded in tragacanth gum, and frozen in methylbutane that was chilled to a slurry on liquid nitrogen. The eyelids were sectioned at 12 μm and stored at −80°C. The sections were processed for the immunohistochemical localization of cd11b-positive cellular infiltrate, specifically neutrophils, monocytes, and macrophages. The tissue sections were fixed for 10 minutes in 10% formalin and quenched in hydrogen peroxide to remove endogenous peroxidase. After a phosphate-buffered saline rinse, the sections were blocked with normal horse serum and incubated with an antibody to cd11b at a dilution of 1:10 (Serotec, Raleigh, NC, U.S.A.). The tissue was incubated with the peroxidase Vectastain Elite ABC kit (Vector Labs, Burlingame, CA, U.S.A.) that was visualized by incubation with diaminobenzidine and heavy metals. The sections were immunostained for fast, developmental, and neonatal myosin heavy chain isoforms. Unfixed sections were blocked in normal horse serum and incubated with an antibody to pan-fast myosin heavy chain (NovoCastra, Burlingame, CA, U.S.A.; 1:40), neonatal (NovoCastra, 1:20), or developmental myosin (NovoCastra, 1:20) and then processed as for the cd11b antibody.

The eyelid sections were analyzed with the use of Bioquant Nova Prime software (Bioquant, Nashville, TN, U.S.A.). CD11b-positive cells were counted in the preseptal region of each eyelid cross section, and at least 4 fields (0.51 mm^2) were measured in this region in each cross section. A standard area measurement for cd11b-positive cells was determined morphometrically by calculation of the average area of 20 to 40 cd11b-positive cells. The computer used this standard area measurement for a cd11b-positive cell to determine the total number of cd11b positive cells for each field measured. Wherever the total area of label was greater than the area measurement for a single cell, the computer divided this by the standard cd11b-positive cell area measurement. This number was the standardized count per field. The validity of this technique was manually confirmed by examination of representative sections. Three to 4 eyelid cross sections were counted in each of the 3 regions of the treated eyelids (12 sections per eyelid), and at least 4 eyelids were examined for each injection parameter.

The sections at each postinjection interval were analyzed to determine total muscle cross-sectional areas, individual myofiber cross-sectional areas, and total myofiber number in the palpebral portion of the eyelids, using the Bioquant Nova Prime and Topographer software (Bioquant, Nashville, TN, U.S.A.). We also assessed the integrity of the skin, vasculature, and peripheral nerves within the injected tissue. Nearby structures in the orbit were examined for histologic changes, to

ensure that there was no spread of the injected drug. All data were analyzed statistically for significance by either Student t tests or analysis of variance and were performed with the use of Prism and Statmate software (Graphpad, San Diego, CA, U.S.A.). Statistical significance was defined as $p < 0.05$.

RESULTS

In the first week after a single eyelid injection of the ricin-mAb35, the eyelids were edematous, but no hair loss or skin lesions developed. The edema resolved by the second week, and the eyelids were normal in appearance during the remainder of the study. There were no apparent systemic reactions to the toxin. One week after immunotoxin injection, there was a significant decrease of 68% ($p < 0.0001$) and 71% ($p < 0.0001$), respectively, in the total number of orbicularis oculi myofibers at the 1/10 and 1/5 maximum tolerated dose for eyelids injected with ricin-mAb35 compared with the saline-injected controls (Fig. 1). There was no significant difference between the overall muscle toxicity when the two doses were compared ($p = 0.3977$) (Fig. 1). However, there was a more even distribution of muscle loss across the treated eyelid at the higher dose of ricin-mAb35 when sections were examined from the medial, central, and lateral portions of the treated eyelids from the medial to lateral canthal dimension (Fig. 2). This suggests that it might be possible to increase myotoxicity in the eyelid with the lower dose if access to the muscle fibers was improved. One month after a single injection of ricin-mAb35, muscle loss was still significant compared with the saline-injected control muscles, with 58% loss of muscle fibers compared with the normal eyelid control (Fig. 3). There was no statistical difference between the total muscle loss at 1 week after treatment compared with that seen at 1 month ($p = 0.09$). At 1 month, the myofibers were small in cross-sectional area, and expression of developmental myosin was upregulated in these muscles compared with normal controls (Fig. 4). No changes were seen in the skin or other tissues within the eyelid sections at either of the time intervals examined. Six months after a single injection of ricin-mAb35 in the eyelid, muscle loss was still significant and similar to that seen at 1 month when compared with the contralateral control (Fig. 3).

The muscles were examined at both 1 week and 1 month for evidence of inflammatory cell infiltrate as

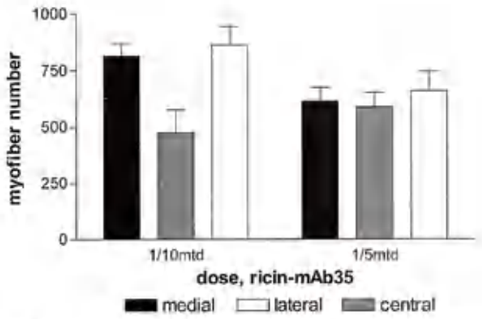

FIG. 2. Quantification of muscle loss from sections taken close to the medial canthus, from the center, and from close to the lateral canthus in eyelids injected with 1/10 maximum tolerated dose ricin-mAb35.

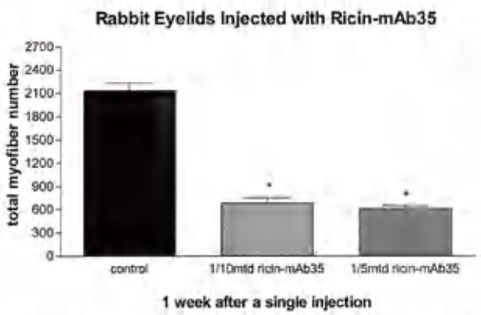

FIG. 1. Quantification of muscle loss of eyelids treated with ricin-mAb35 at 1/10 and 1/5 maximum tolerated dose as determined in mice. *Significant difference from control.

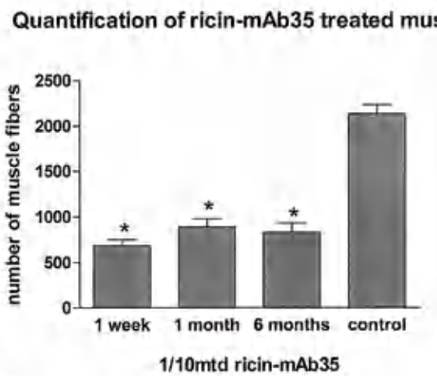

FIG. 3. Quantification of muscle loss at 1 week and 1 month after single injection of 1/10 maximum tolerated dose ricin-mAb35 compared with normal saline–injected control eyelids. *Significant difference from control.

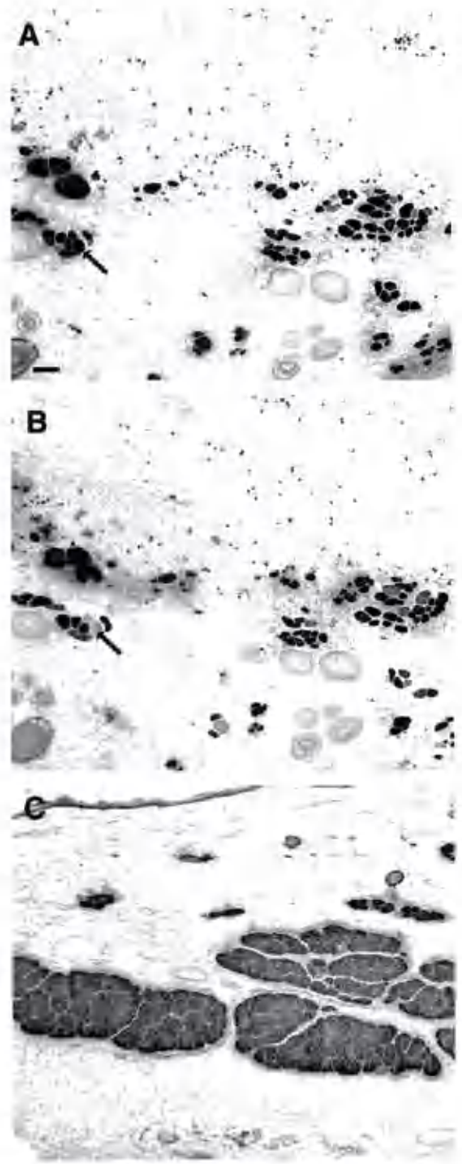

FIG. 4. Photomicrograph of preseptal region of ricin-mAb35-treated eyelid 1 month after single injection. **A.** Myofibers are extremely small in cross-sectional area. **B.** Small groups of myofibers in treated eyelids are positive for developmental myosin heavy chain isoform. **C.** Saline-injected control eyelids immunostained for fastmyosin. Bar is 100 μm.

visualized by positive staining for cd11b (Fig. 5). There was a significant increase in inflammatory cell infiltrate at 1 week after a single eyelid injection of ricin-mAb35 ($p < 0.0001$). By 1 month, this was reduced to a level that was only slightly elevated from that seen in normal eyelids.

DISCUSSION

Ricin-mAb35, when injected directly in the eyelids of adult rabbits, resulted in significant acute muscle loss that was maintained for 6 months after a single injection. At 1 month, there was slight evidence for some regeneration. This is confirmed by myofibers with very small cross-sectional areas and by expression of developmental myosin heavy chain isoform in the treated muscle.[11] Despite some evidence of ongoing regeneration, muscle loss was still significant at 6 months after a single injection of the ricin-mAb35.

The lack of significant regeneration at 1 and 6 months is very promising and indicates that ricin-mAb35 may have a much longer therapeutic effect than botulinum toxin A for the treatment of muscle spasm diseases in the face. However, our experience with ricin-mAb35 in extraocular muscle suggests that orbicularis oculi muscle will slowly regenerate with time after treatment.[8] Other agents, including the local anesthetic bupivacaine[12,13] or injection with dihematoporphyrin ether and laser photochemomyectomy,[14] can significantly injure muscle acutely, but the muscle regener-

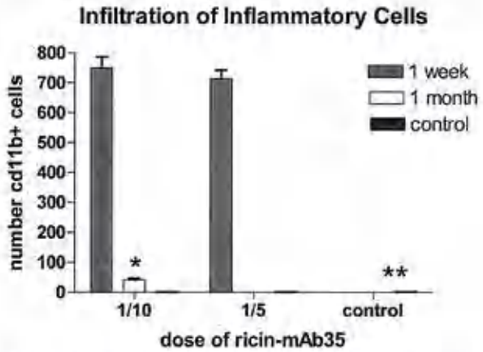

FIG. 5. Quantification of inflammatory cell infiltrate as visualized by antibody to cd11b, which is positive for macrophages, neutrophils, and lymphocytes. There is a significant elevation of inflammatory cell infiltrate 1 week after single injection of ricin mAb35, which is largely back to control levels by 1 month. *Significantly different from control. **Control levels of cd11b-positive infiltrate. These average between 1 and 3 cd11b-positive cells in each eyelid cross section.

ates rapidly. In contrast, both orbicularis myectomy surgery[15] and doxorubicin injection in the eyelid[16] result in permanent muscle loss, but both are associated with eyelid skin injury that many patients find unsatisfactory.

Botulinum toxin A is a well-established and well-accepted treatment for various focal dystonias, including blepharospasm.[1,2] The action of botulinum toxin A is to paralyze the muscle by preventing release of acetylcholine in the neuromuscular junctions. This treatment does not cause permanent muscle weakness, and muscle spasms return in several months.[5] There is also a group of patients, estimated to be between 10% and 25%, who do not respond to botulinum toxin treatment.[6,17–20] Our studies in extraocular muscles demonstrated that a single injection of ricin-mAb35 resulted in both significant long-term muscle loss[8] and muscle weakening.[10] Although further studies are required to determine the long-term efficacy of ricin-mAb35 in weakening the orbicularis oculi muscle, it holds promise as a muscle-weakening agent that might be longer lasting than botulinum toxin treatments.

The differential muscle loss across the eyelid from the medial to lateral canthus at the lower dose of the ricin-mAb35 suggests that it may be possible to increase the myotoxicity of a single injection of the ricin-mAb35 by increasing the infiltration of the drug within the eyelid with the use of hyaluronidase.[21] This might increase the effectiveness of its myotoxicity because the ricin-mAb35 is targeted directly to myofibers by the antibody to the nicotinic acetylcholine receptor. It should be pointed out that although neuromuscular junctions in the orbicularis oculi of rabbits are concentrated in the medial and lateral canthal regions, they are also diffusely located across the entire medial to lateral extent of the muscle.[22] This is particularly true in the pretarsal portion of this muscle. Thus, access to the muscle fibers is critical for its effectiveness. Drugs such as collagenase injected together with the ricin-mAb35 should increase access to the myofibers in the eyelid, which are surrounded by dense connective tissue.

Ricin-mAb35 appears to be as selectively myotoxic in the eyelid as it is in the orbit. Light microscopic examination demonstrated that the nerves, skin, and capillaries within the ricin-mAb35–treated tissue were normal. This suggests that neurotoxicity will not play a significant role in the pharmacologic effects of the immunotoxin. Muscle-specific binding of the immunotoxin should also limit its spread outside of the direct injection site, making it unlikely that orbital or ocular cytotoxicity will be a significant concern.

In summary, a single injection of ricin-mAb35 in the eyelid results in significant muscle loss in the treated lids and a limited inflammatory reaction. We are currently in the process of examining its ability to weaken the orbicularis muscle and its long-term effectiveness, both of which are critical to its potential use as a treatment for blepharospasm and other dystonias.

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EXPERT REVIEWS

Controversies and advances in the management of congenital ptosis

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The management issues associated with pediatric ptosis begin with determining the etiology of the ptosis, and considering how the eyelid position affects the child's visual and psychosocial development. These ultimately determine if and when surgical management should be undertaken. Surgical challenges include the lack of intraoperative feedback regarding the dynamic eyelid height and contour under general anesthesia. When the eyelid elevators do not function or if there is little drive to lift the involved eyelid, obtaining good surgical outcomes can be extremely challenging. A plethora of surgical techniques and materials have been developed, each with their own benefits and drawbacks. Careful preoperative evaluation, planning and counseling can usually result in satisfactory surgical results with happy parents and patients. Families should always be aware that the child will need to be followed long term for visual development, ocular health, and they need to be counseled regarding the possibility of revision surgery.

Keywords: blepharoptosis • childhood ptosis • congenital ptosis • frontalis sling • pediatric ptosis

Pediatric congenital ptosis, while commonly encountered by the pediatric ophthalmologist and oculofacial plastic surgeon, continues to be a challenging management issue. The challenges begin with the evaluation of a preverbal child in the presence of anxious parents. Any red flags need to be teased out, and a decision regarding ptosis repair is made. Timing of ptosis repair or intervals for follow-up become another issue. Finally, if surgical repair is decided upon, there are numerous surgical techniques available, each with unique advantages and drawbacks. Special consideration needs to be given to the risk of amblyopia as well as psychosocial development of the child. In recent decades, numerous modifications have been described to the classic procedures in an effort to improve surgical outcomes.

Background

Data about the incidence of childhood ptosis are limited, with a population-based study out of Olmsted County, Minnesota, finding an incidence of 7.9 per 100,000 children under the age of 19. Of these, 89.7% were congenital, of which 84.3% were diagnosed as simple congenital ptosis [1].

Categorization of childhood ptosis

Childhood ptosis can be classified as aponeurotic, myogenic, neurogenic, mechanical and pseudoptosis. A multifactorial ptosis can also be encountered.

Aponeurotic ptosis, most commonly associated with adult ptosis, suggests a normal levator palpebrae superioris muscle, with normal function. A diaphanous tendon is unable to translate the contraction of the muscle to complete elevation of the eyelid. In children, this form of ptosis can be seen with birth or other trauma, or with chronic contact lens wear.

Myogenic ptosis, which is the most common etiology of congenital ptosis, indicates a congenital abnormality of the levator muscle itself. Injury to the eyelid *in utero* can cause a secondary myogenic ptosis, such as can be seen with amniocentesis. Intraoperatively, these muscles tend to look fibro-fatty infiltrated and are quite inelastic [2]. This results in both an inability to lift the eyelid and retraction of the eyelid in downgaze and lagophthalmos. Non-congenital forms of myogenic ptosis include muscular dystrophy and chronic progressive external ophthalmoplegia, and while they are

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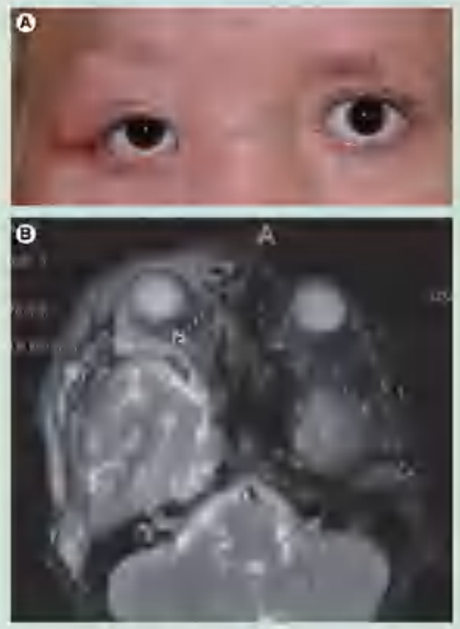

Figure 1. A 7-year-old child with neurofibromatosis. She has a dysplastic greater wing of the sphenoid on the right, and a neurofibroma involving the right superior orbit and upper eyelid as seen on imaging.

classically encountered in adulthood, they may occasionally manifest during childhood.

Neurogenic ptosis most commonly results from an abnormality of the oculomotor nerve as it supplies the levator palpebrae muscle or a problem with sympathetic innervation of Müller's muscle. This can be congenital or acquired. Synkinetic syndromes can also be classified as neurogenic. Every examination should include thorough evaluation of pupils and ocular motility. Aberrant regeneration, such as elevation of the ptotic lid with depression, abduction or adduction, is highly suggestive of acquired oculomotor paralysis. Pupil exam should not only consist of size and reaction, but iris heterochromia should also be noted, which would suggest a congenital Horner syndrome. Myasthenia gravis also rarely presents in childhood as acquired ptosis.

Mechanical ptosis suggests the eyelid is unable to be opened secondary to a mass or being tethered downward. In children, this can be due to brow ptosis, a mass, infiltration, inflammation, foreign body, adhesions and cicatrix. Classic masses causing mechanical ptosis include neurofibroma (Figure 1) and capillary hemangioma.

Pseudoptosis can be a term used for 'other' etiologies of apparent ptosis. This can be secondary to enophthalmos, microphthalmos, anophthalmos, phthisis or contralateral eyelid retraction.

Numerous craniofacial syndromes and cranial dysinnervation disorders can be associated with childhood ptosis. Classic syndromes associated with congenital or childhood ptosis, often requiring greater thought in management and surgical planning, include Duane retraction syndrome, blepharophimosis, congenital fibrosis of the extraocular muscles and Marcus Gunn jaw-winking syndrome. While discussion of each of these individual syndromes is beyond the scope of this manuscript, every surgeon managing childhood ptosis should be familiar with them and the challenges they each present in management.

Preoperative considerations

The inability of the very young to cooperate as well as anxious parents can complicate the evaluation of the ptotic child. Decision to operate needs to take into consideration whether the eyelid position is amblyogenic, responsible for a chin-up position and how the eyelid position may affect the child's social interactions. In the setting of amblyogenic ptosis, there is little question as to the appropriate timing of ptosis surgery. Controversy exists for timing of non-amblyogenic ptosis. Many surgeons decide to proceed with surgical correction prior to the child beginning kindergarten in an effort to prevent comments from peers that may make the child more self-conscious. Waiting until age 4 or 5 allows for a more cooperative examination. Others advocate a more aggressive approach with early surgery typically around the age of 1, arguing that enough clinical information can be ascertained at that age, that there is more emotional trauma associated with surgery later in childhood and that children may encounter hurtful comments while playing with other children prior to kindergarten [3].

Other salient preoperative considerations include whether the child has the drive to recruit frontalis to compensate for the ptotic eyelid or if they are completely ignoring it, variability of eyelid position, presence of strabismus and synkinetic movements. If there is no frontalis recruitment on the ptotic side in a child with poor function ptosis, frontalis sling procedures become less predictable, and one may consider supramaximal levator resection in their place. The author's preference, in this setting, is resection of 2–3 mm of tarsus and 4–6 mm of conjunctiva and Müller's muscle, in addition to levator advancement. If there is apparent unilateral ptosis, consideration should be given to the presence of asymmetric ptosis, which frequently occurs but is masked by a strong central drive to open the ptotic eyelid, and aggressive frontalis recruitment; such masked cases will become evident in the postoperative period when the strong drive to raise the more ptotic eyelid is lost.

As with adults, making note of the marginal reflex distance (MRD1) is important, but of paramount importance in surgical planning is the degree of upper eyelid excursion, often referred to as levator function. This is the difference between the position of the upper eyelid in downgaze and upgaze, with the brow immobilized. Beard categorized levator function as good, fair or poor (Table 1) [4]. We consider >14 mm of function as normal. Determining the response of the eyelid position to instillation of phenylephrine drops (10 or 2.5%) [5] is helpful in planning an appropriate procedure [6,7]. Other subtleties should be evaluated, including how much effort the child exudes to utilize the involved eye, presence or absence of the Bell's phenomenon (elevation and slight abduction of the eye on attempted lid closure) and the strength of the eyelid crease. While children generally tolerate corneal exposure better than adults, in the absence of a good Bell's phenomenon, the authors prefer to be less aggressive surgically to minimize the risk of postoperative corneal complications.

Finally, preoperative counseling and setting expectations is crucial. Parents should understand that the eyelids may never be exactly symmetric, that there may be complications associated with the surgery and that there is a relatively high rate of revisions. In one large series of 186 eyes of 155 children, there was a 19.89% revision rate, with a further 9.14% who declined further revision [8]. Additionally, the parents should be aware that as the child grows, despite their eyelid surgery, they might need to be followed for refractive error and amblyopia.

Table 1. Beard's classification of levator function.

Levator function	Eyelid excursion
Good	8–16 mm
Fair	5–7 mm
Poor	4 mm or less

Surgical procedures

Determining an appropriate procedure should be individualized, and obtaining ideal surgical outcomes can be both challenging and controversial. One can classify surgical procedures anatomically or based on what degree of ptosis they can be utilized for. We will base our discussion on levator function. We consider good levator function 10 mm or greater excursion, moderate 7–10 mm, fair 5–7 mm and poor less than 5 mm of excursion. It must be noted that numerous procedures and modifications have been described and continue to be utilized; the below only addresses some of the most commonly used.

Good levator function

Over the past decade, the use of 2.5% phenylephrine ophthalmic drops in preoperative evaluation of children with relatively good levator function has become routine in our practice. The addition of Müller's muscle conjunctival resection, with or without superior tarsectomy, to the armamentarium of procedures to address pediatric ptosis has allowed for quite predictable and pleasing results in children whose eyelid elevates in response to the drop. There are numerous nomograms, and the amount of resection should be tailored and modified based on the surgeon's personal results. Our current practice is to resect 9 mm of conjunctiva and Müller's muscle if the elevation is perfect. The amount of resection can be anywhere between 6.5 and 9.5 mm based on the degree of ptosis and response to phenylephrine. Superior tarsectomy can be added to the procedure, to provide an additional 1–2 mm of lift. Our current practice is to resect 1 mm of additional tarsus for each 1 mm of desired additional lift. Müller's muscle conjunctival resection is not considered a repeatable procedure. Critics of the procedure argue resecting normal conjunctiva will worsen dry eye by removing goblet cells, and that it does little to address the anatomical problem, which is with the levator palpebrae muscle [9]. In our hands, we have not had trouble with dry eyes in the pediatric population, and the predictable outcome without intraoperative adjustment and pleasing eyelid contour has made this our procedure of choice in the setting of mild congenital ptosis, with good response to phenylephrine drops.

Utilization of the Fasanella–Servat procedure [10] also has a role in management of up to 2.5 mm of congenital or acquired ptosis. This has become a favored procedure for children with mild degrees of ptosis who have minimal response to phenylephrine or who have mild residual ptosis following prior Müller's muscle conjunctival resection. The ratio of tarsectomy to eyelid elevation is 2 mm of tarsectomy to 1 mm of desired elevation [11]. Given most children require general anesthetic, Müller's muscle conjunctival resection and Fasanella–Servat procedure allow graded surgery based on preoperative measurements rather than intraoperative observations, which may be skewed by local anesthetic and the depth of anesthesia. Children with congenital ptosis frequently have a poor eyelid crease, and this may limit the aesthetic result even if the eyelid height and contour is perfectly symmetrical. The Fasanella–Servat and Müller's muscle conjunctival resection procedures do little to create an eyelid crease.

Fair to good levator function

While Müller's muscle surgery has become our preferred workhorse for mild degrees of congenital ptosis, levator surgery is necessary for those with fair levator function, good levator function and inadequate response to phenylephrine, or those who have previously undergone resection of Müller's muscle and/or tarsus and require further revision.

With the added benefit of allowing creation or accentuation of a lid crease, a significant drawback of all procedures other than Müller's muscle surgery is the question of where to position the eyelid under general anesthesia. While those with good levator function typically require advancement of the levator aponeurosis, in cases of moderate or fair levator function, levator resection also becomes necessary. Beard described a method in which the amount of levator resection is based on the degree of ptosis and eyelid excursion [12]. This can be difficult to incorporate into any given surgeon's practice as the amount resected is influenced by surgical technique and tension on the levator muscle. Berke provided guidelines on where to set the upper eyelid under general anesthesia based on upper eyelid excursion [13], and there have been minor modifications since (Table 2) [14].

Table 2. Intraoperative eyelid height under general anesthesia based on upper eyelid excursion for levator surgery.

Levator function	Lid position on cornea
>10 mm	2–4 mm below the limbus
8–9 mm	3 mm below the limbus
6–7 mm of function	2 mm below the limbus
5–6 mm of function	1 mm below the limbus
0–4 mm of function	Recommend frontalis suspension

Adapted from [14].

Poor levator function

The most source of controversy surrounding congenital ptosis is in the management of children with poor levator function. While some advocate supramaximal levator resection in the setting of poor levator function, we have found utilization of a frontalis sling to yield the most satisfactory results. The material used and technique for placement of a frontalis sling continues to evolve.

Autogenous tensor tendon fascia lata, while considered the gold standard, carries the disadvantage of a second surgical site. Furthermore, the tendon is incompletely developed in young children and should be avoided in children younger than 4 years. While banked fascia is available, we have transitioned almost exclusively to utilization of synthetic materials and silicone in particular. Available synthetic suspension materials include nylon, polyester, polytetrafluoroethylene, polypropylene and silicone. Ben Simon *et al.* reviewed their experience with a variety of autologous, banked and synthetic materials and found their recurrence rate of ptosis to be 26% at a mean of 12 months, with no difference between suture materials or loop shape [15]. This supports the widely held belief that ultimately it is scar tissue that surrounds the suspension material that is responsible for transferring lift from the frontalis to the eyelid. Currently, we have been most satisfied with the characteristics of silicone as the suspension material (Figure 2). Advantages include its elasticity, theoretically allowing for more dynamic movement of the lid compared to stiff materials; it is adjustable, often through opening a single brow incision, and can be easily removed should problems arise.

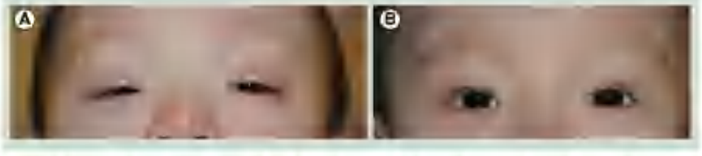

Figure 2. Poor function ptosis. (A) An 8-month-old child with severe bilateral ptosis, which had resulted in a significant chin-up position. **(B)** One week after bilateral upper eyelid ptosis repair with silicone rod frontalis sling.

Complications associated with frontalis sling surgery include exposure keratopathy, recurrence of ptosis and irregular contour of the lid. Often, patients will be unhappy with the surgical outcome despite excellent lift if an eyelid crease is not created or is asymmetric. Additionally depending on the vector of forces, brow recruitment may lead to undesirable peaking of the eyelid or elevation of the lid off of the globe. Use of non-autogenous materials can increase the risk of pyogenic granuloma formation, inflammatory response to implanted materials as well as infection. Exposure of sutures or sling material through the conjunctiva can result in a chronic conjunctivitis, which may initially be mistaken for exposure keratopathy.

Even when placement of a frontalis sling results in excellent symmetry in forward gaze, the lid tends to hang up in downgaze. Additionally when a child is amblyopic on the ptotic side, there may be little drive to recruit frontalis to engage the suspended eyelid. To overcome this, Beard suggested disinsertion of levator on the uninvolved side and placement of bilateral slings [16]. Others have advocated bilateral sling procedures without extirpation of levator [17], often referred to as the 'Chicken Beard' procedure. While this overcomes some of the issues associated with asymmetry, it is difficult for parents to agree to operate on a normal eyelid. Furthermore, operating on the normal side does have inherent risk, particularly if the side with ptosis is densely amblyopic, severe exposure keratopathy or infection on the normal side could be devastating. As mentioned earlier, in the setting of no frontalis recruitment on the side of the ptotic eyelid, if there is some levator function, the author's preference is to combine levator advancement with resection of 2–3 mm of tarsus and 4–6 mm of conjunctiva and Muller's muscle. Ultimately, many surgeons have found the cosmesis in primary gaze with unilateral frontalis suspension for unilateral ptosis to be the most acceptable approach to both the surgeon and patient [18,19].

Expert commentary & five-year view

While surgical technique and materials have continued to evolve over the decades, a better understanding of the embryology and molecular genetics of how a child is born with ptosis may lead to the most radical changes in how congenital ptosis, as well as other craniofacial anomalies are approached in the future. Vestal *et al.* reviewed the literature for cases of congenital ptosis in monozygotic twins and found a heritability index of 0.75 (0–1), indicating a strong genetic contribution to the phenotype of congenital ptosis [20]. Since then, an autosomal dominant gene for isolated congenital ptosis was mapped to a 3-cM region in 1p32-p4.1, utilizing a large pedigree, and additional loci have been identified on chromosome 8, 14 as well as the X chromosome [21–23]. It remains to be seen how these and other candidate genes, in combination with environmental factors, result in congenital ptosis, and perhaps this understanding will allow more tailored approaches to the management of children with ptosis.

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Key issues

- Congenital ptosis refers to a lower-than-expected upper eyelid height noted shortly after birth.
- Congenital ptosis can be unilateral or bilateral.
- There is a high heritability index among monozygotic twins, indicating a strong genetic contribution.
- Congenital ptosis can be isolated or associated with other ocular, craniofacial or systemic syndromes.
- Whether or not to repair the ptosis, and its timing, is dependent on the degree of ptosis, visual and psychosocial impact.
- The appropriate surgical procedure is dependent on the degree of ptosis, levator function, presence of synkinesis, surgeon comfort and outcomes with a variety of techniques and materials.

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Effect of Hyperthyroidism on the Orbicularis Oculi Muscle in Rabbits

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Purpose: To determine the effect of hyperthyroidism on both myofiber number and myosin heavy-chain isoform composition within the palpebral orbicularis oculi muscle in rabbits.

Methods: Four New Zealand White rabbits were made hyperthyroid by injection of 3,3,3'-triiodothyroinine intraperitoneally every other day for 1 month. Four rabbits were used as control animals. After 1 month the rabbits were euthanized, and the eyelids were excised and sectioned in a cryostat. The sections were immunostained to determine the presence of fast, slow, and neonatal myosin heavy-chain isoforms. To determine alterations in myofiber number, differential counts of myofiber number and the cross-sectional areas of the muscle fibers were performed with the use of computerized morphometry.

Results: The orbicularis oculi muscle in the palpebral portion of the eyelids from hyperthyroid rabbits had significantly fewer myofibers compared with control eyelids, predominantly as the result of a loss of myofibers in the preseptal region. The remaining fibers showed continued expression of fast myosin but upregulated coexpression of slow myosin isoform.

Conclusions: Hyperthyroidism led to reduced orbicularis oculi muscle in the rabbit model and an alteration in the myosin heavy-chain isoform composition. This finding may help explain the clinical finding of eyelid retraction in patients with Graves orbitopathy.

Graves disease is an autoimmune process often associated with an endocrinopathy that leads to an inflammatory orbitopathy with proptosis, strabismus, and eyelid retraction.[1,2] The histologic changes in the extraocular muscles, orbital fat, levator superioris, and the Müller muscle have been well described.[3–5] To the best of our knowledge, no prior histologic studies have examined the effects of hyperthyroidism on the orbicularis oculi muscle. The current study begins to fill that void.

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There is no satisfactory animal model for the autoimmune process that leads to Graves disease. Although hyperthyroidism is not always associated with Graves ophthalmopathy, its frequent association lends credibility to the study of the effects of hyperthyroidism on the ocular and nonocular skeletal muscles in other species. A number of studies have been performed with animal models of elevated thyroid hormone to study various muscle-specific aspects caused by this condition.[6–15] The purpose of this study was to evaluate the effect of elevated thyroid hormone levels on orbicularis oculi muscle in a rabbit model.

METHODS

Eight New Zealand White rabbits obtained from Birchwood Valley Farms (Red Wing, Minn.) were housed with Research Animal Resources at the University of Minnesota. All research conformed to the Guidelines of the National Institutes of Health for the Use of Animals in Research.

Four rabbits were made hyperthyroid by intraperitoneal injection of a sterile solution prepared at a concentration of 0.1 mg 3,5,3'-triiodothyroinine (T3) (Sigma, St. Louis, Mo.) in 1 mL of sterile isotonic saline every other day for 1 month. Rabbits received a dose of 0.2 mg/kg body wt. This dose was based on the standard protocol for producing clinical hyperthyroidism in laboratory animals.[6–11] At this point, significance was obtained in the morphometric analyses being performed. Baseline and treated levels of T3 and T4 were determined at 1 week, 2 weeks, 1 month, and at the time of euthanasia for control rabbits and for those receiving T3 injections. All animals showed significant elevations of T3 and T4 levels over baseline and over levels in control rabbits. As required by the institutional review board at the University of Minnesota, the rabbits were monitored daily for signs of hyperthyroidism including weight, food intake, water intake, diarrhea, and irritability. Rabbits were given access to food ad libitum. Rabbit weight dropped from an average of 2.23 kg to 1.37 kg (Fig. 1). The majority of the weight loss occurred within the first 2 weeks of treatment. The weight stabilized over the next 2 weeks of treatment, and during this interval the average weight of the treated rabbits fluctuated between 1.37 and 1.48 kg.

At the end of 1 month, the rabbits were euthanized with an overdose of barbiturate anesthesia. The eyelids were removed and placed in embedding molds containing tragacanth gum. The specimens were frozen in methylbutane and chilled to a slurry on liquid nitrogen. Serial sections at 12 μm were prepared in a cryostat in preparation for immunohistochemistry. Sections were immunostained for either fast, slow, neonatal, or developmental myosin heavy-chain (MHC) isoforms (NovoCastra Labs, Vector, Burlingame, Calif.). After incubation in blocking serum, the sections were incubated in the primary antibody for 1 hour at a dilution of 1:40 for the antibodies to fast and slow MHC isoforms and 1:20 for the antibodies to neonatal and developmental MHC isoforms. Control slides were processed by use of the same protocol except that the primary antibody step was omitted. These slides were negative for myosin staining. The sections were rinsed and incubated with the reagents of the Vectastain Elite ABC kit (Vector Labs, Burlingame, Calif.) containing biotin-avidin-peroxidase complexes. The reacted tissue sections were processed with the use of the heavy metal–intensified diaminobenzidine procedure.

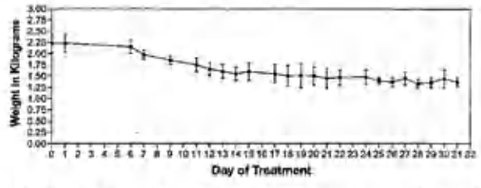

FIG. 1. Daily weights of adult rabbits during course of thyroid hormone treatments. Each point is the average of 4 treated rabbits (±SEM).

The individual muscle fibers were traced and quantified with the use of the Bioquant digitizing morphometry program (R and M Biometrics, Inc., Nashville, Tenn.) to determine the number of muscle fibers in each eyelid section. Previous studies have demonstrated that orbicularis oculi myofibers do not span from the medial to the lateral canthus[16,17]; thus eyelid samples were prepared from the medial, central, and lateral regions of each eyelid. All myofibers were individually traced in 3 different cross-sections in each of the three regions sampled. Since the orbital portion of the orbicularis oculi muscle is difficult to define, only the palpebral portion of the eyelids was counted. We defined the palpebral portion from the eyelid margin to the end of the palpebral conjunctiva. Averages were then obtained from the average number of myofibers in each of the 9 sections counted. The average of these was determined for the eyelids from the 4 control and 4 treated rabbits. Differential counts were made of the number of cross-sectional areas of myofibers positive for each of the three MHC isoforms examined (fast, slow, and neonatal myosin). These data were used to determine the percent positive for each myosin isoform from the total number of myofibers for that particular specimen. Averages were deter-

TABLE 1. *Palpebral orbicularis oculi fiber counts and area measurements*

Control fiber number	Hyperthyroid fiber number	Control fiber area	Hyperthyroid fiber area
2100	374	556	650
2259	577	600	576
1979	524	809	899
1880	368†	708	972†
2400	422†	677	910†
Mean = 2194	Mean = 453*	Mean = 670	Mean = 626
SEM = 94	SEM = 42	SEM = 44	SEM = 45

Hyperthyroid indicates hyperthyroid rabbit eyelid; Control, control rabbit eyelid.
*Statistically significant difference from control.
†Right and left lids of the same rabbit.

mined for each rabbit, and these were used to determine the averages of the 4 control and 4 experimental eyelids. Data were analyzed with the use of Prism software (Graphpad, San Diego, Calif.). Results were considered significantly different at $P<0.05$.

RESULTS

The eyelids from hyperthyroid rabbits had 79.4% fewer orbicularis oculi fibers compared with the control rabbit eyelids (Table 1 and Figs. 2 and 3). This was a statistically significant reduction ($P<0.05$). Almost all of the remaining muscle fibers were in the pretarsal region of the eyelids. Although myofiber number was reduced in the orbicularis oculi muscle from the hyperthyroid rabbits, the average myofiber cross-sectional area was not significantly different from control muscles (Table 1). The remaining myofibers within the orbicularis oculi muscle from the hyperthyroid rabbits showed an increase in the proportion that also expressed either slow myosin

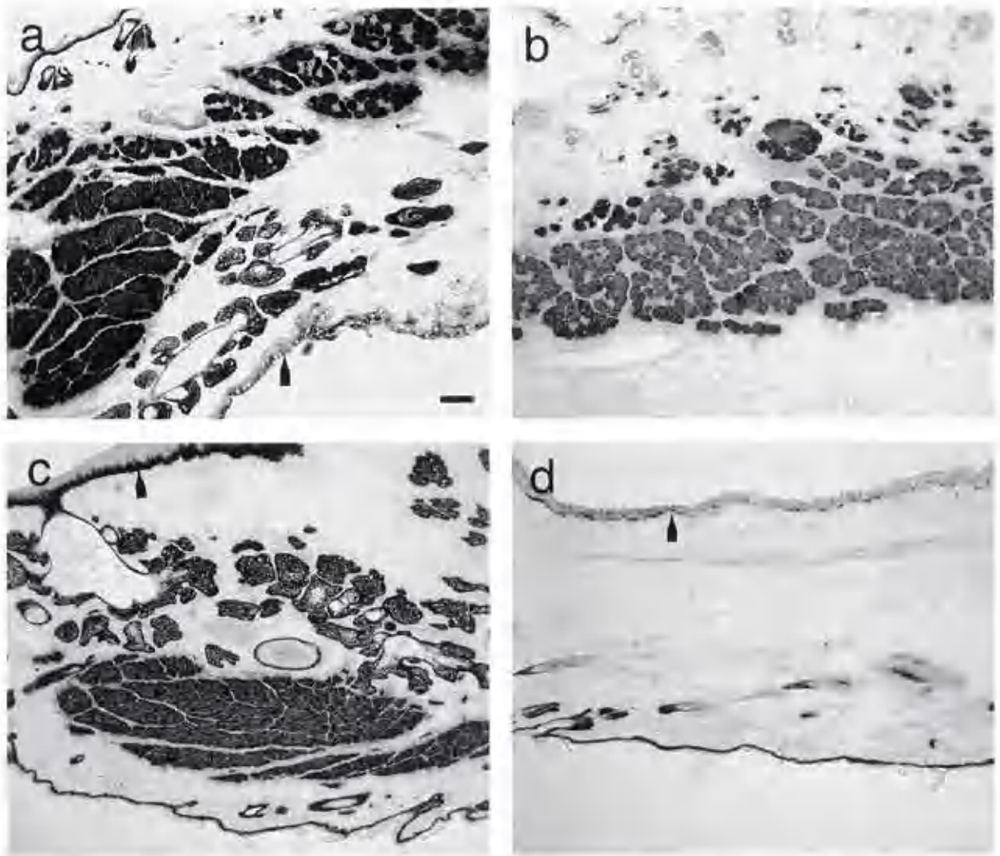

FIG. 2. Cross sections of the palpebral portion of rabbit eyelid stained with the alkaline myosin ATPase procedure. Fast myofibers stain dark in this procedure. **a,** control rabbit pretarsal orbicularis; **b,** control rabbit preseptal orbicularis; **c,** hyperthyroid rabbit pretarsal orbicularis; **d,** hyperthyroid rabbit preseptal orbicularis. All specimens are oriented with the eyelid margin to the left. Arrows indicate conjunctival surface of eyelids. Note reduction of the apparent number of myofibers in both pretarsal and preseptal portions of the hyperthyroid specimen. Although the preseptal portion of this eyelid was totally devoid of myofibers, eyelids from other hyperthyroid rabbits often retained scattered myofibers within this region. Bar is 100 μm.

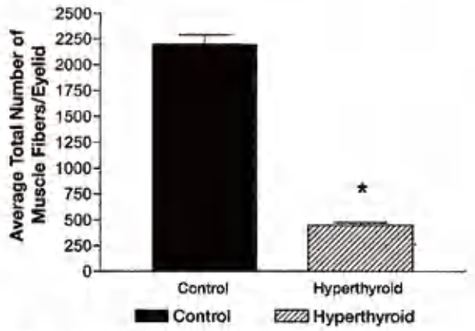

FIG. 3. Palpebral orbicularis oculi myofiber number in control and hyperthyroid rabbit eyelid sections. *Statistically significant.

or coexpressed both slow and fast myosin within single myofibers (Table 2 and Figs. 4 and 5). There was a trend toward increased expression of slow myosin in the pretarsal orbicularis oculi muscle, and this was statistically significant ($P<0.05$) in the preseptal muscle.

DISCUSSION

These results clearly demonstrate that elevated levels of thyroid hormone lead to significantly reduced numbers of palpebral orbicularis oculi muscle fibers after a 1-month period in rabbits. One possible mechanism is increased proteolysis induced by the hyperthyroidism, which has been previously demonstrated in a rat model.[18] Previous studies have shown other skeletal muscle dysfunction in human beings with hyperthyroidism secondary to Graves disease.[19] This finding was thought to be the result of elevated levels of thyroid hormone and circulating catecholamines. It is also interesting that elevated thyroid hormones were reported to hinder muscle repair and cause skeletal muscle atrophy in a mouse model of muscular dystophy.[20] This increase in thyroid hormone levels directly affects the energy metabolism of muscles, but in a muscle-specific manner.[7] In one study, the soleus muscle, composed largely of slow myofiber types, showed a significant alteration in energy metabolism, whereas the extensor digitorum longus, a muscle composed largely of fast myofiber types, did not.[7] However, neither of these muscles from the treated rabbits showed a decrease in myofiber number. These catabolic effects were seen in extraocular muscle as well, in which elevated thyroid hormones resulted in a decrease in muscle mass of approximately 50%.[21] Interestingly, recent studies demonstrated a direct effect of triiodothyronine on apoptosis in primary muscle cells in vitro.[22,23] These studies demonstrate the catabolic nature of elevated thyroid hormone and support our finding of orbicularis oculi myofiber loss in the hyperthyroid rabbit model in the current study.

Few studies have evaluated the effect of Graves disease on the orbicularis oculi muscle in human beings. Frueh et al.[24] evaluated the posterior force generated by the eyelid protractors of patients with Graves disease and found it to be significantly lower than that found in normal eyelids. They postulated that orbicularis atrophy was occurring in the patients with Graves disease, probably secondary to chronic eyelid inflammation. This study supports our finding of significant orbicularis oculi myofiber loss in hyperthyroid rabbits. Oestreicher and Frueh[25] found that the elastic modulus of orbicularis in patients with thyroid-associated eye disease was similar to that in normal patients. These results supported the fact that there was no functionally significant fibrosis

TABLE 2. *Myosin heavy chain expression in orbicularis oculi muscle from control and hyperthyroid rabbits*

	Percentage of myofibers positive for each MHC ± SEM	
	Pretarsal orbicularis	Preseptal orbicularis
Fast control	96.00 ± 0.500	76.50 ± 0.500
Fast hyperthyroid	98.70 ± 0.480	96.50 ± 0.808*
Slow control	4.0 ± 0.200	23.5 ± 0.800
Slow hyperthyroid	8.92 ± 3.97	61.167 ± 10.164*
Neonatal control	22.90 ± 0.176	37.60 ± 0.580
Neonatal hyperthyroid	28.00 ± 9.096	37.70 ± 4.000

Percentages do not add up to 100% because muscle fibers coexpress more than one MHC isoform.
*Statistically different from control eyelids.

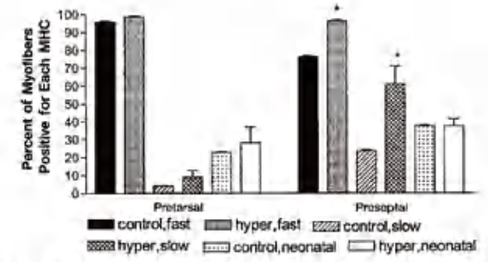

FIG. 4. Myosin heavy chain (MHC) isoform content of all myofibers within orbicularis oculi muscles from both control and hyperthyroid rabbits, including both pretarsal and preseptal regions. *Statistically different from control eyelids. Each bar represents data from 4 eyelids (mean ± SEM).

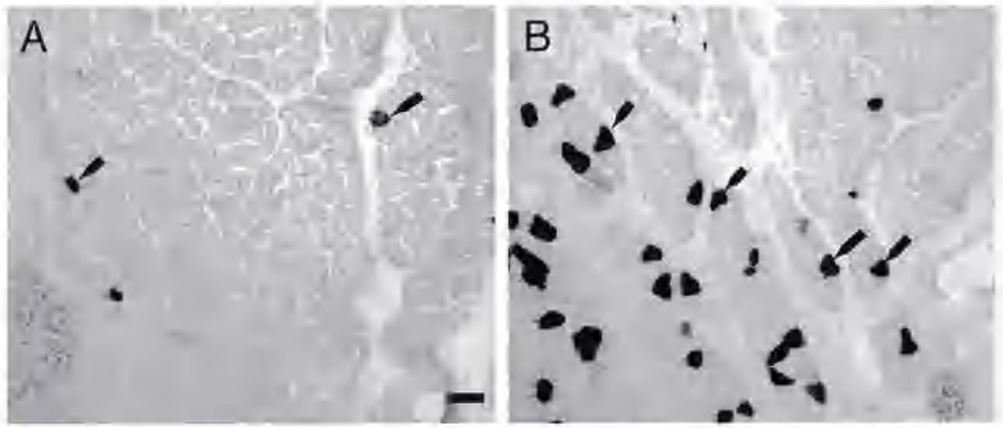

FIG. 5. Serial sections indicating coexpression of myosin heavy chain (MHC) isoforms in individual myofibers from the pretarsal region of the orbicularis oculi of **A,** control, and **B,** hyperthyroid rabbit eyelid. Cross sections are immunostained for slow MHC. Arrows indicate myofibers positive for slow MHC. Bar indicates 100 μm.

within the orbicularis muscle in these patients. Our specimens also showed no signs of fibrosis in the orbicularis oculi muscle and surrounding eyelid tissue.

Retraction of the upper eyelid in thyroid eye disease is a well-described clinical finding without a singular pathophysiologic explanation. Multiple authors have suggested a variety of mechanisms including increased sympathetic tone in the Müller and levator muscles,[26] levator muscle contraction and fibrosis, abnormal adhesions between levator muscle and orbital connective tissue and fat,[27] levator muscle hypertrophy,[24,28] and fixation duress secondary to inferior rectus restriction.[29,30] No correlation was shown between the amount of eyelid retraction and enlargement of the levator/superior rectus complex.[5,31] We believe another factor that may contribute to upper eyelid retraction is weakness of the antagonist protractor muscle, that is, the orbicularis oculi. Although not directly determined, a previous study supports this hypothesis as well.[24]

Our study does not address the finding of eyelid retraction in patients with euthyroid Graves opthalmolopathy. Although patients with no prior history of treatment for hyperthyroidism make up 8% to 21% of the patients with Graves ophthalmopathy, it has been demonstrated that between 22% and 88% of these patients have a palpable thyroid abnormality.[32] Another 62% of these patients have blunted responsiveness to thyroid-stimulating hormone.[32] Thus, although thyroid hormone abnormalities of these patients may be subtle, one cannot easily preclude thyroid-associated abnormalities in what otherwise appears to be euthyroid patients. Finally, eyelid retraction probably is a multifactorial process, of which orbicularis oculi weakness is one factor.

Of the myofibers that remained in the eyelids of the hyperthyroid rabbits, many coexpressed fast and slow MHC isoforms. Normal orbicularis oculi is composed primarily of fast-myofibers.[17] An increased percentage of myofibers expressing slow myosin would result in muscles that are more fatigue-resistant and have slower contractile properties, which may correlate with the development of eyelid lag seen in patients with Graves ophthalmopathy.

The effect of elevated thyroid hormone levels has been studied in other animal adult skeletal muscles with various results. In soleus, a muscle containing largely slow myofibers, elevated thyroid hormone levels resulted in a shift to an increased number of myofibers positive for fast myosin in rats.[12,13] In plantaris, a muscle containing large fast myofibers, elevated thyroid hormone resulted in a shift to increased numbers of slow myofibers in rats.[14] In other muscles, elevated thyroid hormone levels caused changes in expression of all 6 genes in the MHC multigene family, and the same MHC gene could be regulated in different directions in different muscles.[15] Thus, there is precedence in the literature for elevated levels of thyroid hormone to cause MHC isoform transitions like those in the current study.

Clearly, the rabbit model that we used does not perfectly parallel the changes in Graves orbitopathy. This complex autoimmune inflammatory response is not the same as simple hyperthyroidism. Since there is currently no animal model of Graves orbitopathy, we chose to study the orbicularis oculi in hyperthyroid animals because the majority of patients with Graves disease have hyperthyroidism during the course of their illness. Previous studies have demonstrated the use of the hyperthyroid rabbit model.[10,11] An animal model of hyperthyroidism has been used to study the eyelid changes seen in patients with Graves orbitopathy.[6] It is evident from our study that hyperthyroidism itself may lead to significant changes in the orbicularis oculi muscle. The development of eyelid retraction in patients with Graves disease is probably due to a multifactorial effect of elevated thyroid hormones on the orbicularis oculi, Müller muscle, and the levator muscle. In the future, we plan to examine the orbicularis oculi muscle from patients with Graves disease.

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ASOPRS oculofacial surgeon practice distribution and neighborhood deprivation

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Abstract

Purpose: This study explores the relationship between the distribution of active American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) oculofacial surgeons in the United States and the socioeconomic characteristics of their practice locations, as measured by the Area Deprivation Index (ADI).

Methods: In this cross-sectional study, active ASOPRS oculofacial surgeons in the United States were identified using the Oculofacial Society surgeon directory. Data on physician demographics, career stage, and practice type and location were compiled from publicly available sources. The ADI was extracted for each practice address. Chi-squared testing was performed for qualitative analysis.

Results: Overall, 580 physician addresses had obtainable state and national ADI values. The average ADI state decile was 3.5 and average national percentile was 29.9. The majority of surgeons (58.4%) practiced within the first state decile and national percentile quartile (*i.e.*, the lowest socioeconomic disadvantage). Practice locations in 41 states had average state decile values categorized as "low", while practice locations in 36 states had average national percentile values categorized as "low." There was no statistically significant difference between male and female presence, career stage, and practice type in low versus high ADI areas.

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Conclusion: The majority of ASOPRS oculofacial surgeons practice in neighborhoods with less socioeconomic disadvantage, as indicated by lower ADI state deciles and national percentiles, potentially contributing to healthcare disparities. Further research is warranted to understand other factors that may contribute to the ADI distribution of physicians and the role of ADI in pinpointing health care inequities.

Keywords: area deprivation index, health equity, neighborhood disparity, oculofacial, surgeon distribution

Introduction

With a growing aging population and expanding urban-rural gap, geographic disparities in provider distribution may impact access to eye care.[1-3] Proximity to and ability to afford or reliably access care may particularly affect patients requiring oculofacial surgeon services, given the subspecialty's small size.[2] Prior research demonstrates that social determinants of health (*i.e.*, non-medical factors, such as environment, education, employment, and access to resources, that may have a significant impact on a person's health) further contribute to discrepancies in access to oculofacial care, with one study showing that counties with lower income, lower cost of living, and limited access to the internet were less likely to have access to an oculofacial surgeon.[4]

As one of the primary determinants impacting health outcomes is an individual's residential neighborhood, health interventions and policies that fail to account for neighborhood disadvantage may inadequately or incompletely address the issue.[5] The Area Deprivation Index (ADI) is a validated scientific tool that combines 17 social determinants of health measures to provide a quantitative value that can be utilized to evaluate the socioeconomic disadvantage of a United States census block group, the smallest geographic division for which the United States census provides data.[6] Research thus far utilizing ADI has shown that greater neighborhood disadvantage is associated with increased hospital readmission rates, increased risk of mortality from COVID-19, and decreased clinic attendance after surgery.[7-9]

Consideration of socioeconomic disadvantage in surgeon practice location, rather than individual patient-level factors or large geographic trends, may allow for identification of inequities in access to oculofacial care in the United States. This study explores the relationship between the distribution of active oculofacial surgeons in the United States and the socioeconomic characteristics of their practice locations, as measured by the ADI. It also considers potential strategies for mitigating these disparities.

Methods

In this cross-sectional investigation, active American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) oculofacial surgeons in the United States, as of December 2024, were identified using the Oculofacial Society surgeon directory.[10] Data on physician demographics, career stage, and practice type was compiled from publicly available sources, which included the American Academy of Ophthalmology, Castle Connolly, LinkedIn, US News Health, and physician's institutional websites.[11-14] Physicians were categorized as early- (0–10 years), mid- (11–20 years), or late-career (20 or more years) based on years in practice after oculoplastic fellowship completion. Practice address, including state and zip code, was compiled from the listed address on the Oculofacial Society surgeon directory.

ADI is a mapping tool which considers 17 different measures, including metrics of income, housing quality, education, and employment to rank neighborhoods by socioeconomic disadvantage based on United States Census Blocks. The Neighborhood Atlas is a compiled database, with data from 2017–2022, created by the University of Wisconsin Madison to identify the ADI for any given United States address.[6] When an address is inputted into the Neighborhood Atlas, its neighborhood is given both a state decile (1–10) and a national percentile (1–100), with lower values indicating areas with less disadvantaged block groups. In areas of high group quarters (such as on college campuses, residential treatment centers, group homes, correctional facilities, or military barracks), low population, low housing, or questionable data integrity, the ADI tool delivers a result of "Suppression" and the reason for suppression. Suppressed values of ADI were excluded from this analysis.

Using the physicians' practice addresses, state decile and national percentile ADI values were obtained. These values were organized into quartiles at the state (1–3, 4–5, 6–7, 8–10) and national (1–25, 26–50, 51–75, 76–100) levels. Additionally, ADI values were categorized as "low" (state 1–5 or national 1–50) and "high" (state 6–10 or national 51–100) for comparison with qualitative factors. Mean and range of state decile and national percentiles were calculated for each state. Chi-squared analysis was performed for qualitative analysis of ADI's relation to gender, physician training length, and practice type in Microsoft Excel. Significance was determined as $p < 0.05$.

Results

The Oculofacial Society surgeon directory identified 660 active ASOPRS oculofacial surgeons in the United States. Among these surgeons, 80 practice locations received a "Suppressed" result from the tool—indicating areas of high group quarter populations, low population, low housing, or questionable data integrity—and were removed from analysis, leaving a total of 580 physician practice addresses with extractable state and national ADI values.

The average ADI state decile for oculofacial surgeon practice location was 3.5 and average national percentile was 29.9 (Table 1). The majority of surgeons (58.4%) practiced within the lowest state decile quartile (*i.e.*, the lowest socioeconomic disadvantage). This trend was reflected in the national percentiles as well, with 50.3% of practice locations in the lowest quartile. There was a statistically significant difference between the number of oculoplastic surgeons in low versus high ADI settings at the state (75.5% vs. 24.4%, χ^2=151.04, $p < 0.001$) and national levels (79.7% versus 20.3%, $\chi^2 = 204.4$, $p < 0.001$).

Overall, 46 states (including the District of Columbia) had at least 1 active ASOPRS oculofacial surgeon listed in the Oculofacial Society surgeon directory (Appendix); Montana, Wyoming, North Dakota, South Dakota, and New Mexico did not have any listed oculofacial surgeons. Alaska, District of Columbia, Iowa, and Oklahoma comprised the states with oculofacial surgeon practice locations at the lowest state decile (state decile = 1) and Rhode Island and Hawaii represented the states with oculofacial surgeon practice locations at the highest state decile (state decile = 10). Provider location in District of Columbia was associated with the lowest national percentile at 1, while provider locations in Rhode Island, Maine, and Arkansas were associated with the 3 highest national percentiles, at 86.0, 76.0, and 70.7, respectively. Practice locations in 41 states had average state decile values categorized as "low" (less than or equal to 5) and practice locations in 36 states had average national percentile values categorized as "low" (less than or equal to 50).

There was no statistically significant difference between male and female presence in low vs. high ADI areas at both state ($\chi^2 = 0.172$, $p = 0.678$) and national ($\chi^2 = 0.781$, $p = 0.377$) levels (Table 2). Additionally, physician designation of early-, mid-, or late-career had no statistically significant relationship with their likelihood of practicing within low versus high ADI areas at both the state ($\chi^2 = 2.157$, $p = 0.342$) and national ($\chi^2 = 0.629$, $p = 0.730$) levels. Finally, practice type had no statistically significant relationship with low versus high ADI areas at the state ($\chi^2 = 3.833$, $p = 0.147$) and national level ($\chi^2 = 3.336$, $p = 0.189$).

Discussion

Oculofacial surgeons are significantly more likely to practice in areas of low neighborhood deprivation, as verified by ADI value analysis, both within an individual state and across the country. Surgeon demographic factors, such as gender and career stage, and practice type had no significant impact on a surgeon's likelihood of practicing in a low versus high ADI area. These results are concordant with prior reports noting a higher oculofacial surgeon concentration in urban areas and an association between lower socioeconomic status and less access to oculofacial surgeon care.[3,4]

Table 1. Number and proportion of ASOPRS oculofacial surgeon practice locations by Area Deprivation Index state and national quartiles

Area Deprivation Index metric	Number and proportion of surgeons, *N* (%)
State quartile	
1 (1–3.25)	339 (58.5)
2 (3.25–5.5)	99 (17.1)
3 (5.5–7.75)	76 (13.1)
4 (7.75–10)	66 (11.4)
National quartile	
1 (1–25.75)	292 (50.3)
2 (25.75–50.5)	170 (29.3)
3 (50.5–75.25)	89 (15.3)
4 (75.25–100)	29 (5.0)

Table 2. Physician demographics and practice type by practice location Area Deprivation Index

Variable	Average State Decile	Average National Percentile
Gender		
Male	3.5	30.6
Female	3.5	28.4
Career stage		
Early-career	3.6	30.0
Mid-career	3.6	29.7
Late-career	3.4	30.2
Practice Type		
Private practice	3.5	29.9
Academic	3.9	33.4
Private and academic	3.0	25.3
Military	6.0	45.0

Socioeconomic deprivation has been associated with lower access to cataract surgery, negatively impacted visual outcomes after viral retinitis and retinal detachment, and lower rates of glaucoma testing, highlighting the need to consider this social determinant of health within the field of ophthalmology.[15–17] Among oculoplastic concerns, multiple studies have found significant connections between socioeconomic status and patient health outcomes. One study found that higher socioeconomic status, private insurance, and treatment at a high-volume facility were all factors that significantly influenced 10-year-survival in eyelid melanoma patients.[18] When managing facial trauma concerns, a study found that patients with private insurance were more likely to receive an ophthalmology consult than those without.[19] Another study found that higher annual income, employment, and higher educational level were associated with less risk of eye loss after ocular tumor and trauma.[20,21] Socioeconomic status of patients must be a factor of consideration throughout the clinic, perioperative, and postoperative evaluation for patients utilizing oculoplastic services. The current lack of oculoplastic surgeon presence in areas of higher neighborhood deprivation may represent a notable cause of disparities in care outcomes as already vulnerable populations have less access to key services, potentially impacting their visual, eye health, and mortality outcomes.

Developing strategies to mitigate these distribution discrepancies is imperative. As observed, oculofacial surgeons tend to practice in areas of low ADI or high affluence. This may, in part, be a result of desired area of private residence, target patient population, higher patient volumes, and access to large hospital systems and referring providers. In the literature, described strategies to promote practice migration or involvement to areas of higher ADI include increasing reimbursements for oculoplastic procedures, increasing patient understanding and education of offered services, and building robust telehealth connections.[4] Increasing and/or optimizing reimbursements may provide surgeons with an incentive to establish practice locations in areas of greater neighborhood disadvantage.[22] Expanding patient education on periocular pathologies and highlighting the importance of targeted care for qualifying individuals could encourage use of oculoplastic services and allow for expansion of geographic impact; utilization of social media may also play a role in increasing visibility to a larger and more diverse audience of patients.[23,24] An additional technological solution includes telemedicine, an often-proposed strategy to bridge the gap of requiring transportation and time to meet with a provider. Postoperative visits, functional non-surgical evaluations, eyelid lesion evaluations, and eyelid malposition assessments are a few of the potential visit categories that could be addressed during a telemedicine encounter.[25] Notably, the communities that may benefit the most from telehealth visits are often less likely to have access to the internet or have knowledge on how to utilize these services.[26] Infrastructure to improve patient access to telehealth technology and education on how to navigate services could be one strategy to alleviate these concerns. Community centers for computer access in private areas or use of image-based

eyelid lesion management services, which could enroll community-based optometrists for image procurement, are potential ideas.[27] Finally, there is an area of opportunity for the creation of a curriculum within the ASOPRS framework for education on health disparities within the field. Such a curriculum could highlight the impact of social determinants of health, such as income, access to transportation, food security, or housing, on patient considerations and outcomes in clinic and surgical settings.[28,29]

This investigation has several limitations. Active oculofacial surgeons and their practice locations in the United States were identified using the Oculofacial Society surgeon directory. Errors in data reporting or data extraction may influence the reported distribution and representation of surgeons. Further, surgeons may practice at additional locations not listed in the database or change their location mid-practice, limiting a complete analysis of geographic distribution. The Neighborhood Atlas was last updated in 2022 and has compiled information from the 5 preceding years, 2017–2022, which may not fully represent geographic trends. Finally, ADI was used as a proxy for neighborhood deprivation and socioeconomic status in this study. Although individual and regional variation is possible, it is a validated tool and has the advantage of including multiple factors such as education, employment, income, and housing quality.

Conclusion and future perspectives

The majority of ASOPRS oculofacial surgeons practice within neighborhoods with less socioeconomic disadvantage, as indicated by lower ADI state deciles and national percentiles, potentially contributing to healthcare disparities. Demographic factors such as gender, career stage, and practice type are not correlated with choice of practice location neighborhood deprivation. Further research is warranted to understand other factors that may contribute to the geographic distribution of physicians and the role of ADI in pinpointing health care inequities.

Declarations

Ethics approval and consent to participate
None required.

Competing interests
None to declare.

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Appendix

A. Deprivation index state and national metrics by state

State	Min state decile	Max state decile	Average state decile	Min national percentile	Max national percentile	Average national percentile
Alabama	2	10	4.0	47	99	61.8
Alaska	1	1	1.0	6	6	6.0
Arizona	2	10	4.3	19	100	38.9
Arkansas	2	8	4.3	54	92	70.7
California	1	10	3.4	1	71	10.8
Colorado	1	10	4.7	6	99	26.5
Connecticut	1	10	3.5	1	76	26.1
Delaware	1	9	5.3	17	63	42.0
District of Columbia	1	1	1.0	1	1	1.0
Florida	1	8	4.1	3	69	37.3
Georgia	1	8	3.0	8	99	37.9
Hawaii	10	10	10	39	39	39.0
Idaho	1	8	4.2	12	57	35.0
Illinois	1	9	3.3	9	90	37.3
Indiana	1	7	2.0	6	80	22.0
Iowa	1	1	1.0	16	35	29.5
Kansas	1	4	2.0	11	63	34.4
Kentucky	1	8	3.3	30	91	52.7
Louisiana	1	3	1.8	5	56	27.3
Maine	8	8	8.0	76	76	76.0
Maryland	1	8	5.0	2	55	30.8
Massachusetts	1	10	4.4	2	81	20.8
Michigan	1	6	3.5	29	74	51.4
Minnesota	1	9	5.3	12	71	44.7
Mississippi	1	2	1.3	12	62	42.3

ASOPRS practice distribution

State	Min state decile	Max state decile	Average state decile	Min national percentile	Max national percentile	Average national percentile
Missouri	1	10	2.6	6	97	37.1
Nebraska	2	7	4.0	40	73	55.7
Nevada	2	4	3.0	22	30	26.0
New Hampshire	1	7	3.8	15	49	31.0
New Jersey	1	8	3.6	1	44	18.8
New York	1	9	3.3	1	80	17.8
North Carolina	1	10	2.8	9	98	34.9
Ohio	1	6	2.5	16	74	40.9
Oklahoma	1	1	1.0	23	41	32.0
Oregon	1	7	2.5	7	40	15.7
Pennsylvania	1	9	2.7	2	88	34.6
Rhode Island	10	10	10	86	86	86.0
South Carolina	1	5	2.8	9	64	39.8
Tennessee	1	7	4.5	23	76	57.3
Texas	1	10	2.6	1	96	28.7
Utah	5	9	6.9	30	46	37.8
Vermont	7	7	7.0	57	57	57.0
Virginia	1	7	3.2	3	57	23.9
Washington	1	9	4.8	1	45	20.7
West Virginia	2	2	2.0	60	60	60.0
Wisconsin	1	7	3.3	7	67	38.9
Total	**1**	**10**	**3.5**	**1**	**100**	**29.9**

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Artificial intelligence in practice: measuring its medical accuracy in oculoplastics consultations

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Abstract

Purpose: The aim of this study was to investigate the medical accuracy of responses produced by Chat Generative Pretrained Transformer 4 (Chat GPT-4) and DALLE-2 in relation to common questions encountered during oculoplastic consultations.
Methods: The 5 most frequently discussed oculoplastic procedures on social media were selected for evaluation using Chat GPT-4 and DALLE-2. Questions were formulated from common patient concerns and inputted into Chat GPT-4, and responses were assessed on a 3-point scale. For procedure imagery, descriptions were submitted to DALLE-2, and the resulted images were graded for anatomical and surgical accuracy. Grading was completed by 5 oculoplastic surgeons through a 110-question survey.
Results: Overall, 87.3% of Chat GPT-4's responses achieved a score of 2 or 3 points, denoting a good to high level of accuracy. Across all procedures, questions about pain, bruising, procedure risk, and adverse events garnered high scores. Conversely, responses regarding specific case scenarios, procedure longevity, and procedure definitions were less accurate. Images produced by DALLE-2-were notably subpar, often failing to accurately depict surgical outcomes and realistic details.
Conclusions: Chat GPT-4 demonstrated a creditable level of accuracy in addressing common oculoplastic procedure concerns. However, its limitations in handling case-based scenarios suggests that it is best suited as a supplementary source of information rather than a primary diagnostic or consultative tool. The current state

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of medical imagery generated by means of artificial intelligence lacks anatomical accuracy. Significant technological advancements are necessary before such imagery can complement oculoplastic consultations effectively.

Keywords: artificial intelligence, Chat GPT, DALLE, oculoplastics, patient information

1. Introduction

In recent years, the demand for oculoplastic services and related educational resources has significantly increased across the United States.[1] In accordance with this trend, the American Society of Ophthalmic Plastic and Reconstructive Surgery has produced patient education brochures on many oculoplastic conditions and pathologies to inform patients of their diagnoses and treatment options. However, studies demonstrate that these resources and other online oculoplastic educational materials may be written at inappropriate reading levels and demonstrate low accountability.[2,3]

Prospective oculoplastics patients often resort to social media platforms to review and discuss various cosmetic and reconstructive surgeries.[4,5] In today's digitally connected world, social media has emerged as a primary source of information for individuals seeking health advice, second opinions, and information about physicians. However, the prevalence of misinformation and unreliable sources on social media platforms may misguide patients, potentially leading them away from making scientifically and medically informed decisions.[5]

The Chat Generative Pretrained Transformer 4 (Chat GPT-4) is the latest artificial intelligence (AI) chatbot developed by OpenAI, an AI research laboratory. This large language model leverages deep-learning neural network software to generate contextually relevant responses to user prompts, basing its responses on a vast majority of digitally accessible, text-based information up to its last training date, September 2021. Chat GPT-4's ability to generate detailed responses to complex inquiries has propelled it to become the fastest-growing consumer application in history.[6] Given its increasing popularity, it is anticipated that patients will likely resort to Chat GPT-4 for medical advice.

Prospective patients also often query social media and other websites to view before-and-after procedure photographs, which are cited as one of the most influential factors in deciding whether to undergo a procedure.[7] Some patients may soon turn to generative AI models like DALLE-2—a text-to-image AI system developed by OpenAI—to create novel before-and-after photographs.

To the authors' knowledge, there has not yet been an investigation into the medical accuracy of responses generated by Chat GPT-4 and DALLE-2 with regards to oculoplastics concerns. In this study, we present an analysis of Chat GPT-4-generated responses regarding the 5 most commonly discussed oculoplastics procedures and evaluate the accuracy of AI-generated pre- and post-procedure photographs, aiming to assess the medical accuracy of OpenAI technology.

2. Methods

Based on a cross-sectional study by Schmuter *et al.*,[3] we selected the top 5 most frequently discussed oculoplastic procedures on social media to represent the topics most likely to be queried on Chat GPT-4. These procedures included facial filler, botulinum toxin injection, lower blepharoplasty, upper blepharoplasty, and ptosis repair. For each procedure, 9 categories of prompts were formulated based on common patient questions or concerns during clinic encounters. Four prompts corresponded to preoperative assessment questions (*e.g.*, related to procedure definition, risks, cost, and condition etiology), 4 related to postoperative outcome inquiries (*e.g.*, related to procedure pain, bruising, scarring, and longevity), and one was a case-based question. All prompts were written from the patient's perspective.

All questions were posed to Chat GPT-4 in a new session to mitigate any potential learning or contextualization from previous queries. This approach was used to simulate a first-time interaction for each question. To account for variability and randomness in responses, each question was inputted into Chat GPT-4 twice. Each output was recorded for analysis. Responses were evaluated based on a 3-point grading scale:

- 3 points for detailed and highly accurate answers that covered all aspects of the question.
- 2 points for answers that were mostly accurate but may have minor omissions.
- 1 point for those that provided some accurate information but missed several key points.
- 0 points for answers that were largely inaccurate or failed to address important aspects of the question.

To evaluate the accuracy of AI-generated procedure imagery, a short, nonspecific, text description of an image was written for each procedure. The descriptions varied between before-and-after photos and postoperative recovery images. The prompts were submitted to DALLE-2 in independent sessions, and it produced 4 images corresponding to the given description. The 4 images were submitted for analysis and graded on a 3-point scale:

- 3 points for accurate, clear, and anatomically realistic representations of surgical outcomes.
- 2 points for adequate depictions with satisfactory anatomical realism.
- 1 point for limited or vague portrayals with minimal anatomical accuracy.
- 0 points for images that inadequately represented the surgical outcome.

A 110-question, web-based, point-based survey was created using Google Forms (Alphabet Inc., Mountain View, CA, USA) and distributed by e-mail to 5 oculoplastic surgeons certified by the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). These surgeons independently assessed the suitability of all 90 Chat GPT-4 responses and 20 DALLE-2 images, producing a total of 550 evaluations. The survey data was collected in an anonymous fashion. The statistics were performed using DATAtab: Online Statistics Calculator (datatab.net, Graz, Austria).[8] When applicable, the alpha level was selected to be 0.05.

We calculated the overarching percentages of scores attributed to all questions and the scoring distribution by procedure. A detailed breakdown by prompt category for each procedure was evaluated to highlight specific areas of strength or concern in Chat GPT-4 responses. Inter-rater reliability among the oculoplastic surgeons was assessed using Kendall's coefficient of concordance, a measure well suited for ordinal data such as our 3-point grading scale. To determine if there were consistent differences between 2 sets of responses, the Wilcoxon test was used to analyze the variability of scores from duplicate Chat GPT-4 responses. The Jaccard similarity coefficient, calculated using an online algorithm from Tilores (tilores.io, Berlin, Germany), quantified the text similarity of the duplicated responses from Chat GPT-4.[9] Finally, the Friedman test compared the scores across images generated by DALLE-2 to determine whether there were notable differences in ratings for images associated with the same prompt. This study design did not require ethics review by an institutional review board.

3. Results

The full list of question and image prompts, and associated responses, can be accessed in the Appendix. A summary of average scores for Chat GPT-4 and DALLE-2 responses to the prompts utilized in this investigation is provided in Table 1.

Of the 450 evaluations of Chat GPT-4 responses, 172 evaluations (38.2%) received a score of 3 points, while 221 evaluations (49.1%) received a score of 2 points, 52 evaluations (11.6%) received a score of 1 point, and 5 evaluations (1.1%) received a score of 0 points.

Overall, Chat GPT-4 scores were comparable for all procedures, ranging between 2.13 and 2.38 points. The highest average score pertained to the answer given regarding upper blepharoplasty pain and bruising (2.7 points), while the lowest score was associated with a facial filler case-based question (0.9 points). Chat GPT-4 scored the highest on prompts addressing "procedure pain" (2.52 points), "risks/adverse events" (2.4 -points), and "procedure bruising" (2.46 points). In contrast, prompts related to "case scenarios" (1.80 points), "procedure longevity" (2.02 points), and "procedure definition" (2.12 points) received the lowest average scores (Table 1).

Table 1. Chat GPT-4 prompt category and procedure average scores (0–3 points)

Procedure	Facial filler	Botulinum toxin injection	Lower blepharoplasty	Upper blepharoplasty	Ptosis repair	**Category average score**
Prompt category						
Procedure definition	2.3	1.9	2.2	2.2	2.0	2.12
Risks/adverse events	2.6	2.2	2.5	2.6	2.4	2.46
Etiology of condition	2.4	2.1	2.2	2.6	2.4	2.34
Cost of procedure	2.4	2.3	2.1	1.9	2.4	2.22
Procedure pain	2.6	2.4	2.5	2.7	2.4	2.52
Procedure bruising	2.4	2.4	2.5	2.7	2.3	2.46
Procedure scarring	2.2	2.5	2.4	2.5	1.7	2.26
Procedure longevity	2.4	1.7	2.3	1.8	1.9	2.02
Case scenario	0.9	1.8	2.2	2.4	1.7	1.80
Procedure average score	2.24	2.14	2.32	2.38	2.13	

The same responses were evaluated by multiple reviewers. Inter-rater reliability analysis revealed a Kendall's coefficient of concordance of 0.57, indicating moderate agreement among the reviewers.

A Wilcoxon test determined the consistency of Chat GPT-4's responses. There was no significant difference between the scores for the first and second set of responses for the same question ($W = 1149$, $p = 0.77$), highlighting the stability of Chat GPT-4's responses. The Jaccard similarity coefficient further emphasized this consistency ($J = 0.84$), indicating that 84% of the observed attributes overlapped between the 2 response sets.

For image-generator prompts, 4 unique images were generated from each submission. As an example, DALLE-2's image-generated interpretation of the prompt, "Full face before-and-after photos of a 50-year-old person who underwent tear trough filler" is viewable in Figure 1. Of the 100 total evaluations, the overall

Fig. 1. DALLE-2's image-generated interpretation of the prompt "Full face before-and-after photos of a 50-year-old person who underwent tear trough filler."

Table 2. DALLE-2 image set average scores (0–3 points)

Procedure	Facial filler	Botulinum toxin injection	Lower blephar-oplasty	Upper blephar-oplasty	Ptosis repair	Total average score
Image Set Average Score	0.50	0.45	0.70	0.45	0.25	0.47

average score was 0.47 points, with individual image sets ranging from 0.25 to 0.70 points (Table 2).

A Friedman test assessed score differences across the 4 images within each prompt. It revealed no significant score variations among images from the same prompt ($p > 0.05$ for all), indicating consistent reviewer perceptions of the images' realism.

5. Discussion

As interest in AI integration within the broader healthcare system increases, understanding its capabilities and limitations is vital to prevent potential misinformation leading to confusion or harmful outcomes. The efficiency and convenience of Chat GPT-4 has contributed to its rapid adoption, but its trustworthiness to provide accurate medical information remains under scrutiny. This survey aimed to evaluate the accuracy and reliability of OpenAI technology in answering common oculoplastic procedure questions and expand upon its potential application in the clinical setting. It is also the first cross-sectional study assessing the accuracy of pre- and post-procedure, AI-generated images.

Overall, the vast majority (87.3%) of Chat GPT-4's responses achieved a score of 2 or 3 points, denoting a good to high level of accuracy, with minor omissions of essential details. Comparable scores were also found for the overall average response scores of each procedure. This suggests that Chat GPT-4 has the potential to provide fairly accurate general medical information. It may serve as a valuable resource for information in regions lacking immediate medical expertise.

Across the literature, several surveys have assessed the accuracy of Chat GPT's responses to medical questions, often employing a point-system or Likert-scale for evaluation. These studies commonly state that the AI-generated responses are generally of acceptable quality. Reported rates of Chat GPT-4 answers scoring "appropriate", "very good," or "good" in other studies ranged from 73% to 96%.[10-16] The results of this survey align with these rates, which highlight Chat GPT-4's potential as a supplementary resource for healthcare professionals and as an educational aid for patients. However, these studies, including our own, have identified instances of misinformation, suggesting a need for vigilant verification of AI-generated content. The consensus among researchers is that AI-generated information requires additional validation studies on accuracy and patient safety before its integration into clinical practice can proceed.

The highest scored responses pertained to anticipated pain and bruising for upper blepharoplasty (2.7 points). Across all procedures, prompts related to pain and bruising scored high (2.52 and 2.46 points, respectively), as did prompts regarding procedure risks and potential adverse events (2.46 points). The higher scores in these areas may result from a higher quantity and standardization of

associated data pertaining to these topics in the medical literature. As pain, bruising, and risks of a procedure are common concerns for patients, Chat GPT-4's accuracy in these areas is reassuring; this platform may be able to effectively provide basic information in these areas.

On the other hand, responses regarding specific case scenarios (average score of 1.80 points), procedure longevity (2.0 points), and procedure definition (2.12 points) received the lowest scores. The poor performance with specific case scenarios highlights Chat GPT-4's limitations and the ongoing necessity for human medical judgment and regulation. In the majority of cases, Chat GPT-4 avoided directly answering the patients' question, instead offering general information and suggesting that the patient pursue a professional consultation. Recommendations for patient-specific scenarios require nuanced insights, which at this moment appear to be a limitation in Chat GPT-4's skill set.

Chat GPT-4 is designed to introduce variability in responses to identical inputs. This is due to the inherent randomness introduced during the sampling process when the model produces outputs. Both the Wilcoxon test and the Jaccard similarity coefficient offered a multidimensional perspective on the consistency and similarity of Chat GPT-4's outputs. The Wilcoxon test found no significant difference in scores given by reviewers between the first and second response to a prompt ($W = 1149$, $p = 0.77$), and a Jaccard similarity coefficient of 0.84 implied that 84% of the textual content of the paired responses overlapped. This consistency enhances the reliability of Chat GPT-4 and assures patients and medical professionals that repeated inquiries would yield similar quality responses.

Overall, DALLE-2's AI-generated images scored low; the average score among all images was 0.47 points. The average score for the 5 image sets ranged from 0.25 points to 0.70 points. These images failed to depict accurate surgical outcomes and lacked realistic detail. Given the importance of before-and-after images in setting patient expectations, this finding highlights a gap in DALLE-2's present capabilities. Common shortcomings of these photos included failure to show all relevant aspects of the face, failure to maintain ipsilaterality for linked images, and reversal of the order of before-and-after photos. Patients relying on such images to make an informed decision may be misled by portrayed surgical outcomes or postoperative states.

In assessing the perceived realism of AI-generated photos across the 4 images per prompt, the Friedman test revealed no significant differences in scores among the images from the same prompt ($p > 0.05$ for all). This suggests, the images were perceived as similarly poor, and the reviewers did not consistently rank one image as more realistic than the others. This also implies a degree of consistency among the reviewers in their assessments of the photos.

Training data for AI largely influences the quality and characteristics of the generated images. The limited availability of real pre- and postoperative images due to protections regarding patient health information might be contributing to the shortfall in pre- and post-procedure image realism.[17] It is also possible that the complexities of postoperative healing are too intricate for DALLE-2's current rendition.

The primary limitation of this study was the limited number of reviewers. While all 5 reviewers were board-certified ASOPRS surgeons, a small number of reviewers raises concerns about potential biases. Reviewers were not blinded to the source of the generated answers and photos. This knowledge was inevitable given the nature of the study, and preconceived notions about OpenAI technology may have influenced their responses. Additionally, the study's narrow focus on oculoplastic procedures limits the results' generalizability to other fields of medicine. Another limitation was the use of a single IP address for all question sessions. While new user sessions were initiated for each query to simulate first-time interactions, the consistent IP address may have influenced the AI model's learning and response generation.

While Chat GPT-4 demonstrated acceptable responses for several generic prompts, it fell short in offering personalized advice. Meanwhile, DALLE-2's poor ability to generate medical imagery underscores the challenges with creating accurate and realistic medical images. These findings highlight the current capabilities of OpenAI technology, which support its use as a basic educational tool for helping patients learn about oculoplastic procedures. The model's performance on case-based scenarios revealed a key opportunity for improvement. Both Chat GPT-4 and DALLE-2 should be viewed as supplementary tools rather than primary diagnostic or consultative platforms. In their current form, these AI tools cannot replace evaluation and guidance by a physician.

Future collaborations with medical institutions and feedback from medical professionals may enhance AI's performance and image generation capabilities. With additional research in machine learning and the use of larger datasets, these tools may eventually be able to provide second opinions for oculoplastic patients, especially those living in remote locations. The goal is for AI to empower healthcare providers and guide patients with reliable and up-to-date information to make evidenced-based decisions. This study offers a preliminary evaluation of the accuracy and consistency of information generated by Chat GPT-4 and DALLE-2 in the context of common oculoplastic concerns. Further research with a more expansive dataset is essential to develop a definitive understanding of their capabilities and limitations as medical tools.

Declarations

Ethics approval and consent to participate
Not required.

Competing interests
Adam J. Neuhouser, Alisha Kamboj, and Ali Mokhtarzadeh have no competing interests to declare. Andrew R. Harrison is speaker and consultant for Horizon Pharmaceuticals and RVL Pharmaceuticals.

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Predictors of Ophthalmology Resident Performance From Medical Student Application Materials

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OBJECTIVE: To determine whether elements in ophthalmology residency applications are predictors of future resident performance.

DESIGN: This multi-institutional, cross-sectional, observational study retrospectively reviewed the residency application materials of ophthalmology residents who graduated from residency from 2006 through 2018. Resident performance was scored by 2 faculty reviewers in 4 domains (clinical, surgical, academic, and global performance). Correlation between specific elements of the residency application and resident performance was assessed by Spearman correlation coefficients (univariate) and linear regression (multivariate) for continuous variables and logistic regression (multivariate) for categorical variables.

SETTING: Seven ophthalmology residency programs in the US.

PARTICIPANTS: Ophthalmology residents who graduated from their residency program.

RESULTS: High-performing residents were a diverse group, in terms of sex, ethnicity, visa status, and educational background. Residents with United States Medical Licensing Examination Step 1 scores higher than the national average for that year had significantly higher scores in all 4 performance domains than those who scored at or below the mean (all domains $P < 0.05$). Residents who had honors in at least 4 core clerkships and who were members of Alpha Omega Alpha Medical Honor Society also had higher scores in all 4 performance domains (all domains $P \leq 0.04$). Step 1 score (ρ=0.26, $P < 0.001$) and the difference between Step 1 score and the national average for that year (ρ=0.19, P = 0.009) positively correlated with total resident performance scores. Residents who passed the American Board of Ophthalmology Written Qualifying Examination or Oral Examination on their first attempt had significantly higher Step 1/2 scores ($P \leq 0.005$), Ophthalmology Knowledge Assessment Program scores (P = 0.001), and resident performance scores ($P \leq 0.004$).

CONCLUSIONS: In this new landscape of increasing numbers of applicants to residency programs and changing of the Step 1 score to pass/fail, our findings may help guide selection committees as they holistically review applicants to select exceptional future residents in ophthalmology. (J Surg Ed 81:151–160. © 2023 Association of Program Directors in Surgery. Published by Elsevier Inc. All rights reserved.)

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ABBREVIATIONS: ABO, American Board of Ophthalmology, AΩA, Alpha Omega Alpha Honor Society, GHHS, Gold Humanism Honor Society, OKAP, Ophthalmology Knowledge Assessment Program, SF Match, San Francisco Match, URM, underrepresented in medicine, USMLE, United States Medical Licensing Examination, *USNWR*, *US News & World Report*, WQE, Written Qualifying Examination

KEY WORDS: internship and residency, medical education, medical residency, ophthalmology

COMPETENCIES: Medical Knowledge, Professionalism, Interpersonal and Communication Skills

INTRODUCTION

Ophthalmology is one of the most competitive specialties in the US, with residency applicant match rates of 70% to 80%.[1] Medical students apply to an increasing number of programs each year, such that these programs now commonly review more than 100 applications for each residency position.[2] Both objective and subjective factors contribute to the overall perceived strength of an application during the interview and matching process. These include United States Medical Licensing Examination (USMLE) scores, academic pedigree, clinical grades, letters of recommendation, performance during a visiting rotation/clerkship, research publications, personal statement, and extracurricular activities.[3–5] How these factors ultimately translate into performance or success during and after residency, however, remain poorly understood, as does the definition of success.[6,7]

Prior studies in other specialties have shown that noncognitive domains, including work ethic, professionalism, honesty, and interpersonal skills, are critically important and predictive of resident success.[8,9] Cognitive metrics such as standardized test scores correlate well with in-training/board examinations but less so with faculty evaluations or other metrics of performance.[10–14] As the limitations of traditional resident selection systems for predicting resident performance become increasingly evident, new and ophthalmology-specific data will be needed to guide the resident selection process.[7] The purpose of this study was to identify elements in ophthalmology residency application materials that may be predictive of future performance. We developed a categorical performance assessment system to classify both high- and low-performing residents on the basis of objective and subjective criteria. Because training programs no longer use USMLE Step 1 numerical scores, there is increased motivation to consider applications from a more holistic perspective.

METHODS

This study received institutional review board approval at each participating institution, complied with the Family Educational Rights and Privacy Act, the Health Insurance Portability and Accountability Act, and the tenants of the Declaration of Helsinki. The requirement for informed consent was waived.

Study Design

We retrospectively reviewed San Francisco Match (SF Match) Ophthalmology Residency Matching Program application materials from ophthalmology residents who graduated from the 7 programs participating in our study from 2006 through 2018. These participating institutions included Mayo Clinic, Rochester, Minnesota; Vanderbilt University, Nashville, Tennessee; Weill Cornell Medical College, New York, New York; University of Minnesota, Minneapolis, Minnesota; Saint Louis University, St. Louis, Missouri; University of California Irvine, Irvine, California; and New York University, New York, New York. Residents were excluded from analysis if they did not graduate from their residency program.

Residency Application Information

We abstracted the following application data for each resident: sex, underrepresented in medicine (URM) status, visa status, USMLE Step 1 and 2 scores (including the national average for that year to account for annual fluctuation and inflation of scores), undergraduate institution and whether it ranked in the top 50 of the *US News & World Report* (*USNWR*) college rankings during the year of the application, academic major, grade point average, honors status (e.g., cum laude or higher), varsity athlete, years off between college and medical school, advanced degrees (e.g., PhD and MBA), medical school and whether it ranked in the *USNWR* top 25 from 2006 through 2018, Alpha Omega Alpha Medical Honor Society (AΩA) selection, Gold Humanism Honor Society (GHHS) selection, whether the applicant completed a visiting rotation/clerkship at the matched institution, grades in core medical school clerkships (i.e., internal medicine, pediatrics, surgery, obstetrics and gynecology, neurology, psychiatry, and ophthalmology), and authorship of 1 or more PubMed-indexed publications at the time of application. Clinical clerkship grades were categorized as *honors* or *nonhonors* with numeric scores (10 of 10 points), and notations of high honors and/or grades of A+ were considered honors. Descriptive grades, including excellent, outstanding, and commendable, were excluded unless a clear distinction was made to indicate which term represented the highest grade possible. We also recorded American Academy of

Ophthalmology–standardized Ophthalmology Knowledge Assessment Program (OKAP) in-training examination scores and American Board of Ophthalmology (ABO) Written Qualifying Examination (WQE) and Oral Examination first-time passage rates.

Resident Performance Assessment

Resident performance was independently assessed by 2 faculty members at each institution, most commonly a program director, associate program director, or another faculty member who had worked closely with residents during the study period. Faculty scorers were selected by each participating institution. Residents were scored on a scale of 1 through 5, with 1 representing the bottom 20% of residents and 5 representing the top 20% of residents in the following performance domains: (1) clinical (i.e., preparation for clinic, ability to formulate an assessment and plan, diagnosis, and management), (2) surgical (i.e., technical skills, intraoperative judgment, and preoperative planning), (3) academic (i.e., peer-reviewed publications, podium presentations, and OKAP scores), and (4) global (i.e., professionalism, common sense, reliability, judgment, and ability to work in a team environment). Scorers were trained before scoring according to the above descriptions for each performance domain but were masked to resident application data (application details, OKAP scores, and ABO examination passage), although the scorers may have had recall of these data. Scorers from the same institution were blinded to each other's scores. Scorers were also coached to link numeric scores to a resident's assessed performance quintile for each domain (i.e., to reserve a score of 5 for residents performing in the top 20% of all trainees). If scores differed between the 2 faculty scorers by more than 1 point, a third scorer independently assigned a score, and the 3 scores were averaged.

Statistical Analysis

Between-group comparisons for categorical variables were performed by using the χ^2 test. Between-group comparisons for continuous variables were performed with Wilcoxon rank sum tests. Because performance scores were non-normally distributed, medians were used to summarize these data. The correlation between resident performance and USMLE Step scores was ascertained with Spearman correlation coefficients (ρ). Linear regression was used to interrogate multivariate models that included the different performance scores. A rank transformation was used to increase the normality of the data for these models. Statistical analyses were performed with SAS software, v9.4 (SAS Institute Inc). All P values were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

We analyzed 259 residency applications by residents at our 7 institutions from 2006 through 2018. Three residents did not graduate from residency because of early transfers to other specialties or prolonged leaves of absence and were excluded from analysis. Applicant demographics are summarized in Table 1. Of the 256 residents included in our study, 151 (59.0%) were men. Of 202 residents with undergraduate training indicated in their application, 115 (56.9%) graduated from an undergraduate university ranked in the top 50 by *USNWR*. Most residents (52.7%) earned the distinction of cum laude or higher from their undergraduate institution, and 7% of residents were varsity athletes. Approximately 30% of residents attended a medical school ranked in the top 25 by *USNWR*, and 22 (9.1%) residents had dual MD/PhD degrees. Nine residents had other degrees (MBA, MPH, and JD), but these were not analyzed separately because of their small sample size. Of 243 residents with AΩA membership status documented in their application, 50 (20.6%) were AΩA members, although junior vs senior membership was not distinguished. Fifteen residents (6.2%) were documented GHHS members.

Performance Scores

Agreement between faculty scorers was high, with only 76 of 1,036 score pairs (7.3%) differing by more than 1 point and necessitating a third blinded scorer. Median total scores of each performance domain (clinical, surgical, academic, and global) ranged from 3.0 to 4.5 (Table 2). Men had a significantly higher median global score than did women (4.0 vs 3.5, $P = 0.049$). Residents had significantly higher performance scores for all 4 domains if they had USMLE Step 1 scores higher than the national average (vs at or below national average), were AΩA members (vs nonmembers), and had honors in at least 4 clerkships (vs honors in <4 clerkships) (all $P < 0.05$). Interestingly, residents with dual MD/PhD degrees had significantly lower clinical, surgical, and global performance scores than did residents who did not have a PhD ($P \leq 0.02$). Residents who were GHHS members had significantly higher clinical, surgical, and global scores than did nonmembers ($P \leq 0.02$). Performance scores for any of the 4 domains did not significantly differ according to visa status, URM status, or number of publications ($P \geq 0.11$).

USMLE Step 1/2 Scores

USMLE Step 1 score, the difference between Step 1 score and the national average that year, and Step 2 score were all correlated with higher total performance scores ($P \leq 0.009$) (Table 3). Step 1 score was positively correlated with total residence performance score ($\rho = 0.26$, $P < 0.001$) and scores in all 4 performance domains ($\rho \geq 0.16$, $P \leq 0.01$). A representative Spearman correlation plot between total performance score and the difference between Step 1 score and the national average is shown in Figure 1. Step 2 scores were only analyzed if they were included in the SF Match application materials (n = 64, 25%). Step 2 scores were positively correlated with total ($\rho = 0.33$, $P = 0.008$) and academic ($\rho = 0.51$, $P < 0.001$) performance scores.

TABLE 1. Applicant Demographics[a]

Demographic	n	Value
Sex	256	
Men		151 (59.0)
Women		105 (41.0)
Visa noted on application	250	15 (6.0)
Identified as URM	241	13 (5.4)
Undergraduate university in top 50[b]	202	115 (56.9)
Varsity athlete	199	14 (7.0)
Undergraduate major	242	
Biology		93 (38.4)
Biochemistry/molecular biology		27 (11.2)
Neuroscience		16 (6.6)
Chemistry		14 (5.8)
Biomedical engineering		12 (5.0)
Premedical		12 (5.0)
Psychology		11 (4.5)
Other science/math		24 (9.9)
Nonscience		24 (9.9)
PhD	243	22 (9.1)
Graduated cum laude	239	126 (52.7)
Medical school in top 25[b]	243	71 (29.2)
AΩA member	243	50 (20.6)
GHHS member	243	15 (6.2)
USMLE Step 1 score	243	236.1 (16.2)
Difference between Step 1 score and national average that year	187	18 (−39 to 51)
USMLE Step 2 score	64	239.9 (15.4)
Clerkship/rotation at institution	197	65 (33.0)
Clerkship honors	201	
Medicine		76 (37.8)
Surgery		79 (39.3)
Pediatrics		68 (33.8)
Obstetrics/gynecology		70 (34.8)
Neurology		47 (23.4)
Psychiatry		62 (30.8)
≥4 clerkships		43 (21.4)
Publications	226	
0		98 (43.4)
1		77 (34.1)
≥2		51 (22.6)

Abbreviations: AΩA, Alpha Omega Alpha Honor Society; GHHS, Gold Humanism Honor Society; URM, underrepresented in medicine; USMLE, United States Medical Licensing Examination.
[a]Categorical data are summarized as No. (%) of residents. USMLE Step 1 and Step 2 scores are summarized as mean (SD), and the difference between Step 1 score and the national average that year is summarized as median (range).
[b]Ranked by *US News & World Report* from 2006 through 2018.

ABO Examination Performance

Of 221 residents with documented ABO WQE scores and 172 with Oral Examination scores, 200 (90.5%) and 149 (86.6%), respectively, passed on their first attempt (Table 4). Those who passed the ABO WQE on their first attempt had significantly higher median (IQR) Step 1 (238 [230-246] vs 221 [206-236], $P = 0.005$), Step 2 (241 [232-251] vs 220 [204-232], $P = 0.004$), and OKAP (51 [31-70] vs 31 [10-38], $P = 0.001$) scores than did those who failed on their first attempt. Academic performance score was also significantly higher for those who passed the ABO WQE on the first attempt than for those who failed their first attempt (3.4 vs 2.7, $P = 0.002$). Of residents who passed the ABO Oral Examination on their first attempt, significantly more were AΩA members (91% vs 10%, $P = 0.03$) and attended a medical school ranked in the top 25 by *USNWR* (90% vs 10%, $P = 0.002$) than were those who failed on their first attempt. In addition, USMLE Step 1 and 2 scores, OKAP scores, and performance scores in all 4 domains (clinical, surgical, academic, and global) were significantly higher for residents who passed the ABO Oral Examination on their first attempt than for those who failed ($P \leq 0.002$). All available Step 2 scores were included in our analysis of ABO examination performance, even if taken after the residency application cycle.

DISCUSSION

To our knowledge, this multi-institutional study is the largest analysis of ophthalmology residency application materials and future resident performance. High-performing residents were a diverse group, in terms of sex, ethnicity, visa status, and educational background. High performers had academic rigor evidenced by cognitive-based objective data, which included Step 1 and 2 scores and clerkship grades. These students succeeded at their respective medical schools and were often recognized by AΩA or GHHS selection but did not necessarily publish extensively, travel for rotations, attend highly ranked institutions, or pursue advanced degrees such as a PhD. These data may help guide a holistic review for residency selection committees.

To quantitatively measure resident performance, we devised a categorical system to classify resident performance, which had high interrater reliability and generated metrics to establish correlations. The clinical, surgical, academic, and global performance domains

TABLE 2. Resident Performance Scores in Each Domain According to SF Match Application Factors.[a]

Factor	Total	P	Surgical	P	Academic	P	Clinical	P	Global	P
All applicants	3.6 (3.6)		3.7 (4.0)		3.3 (3.0)		3.6 (4.0)		3.6 (4.0)	
Men	3.6 (3.8)	0.06	3.8 (4.0)	0.23	3.4 (3.3)	0.11	3.7 (4.0)	0.049	3.7 (4.0)	0.049
Women	3.5 (3.5)		3.7 (4.0)		3.1 (3.0)		3.6 (3.5)		3.6 (3.5)	
Visa noted on application	3.9 (4.0)	0.11	3.9 (4.0)	0.23	3.8 (4.0)	0.06	3.9 (4.0)	0.11	3.9 (4.0)	0.11
Identified as URM	3.4 (3.5)	0.65	3.4 (3.5)	0.40	3.5 (3.5)	0.46	3.4 (3.5)	0.60	3.4 (4.0)	0.60
Undergraduate university in top 50	3.5 (3.5)	0.36	3.6 (4.0)	0.10	3.2 (3.0)	0.81	3.5 (3.5)	0.56	3.6 (3.5)	0.56
Varsity athlete	3.6 (3.6)	0.93	3.9 (4.0)	0.49	3.2 (3.0)	0.77	3.6 (3.8)	0.72	3.6 (3.5)	0.72
Graduated cum laude	3.6 (3.7)	0.55	3.7 (4.0)	0.90	3.4 (3.5)	0.15	3.7 (4.0)	0.89	3.7 (4.0)	0.89
PhD	3.3 (3.2)	0.06	3.4 (3.5)	0.01[b]	3.3 (3.3)	0.75	3.1 (3.0)	0.02[b]	3.2 (3.3)	0.02[b]
Medical school in top 25	3.4 (3.4)	0.02[b]	3.5 (3.5)	0.01[b]	3.2 (3.5)	0.95	3.5 (3.5)	0.05[b]	3.5 (3.5)	0.05[b]
USMLE Step 1 score		0.002		0.009		0.002		0.002		0.049
At or below national average	3.0 (3.1)		3.2 (3.5)		2.7 (2.6)		3.0 (3.0)		3.2 (3.3)	
1-20 points higher than national average	3.6 (4.0)		3.7 (4.0)		3.2 (3.0)		3.6 (4.0)		3.6 (3.9)	
≥21 points higher than national average	3.7 (4.0)		3.9 (4.0)		3.5 (3.5)		3.8 (4.0)		3.7 (4.0)	
AΩA member	3.9 (4.0)	0.001	4.1 (4.0)	0.002	3.6 (3.5)	0.01	4.0 (4.0)	0.001	4.0 (4.0)	0.01
GHHS member	4.0 (4.3)	0.03	4.2 (4.0)	0.03	3.6 (4.0)	0.26	4.1 (4.5)	0.03	4.1 (4.3)	0.02
Clerkship/rotation at institution	3.6 (3.6)	0.81	3.7 (4.0)	0.96	3.3 (3.3)	0.97	3.6 (4.0)	0.76	3.7 (4.0)	0.61
Honors in ≥4 clerkships	3.9 (3.9)	0.007	4.0 (4.0)	0.01	3.6 (3.5)	0.008	3.9 (4.0)	0.02	3.9 (4.0)	0.04
Publications		0.73		0.25		0.51		0.85		0.50
0	3.6 (3.6)		3.7 (4.0)		3.2 (3.0)		3.7 (4.0)		3.6 (4.0)	
1	3.7 (3.7)		3.9 (4.0)		3.2 (3.0)		3.8 (4.0)		3.8 (4.0)	
≥2	3.6 (3.6)		3.7 (4.0)		3.4 (3.5)		3.7 (4.0)		3.7 (4.0)	

Abbreviations: AΩA, Alpha Omega Alpha Honor Society; GHHS, Gold Humanism Honor Society; SF Match, San Francisco Match; URM, underrepresented in medicine; USMLE, United States Medical Licensing Examination.

[a]Each performance score domain is summarized as mean (median).

[b]Denotes a statistically significant lower score when compared with the control group. All other variables with $P < .05$ have significantly higher scores than those of the control group.

TABLE 3. Correlation Between Resident Performance and USMLE Step Scores.[a]

USMLE Step score	Correlation with resident performance, ρ									
	Total	P	Clinical	P	Surgical	P	Academic	P	Global	P
Step 1 (n=243)	0.26	<0.001	0.20	<0.001	0.20	<0.001	0.33	<0.001	0.16	0.01
Difference between Step 1 score and national average (n=187)	0.19	0.009	0.16	0.03	0.15	0.04	0.24	<0.001	0.11	0.15
Step 2 (n=64)	0.33	0.008	0.25	0.05	0.15	0.23	0.51	<0.001	0.22	0.08

Abbreviation: USMLE, United States Medical Licensing Examination.

[a]Spearman correlation coefficients (ρ) indicate the correlation between resident performance (total and individual domains) score and USMLE Step scores.

were chosen to reflect the Accreditation Council for Graduate Medical Education/American Board of Medical Specialties core competencies and may be used as a proxy for these current milestones in ophthalmology training.[15] Studies outside of ophthalmology have used similar scales to rate residents with good interrater reliability.[6,10,14] Although this assessment methodology is subjective and prone to potential bias, it allows for holistic evaluation of multiple disparate domains of resident performance (avoiding overemphasis on limited and predominantly cognitive-based objective data) and has shown consistency in the mean and distribution of scores across institutions.

Studies of ophthalmology resident performance are limited, possibly because of the inherent challenges of analyzing such relatively small trainee class sizes. Furthermore, assessing resident performance and defining a *successful* resident is inherently challenging. Resident performance is multifactorial, and some characteristics of high-performing residents may vary across institutions. Past studies of resident performance have used in-training examinations and clinical evaluations to assess overall resident performance.[15] These metrics, however, may overemphasize cognitive performance and overlook the subjective, holistic qualities that characterize a competent physician. Residents with excellent clinical judgment and surgical skills and who are reliable and work well in teams may not be the highest performers on in-training examinations or the most prolific contributors to scholarly activity.

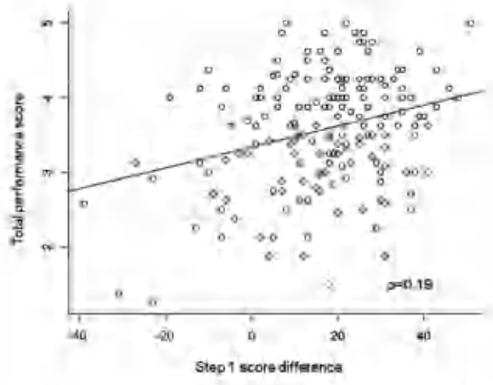

FIGURE 1. Difference Between United States Medical Licensing Examination Step 1 Score and the National Average for Each Corresponding Year vs Total Resident Performance Score. The Spearman correlation coefficient (ρ) is indicated for the linear trend in correlation.

Although resident selection is challenging for all medical specialties, USMLE scores and clerkship grades traditionally have been among the most heavily weighted factors in the applicant evaluation process.[4,16,17] In this study, both Step 1 and 2 scores were highly associated with future ophthalmology resident performance. Prior studies in other medical specialties investigating the association between Step 1 score and resident performance have yielded mixed results, with several studies reporting no association.[6,18,19] Other studies have reported that Step 1 and 2 scores are predictive of future success, although this success was mostly correlated with only cognitive-based measures of performance, such as in-training examinations.[16–20] Although Step 1 scores were associated with higher performing residents in our study, the mean Step 1 score for high-performing residents in each performance domain ranged between 238 and 243, which was approximately 20 to 21 points higher than the national average that year. This range of Step 1 scores aligns with the mean of matched ophthalmology applicants overall, which may be reassuring to residency selection committees.[1] Ophthalmology residency is an academically taxing specialty. With the transition of Step 1 scores to pass/fail, resident selection committees may need to review applications for other indicators of academic fortitude to predict future success. Additionally, although higher Step 1 and 2 scores were associated with residency performance in our study, some of the correlation coefficients were small, which suggests that other important determinants of success contribute to resident performance. Our findings do not provide direct evidence that Step 1 or 2

TABLE 4. American Board of Ophthalmology Examination Performance on First Attempt According to SF Match Application Factors and Resident Performance.[a]

Factor/performance score	Written Qualifying Examination				Oral Examination			
	n	Pass	Fail	P	n	Pass	Fail	P
All applicants	221	90.5	9.5		172	86.6	13.4	
AΩA member	39	96	4	0.03	39	91	10	0.03
GHHS member	10	100	0	>0.99	10	97	3	>0.99
Medical school in top 25	57	92	8	0.002	57	90	10	0.002
USMLE Step 1 score[b]	213	238 (230-246)	221 (206-236)	0.001	164	239 (231-246)	222 (211-241)	0.005
USMLE Step 2 score[b]	114	241 (232-251)	220 (204-232)	0.02	99	241 (230-251)	228 (217-238)	0.004
OKAP score	178	51 (31-70)	31 (10-38)	0.001	130	52 (34-70)	31 (18-40)	0.001
Clinical performance	221	3.7	3.5	<0.001	172	3.8	3.1	<0.001
Surgical performance	221	3.8	3.6	<0.001	172	3.9	3.2	<0.001
Academic performance	221	3.4	2.7	0.004	172	3.4	2.8	0.004
Global performance	221	3.8	3.5	0.002	172	3.8	3.2	0.002

Abbreviations: AΩA, Alpha Omega Alpha Honor Society; GHHS, Gold Humanism Honor Society; OKAP, Ophthalmology Knowledge Assessment Program; SF Match, San Francisco Match; USMLE, United States Medical Licensing Examination.

[a]Data are summarized as either the percentage of residents who passed/failed the American Board of Ophthalmology Examination on the first attempt or as median (IQR) score.

[b]Step 2 scores were included from residents with scores available even if Step 2 was taken after SF Match application. In earlier analysis, Step 2 scores were included only if present on the SF Match application.

scores are able to identify the best performing applicants. Indeed, others have reported that evidence for the predictive value of USMLE scores for resident success is inconclusive.[23]

Induction into AΩA is accorded to up to 20% of a graduating medical school class and signifies commitment to professionalism, leadership, scholarship, research, and community service.[22] AΩA recognition is correlated with resident performance, both objectively and subjectively, in many specialties.[1,9,10,24,25] Similarly, GHHS was established in 2002 to recognize humanistic health care professionals.[26] The honor ostensibly reflects high emotional intelligence (integrity, honesty, and teamwork), in addition to professionalism, systems-based practice, and interpersonal and communication skills. Our analysis of honor society status may be limited by the aggregation of junior and senior AΩA status, which may carry different predictive value, the small number of GHHS members analyzed, and the unavailability of AΩA/GHHS selection at some medical schools. Moreover, more than 60 GHHS chapters were established after 2012; therefore, many residents may not have had this honor available to them at the time of their application.[2,4,25] Additionally, selection committees should remain cognizant of the potential for bias in the honor society selection process.

Assessment of clerkship grades has several important caveats and limitations. Although high-performing residents had honors in 4 or more clerkships, clinical grading scales and the proportion of students receiving the highest possible grade varies considerably among institutions.[20] We categorized honors as a numeric score of 10 of 10 or as a grade of A+. This method undoubtedly failed to identify students who would have had high grades if classified by another system (i.e., pass/fail). Additionally, our method inflated the performance of students from schools in which most students receive honors grades. Because of the inherent challenges and limitations of all potential methods of evaluating clinical grades,[27] we rationalized that analyzing clinical grades at face value with a binary system (honors vs nonhonors) was the most reasonable and realistic approach.

Research publications are increasingly viewed as an important component of a competitive residency application in many medical specialties, and we identified a marked increase in PubMed-indexed publications in the latter years of the study period. However, our findings align with prior studies that show additional published research at the time of application does not correlate with future resident performance.[28]

Medical education at highly ranked institutions and PhD training may be viewed favorably by some resident selection committees. However, performance of MD/PhD residents may vary according to program-specific environmental factors, and the relatively small number of MD/PhD residents in our study may have limited subgroup analysis. In a survey of ophthalmology residency program directors, most rated prior PhD training as not important in their resident selection process, but medical school ranking was rated of high importance.[3] Our findings showed that applicants from *USNWR*-ranked medical schools in the top 25 had lower clinical, surgical, global, and total performance scores and were less likely to pass the ABO Oral Examination on the first attempt. Similar findings were reported by a study of urology residents that showed attending a low-ranked medical school was associated with higher performance scores.[11] Although some highly regarded application criteria may be positively associated with performance during residency, if these factors are overweighted by recruitment committees relative to other potentially stronger predictors, a spurious negative association with performance may result. Our trainees generally excelled during residency without specific institutional pedigree or advanced degree training prerequisites. This finding may embolden selection committees to broadly search for applicants with or without additional degrees from diverse backgrounds and schools.

Our study is limited by its retrospective nature, the limitations and accuracy of the abstracted data, and various potential biases related to sex, race, and ethnicity during medical school and residency assessments, and by other aspects of the original matching process. Although 7 residency programs with wide geographic representation and differing program sizes participated in this study, the generalizability of our findings to all programs may be limited. Despite the consistency between scorers and the need for a third scorer remediation in only 7% of cases, scorers relied heavily on recall. No uniform methodology was used for scoring other than the guidance given to link performance scores to the associated quintile of residents in the individual program with time. Importantly, the residents who were assessed in our study were not randomly assigned but were matched according to the original assessments of their candidacy by the residency programs and resident preferences for training. The relative weight that programs placed initially on various application factors (e.g., attendance at a highly ranked medical school) may have affected our findings if they were markedly overweighted or underweighted with respect to their actual value in predicting future resident performance.

In summary, we conducted a multi-institutional study of ophthalmology residency applications to glean predictors of resident performance. We also developed a system to characterize and quantify resident performance. Our findings show that USMLE Step 1 and Step 2 scores were correlated with future success, and high-performing residents had a high frequency of institutionally assigned honors (clerkship grades and AΩA/GHHS membership). Other metrics, such as undergraduate or medical institution prestige, PhD degree, and research publications, were not apparent predictors of future performance. In our efforts to increase diversity, equity, and inclusion in ophthalmology residency training programs, and ultimately among practicing ophthalmologists, recognizing the potential for bias (racial, socioeconomic, cultural, and other biases) in both medical school–related application materials and performance assessments during residency is imperative.[29,30] Applicant experiences and attributes outside of academic metrics are also important considerations for creating a diverse cohort of ophthalmologists that reflects an expanding, diverse patient population. Our findings may help guide selection committees as they holistically evaluate applicants, with the goal of selecting exceptional future residents.

DATA STATEMENT

All relevant data supporting the findings of this study are reported in the article.

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not been detected by sterilizing services unit staff when inspecting and wrapping the tray for sterilization. We decided to test whether a hair or suture material accidentally retained in a tray prior to processing would potentially compromise the sterility of the instruments or tray.

Two × 5-cm strands of hair and 2 × 5-cm lengths of postsurgical used nylon suture and postsurgical used silk suture were dipped in 0.5 McFarland (10^8 colony-forming units per milliliter) *Staphylococcus aureus* (ATCC 25923) solution. The nylon suture and the silk suture (the hair was set aside) were then processed through the washer to replicate the most likely procedure in practice.

One sample of hair, silk suture, and nylon suture was then placed in Tryptic Soy Broth as a control, and the other sample of each hair, silk suture, and nylon suture was placed in individual steripeel wraps and processed in the steam prevacuum sterilizer.

After sterilization, each sample of hair, silk suture, and nylon suture was removed from the steripeel wrap using a sterile technique and place into sterile Tryptic Soy Broth at 35°C and checked for growth at 24 hours, 48 hours, and 1 week.

The control sample of hair, nylon suture, and silk suture all grew the control strain within 24 hours. The test sample of hair, nylon suture, and silk suture that had all been dipped and then processed in the prevacuum sterilizer showed no growth after 1 week.

The results of our study demonstrate that hair, silk suture, and nylon suture can be rendered free from pathogenic activity by sterilization because there was no growth from all 3 items after processing. Sterilization is the process that kills all types of microorganisms, including bacterial spores.[2,3] It provides an acceptably low probability that any microorganism will survive the treatment. Our study demonstrates that it is possible for highly contaminated suture material to be processed and sterilized and be free of microorganisms at the end of the process.

The Australian Standard for cleaning, disinfecting, and sterilizing reusable equipment requires thorough cleaning of all instruments and equipment. This is an essential prerequisite in sterilization and disinfection processes to ensure the removal of adherent protein soil and biofilm. Cleaning performance must be continually monitored and documented. Visual inspection is used to monitor cleaning outcomes.[4]

Clearly, the retention of a piece of suture material suggests that visual inspection can, at times, be flawed. It is a requirement of the instrument nurse to remove all used disposable items from the instrument tray before returning the tray to the sterilizing service for reprocessing. Visual inspection and removal of items such as suture material are frequently incomplete by instrument nurses, which then places an added burden on the role of the staff in the sterilizing services unit.

Both the instrument nurse and sterilizing services staff would not knowingly retain a piece of suture in a tray for reprocessing. Once sited, the item would be removed immediately and the item reprocessed.

A review of inspection processes of instruments immediately prior to packaging, similar to other reports,[5] has not completely resolved the problem of retained suture material. However, where the suture has inadvertently been retained and reprocessed with the instruments or equipment, our study demonstrates that it can be cleaned and reprocessed to a level that is free from contamination.

In instances in which cancellation of the surgery is of high risk to the patient, there should be careful consideration if there is no risk of infection from an instrument tray with a retained piece of suture or hair. The results of our study may assist with decision making by administrators faced with such a dilemma.

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Isopropyl alcohol skin antisepsis does not reduce incidence of infection following insulin injection

To the Editor:

Current guidelines for the practice of insulin injection recommend a clean injection site on the skin; however, disinfection with isopropyl alcohol is not typically necessary.[1,2] Despite these guidelines, many resources still recommend isopropyl alcohol skin antisepsis prior to insulin injection. Alcohol has traditionally been advocated as a method of skin preparation to decrease infection risk despite several studies to the contrary.[3,4] Although evidence exists that alcohol antisepsis reduces bacterial counts, this does not translate into lower infection rates.[3] Health care systems or individuals requiring chronic insulin injections may benefit from abandoning routine alcohol antisepsis, thereby reducing expense and avoiding patient discomfort sometimes associated with alcohol antisepsis.[1,5]

We conducted an Institutional Review Board-approved survey of 225 patients with insulin-dependent diabetes mellitus. Based on responses, we estimated 9,472,040 total insulin injections during their lifetime. Patients disclosed information regarding disease history, injection practices (specifically how often isopropyl alcohol swabs were used to sanitize the skin prior to injection), and history of complications resulting from their insulin injections.

Of the 8,134,995 estimated injections among those who reported "never" or "sometimes" use of alcohol antisepsis, there were 14 cases of infection (incidence = 1.72 infections per million injections). Of the 1,337,045 total estimated injections performed in diabetics who reported "often," "very often," or "always" use of alcohol antisepsis, there were 10 cases of infection (incidence = 7.48 per million injections). When comparing the 2 groups, the rate of infection was higher among individuals using alcohol antisepsis ($P = .001$).

Our data strongly suggest that alcohol antisepsis prior to insulin injection in diabetics does not reduce the incidence of infection at the injection site. Our conclusions support those of several other studies that analyzed smaller numbers of total injections.[3-5]

Why would infections occur more commonly in the alcohol antisepsis group? Participant recall bias can significantly limit survey-based studies and likely contributes to this observation. Those who routinely use alcohol antisepsis may be more concerned about infections and therefore be more likely to remember them. Alternatively, frequent alcohol antisepsis users may be more apt to describe a change as infectious compared with non-alcohol antisepsis users. Although prospective studies could more definitively assess the effectiveness of alcohol antisepsis, this would likely never take place given the low natural infection rate. Despite these limitations, we believe that our findings are valid. The infection rate following all insulin injections is impressively low, and the lack of alcohol antisepsis does not increase the risk of infection.

The principal investigator had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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非手术治疗

Non-Surgical Treatment

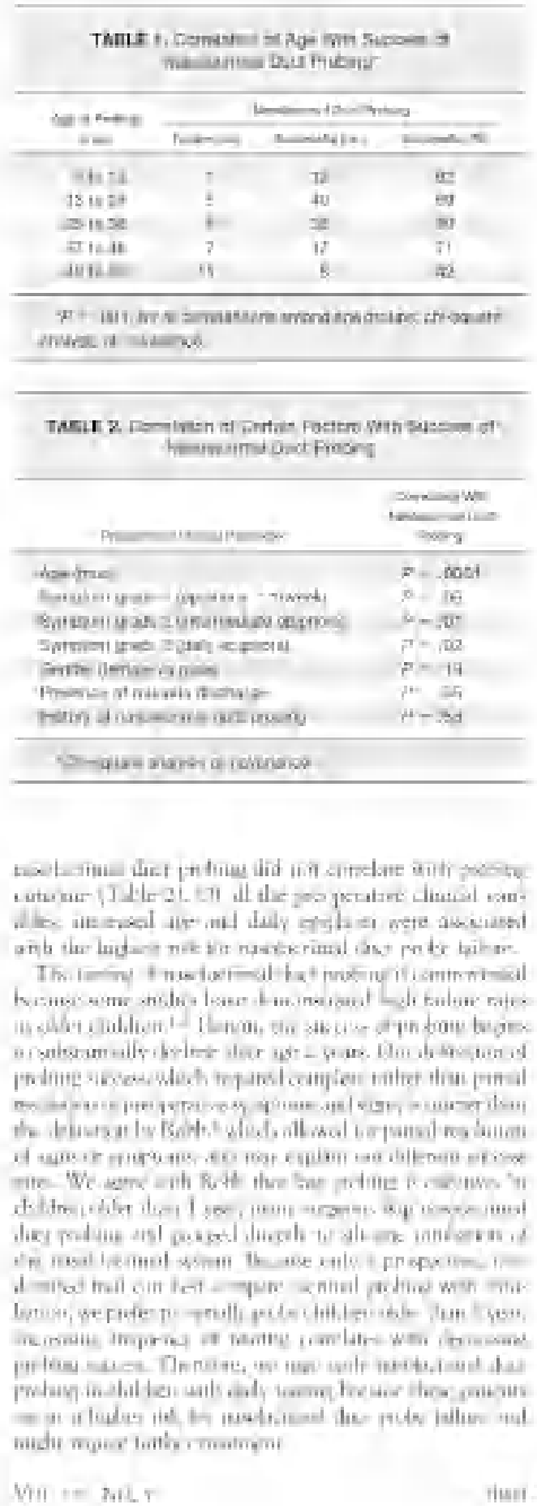

TABLE 1. Correlation of Age With Success of Nasolacrimal Duct Probing*

Age at Probing (mos)	Simultaneous Duct Probing		
	Postoperative	Successful (n)	Success (%)
0 to 12	7	12	92
13 to 24	5	40	89
25 to 36	6	28	82
37 to 48	7	17	71
49 to 60	11	5	62

*P = .001 by chi-square analysis of trend.

TABLE 2. Correlation of Certain Factors With Success of Nasolacrimal Duct Probing

Preoperative Factor Evaluated	Correlating With Nasolacrimal Duct Probing
Age (mos)	P = .0001
Symptom grade 1 (epiphora < 1 week)	P = .16
Symptom grade 2 (intermittent epiphora)	P = .07
Symptom grade 3 (daily epiphora)	P = .02
Beetle Dehlen lg index	P = .19
Presence of mucoid discharge	P = .05
History of conjunctivitis (red eyes)	P = .36

*Chi-square analysis of correlation.

nasolacrimal duct probing did not correlate with positive outcome (Table 2). Of all the preoperative clinical variables assessed, age and daily epiphora were associated with the highest risk for nasolacrimal duct probe failure.

The timing of nasolacrimal duct probing is controversial because some studies have demonstrated high failure rates in older children.[1–3] Herein, the success of probing begins to substantially decline after age 1 year. Our data suggest probing should be performed earlier rather than later in the first year of life. We agree with Robb that late probing is ominous in children older than 1 year, many surgeons may consider nasal duct probing not to be indicated. Despite only a prospective, time-limited trial can best compare nasal probing with intubation, we prefer to initially probe children older than 1 year, because the importance of treating canaliculitis with dacryocystitis makes. Therefore, we may only intubate nasal duct probing in children until daily tearing because these patients are at a higher risk for nondrained duct probe failure and might require tube exchanges.

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Isolated Inferior Rectus Paresis Secondary to a Mesencephalic Cavernous Angioma

Andrew R. Harrison, MD; and Jonathan D. Wirtschafter, MD, FACS

PURPOSE: To report a case of recurrent binocular, vertical diplopia presenting as an isolated, unilateral inferior rectus paresis occurring in a patient with a mesencephalic tegmental cavernous angioma.

METHOD: Case report. A 30-year-old man with recurrent vertical diplopia underwent neuro-ophthalmic examination, laboratory examination, pharmacologic testing, and magnetic resonance imaging and angiography.

RESULTS: Magnetic resonance imaging disclosed a lesion in the mesencephalon consistent with a cavernous angioma. Magnetic resonance angiography was negative.

CONCLUSIONS: Isolated inferior rectus paresis is a rare phenomenon. This unique case involved a patient with recurrent inferior rectus paresis secondary to a mesencephalic cavernous angioma. The disparity between the extent of the lesion and the neuro-ophthalmologic consequences is remarkable. (Am J Ophthalmol 1999; 127:617–619. © 1999 by Elsevier Science Inc. All rights reserved.)

THE CAVERNOUS MALFORMATION IN A VARIETY of locations in the central neuraxis. Each subtle applied by the appearance name is thought to be governed by subpopulations of cells, showing [illegible]

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FIGURE 1. Version show left inferior rectus palsy. Note secondary overaction of right superior oblique and underaction of right inferior oblique.

with the exception of the levator palpebrae superioris muscles, which have a solitary midline subnucleus. Subnuclear oculomotor lesions are rare. We report a case of isolated inferior rectus palsy secondary to a midbrain cavernous angioma.

A 30-year-old man was referred to the Neuro-ophthalmology Clinic at the University of Minnesota for evaluation of binocular vertical diplopia in left gaze. Ten years before his examination, he had a similar episode of binocular vertical diplopia in left gaze that resolved spontaneously over 4 months. Six years before this examination, the patient had another episode that resolved in a similar fashion. Five months before his examination, he again noted binocular vertical diplopia in left gaze. He noted diplopia in primary gaze only when tired. He denied any blepharoptosis. His ocular, neurologic, and systemic histories and reviews of systems were negative. He was taking no medications.

Visual acuity was 20/20 without correction. Pupils were equal, round, and briskly reactive to light, with no relative afferent pupillary defect. Dilation of the right eye were normal. The left eye had moderately severe limitation of depression when the eye was abducted (Figure 1). In primary gaze, there were 4 prism diopters of left hypertropia. This increased with left gaze and with left head tilt. No blepharoptosis or any sign of aberrant regeneration of the third cranial nerve was present. Bilateral Maddox rod testing disclosed no excyclotropia. Pentagonating and ophthalmokinetic testing were negative. Cranial nerve testing and neurologic examination were otherwise unremarkable. Ophthalmoscopic findings were normal bilaterally. Lens-sensor diplopia testing was performed and showed left inferior rectus paresis. Forced duction testing was normal. Acetylcholine receptor binding antibodies and thyroid stimulating hormone levels were normal.

Magnetic resonance imaging disclosed a round 1-cm lesion in the left midbrain, impinging slightly on the midline. The mass had a core of hypointensity with a rim of hyperintensity on the T$_2$-weighted gradient echo images (Figure 2). The lesion did not invariably enhance with the administration of gadolinium. Magnetic resonance angiogram was negative. The diagnosis of cavernous angioma of the midbrain was made, and the patient was referred for neurosurgical evaluation. His case is being managed with conservative observation.

Apart from focal neurologic deficits, other clinical presentations of cavernous angioma include seizures and headache. The annualized bleeding rate is less than 1%. Occult hemorrhages occur more frequently than overt hemorrhage.

Isolated inferior rectus palsy without mechanical abnormalities is a relatively rare phenomenon. The diagnosis of isolated inferior rectus paresis is based on evaluation of duction and versions. Ancillary clinical signs such as the

FIGURE 2. T$_2$-weighted sagittal magnetic resonance image shows a 1-cm mass lesion of mixed signal intensity with central hyperintense signal surrounded by a hypointense ring in the tectum-cerebellum at the level of the superior colliculus.

Convergence level of the eyes and the presence of cyclodeviation are rarely helpful in diagnosing this condition.[1] In our patient, the head tilt test gave the predictable response of increased deviation with tilt to the ipsilateral side. Isolated inferior rectus palsy has been described with myasthenia gravis.[2] Fisher reported cases in the literature are thought to be caused by midbrain infarction.[3,4] The reported cases of available vascular, demyelinating, and metastatic disease. Skew deviation was not considered in this case because of the medical examinations of the cerebellum. Cases of midbrain cavernous angiomas have been reported that cause dysconjugate gaze palsy, vertical gaze palsy, and other.[5] The present case extends the clinical spectrum of large solitary cavernous hemangiomas to cause isolated or relatively isolated extraocular muscle involvement by the third cranial nerve.

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Orbital Chondrosarcoma Developing in a Patient With Paget Disease

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PURPOSE: To describe the radiologic, histopathologic, and cytogenetic features of an orbital chondrosarcoma developing in a patient with Paget disease.

METHODS: A 66-year-old woman presented with rapidly progressive proptosis of her right eye. Computed tomographic scans, histopathologic examination, and cytogenetic analysis were performed.

RESULTS: Computed tomographic scans disclosed osseous changes of the temporal and frontal bones, with areas of high density consistent with Paget disease. A soft-tissue tumor in the right lateral orbital wall was consistent with Paget sarcoma. On histology, a chondrosarcoma was diagnosed, which was confirmed by fluorescent in situ hybridization.

CONCLUSION: This is a unique case of orbital chondrosarcoma developing in a patient with Paget disease. [Am J Ophthalmol 1996;122:619–621. © 1996 by Elsevier Science Inc. All rights reserved.]

The [illegible] Paget disease is well established. The overall frequency [illegible] changes is low (1% to 3%).[1]

A 66-year-old woman with a 2-month history of progressive and painful proptosis of the right eye, restricted eye movements, and diplopia was referred to the Eye Hospital Rotterdam. Her head ophthalmologist found that she had a visual acuity of 20/40 20/20, normal pupillary reflexes, and normal findings on ophthalmoscopy. Her intraocular pressure was RE 23 mm Hg. A tumor in the right orbit was diagnosed. Upon referral, she had total loss of light perception in the right eye, proptosis that increased from 3 to 12 mm, and the globe was displaced medially and inferiorly. She had progressively severe pain accompanied with [illegible] [illegible] conjunctival chemosis, and vascular congestion caused by compression in the temporal bone and the lacrimal gland area. [illegible] were found also palpable.

The initial computed tomographic scan disclosed osseous changes of the entire skull, with cranium bone thickness

Accepted for publication [illegible] 1995.

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This paper was presented at the Dutch Ophthalmic Society, May 28 to 31, 1995, Noordwijk, Rhenen.

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AFTERIMAGES

ANDREW HARRISON AND MICHAEL LEE, EDITORS

The Woman Who Needed a Pet

Michelle Atchison, BA,[1] Andrew R. Harrison, MD,[1,2] and Michael S. Lee, MD[2]

[1]Department of Ophthalmology, and [2]Otolaryngology, University of Minnesota, Minneapolis, Minnesota, USA

Abstract. A 72-year-old woman developed difficulty reading, driving, and playing dominoes. Ophthalmologic examination revealed a homonymous hemianopia, but brain MRI showed no abnormality to explain the visual field defect. Neuropsychiatric testing demonstrated severely impaired visual processing (simultagnosia, visual apraxia, visuospatial difficulty). Positron emission tomography revealed hypometabolism of both parietal and occipital lobes consistent with posterior cortical atrophy or the visual variant of Alzheimer disease. Functional neuroimaging should be considered in the setting of a normal MRI finding patients with signs and symptoms of the visual variant Alzheimer disease. (**Surv Ophthalmol 51:**155–159, 2006. © 2006 Elsevier Inc. All rights reserved.)

Key words. homonymous hemianopia • positron emission tomography • posterior cortical atrophy • visual variant of Alzheimer disease

Introduction

Posterior cortical atrophy, a form of Alzheimer disease, presents with visual symptoms that develop years before dementia. In recent years, it has also been described as the visual variant of AD (VVAD).[1] It develops in late middle age, with a mean age of onset of 60.8 years,[1,2] whereas AD typically develops much later in life with a mean onset at 82.3 years.[1,3] Although VVAD develops earlier than Alzheimer disease, the course progresses more slowly, with global dementia symptoms developing after approximately 5.0 years.[1]

The visual symptoms commonly consist of difficulty reading and reading despite a structurally normal eye examination with normal visual acuity. Other features include an inability to name a visualized object (visual agnosia), an inability to recognize a complex scene (simultagnosia), difficulty dressing, and visuospatial environmental disorientation. Although patients with Alzheimer disease may also demonstrate the above visual symptoms,[1] patients with VVAD do not develop more typical findings of Alzheimer disease such as memory dysfunction or disruption of language fluency until much later in the disease course.[1,2,4,5,6,7,8,9,10] Visual field testing in VVAD may reveal a homonymous hemianopia or constriction of the visual fields in the setting of a normal magnetic resonance imaging (MRI) of the brain.[9]

We report a woman with prominent visual symptoms and normal neuroimaging. Positron emission testing (PET) and neuropsychiatric testing revealed the typical findings of VVAD.

Case Report

A 72-year-old white woman presented with difficulty reading, trouble finding objects, and loss of visual contrast beginning 1 year prior. She described her difficulty with reading as "the words run together or overlap." This visual disturbance caused her to give up reading, driving, and playing bridge and dominoes. The patient denied any difficulty with her memory.

Her past medical history included osteoarthritis, mild sensory neuropathy, restless-leg syndrome, and hypothyroidism for which she took celecoxib, tizanidine, amitriptyline, sertraline, and levothyroxine. Her family history was significant for a brother that died at age 68 with frontotemporal dementia (Pick disease).

On examination, she was alert and oriented, with normal attention, concentration, language, memory, and fund of knowledge. Ophthalmologic examination revealed best corrected visual acuity of 20/70 OD and 20/30 OS. The pupillary examination was normal. The patient could identify only the control Ishihara color plate, but successfully identified 5/5 large colored objects with each eye. Upon Amsler grid testing, the patient had difficulty comprehending what she saw on the grid. Automated perimetry revealed an incongruous left homonymous hemianopia (Fig. 1). Fundus examination demonstrated healthy optic nerves bilaterally with evidence of mild macular drusen. Slit-lamp examination revealed lenticular changes consistent with her visual acuity. A pattern stimulated visual cortical response revealed amplitudes and latencies for each eye that fell within normal limits.

MRI of the brain and orbits with and without gadolinium showed minimal chronic white matter disease (Fig. 2). A PET scan of the brain demonstrated bilateral hypometabolism of the occipital and parietal regions, right more severe than left (Figs. 3 and 4). She underwent formal neuropsychological testing. Her performance was within normal limits for the Boston naming test, Wisconsin card sorting test, Wechsler memory and adult intelligence tests, the trail making test, and semantic fluency tests indicating that her verbal

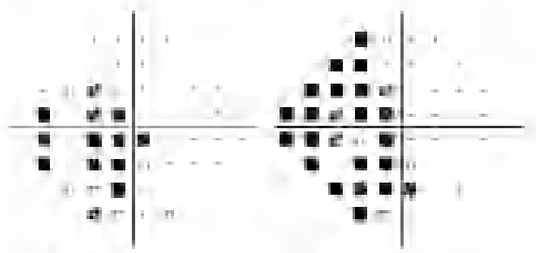

Fig. 1. Patient displays posterior cortical atrophy with incongruous homonymous hemianopia. The right visual field (right hemisphere) is more affected than the left (left hemisphere).

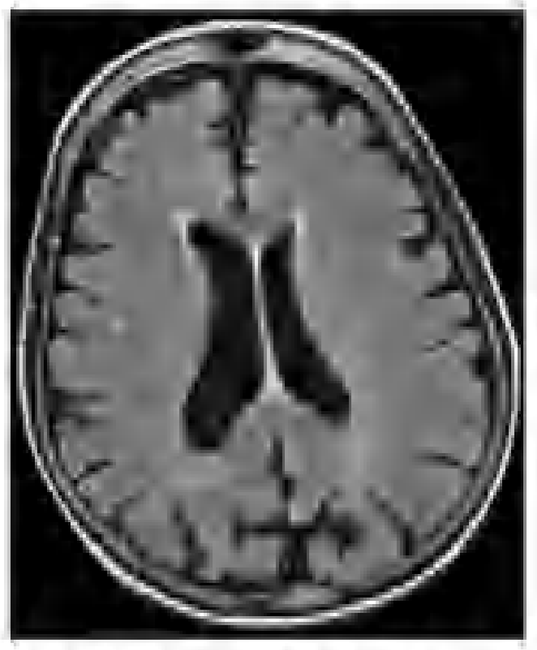

Fig. 2. Axial fluid-attenuated inversion recovery (FLAIR) gadolinium-enhanced MRI demonstrates age-related, mild white-matter disease and generalized atrophy.

functioning and memory were relatively intact. Novel problem solving including strategies and solutions fell within the normal range for her age and education. Basic visual perception including matching lines, angles and geometric shapes was within normal limits for her age. Complex visual processing was severely impaired including mental rotation of objects (visuospatial difficulty), completion of complex designs (visual construction difficulty), confrontation naming (visual agnosia), and description of complex scenes (simultagnosia). Her ability to identify colors but not the Ishihara color plates likely reflected this. Several of her naming difficulties could be overcome with verbal cues. This pattern of impairment was consistent with posterior cerebral involvement from VVAD.

Discussion

The visual symptoms of VVAD presumably result from interference of visual projections to the dorsal stream or visual processing found in the parietal and occipital lobes.[11] Histopathologic examination of cerebral tissue from patients with VVAD has revealed the same changes seen in Alzheimer disease: senile plaques and neurofibrillary tangles.[1] Gamboa-Gomez et al reported that the visual loss of Alzheimer

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doi:10.1016/j.survophthal.2006.08.009

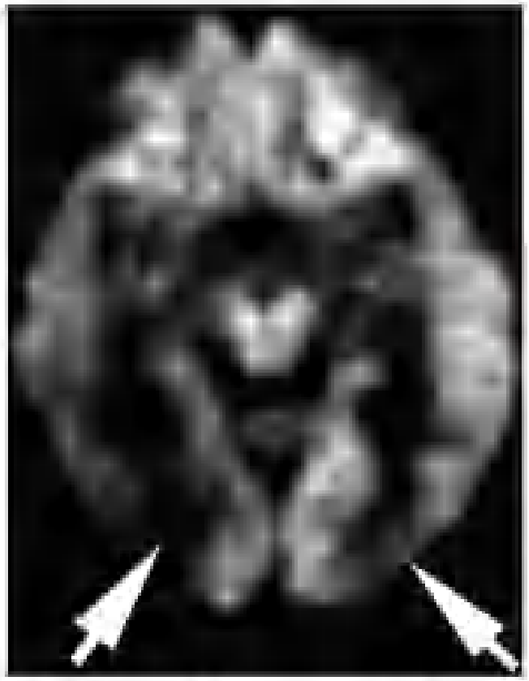

Fig. 3. PET shows hypometabolism in the parieto-occipital lobes bilaterally (arrows). The right parieto-occipital lobe (left arrow) displays much less activity than the contralateral side.

disease resulted from the density of neurofibrillary tangles in the visual association cortex, and appears unrelated to senile plaques.[3] Thus, VVAD symptoms are likely caused by the development of neurofibrillary tangles within the dorsal visual stream.

Neurofibrillary tangles do not appear on brain MRI. Although neuroimaging studies may be normal, they also may demonstrate focal posterior, bilateral atrophy in the VVAD.[11] When present, localized atrophy may help differentiate VVAD from AD and Pick disease. Although overlap exists, the atrophy of VVAD affects the parieto-occipital lobes. Alzheimer disease tends to affect the parieto-temporal lobes and Pick disease characteristically involves a fronto-temporal distribution.

PET and single-photon emission computed tomography (SPECT) have shown promise for use in diagnosing cortical visual loss. The PET measures tissue uptake of injected radionuclide-tagged molecules by detecting emission of gamma rays that occur after the radionuclide uptake. The most commonly used PET radionuclide is fluorine-tagged glucose, which allows estimation of local metabolic rate of glucose consumption. The SPECT involves injection of gamma-ray emitting radiopharmaceuticals that release gamma rays detected by the CT scanner

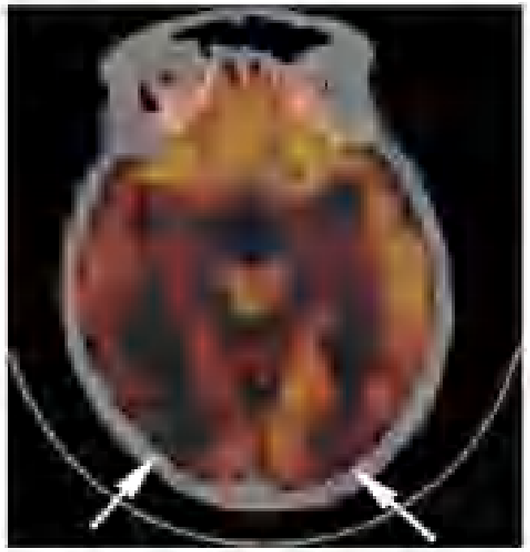

Fig. 4. Fusion of PET and computed tomography (CT) images improves localization and highlights the anatomical localization of hypometabolism in the parieto-occipital lobes (arrows) than PET scanning alone (compare to Fig. 3).

SPECT imaging is used to demonstrate alterations in blood flow within tissues. PET imaging is more sensitive and has better spatial resolution (5–8 mm compared to 7–8 mm for SPECT) but is significantly more expensive than SPECT.[12–14]

These imaging techniques have proven useful in detection of cortical visual loss despite normal MRI imaging. One study showed altered cerebral blood flow through the corresponding visual pathways on SPECT imaging in patients with visual loss due to brain injury, cerebral ischemia, carbon monoxide exposure, status epilepticus, and Alzheimer disease, although MRI scanning was normal or nondiagnostic.[15] Another study reported two patients initially diagnosed with functional vision loss after normal MRI and CT imaging. Subsequent, thereafter, glucose PET scanning revealed that occipital hypometabolism was the source of their visual loss.[16] Other diagnostic consideration with a similar constellation of findings as the patient herein (vision loss, normal neuroimaging, visuospatial deficits, abnormal PET) include progressive multifocal leukoencephalopathy, Creutzfeldt-Jakob disease (CJD), and bilateral stroke.

The pattern herein that a normal brain MRI and PET scanning was essential in making the diagnosis of the VVAD. The PET scan displayed the typical features of bilateral and asymmetric cerebral hypometabolism of the parieto-occipital regions. The right hemisphere is often more severely affected

than the left hemisphere in most patients with VVAD.[14] The hypometabolism seen on PET in patients with VVAD is significantly different from the PET of patients with Alzheimer disease. Thus, the hypometabolism of VVAD cannot be accounted for by atrophy alone, but likely results from a decrease in functional activity of the brain.[1]

Some reports have found that some patients with Alzheimer disease exhibit thinning of the retinal nerve fiber layer (RNFL) and abnormal pattern electroretinogram results.[17] Autopsy results of patients with Alzheimer disease shows a predominant loss of the M cell retinal ganglion cells within the optic nerve.[17] These authors suggest that optic nerve degeneration may cause the abnormal visual fields and visual evoked potentials (VEP) seen in these patients. Our patient did not have Alzheimer disease and we were unable to find a reference to posterior cortical atrophy or VVAD with optic atrophy. We did not obtain optical coherence tomography or ERG testing in our patient, but she had a normal pattern shift VEP, which strongly argues against anterior visual pathway disease.

Autopsy studies and case reports have described neuroimaging results in treating VVAD with anticholinesterase drugs. Patients taking donepezil have shown increased perfusion on SPECT imaging and improved neuropsychological testing.[18]

Conclusion

In this report, we have summarized the presenting symptoms and diagnostic course of a patient with the visual variant of Alzheimer disease. This disorder warrants consideration in older patients complaining of difficulty reading or vague visuospatial disturbances unexplainable by routine ophthalmologic examinations. Although MRI imaging may demonstrate posterior cortical atrophy, some patients with VVAD may have normal MRI results. In these patients, PET scanning may aid in the diagnosis of VVAD by revealing hypometabolism of the parieto-occipital lobes. Early treatment may slow the progression of signs and symptoms related to VVAD.

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Review

A guide to dosing in the treatment of cervical dystonia and blepharospasm with Xeomin®: A new botulinum neurotoxin A

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ABSTRACT

Xeomin® (Incobotulinumtoxin; Merz Pharmaceuticals, Frankfurt-am-Main, Germany) was first introduced in Germany for movement disorders in 2005. In 2010 it was approved for use in the United States by the FDA for the treatment of cervical dystonia (CD) and blepharospasm. It is a unique botulinum type A formulation free of any complexing proteins and contains only the pure 150 kD neurotoxin. Thus, the formation of neutralizing antibodies is not induced even after long-term treatment. The purpose of this report is to review the safety profile and dosing schedule for Xeomin for the treatment of CD and blepharospasm.

The recommended dose for patients with CD is 120 U/treatment, with administration intervals normally between 3 and 6 months. However, clinical studies have found Xeomin to be safe and effective at doses up to 400 U, in both previously treated and treatment-naïve patients. The recommended starting dose in patients with blepharospasm is 2.5–5.0 U/injection site. Patients can be switched using a 1:1 conversion ratio from Botox® (onabotulinumtoxinA, Allergan Inc., Irvine, CA, USA) to Xeomin without any loss of efficacy or safety concerns. Xeomin does not differ from Botox in terms of its tertiary, spread diffusion profile, or duration and waning of effect. It is the only botulinum treatment that is stable for up to 3 years at room temperature. Xeomin offers a new and important (additional) option for movement disorders.

Contents

1. Part I

1.1. Xeomin overview

In the United States incobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals, Frankfurt am Main, Germany) is indicated for the treatment of adults with cervical dystonia (CD) to decrease the severity of abnormal head position and neck pain in both botulinum toxin (BoNT)-naïve and previously treated patients and blepharospasm in adults previously treated with onabotulinumtoxinA (Botox®; Allergan Inc., Irvine, CA, USA) [1].

The clinical effect of Xeomin begins to appear within 4 days of injection, peaks at approximately 4–6 weeks, and is sustained for about 3–4 months. When injected directly into muscles, Xeomin inhibits focal neuromuscular cholinergic transmission, causing

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focal weakness. It binds at motor nerve terminal membrane receptors, is internalized via receptor-mediated endocytosis, and then proteolytically cleaves a protein called SNAP-25, one of several "SNARE" proteins involved in cholinergic discharge of vesicles. This inhibits the release of acetylcholine, causing a localized weakness of the muscle [2].

Xeomin is a highly purified neurotoxin complex produced by Clostridium botulinum type A, free of any accessory complexing proteins, hemagglutinins and non-hemagglutinating components. Xeomin is available as 50 kD neurotoxin and no laboratory immunoassay tests exist for antibodies [3]. However, in trials by Merz, first in 1997 by Dressler, the incidence of neutralizing antibodies was found to be 0% [4]. In another study, monkeys were treated with Xeomin, Botox, or placebo, and then challenged with increasing doses of botulinum toxin A. Monkeys treated with Xeomin developed significantly higher neutralizing antibody titers than those treated with Botox [5]. In a study by Dressler et al., the frequency of antibody formation after onabotulinumtoxinA treatment is very low and infrequently leads to loss of efficacy [6].

A preliminary study in NMD patients demonstrated that adjacent treatment with Xeomin did not reduce the formation of BoNT-A neutralizing antibodies [7]. In an ongoing study evaluating the immunogenicity of Xeomin in all treatment-naïve and all previously treated (i.e., those onabotulinumtoxinA) dystonia patients (n = 1,226), Xeomin (incobotulinumtoxinA) vs. Reloxin® (Dysport® from Ipsen Ltd., Slough, UK; abobotulinumtoxinA) vs. Neurobloc® (Myobloc®, Solstice Neurosciences Inc., Malvern, PA, USA; rimabotulinumtoxinB), fatal dystonia patients were switched to Xeomin. After 2 years, treatment-developed neutralizing immunoresponses to BoNT-A antibodies [8]. Recently reported data from a study in 347 patients with upper limb spasticity showed that even after a mean duration of exposure to Xeomin of approximately 61 weeks (median dose 594 U) upper limb/dose dose 1911 U) no patient developed neutralizing antibodies [9].

Animal studies have established the safety profile of Xeomin in lipolysis-free rodent and non-rodent toxicity models. No unexpected findings were seen that would impact the clinical safety profile [10]. Xeomin did not interact negatively with various commonly co-prescribed pharmacologic agents, including anticholinergics, botulinum toxin type B, and aminoglycoside antibiotics. Xeomin is devoid of systemic effects on the cardiovascular and neuromuscular conduction velocity in cynomolgus monkeys up to dose levels at least 3 times the recommended therapeutic human dose in monkeys [7]. In this, intramuscular (IM) injections of Xeomin at least 3 times higher than the maximum recommended human dose had no effect on gastrocnemius muscle [8]. Finally, in an acute intravenous toxicity study in mice, the lowest dose (50% mortality) was 16,000 times the recommended therapeutic maximum dose of 600 units dose (1,600–2,400 units/kg) by intraperitoneal injection in primates with CD [11].

Animal to the way were not to water for 4 hours at room temperature [12]. In a comprehensive real-time and environmental stability study found no environmental circumstances of Xeomin vials, no abnormal effects on the activity of Xeomin were observed after exposure to temperatures between 40° and 80 °C for up to 1 month [13].

Xeomin is available in 50-U and 100-U vials [14]. One hundred units of Xeomin contains approximately 0.9 ng (900 pg) of clostridial protein, compared with 75 ng for Myobloc, 5 ng for Botox, and 12.5 ng for Dysport [15]. The recommended dose for patients with CD is 120 U per treatment session [1], with administration intervals normally between 3 and 6 months [16].

In patients with blepharospasm, the dose, efficacy and tolerance of treatment should be based on the previous history in naïve. If the dose is not known, the recommended starting dose is 2.5–5 U per injection site [17]. In a placebo-controlled trial in which patients were dosed with the same number of units as they had previously received with Botox, the mean duration was 93.0 days (range 60–240 d), and the mean number of injections per year was 3.9. The maximum dose per eye in the controlled trial was 50 U, with a range of 10–50 U in the controlled trial. Two patients received a total dose of greater than 75 U [18].

There is some variation in dose regimen. After 4 weeks' treatment, 4–16 U of Xeomin administered to the medial (EDB) muscle of healthy volunteers, a dose-response relationship for efficacy and duration of effect was apparent when comparing the lowest dose (4 U) with the highest dose (16 U). But not the intermediate dose (8 U). In a phase III dose-ranging study, the optimum balance between efficacy and safety was observed with the 100-U dose (i.e., 50 U in the corrugator muscle and 50 U in the orbicularis oculi muscle) [19].

Prior to injection, Xeomin should be reconstituted with sterile preservative-free 0.9% Sodium Chloride Injection USP using the diluent volume specified in the product prescribing information [1]. Each reconstituted Xeomin vial is labeled to administer a certain # of units/0.1 mL, from which the desired dose should be calculated. It is important to note that the dilution volume is not the same as the injection volume [20].

As Xeomin is a relatively new product in the United States and investigators may be unfamiliar with dosing, this review will discuss the 1:1 conversion between Xeomin and Botox and the advantages of using Xeomin for treating movement disorders.

2. Part II

2.1. Xeomin clinical trial dosing experience

Xeomin has been used widely in doses of up to 400 units over [illegible] without loss of secondary treatment failure [1]. In patients previously treated with Botox switched to Xeomin, there were no differences in adverse events, treatment and duration of treatment effects, adverse events profile or long-term use profile. The parameters of the Jankovic (TWSTRS) ... 971 and Tsui ... 7) [21] were not statistically different ($p = 0.71$) [19]. The patients were determined using the ED_{50} (average dose ... the dose that ... Botox) ... Xeomin in a blinded fashion. Dose equivalence was performed using the Xeomin reference standard qualified against the WHO standard. The statistical parameters for the 3 assays were within the range specified in the European Pharmacopoeia. A sensitive assay for BoNT/A proteolytic activity [illegible] and potency [illegible] against the Hall A strain of BoNT-A was established in the mouse [illegible] type A, showed that the ratio of lethal potency [illegible] constant (LD ng: ED ng) and that ng of BoNT-A, respectively, with the highest specific activities among BoNT/A [illegible] [22].

Although ED_{50} is usually the assay parameter used to test the biological activity of botulinum neurotoxins, many pharmacologists use very sensitive mouse models. For this reason, the most informative comparisons between BoNT assays has been made in clinical studies in clinical trials in patients. Both CD (total dose) ranged from 70 to 400 U [19] [illegible] ... [illegible] and dystonia (range from 120 [illegible]). Xeomin was as effective and safe as Botox when used at a clinical conversion ratio of 1 U:1 U. Thus, starting doses of Xeomin and Botox can be used allowing conversion of both BoNT drugs in a therapeutic setting [19].

In a prospective, randomized, double-blind, parallel-group study of 18 and 200 U of Xeomin in 233 patients with CD, the change in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores at 4 weeks was significantly greater in patients of Xeomin compared with placebo ($p = 0.0001$). The lack of an efficacy difference between the 2 doses suggested to the study was explained by the fact that the study was not powered to assess

3. Conclusions

Acknowledgements

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Annual Meeting of the American Academy of Neurology: 10–17 April 2010; Toronto, Ontario, Canada.
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Patient use of Visine (tetrahydrozoline) masks Horner syndrome

CASE REPORT

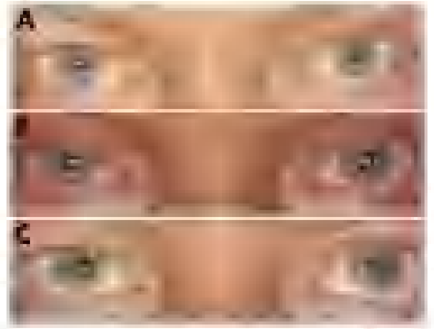

Figure 1 (A) One hour after taking tetrahydrozoline HCl 0.05%, there is no sign of Horner syndrome on observation; the patient's pupils are nearly equal in size with only a slight right miosis. There is no evidence of ptosis or asymmetric conjunctival injection. (B) Twenty-four hours after discontinuing tetrahydrozoline HCl 0.05%, the patient has anisocoria with the right pupil smaller than the left. The right upper lid is hyperaemic and the conjunctiva is injected. There is also now evidence of "upside down" ptosis of the right lower lid compared with the left lower lid. (C) Thirty minutes after the instillation of apraclonidine 0.5%, the anisocoria in room light and right lid ptosis have reversed [illegible] consistent with a right Horner syndrome. The right pupil is now [illegible] larger than the left. Informed consent was obtained for publication of this figure.

REFERENCES

COMMENT

PostScript

REFERENCES

Cocaine-induced chorioretinal infarction

CASE REPORT

COMMENT

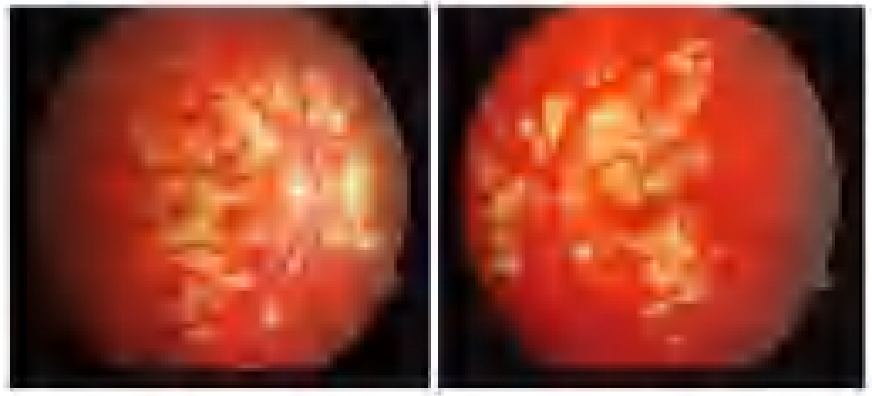

Figure 1 Fundus photographs of right and left eyes of patient showing [illegible]

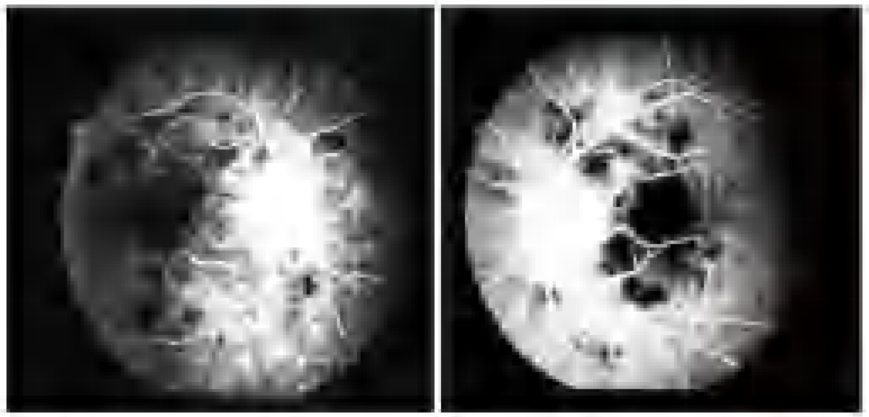

Figure 2 Fundus fluorescein angiograms of right and left eyes of patient showing [illegible]

Dissociating Averageness and Attractiveness: Attractive Faces Are Not Always Average

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phologists (Perrett, Kaping, Moriguchi, & Dittrich, 2003; Wolfe & Maclin, 1991) but the effect of visual expertise in faces is also a common task (e.g., increased eye spacing) on perceptions of novel faces and averaging changes in perception to some function of this central average. Visual adaptation is thought to alter the central tendency for the perception of subsequently viewed faces, such that stimuli that are perceived as more average after adaptation to a face (and adaptation to a face itself) increase both the perceived normality and attractiveness of faces physically similar to those recently seen (Rhodes et al., 2003; Little, DeBruine, & Jones, 2005; Rhodes, Jeffery, Watson, Clifford, & Nakayama, 2003), supporting the averageness hypothesis.

However, rather than attractiveness being solely a function of closeness to an internal prototype, the computational simplicity may be a measure of distance along certain dimensions in face space relevant to an internal prototype (Perrett et al., 1994). As face shape deviates from average in one direction along this dimension, attractiveness will increase. However, deviations from average in the opposite direction on the "shape-related" dimension would reduce attractiveness. Thus, one can even create a positive relationship and distance (not average) between stimuli and a prototype in a certain direction (that is, as the distance between stimuli and prototype increases, attractiveness increases) but maintain distinctiveness and judgments of typicality (i.e., stimuli can be distant from the prototype but still be typical).

Perrett et al. (1994) tested these competing hypotheses in an effort to establish whether averageness or the critical determinants of the attractiveness of faces. Perrett et al. (1994) found that composites of 60 faces were judged as less attractive than composites of 15 faces, but composites of 15 faces were not judged as more attractive than composites of 30 faces. Perrett et al. (1994) concluded that the averageness hypothesis could not explain the attractiveness of faces, but that the shape of faces was important in determining attractiveness. However, Perrett et al. (1994) did not control for the number of faces in the composites when manipulating the distance between the shape of individual faces and the average shape. Therefore, it is unclear whether the decrease in attractiveness with increasing distance from the average face was due to the distance between the shape of individual faces and the average shape or to the number of faces in the composite. Indeed, Perrett et al. (1994) found that composites of 15 faces were rated as more attractive than composites of 2 faces, which is consistent with the averageness hypothesis.

The averageness hypothesis was rejected by Rhodes, Langlois, and Rhyngans (2001). They suggested that if highly attractive faces are mathematically closer to average than composites of 15 highly attractive faces should be, then composites of 15 highly attractive faces should be perceived to have undergone the same transformation (i.e., have moved the same distance) from average as composites of 15 highly attractive faces. Rhodes et al. (2001) failed to replicate the results of Perrett et al. (1994), finding that composites of 15 highly attractive faces were rated as more attractive than composites of 30 highly attractive faces. Rhodes et al. (2001) concluded that the averageness hypothesis could not explain the attractiveness of faces. Perrett et al. (1994) found that composites of 60 faces were judged as less attractive than composites of 15 faces, but composites of 15 faces were not judged as more attractive than composites of 30 faces. Perrett et al. (1994) concluded that the averageness hypothesis could not explain the attractiveness of faces, but that the shape of faces was important in determining attractiveness. However, Perrett et al. (1994) did not control for the number of faces in the composites when manipulating the distance between the shape of individual faces and the average shape. Therefore, it is unclear whether the decrease in attractiveness with increasing distance from the average face was due to the distance between the shape of individual faces and the average shape or to the number of faces in the composite. Indeed, Perrett et al. (1994) found that composites of 15 faces were rated as more attractive than composites of 2 faces, which is consistent with the averageness hypothesis.

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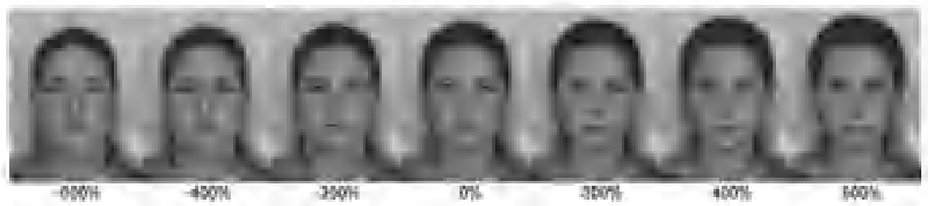
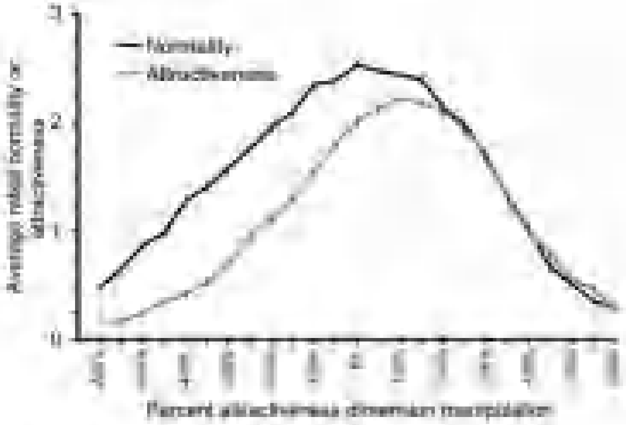


Figure 1. A series of faces ranging from -600% to 600% of the face's shape from average.

Figure 2. The composite of other female faces (A) and the composite of those same faces with the addition of one extra face (B). Adapted from "Is Attractiveness Universal or Culturally Determined? A Meta-Analysis of the Relationship Between Facial Symmetry and Attractiveness Ratings," by G. Rhodes, 2006, *Journal of Evolutionary Psychology, 4*, p. 4. Copyright 2006 by Akadémiai Kiadó.

it may be a population's mean shape that differs from the mathematical average of the faces seen by most people in the population. For example, Mazur et al. (2001) have shown that both men and women of mixed ethnicity tended to have smaller noses in combination with the frequency of negative facial affect. That is, we assume that a certain type of face could result in facial maturity, normality, and sexual dimorphism that are not symmetrically different from the population average (e.g., Perrett et al., 1998) and predictive for mating decisions. One prediction from these findings is that perceived averageness would be based on a mathematical average in the same way that attractiveness judgments are.

Independent variables and predictions. Experiment 1 was identical to Experiment 1 of Rhodes et al. (2001). Rhodes et al. (2001) found that composites of 15 highly attractive faces were more attractive than composites of 30 highly attractive faces. Experiment 1 of Rhodes et al. (2001)



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Discussion

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Experiment 2: Attractiveness of Images Equidistant From Average

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Method

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Results

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Discussion

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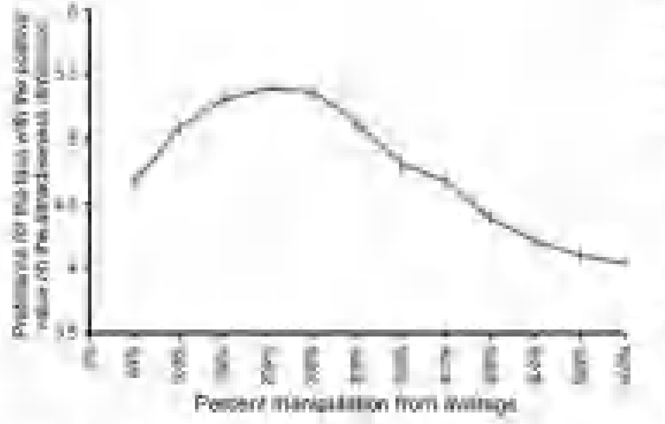

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Experiment 3: Attractiveness of Adjacent Images

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Method

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Results

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Discussion

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Experiment 4: Attractiveness of All Possible Pairs

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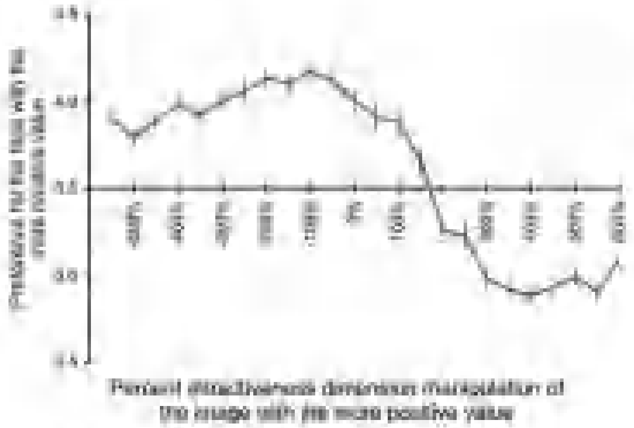
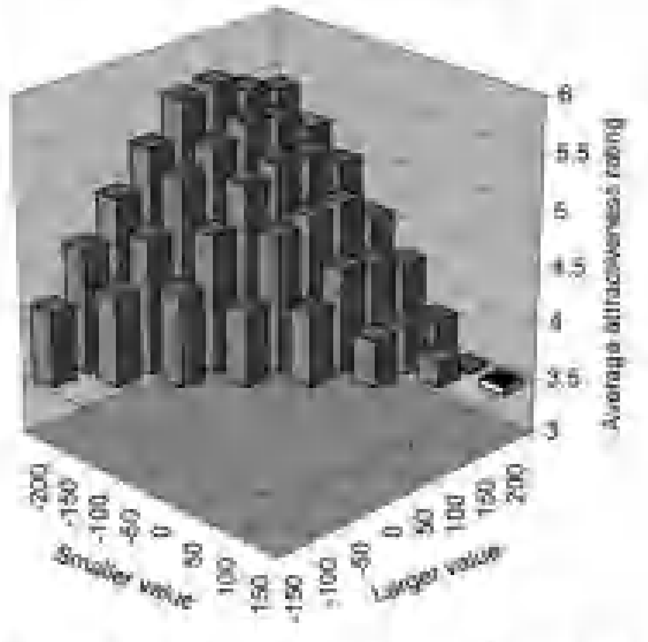


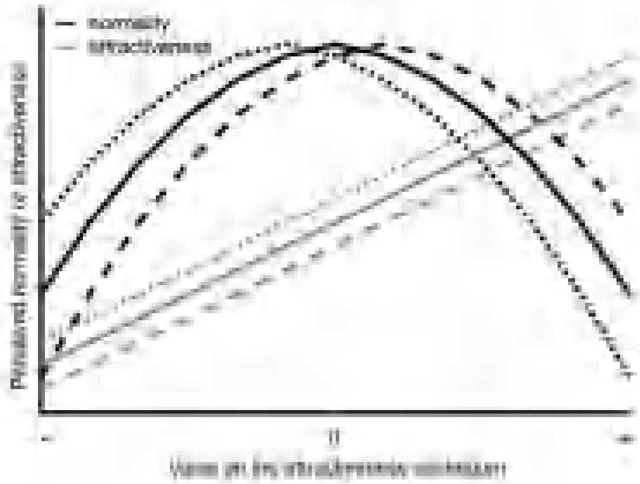
Discussion

Experiment 5: Effects of Visual Adaptation on Attractiveness and Normality

Method

Results





Method

Figure 3. Examples of individual faces morphed to attractiveness (top row) and toward or away from the composite of 20 individuals (average on attractiveness (top right) and distorted in attractiveness (bottom right). A color version of this figure is available on the Web at http://dx.doi.org/10.1037/0096-1523.35.4.1420.supp

ratings of faces (RS such as the attractive and unattractive composite faces (see Figure 3, for stills images) on a scale from 1 to 7. Specifically, participants in the attractiveness rating task were asked, "Please rate how attractive you think this person is by typing a number 1 (very unattractive) to 7 (very attractive)," and participants in the normality rating task were asked, "Please rate how normal you think this face is by typing a number 1 (not normal) to 7 (very normal)." Pressing the other keys also (typing a rating outside the scale) would lead participants to go back to change their answers. The order of trials was fully randomized. Participants completed each trial at their own pace.

Next, participants completed an adaptation phase, which consisted of passive viewing of 20 unfamiliar female faces that had been manipulated by either 150% attractiveness (+150% prototype-face distance) or 50% unattractiveness (−50% prototype-face distance) (see Figure 3). Each face was presented for 3 s in a fixed random order.

In the postadaptation phase, participants repeated the final rating task.

Results

Initial analyses. All data were analyzed using a mixed-design ANOVA, with phase (preadaptation, postadaptation) and composite attractiveness (attractive, unattractive) as within-subjects factors, and exposure type (attractive, unattractive) and judgment (attractiveness, normality) as between-subjects factors. A 3-way interaction among phase, composite attractiveness, exposure type, and judgment, $F(1, 124) = 3.97$, $p = .048$, $\eta^2 = .031$, indicated that exposure to attractive and unattractive individual faces did not affect attractiveness judgments and normality judgments of attractive and unattractive faces in the same way. All other significant effects were qualified by this 3-way interaction.

In other words, the pattern of results for attractiveness judgments differed from that for normality judgments, justifying the analyses described below. Next, we carried out separate analyses for attractiveness and normality judgments to determine the nature of these different patterns.

Attractiveness judgments. Attractiveness judgments were analyzed using a mixed-design ANOVA with phase (preadaptation, postadaptation) and composite attractiveness (attractive, unattractive) as within-subjects factors and exposure type (attractive, unattractive) as the between-subjects factor. A main effect of phase, $F(1, 126) = 6.61$, $p = .005$, $\eta^2 = .052$, was qualified by an interaction between phase and exposure type, $F(1, 126) = 19.5$, $p < .001$, $\eta^2 = .134$ (see Figure 4). A main effect of face attractiveness, $F(1, 126) = 427.7$, $p < .001$, $\eta^2 = .773$, confirmed that the attractive composite was judged as more attractive than the unattractive composite. No other effects were significant (all $Fs < 1.1$, $p > .08$, $\eta^2 < .021$).

To interpret the interaction between phase and exposure type, we carried out paired-sample t tests on the change in attractiveness judgments from pre- to postadaptation tests (i.e., postadaptation minus preadaptation) comparing participants who were exposed to attractive individuals to those who were exposed to unattractive individuals. This was done separately for judgments of the attractive and unattractive composites. Exposure to unattractive faces

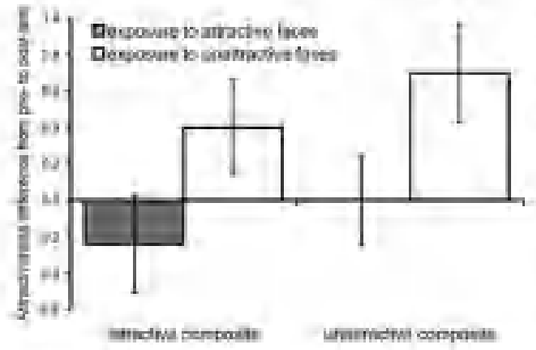


Figure 4. The effects of exposure to attractive and unattractive individuals on the attractiveness ratings of attractive and unattractive composite faces. Error bars show standard error of the means.

increased the attractiveness of attractive faces, $t(148) = 2.78$, $p = .006$, $d = .455$, and the unattractive composite, $t(148) = 3.12$, $p = .001$, $d = .511$, $p < .05$, two-tailed. Normality judgments. Normality judgments were analyzed using the same mixed-design ANOVA, with phase (preadaptation, postadaptation) and composite attractiveness (attractive, unattractive) as within-subjects factors and exposure type (attractive, unattractive) as the between-subjects factor. The only significant effect was an interaction among phase, composite attractiveness, and exposure type, $F(1, 126) = 6.05$, $p = .015$, $\eta^2 = .046$ (see Figure 10). No other effects were significant (all $Fs < 2.17$, $p > .14$, $\eta^2 < .017$).

To interpret the interaction among phase, composite attractiveness, and exposure type, we carried out paired-sample t tests on the change in normality judgments from pre- to postadaptation tests (i.e., postadaptation minus preadaptation) comparing participants who were exposed to attractive individuals to those who were exposed to unattractive individuals. This was done separately for judgments of the attractive and unattractive composites. Exposure to unattractive faces (Whitaker et al., 2008; Skinner et al., 2010).

This pattern contributed to the predictions from the contrast hypothesis. Although Rhodes et al. (2003) have shown that aftereffects are distorted (more affected) both perceived normality and attractiveness in similar ways (see Little et al., 2008), and Jaquet et al. (2008) have shown that exposure to atypically unattractive faces increased preferences for atypical, familiar faces, we did find that exposure to attractive individuals is associated with the decrease in the attractiveness of attractive faces. While this finding is inconsistent with the averageness hypothesis, it is a specific prediction of the contrast hypothesis. Increases perceived averageness (because attractiveness can be distinguished from averageness; see Rhodes et al., 2007) has generally been assumed to underlie the perceptual aftereffects of facial adaptation (Leopold et al., 2001; Rhodes et al., 2003; Webster et al., 2004). Our results show that the aftereffects of facial adaptation are not always attractiveness enhancing. Instead, they can distort face perception in the direction away from averageness and increase attractiveness. What determines the direction of these aftereffects?

Some theories suggest that the exclusive use of highly attractive faces is actually a maladaptive form of exposure, as it encourages a shift away from the norm and, as a consequence, a decrease in attractiveness (Rhodes et al., 2003). This implies that the tipping point at which adaptation to attractive faces is maladaptive (i.e., when it starts to decrease attractiveness) is when the adapting faces are more attractive than the average face. Our results show that exposure to attractive faces can increase attractiveness, even when the adapting faces are more attractive than the average face. Thus, the tipping point is not when the adapting faces are more attractive than the average face, but when the adapting faces are more attractive than the face that is perceived to be most attractive. The results of Experiment 2 show that, for a broad range of values along the attractiveness continuum, the face with the greatest distance in face space from the average face is perceived to be the most attractive face. Thus, the tipping point is when the adapting faces are more attractive than the most attractive face in face space.

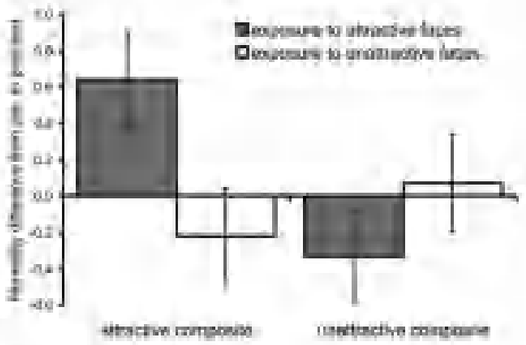


Figure 10. The effects of exposure to attractive and unattractive individuals on the normality ratings of attractive and unattractive composite faces. Error bars show standard error of the means.

General Discussion

The results of the first face-rating experiments (Experiments 1–4) and the visual adaptation experiment (Experiment 5) strongly support the contrast hypothesis, demonstrating that there is a distinction in face space between differences that are attractiveness enhancing, independently of the notion of averageness. That is, moving away from average in one direction in face space (toward attractiveness) can also move you away from average in the opposite direction and decrease attractiveness.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

A review of acquired blepharoptosis: prevalence, diagnosis, and current treatment options

Jason Bacharach[1] · Wendy W. Lee[2] · Andrew R. Harrison[3] · Thomas F. Freddo[4]

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Abstract

Blepharoptosis (ptosis) is among the most common disorders of the upper eyelid encountered in both optometric and ophthalmic practice. The anatomical or functional drooping of the upper eyelid that characterizes ptosis can affect appearance and impair visual function, both of which can negatively impact quality of life. While there are several known forms of congenital ptosis, acquired ptosis (appearing later in life, due to a variety of causes) is the predominant form of the condition. This review summarizes the prevalence, causes, identification, differential diagnosis, and treatment of acquired ptosis. Particular attention is paid to the differential diagnosis of acquired ptosis and emerging treatment options, including surgical and pharmacologic approaches.

Literature search notes

Literature cited in this review was identified via a broad search of the PUBMED online database for English-language, peer-reviewed publications including search terms such as "ptosis," "epidemiology," "etiology," "eyelid," "surgical," "pharmacologic," "Müller's muscle," "aponeurosis," "visual field," and "quality of life." Relevant primary and review articles were reviewed and cited when providing unique primary data or a concise summary of fundamental concepts. After inclusion, when reference were primary or review articles not identified via PUBMED, but cited in publications retrieved via this literature search.

Acquired ptosis overview, prevalence, and impacts

Blepharoptosis, more commonly known as "ptosis," is an abnormal drooping of the upper eyelid with the eye in primary gaze. This drooping can affect one or both eyes, and based on time of appearance, it is broadly classified as either congenital (present at or shortly following birth) or acquired (appearing later in life). Ptosis is broadly recognized as being among the most common disorders of the eyelid encountered in the clinic, however data from large-population-based studies are limited. Estimates of ptosis prevalence are largely based on data from region-specific studies, which report rates between 4.7 and 13.5% in adult populations and support the widespread nature of the condition [1–3]. Furthermore, these studies consistently reveal that within adult populations, the incidence of ptosis increases with age (Table 1 and Acquired ptosis risk factors). Reports of ptosis incidence in surgical populations are consistent with those in broader patient populations. In a study evaluating a cohort of 623 patients referred for surgery in an ocuplastics department in Singapore, ptosis was the most common condition, occurring in 11.7% of patients [4].

Drooping of the upper eyelid due to ptosis can lead to the condition's characteristic "sleepy" appearance as well as asymmetry. In both unilateral and bilateral cases [5, 6], studies reveal that this can have important impacts on patient well-being, including reduced independence and increased appearance-related anxiety and depression [7, 8]. In a study in the United Kingdom, adults referred for ptosis surgery were assessed prior to surgery using validated questionnaires addressing psychosocial factors, including appearance-related distress (the Derriford Appearance Scale (DAS 24)), anxiety and depression (the Hospital Anxiety and Depression Scale (HADS)), fearful or worrying conditions related to the perceived opinions of others (the Fear of Negative Evaluation (FNE) Scale), and self-evaluation of appearance (the Centre for Appearance Research Evaluation (CARVAL) scale). Patients reported levels of appearance-related distress, anxiety, and depression that were higher than typical norms in the general population and similar to levels previously reported in patients with other appearance-altering ophthalmic conditions, such as strabismus [9]. The analysis also identified significant gender differences with respect to DAS 24, HADS, FNE, and CARVAL scores, with female patients reporting higher mean scores than males [7].

From a functional perspective, obstruction of the pupil as a result of ptosis can lead to deficits in the superior visual field detectable via visual field testing and evident even in mild cases [9–11]. An evaluation of the superior visual field using static perimetry testing (Humphrey Visual Field (HVF) Test) in subjects at baseline and after induction of mild or moderate ptosis using eyelid weights found that even mild ptosis was associated with significant depression of all test points along the superior hemifield, and that this worsened as the moderate ptosis condition [11]. Among more recent studies in patients with ptosis, a study validating a novel static perimetry test (the Leicester Peripheral Field Test (LPFT)) revealed that 84 of 85 ptotic eyes had a visual field deficit [10]. Visual field testing methods are described in detail in the section titled Acquired ptosis identification and differential diagnosis.

The effect of ptosis goes beyond diminished performance on visual field tests. Visual field loss is associated with decreases in health-related quality of life (HRQoL) measures [7], indicating meaningful impacts on patients' daily lives. In the Los Angeles Latino Eye Study (LALES), more than 5200 subjects underwent ophthalmic examination and visual field testing. Data from this population revealed that greater visual field loss, measured using the HVF Test, correlated with worse scores on two validated tools to assess HRQoL—the Medical Outcomes Study 12-item Short-Form Health Survey (SF-12) and the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). While bilateral moderate/severe visual field loss was associated with the greatest negative effect on HRQoL measures, decreases in HRQoL were observed in participants with mild unilateral visual field loss [7]. The reductions in HRQoL were found to be, at least in part, due to the reductions in independence (greater difficulty driving and

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Table 1. Studies reporting on the prevalence of ptosis in the general adult population.

Study	Location	Ptosis evaluated	Ptosis prevalence	Data on risk factors
Linxweiler et al. 1988 [12]	United Kingdom	(n = 400 subjects (50 per decade); 20–80 years)	13.5% (54/400 subjects)	Ptosis prevalence increased with age (p < 0.001)
Bacharach et al. 2011 [1]	Singapore	(n = 1232 subjects; 40–80 years)	4.7% (58/1232 subjects)	Ptosis prevalence increased with age (p < 0.001)
Mitchell et al. 1997 [13]	Australia	(n = 3654 subjects; 49+ years)	13.2% (482/3654 subjects)	Ptosis prevalence increased with age (p < 0.001)

performing regular tasks that often rely on visual field details [7]. Studies also show that improvements in subjective and objective visual performance following intervention are associated with improved HRQoL-related measures [12, 13]. In a study of 50 patients who underwent ptosis surgery, patients showed significant improvement versus pre-surgery assessment, with respect to a range of vision-related activities and symptoms, including the ability to perform fine manual work, [illegible] or reach objects above eye level, watch television, and read [12]. Similarly, in a study of 100 patients with unilateral or bilateral ptosis that used the same questionnaire, improvement in the superior visual field following surgery was associated with a greater functional index, and patients had significant improvement with respect to activities including performing their occupation, playing sports, and walking without assistance [13].

The upper eyelid and causes of acquired ptosis

Elevation of the upper eyelid is largely provided by two muscles—the levator palpebrae superioris (levator) and the superior tarsal (Müller's) muscle (Fig. 1). The levator is a voluntary (striated) muscle that originates from the lesser wing of the sphenoid bone at the orbital apex and inserts, through its aponeurosis, onto the anterior surface of the superior tarsal plate. It also has attachments to the skin of the upper eyelid, which contribute to the formation of the lid crease. This insertion is absent or poorly formed in some Asian individuals. The levator is innervated by the superior division of the oculomotor nerve (cranial nerve III), and its contraction provides the majority (~80%) of upper eyelid elevation [5, 14–16]. Müller's muscle arises from the underside of the levator, at the level of the distal aponeurosis, and inserts onto the superior tarsal plate [5, 14, 15]. In contrast to the striated levator muscle, Müller's muscle—like its analogue in the lower eyelid, the inferior tarsal muscle—is an involuntary smooth muscle. With contraction, Müller's muscle helps to sustain upper eyelid elevation provided by the levator, while also supplying 1–2 mm of additional lift [5, 14]. Similarly, in the lower eyelid, the inferior tarsal muscle assists in lowering the lid during downward gaze, though there is no striated muscle analogous to the levator. Both Müller's muscle and the analogous inferior tarsal muscle receive sympathetic innervation from nerve fibers originating in the superior cervical ganglion [5, 14, 15]. A study of adrenergic receptor expression in Müller's muscle revealed a predominance of the α_{2C} subtype, and lower expression of the α_1 and β_2 subtypes [16]. Further examination of receptor subtype expression in Müller's muscle has also demonstrated expression of the α_{1A}, α_{2C}, and β_2 subtypes in patients with ptosis [17, 18]. In contrast to Müller's muscle, the levator predominantly expressed the β_2-adrenergic receptor subtype, with only trace expression of the α_1, α_2, and β_1 subtypes [17].

The frontalis muscle, which inserts at the level of the eyebrows, is innervated by the facial nerve (cranial nerve VII) and its contraction raises the brow, with no direct effect on upper eyelid elevation. In patients with ptosis, however, compensatory raising of the brow via the frontalis muscle can indirectly provide slight elevation of the eyelid as well [19].

Finally, ptosis is classified based on time of onset. Congenital ptosis (present at birth) typically has a unilateral presentation and is most often a result of developmental dystrophy of the levator muscle that affects the levator's ability to contract and raise the upper eyelid [19–21]. Neurogenic forms of congenital ptosis can be caused by cranial nerve III abnormalities or insufficient sympathetic innervation of Müller's muscle. Furthermore, several rare [illegible] syndromes or cranial dysinnervation disorders can also underlie congenital ptosis, including Marcus Gunn jaw-winking syndrome or blepharophimosis [22, 23].

Acquired ptosis, the predominant form of ptosis (Table 2), can be classified by etiology, with cases typically defined as having an aponeurotic, myogenic, neurogenic, mechanical, or traumatic origin. Aponeurotic ptosis,

Fig. 1 Anatomy of the upper eyelid. Adapted from Rodda and Chang, 2011 [14]. The striated levator palpebrae superioris is innervated by the superior division of cranial nerve III and inserts, through its aponeurosis, on the anterior surface of the superior tarsal plate. Except in the eyelids of Asian individuals, the aponeurosis extends fibers through the orbicularis oculi muscle to form the skin crease of the upper eyelid. The smooth Müller's muscle arises from the underside of the levator and inserts on the superior tarsal plate. It is innervated by sympathetic fibers from the superior cervical ganglion [5, 14–16].

Table 2 Summary of common types of acquired ptosis causes and risk factors.

Types of acquired ptosis	
Aponeurotic (involutional)	• Caused by stretching, dehiscence, or detachment of the levator aponeurosis, and is typically associated with aging [5, 10, 24] • Typically presents with reduced MRD-1, high upper eyelid crease, near normal levator function, and decreased PTD [24]
Myogenic	• Caused by primary or secondary myopathy of the levator muscle (e.g., due to OPMD, myotonic dystrophy, or CPEO) [5, 16, 25] • Can present with a weak/absent upper eyelid crease, poor levator function, and [illegible] [25]
Neurogenic	• Relatively rare type of ptosis caused by CNS abnormality or underlying neurological condition affecting the oculomotor or sympathetic nerves [5, 16, 26] • Can have a range of presentations, depending on underlying cause (e.g., Horner's syndrome presents as unilateral ptosis with associated pupil constriction and facial anhidrosis) [5, 16, 26]
Mechanical	• Caused by excess weight on the upper eyelid, usually due to benign or malignant neoplasms (e.g., haemangioma, chalazion, neurofibroma, dermoid cyst) [5, 22] • Can also be "pseudoptosis" (e.g., dermatochalasis, in which levator function is not impaired) [5, 16, 22]
Traumatic	• Caused by trauma to the eyelid retractor muscles, aponeurosis, or neural inputs to the eyelid [22] • Can be myogenic, aponeurotic, or neurogenic in nature [22]
Common environmental risk factors for acquired ptosis	
Age	• In adult populations, prevalence of ptosis increases with age [1–4] • Age-related aponeurotic ptosis is the most common form of ptosis in older adult patients referred for ptosis surgery [10, 11]
Contact lens wear	• Long-term wear of hard or soft contact lenses associated with increased ptosis risk [27–31]
Ocular surgery	• Transient or persistent ptosis associated with a range of procedures, including glaucoma, cataract, [illegible], and [illegible] surgery [10, 32–34] • Risk can be dependent upon surgical technique used [32, 33, 34]
Periocular neurotoxin injection	• Botulinum toxin injections associated with transient upper eyelid ptosis [35–37]

CNS central nervous system, *CPEO* chronic progressive external ophthalmoplegia, *MRD-1* Marginal Reflex Distance 1, *OPMD* oculopharyngeal muscular dystrophy, *PTD* palpebral tissue distance.

the most common acquired form of the condition [24], is caused by stretching, dehiscence, or disinsertion of the levator aponeurosis from its insertion on the tarsus, and is typically associated with aging [5, 10, 24]. Myogenic ptosis is caused by primary or secondary myopathy of the levator muscle, due for example to chronic progressive external ophthalmoplegia (CPEO), oculopharyngeal muscular dystrophy (OPMD), or myotonic dystrophy [5, 16, 25]. Neurogenic ptosis is relatively rare and is typically caused by dysfunction or damage to the oculomotor nerve or to sympathetic nerves innervating the eyelids, or by central mechanisms [5, 16, 26]. Among patients with neurogenic ptosis, the most common underlying causes are oculomotor nerve (3rd cranial nerve) palsy (35.7%), myasthenia gravis (28.6%), aberrant regeneration (14.3%), and Horner's syndrome (7.1%) [26]. Common causes of mechanical ptosis include benign or malignant neoplasms of the eyelid, such as haemangioma, chalazion, neurofibroma, or dermoid cysts, which create excess weight that cannot be raised by the upper eyelid retractor muscles [5, 22]. Finally, acquired ptosis can arise due to trauma to the eyelid retractor muscles, aponeurosis, or neural inputs to the eyelid. Thus, traumatic ptosis can be myogenic, aponeurotic, or neurogenic in nature [22].

Pseudoptosis does not involve pathology of the upper eyelid retractor muscles or aponeurosis, and can be due to mechanical, neurogenic, or anatomical causes. Mechanical causes include dermatochalasis (excessive upper eyelid skin that overhangs the lid margin), brow ptosis (drooping of the eyebrow), and floppy eyelid syndrome (easy eversion of the upper eyelid due to excessive lid laxity). Neurogenic causes include benign essential blepharospasm and hemifacial spasm (unilateral spasm of the upper and lower eyelids). Anatomical causes include microphthalmos (decreased size or volume of the globe) or superior sulcus deformity (deepening of the superior sulcus) [5, 16, 22]. Diagnostic differentiation of acquired ptosis is discussed in the section titled Acquired ptosis identification and differential diagnosis.

Acquired ptosis risk factors

Studies of adult populations consistently reveal age as a significant risk factor for the development of acquired ptosis, with reported prevalence exceeding 20% among patients aged 70 years and older (summarized in the section titled Acquired ptosis—overview, prevalence, and impact).

and in Table 1 [1–6]. In a 1960 study of 468 individuals ≥50 years old in the United Kingdom, 11.5% were determined to have ptosis, with the visible magnitude increasing from 2.4% among individuals aged 50–59 years to 8.5% among individuals aged 60–69 years old and 20.8% among individuals aged ≥70 years [1]. A more recent study of ~6700 Iranian patients 45 to 80 years old reported an incidence of 4.7%, with the lowest prevalence (2.1%) among patients aged 45–49 years and the highest prevalence (7.1%) among patients aged 80–84 years [2]. Another study of 17,200 patients ≥40 years old in Kansai reported an overall prevalence of ptosis of 13.4%, with the lowest prevalence (9.4%) among patients 40–49 years old and the highest prevalence (32.8%) among patients ≥80 years old [3]. Numerous studies also reported higher rates of ptosis in patients with diabetes and hypertension [4–6]. Furthermore, the Kansai study found an association between higher body mass index (BMI) as well as a history of cerebrovascular disease and the presence of ptosis [3]. Individuals with ptosis in this study were also found to be more likely to have hyperopia, cataracts, and tortuosity in comparison to individuals without ptosis [3].

Recent analysis of 284 patients referred for ptosis surgery to an ophthalmic surgery centre in Singapore, aponeurotic ptosis was the most common form of ptosis identified (81.2%). In this study, the median age among patients with aponeurotic ptosis was 62 years. The other most common types observed in the study were myogenic (11.2%), geriatric (4.6%), mechanical (0.8%), neurogenic (0.8%), and myogenic (2.0%) ptosis [7,8]. Similarly, an evaluation of patients presenting to an oculoplastic surgery practice in Australia revealed that involutional aponeurotic ptosis was the most common form among patients over 50 years of age, accounting for 77% of cases among patients aged 51–60 years, 81% of cases among patients aged 61–70 years, and 70% of cases among patients aged ≥71–80 years [9,10].

Clinical trial data which involves eyelid manipulation of the eyelid, and therefore the potential risk of unintentional ptosis development, has also been associated with the development of acquired ptosis. Case studies having demonstrated soft contact lens wear to increased incidence of ptosis [11–13]. A retrospective analysis of 15 lawsuits with ptosis settlements conducted that was revealed that all were bilateral and 13 of 15 had been wearing their lenses for >17 years. Furthermore, in 11 of the 15 patients, thinning or dehiscence of the levator aponeurosis was observed during surgery [13]. A large similar study in Japan matched case-control study of female patients in Japan found that hard contact lens wear significantly increased the risk of ptosis when worn over 10 years (OR 1.9 (95% CI 1.03–3.5)) [14]. A retrospective analysis of 25 patients (and 38 eyes) who presented with ptosis after ophthalmologic surgery found that 28 of the 25 patients had a history of contact lens use and that contact lens wear time (7.6 and 9 years, respectively) [15]. A broad analysis of environmental factors contributing to ptosis in 288 sets of adult twins (range: 18–82 years old) found a significant association between hobbies (not just self-contact lens wear and ptosis, but an association with respect to other environmental factors evaluated, including BMI, smoking status, alcohol consumption, hours of sleep per night, or sun exposure [16]. Conclusions were more inconclusive in a systematic literature review found significant risk associated with hobbies (odds ratio [OR] 2.38 (95% CI 1.71–81.20)) and with contact lens wear (3.66 (95% CI 2.69–4.97)) of contact lens wear [17].

Another known cause of ptosis is cardiac surgery. A systematic literature review reported an 11.3% incidence of ptosis following cardiac surgery, with the highest incidence (13.8%) occurring among patients who underwent giant aneurysm surgery, followed by coronary (10.3%), valvular (10.0%) (mitral [9.4%] and mixed [9.7%] surgeries [18]). Presumptive ptosis incidence also depends on surgical technique [19]. Reported rates of ptosis range from 1 to 44.4% and 0 to 12.8% among patients undergoing endarterectomy and pharmacoinvasive cardiac surgery, respectively. Similarly, moderate glaucoma surgery (7–10% of all glaucoma procedures [9.7–17%]) appears to differ based on the surgical technique used [20]. For glaucoma surgery, peripheral ptosis incidence is higher in trabeculectomy with mitomycin C (13.9% incidence) than when compared to the canal (13.5%) [21]. In cataract surgery, external ptosis incidence with intravitreal steroid injection and intravitreal anti-VEGF injection with subconjunctival injection are reported to be 1.1% and 1.2%, respectively [22].

Ptosis following ocular surgery can be particularly problematic. Unilateral ptosis of a young individual presenting with the appearance of acquired ptosis, with double vision, and/or amblyopia should be investigated immediately as a potentially life-threatening, and therefore urgent, neurological condition [23]. Ptosis can also be a symptom of more permanent neurological pathologies such as neurotrophic keratopathy, which can lead to severe ulceration, perforation, and loss of vision [24]. Ptosis following ocular surgery can be managed conservatively with observation, or surgically with levator resection, frontalis suspension, or brow suspension [25]. Ptosis following ocular surgery can be managed conservatively with observation, or surgically with levator resection, frontalis suspension, or brow suspension [25].

treating transient ptosis resulting from botulinum toxin injection, which, most notably, topical application of the adrenergic agonist apraclonidine provides measurable upper eyelid elevation in some patients [26, 27].

Ptosis can also be secondary to a range of underlying neurological or muscular conditions, including 3rd cranial nerve palsy, CPEO, oculopharyngeal muscular dystrophy, Horner's syndrome, and myasthenia gravis [28–30]. These conditions can range in severity and require different interventions based on primary pathology. For example, underlying conditions can also be emergent and potentially life-threatening, and therefore require rapid management. Ptosis identification and differential diagnosis are summarized in detail in Acquired ptosis identification and differential diagnosis section.

Acquired ptosis identification and differential diagnosis

Accurate acquired ptosis as well as its underlying aetiology and severity is essential in successful management. Thorough clinical examination and differential diagnosis is also needed in order to identify conditions or most importantly symptoms any patients undergoing cosmetic eyelid surgery (unrelated unrelated intervention) (Table 2).

The initial diagnostic step is a review of patient history to ascertain timing of ptosis onset, as a sudden appearance may signal some underlying pathology. If ptosis history suggests that ptosis may be secondary to a more serious condition, subsequent examination for confirmation based on the observable clinical signs. The unilateral neurological or myogenic conditions most commonly associated to acquired ptosis include Horner's syndrome, 3rd cranial (oculomotor) nerve palsy, myasthenia gravis, and CPEO. In a study of patients referred for ptosis surgery, 5.6% of cases had a neurogenic cause and among these cases the majority were due to lesions affecting aetiologies (35.7%) palsy of the 3rd cranial nerve), 28.6% myasthenia gravis, 14.3% aberrant regeneration, 7.1% Horner's syndrome). While myogenic causes (ophthalmoplegic migraine, CPEO, and myotonic dystrophy) were less common in the study population (4.8% overall), 90% of the patients in this group had an underlying diagnosis of CPEO [31].

Horner's syndrome, in its acquired form is usually secondary to interruption of sympathetic innervation of the superior and inferior tarsal muscles due to trauma, certain tumours, or stroke. It is characterized not only by mild unilateral ptosis of the upper eyelid, but also the lower eyelid (i.e., slight elevation of the lower eyelid), ipsilateral pupillary miosis, facial anhidrosis, and a positive pupillary response (dilation in equal physiological (which can be used to differentiate between pre- and post-ganglionic Horner's syndrome) or anisocoria [32–34]. Ptosis caused by 3rd cranial nerve palsy—which innervates several extra muscles, the levator palpebrae superioris—has a profound and variable presentation but is typically accompanied by diplopia and a "down and out" position of the affected eye due to partial or complete muscular paresis [35, 36]. Like with Horner's syndrome, 3rd cranial nerve palsy can be secondary to an aneurysmal event such as intracranial aneurysm, or trauma or compression of the nerve by an expanding mass. Because the 3rd cranial nerve activates many of the parasympathetic fibres destined for the eye, dilation of the ipsilateral pupil can be observed in some cases. Pupillary involvement requires neuroimaging for the presence of an aneurysm or of a tumour that may be compressing the nerve. Lack of pupillary involvement often suggests a microvascular cause, such as diabetes mellitus [37–39].

Ptosis can also be an early symptom of myasthenia gravis, a condition caused by antibodies binding to the postsynaptic receptors, and may be accompanied by normal ophthalmoplegia [40, 41]. Ptosis can present either unilaterally or bilaterally (symmetric or asymmetric), tends to worsen with fatigue, and can be minimized or alleviated by a positive response (upper eyelid elevation) to the ice test or the rest [42–44]. Further diagnosis can be confirmed via serologic testing for anti-acetylcholine receptor antibodies [45]. When myasthenia gravis is suspected, CT scanning is required in order to identify potential thymic hyperplasia or thymoma [46]. Ptosis secondary to CPEO, a mitochondrial syndrome that can be accompanied by extraocular muscle weakness particularly on upgaze, and bilateral loss of reflexes, and requires evaluation for involvement of other systems [5, 15].

Evaluation of the periocular skin and soft tissues is essential to identifying or excluding ptosis secondary to a mass weighing down the upper eyelid [5, 47, 48]. Patients should be examined for suspicious lesions such as basal cell or squamous cell carcinoma of the skin, or unusual masses beneath the skin. A lacrimal gland mass can present as upper eyelid ptosis, and potential neoplasms for lacrimal gland masses include lymphoma, adenoid cystic carcinoma, or pleomorphic adenoma, all of which require biopsy prior to considering ptosis as the diagnosis. Examination should include palpation of the superolateral portion of the upper eyelid beneath the tail of the brow near the orbital rim, and if a mass is suspected, referral to a specialist is recommended.

Also essential to the clinical workup is the exclusion of "pseudoptosis" conditions which involve an pathology of the upper eyelid tissue but unrelated to levator aponeurosis, but instead are due to pathologies of other structures that

Table 3 Diagnostic testing approaches for acquired ptosis.

Basic identification	
Patient history and evaluation for serious underlying conditions	• Evaluate timing of onset • If sudden onset, consider ischemic cause (e.g., Horner's syndrome, 3rd cranial nerve palsy, myasthenia gravis, CPEO); examine for characteristic ophthalmic signs and perform appropriate ancillary testing (e.g., phosphorus or spaghetti test for Horner's syndrome, ice test/Tensilon test, anti-acetylcholine antibody testing for myasthenia gravis) [5, 15, 16, 41]
Evaluation of pseudoptosis	• Evaluate periocular skin and soft tissues to identify occlusive mechanical cause or tumor [5, 15, 32] • If dermatochalasis or brow ptosis present, examine upper eyelid while raising eyebrow skin [16] • Examine the globe for dysplasia, proptosis (exophthalmos, hypertelorism) or asymmetry (phthisis bulbi, microphthalmia) [16] • If contralateral retraction is suspected, consider for thyroid eye disease [16]
Upper eyelid evaluation	
MRD-1	• Distance from the central pupillary light reflex to the central margin of the upper eyelid; provides a measure of ptosis severity [5, 15, 44]
Eyelid crease height	• Distance from the upper eyelid crease to the eyelid margin; increased eyelid crease height can indicate dysfunction of the levator aponeurosis [5, 15]
Palpebral fissure height	• Distance between the upper and lower eyelid margins with the eye in primary gaze; decreased palpebral fissure height can indicate ptosis; the levator aponeurosis from the tarsal plate [15, 44]
Levator function (Berke's method)	• Upper eyelid excursion upon downgaze to upgaze, with the frontalis muscle excluded; decreased excursion indicates greater degree of levator dysfunction [5, 15, 44] >3 mm = normal [44] ≤3 mm = ptosis [44]
Müller's muscle function	• Assessed by instilling phenylephrine and measuring upper eyelid lift; more lift indicates better Müller's muscle function [16, 44, 45]
Visual field testing	
Goldmann Visual Field Test	• Observer-dependent, kinetic perimetry test using Goldmann bowl; visual field mapped manually by the examiner [51]
Humphrey Visual Field Test	• Automated, static perimetry test using Humphrey Visual Field Analyzer; 24°, superior visual field tested, using a 54-point grid (24-2 setting) [16, 51]
Lancaster Peripheral Field Test (LPFT)	• Modified Humphrey Visual Field Test; automated, operator-independent, static perimetry test evaluating a 40° superior field using a 35-point grid (14-point grid in inferior field used in ptosis) [16] • Software for more natural eyelid positioning and validation of compensatory behaviors

CPEO chronic progressive external ophthalmoplegia, MRD-1 marginal reflex distance 1.

indirectly affect eyelid position. Pseudoptosis can also be, for example, due to a range of mechanical abnormalities (e.g., brow ptosis, floppy eyelid syndrome), anatomical (globe dystopia, globe asymmetry, ocular misalignment), or neurogenic (hemifacial spasm, blepharospasm) causes or conditions of poor cosmetic appearance (thyroid eye disease) [5, 15, 16, 20]. The pathologic process for the various forms of pseudoptosis means that treatment targeting the upper eyelid muscles or aponeurosis is unlikely to resolve the condition, as would correcting the upper eyelid ptosis. It is important to identify any causes of pseudoptosis. Dermatochalasis, the presence of redundant upper eyelid skin, can be corrected by lifting the excess eyelid skin and performing an eyelid reconstruction. If eyelid elevation and muscle function are normal, then ptosis is excluded [15]. Evaluation of the globe can identify dysplasia such as enophthalmos, hypophthalmos or asymmetry caused by phthisis bulbi, microphthalmos, or other conditions affecting globe size and giving the appearance of unilateral ptosis [5, 15]. To differentiate ptosis from contralateral eyelid retraction, it is helpful to determine whether the ptotic eyelid can be lifted and the contralateral eye observed for excessive retraction indicative of compensatory hemifacial spasm or ptosis [16]. One may also assess whether there is full lagophthalmos, globe proptosis, indicative of thyroid ophthalmopathy.

After appropriate examination of the ocular and periocular anatomy, assessment of upper eyelid function can be performed with a few simple measurements. The distance from the central pupillary light reflex to the central margin of the upper eyelid margin after dilation (MRD-1) helps define the presence and severity of ptosis in the normal eye. MRD-1 is typically 4–5 mm and a decrease in this distance signals the presence of ptosis [5, 15, 16]. It is common to the context of acquired ptosis as MRD-2 (the distance from the center of the pupillary light reflex to the lower eyelid margin with the eye in primary gaze) and MRD-3 (the distance from the pupillary light reflex to the upper eyelid margin with the eye in extreme upgaze). The MRD-3 measure is used to determine the degree of levator insufficiency expected in patients with congenital ptosis and vertical strabismus [5, 6].

Eyelid crease height, the distance from the upper eyelid crease to the eyelid margin, can likewise be informative. Normal eyelid crease height generally ranges from 7 to 8 mm in males and 9–10 mm in females, and an increase in this measure can indicate dysinsertion of the levator aponeurosis [15, 44]. Palpebral fissure height is a measure of the distance between the upper and lower eyelid margins with the eye in primary gaze, with a normal value of the adult of 10–12 mm. A decrease in palpebral fissure height can be an indicator of dysinsertion of the levator aponeurosis from the tarsal plate [15, 44]. Levator function is most commonly assessed using Berke's method, in which frontalis muscle function is negated by holding the forehead until the patient shifts their gaze from downgaze to upgaze. Levator function is calculated based on the amount of upper eyelid excursion, from poor (0–4 mm full excursion), to fair (5–11 mm), good (12–14 mm), and normal (≥15 mm) [44]. Müller's muscle function can be assessed using the phenylephrine test, in which a drop of the α-adrenergic agonist phenylephrine 2.5% is applied under the ptotic eyelid. A positive response to phenylephrine (eyelid elevation) is indicative of Müller's muscle function and suggests that the patient is a candidate for Müller's muscle-conjunctival resection [15, 16, 44].

Visual field testing is an important tool for assessing any functional deficits caused by ptosis [7, 8, 15, 16]. The Goldmann Visual Field (GVF) Test is a manual, kinetic perimetry test in which the patient fixates on the center of the testing field and indicates when they see moving illuminated targets of varying size and brightness on the peripheral field, and the visual field is mapped by the examiner [16]. The HVF Test is an automated static perimetry test using an HVF analyzer, in which static illuminated targets briefly appear in the field and patients indicate when a target is seen. Most commonly, the HVF Test evaluates a 24° field (24-2 setting) using a 54-point grid [15, 16]. The LPFT is a modified HVF Test, specifically designed to more objectively visual field deficits caused by ptosis, that demonstrates high sensitivity, specificity, and positive/negative predictive value [16]. It is an outpatient, observer-independent, test primarily test that evaluates a 40° range in the superior visual field, using a 35-point grid. The center of fixation on the LPFT is tilted 15° downward to accommodate for the superior field, unlike most central eyelid positioning and proven compensatory behaviors, such as brow elevation [16].

Acquired ptosis treatment

The standard of care for ptosis management is surgical intervention. Elevation of the upper eyelid for functional or cosmetic purposes can be successfully achieved with a variety of techniques targeting the upper eyelid retractor muscles and aponeurosis [5–7, 15], and the procedure or combination of procedures is selected based on underlying ptosis etiology and severity (Table 4) [5, 6, 15, 16]. Indications for a functional indication include measurable reduction in eyelid elevation (typically defined as MRD-1 ≤2 mm) and accompanying superior visual field deficit, demonstrated via visual field testing [5–8]. Common procedures targeting Müller's muscle include Müller's muscle-conjunctival resection, in which Müller's muscle and the overlying conjunctiva are excised using a posterior approach. This procedure is most commonly performed

Table 4 Approaches to acquired ptosis treatment.

Surgical approaches	
Müller's muscle	• Müller's muscle–conjunctival resection or Fasanella-Servat procedure best when ptosis is mild and levator function is good [9, 11, 13]
Levator or frontalis suspension	• Levator advancement (external approach) is used when there is adequate levator excursion and decreased tarsal distance [9, 13] • Levator resection, usually of levator muscle complex with decreasing physiological levator function, Whitnall's ligament suspension and tarsal levator resection is used [9, 13, 14] • Frontalis suspension, sometimes of the frontalis and upper eyelid using a strip of fascia lata, is used in cases of severely impaired levator function (poor and unpredictable response) [9, 13, 14]
Non-surgical approaches	
Observation/"watch and wait"	• Conservative approach for mild ptosis, reassuring to identify progressive acquired ptosis requiring intervention when necessary
Mechanical intervention (e.g. eyelid crutches, eyeglasses)	• Temporary solution with limited benefit and tolerance issues in certain populations
Scleral contact lenses	• Mechanical lacrimation, especially when upper eyelid elevation is increased during less severe [13, 14] • Upper lens irritation, papillary conjunctivitis, corneal ulcers, and corneal pain [13, 14]
Different botulinum neurotoxin serotypes	• Botulinum toxin type A (BoNT-A) and botulinum toxin type B (BoNT-B) have been used off-label for levator aponeurosis, but with caution in Müller's muscle [13] • Studies limited by small sample sizes, variable efficacy, and short duration of effect [13, 14]. Higher doses are associated with more severe complications, such as ptosis, diplopia, and corneal exposure [13, 14, 15]
Topical sympathomimetics	• Apraclonidine and brimonidine (alpha-2 adrenergic agonists) may temporarily increase tone in Müller's muscle [13] • Ophthalmic solution of apraclonidine 0.5% administered twice daily was shown to increase eyelid elevation and visual acuity in patients with Horner's syndrome over 42 days of treatment in phase 2 trials [13]

Horner's syndrome with good levator function. Similarly, in the Fasanella-Servat procedure, the lower part of Müller's muscle, overlying conjunctiva, and upper border of the tarsus are resected. This procedure is also gradually reserved for mild acquired ptosis or Horner's syndrome with good levator function, with the amount of muscle resected dependent on the degree of eyelid droop [9, 11, 13].

If there is dehiscence or dysinsertion of the aponeurosis but levator muscle function remains good, levator muscle advancement (sometimes referred to as anterior or posterior approach, can be performed. Levator resection is used in cases in which levator function is in the fair-to-good range (5–11 mm), with the amount of muscle resected dependent upon the degree of preoperative levator function [9, 14]. If levator function is poor, the desired upper eyelid elevation can be provided via Whitnall's ligament suspension, in which anatomic resection is followed by suturing of Whitnall's ligament to the tarsal plate and suspension of the ligament to the periosteum of the superior orbital rim [13, 14]. If levator function is poor and frontalis function is good, as is the case in many patients with congenital ptosis, a subcutaneous sling to connect the frontalis muscle to the upper eyelid can also be used. This procedure can also be used for acquired ptosis with a myogenic or neurogenic cause [9, 11]. For patients with both ptosis and dermatochalasis, a combination of ptosis repair and upper lid blepharoplasty procedures may be appropriate [13].

Surgical intervention has been demonstrated to improve elevation of the upper eyelid and superior visual field deficits, and these clinical improvements can accordingly improve patients' performance of activities of daily living and HRQoL outcomes. As noted in Acquired ptosis overview, prevalence, and impacts above, patients who undergo ptosis surgery report improved ability to perform common visual tasks and activities of daily living, leading to an improved functional index [9, 10, 14]. Despite these well-established benefits of surgery, however, it is not an ideal approach for some patients. In many cases, ptosis is not severe enough, with respect to appearance or functional deficits, in the view of the surgeon, patient, or payer to warrant surgical intervention. Furthermore, the potential benefits of surgical intervention must be weighed against risks of unwanted side effects or outcomes. The most common risks associated with ptosis surgery range from temporary adverse events (AEs) such as bleeding, bruising, and infection, to more persistent AEs such as scarring, eyelid crease abnormalities, over- or under-corrections, and eyelid asymmetry. There are also secondary risks to over-correction, including lagophthalmos and exposure keratopathy [14]. Unilateral ptosis in particular can present unique challenges with respect to achieving desired symmetry. The levator muscles are yoke muscles bilaterally innervated by the same afferent input, which increases when one or both eyes is ptotic. In the case of unilateral ptosis, afferent input

to the levator muscle of both eyes increases, resulting in elevation of the ptotic eyelid, but also contralateral eyelid (pseudoptosis). Following unilateral ptosis surgery, the compensatory decrease in afferent input to the formerly ptotic eyelid is paralleled by a decrease in input to the contralateral eye, causing it to droop and result in secondary contralateral ptosis (Hering's phenomenon) and the potential need for revision surgery [9, 14]. A thorough examination for pseudoptosis is therefore essential in cases of unilateral ptosis that are candidates for surgery.

A retrospective analysis of 1509 patients who underwent ptosis surgery revealed that revision was required in 6.7% of cases, with a 6.8% revision rate in patients who underwent a posterior/müllerectomy procedure and a 3.9% revision rate in those who underwent an anterior approach procedure [12]. Undercorrection and overcorrection were identified as the predominant reasons for revision, and the mean time to revision was 2.6 ± 2.4 years [12]. Among subjects who underwent ptosis surgery (BPS total ≥ 19) and a preoperative assessment given the prospect revision surgery [12].

Pharmacological approaches to managing ptosis—and clinical evidence supporting any of these approaches—have been comparatively limited (Table 4). The most prominent approaches include the use of topical sympathomimetic agents, including phenylephrine, apraclonidine, brimonidine, and naphazoline. Ophthalmic applications include drops of phenylephrine, but have been evaluated for their effects on the ptotic upper eyelid based on their potential to activate Müller's muscle, which has been shown to express alpha-1 and alpha-2 receptor subtypes [13, 14]. A retrospective study of patients with unilateral or bilateral ptosis who received topical apraclonidine 0.5% ophthalmic solution twice daily for 42 days showed a positive response (i.e., an increase in MRD-1), and that responsiveness did not depend on ptosis severity or levator function. There was an association between responsiveness and ptosis aetiology, however, with a 77% of eyes with ptosis caused by previous ocular surgery showing ≥1.5 mm increase in MRD-1, versus 42% of eyes with aging as the only identifiable cause (such as the same degree in severity [13]. While these effects on the upper eyelid are intriguing, clinically significant pupil dilation is also observed in the majority of patients following phenylephrine instillation [14], limiting its utility for ptosis treatment.

Apraclonidine's demonstrated alpha agonist activity in the sympathetic receptors and weaker agonist activity at the alpha-2 receptors [13, 14]. Via its sympathomimetic mechanism of action, topical apraclonidine can temporarily reverse ptosis due to Horner's syndrome, thus supporting the diagnosis [13, 14]. A case report also revealed resolution of the upper eyelid in three patients with Horner's syndrome after instillation of 0.5% apraclonidine [13]. A larger evaluation of the effects of apraclonidine on upper eyelid elevation was conducted in 100 non-ptotic subjects, demonstrating small mean increases in MRD-1 at 30 and 45 min post-administration were hypothesized to be a result of stimulation of postganglionic sympathetic receptors [13].

Apraclonidine's effect in ptotic patients has also been evaluated in a number of small-scale studies. A non-masked case series examined 7 patients with upper lid-lowering ocular conditions (ptosis or pseudoptosis) and found effect of apraclonidine 0.5% on ptosis but only when used within 4–6 weeks of ptosis establishment, suggesting that opportunities response might help predict treatment time [13]. A later case series evaluated the effect of administration two doses of apraclonidine 0.5% in a cohort of 6 patients with ptosis resulting from botulinum toxin injection and another with Horner's syndrome, showing improvement in upper eyelid elevation 20–40 min following administration [13]. A prospective study enrolling 26 patients scheduled for ptosis surgery revealed variability in upper eyelid responsiveness to apraclonidine 0.5% and statistically significant correlation between the magnitude of reduced Müller's muscle ptosis revealed higher expression of the α_{2C} adrenergic receptor subtype in responsive tissue, suggesting that its

drug's effect on the upper eyelid is mediated at least in part by agonism of α_{2C} receptors [16].

While studies of limited sample size/dosing in patients with ptosis have shown no notable safety concerns, prospective studies will be clinically useful for other ophthalmic applications (glaucoma, ocular hypertension) have reported ocular (including decreased visual acuity and allergic conjunctivitis) and non-ocular (such as dry mouth and cardiac disturbance) side effects that have led to discontinuation of [illegible]. In the context of treating ptosis this side effect profile is likely undesirable to patients and practitioners.

Other adrenergic agents have also been evaluated for potential application in ptosis. A study of 20 healthy adult volunteers found significant elevation of the upper eyelid for up to 2 h following instillation of naphazoline 0.05% (a preferential α_1-adrenergic receptor agonist) but not brimonidine 0.1% or phenylephrine 0.12% [17]. Topical naphazoline was also reported to improve upper eyelid elevation in a cohort of 12 patients with myopathic ptosis with limited ocular side effects; but tachyphylaxis was observed with frequent daily dosing over a period of 2 weeks [18]. Significant ocular side effects have been reported in cases treated with oxymetazoline, with topical use provoking observable ptosis of the eye in 70% of studied patients [19]. A case series in a small cohort with adverse hemodynamic-related Horner's syndrome revealed a positive effect of [illegible] unilateral administration of brimonidine tartrate 0.15% [20]. In 3 studies [21–23] [illegible] suggestive of possible applications in treating some cases of ptosis, the data regarding the adrenergic agents phenylephrine, apraclonidine, and oxymetazoline are limited to single-dose use of these agents are approved for the treatment of ptosis. An important consideration in the context of treating ptosis is the chronic use of some sympathomimetic agents for glaucoma and the lowering of intraocular pressure in patients with glaucoma can be associated with tachyphylaxis and this may depend on the agent's pharmacologic receptor subtype activity [illegible].

More recently, the efficacy and safety of an oxymetazoline 0.1% ophthalmic solution approved for the treatment of acquired ptosis (Upneeq®; RVL Pharmaceuticals, Inc., Bridgewater, NJ, USA) has been reported. Oxymetazoline is a direct-acting α_1- and α_2-adrenergic receptor agonist [24, 25]. Like other α-adrenergic agents, oxymetazoline is thought to act by stimulating contraction of Müller's muscle. Evidence from two phase 3 clinical trials revealed that once-daily treatment with oxymetazoline 0.1% for 42 days significantly improved the superior visual field and upper eyelid elevation in patients with acquired ptosis and accompanying superior visual field deficit [26]. Using the LPFT, these studies demonstrated mean [illegible] and [illegible] mm improvements in the superior visual field on treatment days 1 and 28 (primary and [illegible] endpoints, respectively), both of which were statistically superior to the mean change observed with vehicle at the corresponding time points (day 1: 1.8 ± 0.3 points; day 14: 2.4 ± 3.5 points). Similarly, MRD-1 measurements showed 0.98 ± 0.89 mm and 1.30 ± 0.97 mm improvement with oxymetazoline 0.1% on treatment days 1 and 14, respectively, in comparison to 0.50 ± 0.81 mm and 0.50 ± 0.80 mm with vehicle at the same time points [26]. Importantly, these studies found that oxymetazoline 0.1% was effective after administration of a single drop treatment (no treatment may 3 minutes 6 h post-installation) and was associated with relatively low AE rates, making it a particularly intriguing non-invasive treatment option for acquired ptosis [27]. No tachyphylaxis was reported over 42 days of once-daily use in these studies of oxymetazoline 0.1%, however future duration evaluation is required to more thoroughly explore the potential effects of chronic use.

Summary, conclusions, and future directions

The prevalence and wide-ranging clinical and functional significance of acquired ptosis make timely and accurate diagnosis and treatment important for eye care practitioners. Acquired ptosis is most often due to aponeurotic changes in the upper eyelid retractor muscles [28, 29], but underlying causes are varied, and many previous and interventions common in eye care today—such as cataract surgery and cataract and glaucoma procedures, can be risk conditions for the development of transient or more persistent forms of ptosis [30–32]. Along with other undesirable abnormal eyelid findings, all warrant full examination and evaluation of treatment opportunities.

Surgery is an effective treatment option for ptosis, but non-surgical approaches have been limited in both number and effectiveness. Routine treatment via surgical intervention may be limited to a relatively small proportion of patients, finding ways to incorporate novel non-surgical therapeutic options into practice presents the potential to treat a wider range of patients. The evidence regarding a newly approved pharmacologic agent for the treatment of acquired ptosis [26] is extensive, encouraging, and suggests the opportunity to offer effective non-surgical treatment. For eye care practitioners—and indeed a team of health care professionals—the availability of an approved pharmacological option might help shift from a "reactive and referral" approach to a "diagnose and treatment" approach, with referral for surgery when appropriate. Furthermore the expansion of therapeutic options may help to improve the patient focus of treatment, by allowing for the use of surgical and non-surgical approaches as appropriate based on underlying ptosis aetiology, severity, and practice preference.

While advances in ptosis treatment are encouraging, these remain only part of the clinical equation. Ef-

fectively treating ptosis starts with accurate diagnosis is essential. In particular, comprehensive clinical examination and differential diagnosis are critical in understanding whether a patient's ptosis is due to primary pathology of the upper eyelid retractor muscles—and can thus be effectively managed by surgical or pharmacological means targeting the upper eyelids—or whether the underlying cause is a more serious underlying neurological condition requiring different intervention. While in many cases ptosis might not be evaluated and treated when its onset is sudden or severity is high, examination of the upper eyelid for subtle evidence of progressive ptosis can be incorporated into the comprehensive eye exam with relative ease. Together with a focus on awareness and diagnosis, focused surgical or non-surgical treatment based on the clinical evidence offers the promise of [illegible] for many patients.

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Compliance with ethical standards

Conflict of interest DH reports [illegible] from RVL Pharmaceuticals, Aerie, Allergan, Bausch & Lomb, Eyevance, Icon, Ocular Therapeutix, and Sun Pharmaceutical Industries Inc.; consultant fees from Aerie Pharmaceuticals, Alcon, Allergan, Bausch & Lomb, Dompé, Eyevance, Icon, Ocular Therapeutix, RVL Pharmaceuticals, Sun Pharmaceutical Industries Inc., and Tarsus Pharmaceuticals; speaker's bureau fees from Allergan, Aerie Pharmaceuticals, Alcon, Novartis, Shire, Ocular Therapeutix, WWL; expert consulting fees from Allergan, Eyevance, Horizon Pharmaceuticals, Mallinckrodt, Novartis Pharmaceuticals, Revance, and Tarsus; and research support from Dompé Pharmaceuticals and Horizon Pharmaceuticals; and equity fees from Ocular Therapeutix. DAH reports consulting fees from Horizon Pharmaceuticals.

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ARTICLE OPEN ACCESS

Teprotumumab for the treatment of chronic thyroid eye disease

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BACKGROUND: Teprotumumab, a novel IGF-1R antibody was recently shown to significantly reduce the signs of active Thyroid eye disease (TED). The current study reviews its efficacy in chronic TED.

METHODS: In this retrospective review, consecutive patients with chronic TED (≥1 year) who had received ≥ 8 infusions of teprotumumab were included. All patients had measurements of proptosis and calculation of the CAS and diplopia score before and after therapy. Endpoints examined were: the clinical activity score, ophthalmology and 6 weeks post therapy underwent orbital CT volumetric analysis.

RESULTS: Thirty-one patients met the inclusion criteria. The mean (SD) duration of TED was 8.1 years (5.6) and the mean (SD) number of infusions received by each patient was 7 (2). Mean (SD) reduction in proptosis for each study orbit was 3.3 mm (0.4) and 3.1 mm (0.6) for the fellow eyes. The CAS response was 90% for the study orbit and 87% for the fellow orbit. Of the 7% patients who had diplopia at baseline, 67% had a clinically significant response, while 47% had complete resolution following treatment.

Following teprotumumab mean (SD) reduction of muscle tissue was 2017 mm³ (1497) in the study orbit and 1 mm³ (2159) in the fellow orbit. The mean (SD) reduction of fat volume was 2197 mm³ (1663) in the study orbit and 1378 mm³ (2787) in the fellow orbit.

CONCLUSION: Teprotumumab significantly reduces proptosis, inflammation, diplopia, shortens and orbital soft tissue volume in patients with chronic TED.

Thyroid eye disease (TED) is a complex, debilitating autoimmune condition most commonly associated with Graves' disease that can cause significant disfigurement, vision loss and psychosocial sequelae [1]. Approximately 40% of patients with Graves' disease (GD) will develop ocular involvement with signs and symptoms that range from mild to severe [2]. At presentation, common symptoms include pain, diplopia, tearing, redness and decreased vision [3]. Exam findings may include dry eye, eyelid retraction, proptosis, lagophthalmos, extraocular dysmotility, inflammation and redness of the caruncle and conjunctiva, and signs of optic nerve compromise [4]. Classic radiographic findings include orbital fat expansion [5], enlargement of the extraocular muscles and expansion of the bony orbital cavity [6].

The current consensus suggests that the natural history of the disease is biphasic. It begins with an active phase with inflammatory signs and/or soft tissue expansion followed without resolution, by a chronic phase characterized by fibrosis with a lack of further soft tissue expansion and a reduction of inflammatory signs [3]. Conventional management for the active phase has been directed almost exclusively to immune suppression with agents such as corticosteroids [6, 7]. Present day treatments have failed to reverse orbital fibroblast (OF) activation, which is responsible for the majority of soft tissue expansion through the production of extracellular matrix (ECM) proteins [8]. Since immune activation forms only one facet of disease progression, these treatments have been shown to reduce inflammatory signs but not significantly alter proptosis [6, 9]. Similarly, some biologic-like immunomodulatory agents such as Rituximab have been found to be temporarily useful in the inflammatory phase, but with limited effect on long-term disease outcomes such as proptosis and diplopia [10]. Given the underlying pathophysiologic event in TED, IL-6R activation resulting in soft tissue expansion, differentiation to fat cells and myofibroblasts in conjunction with hyaluronic acid (HA) production, debulking treatment, such as decompression procedures have been the mainstay of therapy for proptosis in the chronic non-inflammatory phase [11].

A key pathological feature of TED, regardless of disease phase, is the overexpression of the insulin-like growth factor-1 receptor (IGF-1R) and its interaction with the thyrotropin receptor (TSH-R) [12]. Both receptors form a functional complex on the cell membrane of OFs, B cells and T cells [13]. In TED, autoantibodies to IGF-1R bind to the complex, leading to increased production of the proinflammatory cytokines IL-6, IL-2 [14], TNF-α [15] and IL-8 [16] by T cells and monocytes and hyaluronan by OFs [17]. In the

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...ultimately halt TED, which has not been supported by the data mentioned above [6, 9].

This study evaluated the response of teprotumumab therapy in consecutive patients with more chronic TED (≥1 year) to determine if the response was similar to those with more acute disease.

Patients

This was a multicenter study with patients being recruited from two tertiary TED centers (Wills Eye, UCLA). Patients that presented for evaluation for the treatment of symptomatic TED were considered for study eligibility. Consecutive patients who had been diagnosed with TED, formerly had a prior (≥1 year) clinical activity score (CAS) ≥ 4 (scoring system described in the methods section) that persisted despite conventional therapy, and who had completed the initial set (8 infusions) of teprotumumab, were included in the study. Patients were excluded if they had received any prior orbital radiation therapy, had undergone orbital surgery (orbital decompression, strabismus surgery or eyelid surgery) within 6 months prior to the first infusion of teprotumumab, or had not completed 8 infusions over 24 weeks.

Measurement of clinical outcome

The primary outcome measure was a reduction in proptosis of ≥2 mm from baseline in the study eye without a corresponding increase in proptosis of ≥2 mm in the fellow eye. The secondary outcome measures were proptosis reduction and orbital soft tissue volume measurement, while secondary outcome measures included the CAS and resolution of diplopia and epiphora.

Image analysis

Thin-cut axial non-contrast CT orbital images were retrospectively collected for patients with active TED who had been treated with teprotumumab. The primary analysis was used to the greatest change in muscle and orbital fat volumes in patients with chronic TED who were compared before and after treatment with teprotumumab. Patients with prior orbital surgery or radiation therapy were excluded. If there was no pre-treatment CT orbit, patients were excluded. Only patients with both pre-treatment and within 6 weeks post-therapy CT orbit scans were included.

Three dimensional volumetric analysis of the orbits for soft tissue volumes were performed using the open-source software 3D Slicer (version 4.10.2, https://www.slicer.org/). Each orbit was manually segmented by a single rater (Shweta Ugradar) who was masked to the patient's clinical information and the timing of the scan (pre- or post-treatment). Segmentation was performed using the axial images and coronal and sagittal reformats were used to ensure the accuracy of the segmentation. The orbital soft tissue volumes were calculated by summing the number of voxels (3D pixels) within the segmented region and multiplying by the voxel volume. The orbital soft tissue was segmented into muscle and fat tissue using a semi-automated segmentation algorithm based on the Hounsfield unit (HU) values of each tissue type. Muscle tissue was defined as tissue with HU values between 40 and 90, while fat tissue was defined as tissue with HU values between −200 and −30. Manual segmentation was performed to remove any tissue that was not muscle or fat, such as bone or air. The segmentation was performed in the axial plane and then reviewed in the coronal and sagittal planes to ensure accuracy. The segmentation was performed by a single rater (Shweta Ugradar) who was masked to the patient's clinical information and the timing of the scan (pre- or post-treatment). The segmentation was performed using the open-source software 3D Slicer (version 4.10.2, https://www.slicer.org/). The segmentation was performed by a single rater (Shweta Ugradar) who was masked to the patient's clinical information and the timing of the scan (pre- or post-treatment).

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM, Inc., Chicago, Illinois, USA). Differences in continuous measurements before and after commencing therapy were assessed using a dependent t-test, while differences between CAS and diplopia scores at different time points were assessed using the Wilcoxon Signed Rank test. Due to the symmetry of asymmetric TED, each orbit was treated as a separate entity. Statistical significance was defined as $p < 0.05$. In each patient, a single rater (Shweta Ugradar) blinded to the patient's clinical information and the timing of the scan (pre- or post-treatment) performed the segmentation. Intra-rater reliability was assessed by re-segmenting the orbits of 10 randomly selected patients (20 orbits) after a 2-week interval. Intra-rater reliability was assessed using the intraclass correlation coefficient (ICC) with a two-way mixed-effects model and absolute agreement. The segmentation was performed by a single rater (Shweta Ugradar) who was masked to the patient's clinical information and the timing of the scan (pre- or post-treatment). The segmentation was performed using the open-source software 3D Slicer (version 4.10.2, https://www.slicer.org/). The segmentation was performed by a single rater (Shweta Ugradar) who was masked to the patient's clinical information and the timing of the scan (pre- or post-treatment).

RESULTS

Patients

A total of 31 consecutive patients (9 males, 22 females) were included in the study. The mean (SD) age was 47 (10). The mean (SD) duration of TED prior to presentation was 8.1 months (5.6). The mean (SD) number of infusions received by each patient was 7 (2). All patients were surveyed and none of the patients were current smokers. Further, 58% (17/31) of patients had completed 8 infusions of teprotumumab therapy at the time of review. No patients discontinued therapy due to adverse events.

CLINICAL OUTCOMES

Proptosis

Prior to therapy, the mean (SD) exophthalmometry in the study orbit was 24 mm (3.3) and 21 mm (3.4) in the fellow orbit ($p < 0.01$). In the fellow orbit, at baseline, mean (SD) exophthalmometry was 22 mm (3.4) and 20 mm (3.7) following therapy ($p < 0.01$).

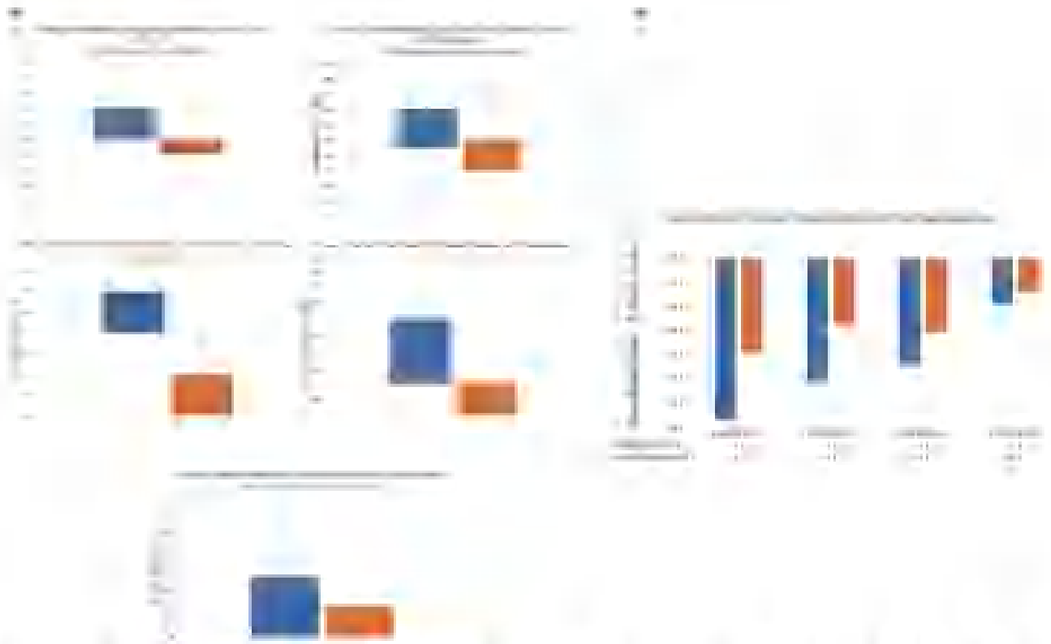

Fig. 1 Clinical measurements before and after Teprotumumab. **a** Changes in exophthalmometry, the CAS and Gorman diplopia scores before and after therapy. **b** Changes in gaze restriction for each of the rectus muscles before and after Teprotumumab therapy.

Mean (SD) reduction in proptosis for each study orbit was 3.5 mm (0.4) and 3 mm (0.3) for the fellow orbits. Ninety percent of study orbits had a clinically significant (≥2 mm) reduction in proptosis, while 84% of fellow orbits had a significant reduction in proptosis. Prior to therapy, five patients had asymmetric disease (proptosis difference ≥2 mm between orbits), while after treatment, four patients had asymmetric disease (Fig. 1a and Table 1).

Clinical activity score

In the study orbit, mean (SD) CAS was 2.3 (0.9) before therapy and 0.5 (0.7) following therapy ($p < 0.001$). The mean (SD) reduction in CAS was 1.8 (1). In the fellow orbit, mean (SD) CAS was 2.3 (0.9) before therapy and 0.5 (0.8) following therapy ($p < 0.001$). The mean (SD) reduction in CAS was 1.8 (1). For the study orbits, the CAS response was 90% for the study orbit (28/31) and 87% (27/31) for the fellow orbit (Fig. 1a and Table 1).

Diplopia

At baseline, the mean (SD) Gorman score was 1 (1.4) and improved to 0.5 (1) following therapy ($p = 0.02$) (Fig. 1a and Table 1). From the 16 patients who had diplopia at baseline, 10 (63%) had a clinically significant response, while 7 (44%) patients had complete resolution following treatment (Fig. 1a and Table 1). Using a 6-point strabismus scale, the greatest reduction in strabismus was seen in upgaze. Prior to therapy, the mean (SD) strabismus score for upgaze (superior rectus) was −0.7 (1) and −0.4 (1) following therapy ($p < 0.01$). Before therapy, the mean (SD) strabismus score for downgaze (inferior rectus) was −0.19 (0.7) and −0.14 (0.7) following therapy ($p = 0.16$). The mean (SD) score for gaze associated with the lateral rectus was −0.5 (1) prior to therapy and −0.3 (0.7) following therapy ($p = 0.07$). Finally, the score for gaze associated with the medial rectus was −0.5 (0.8) prior to therapy and −0.4 (0.7) following therapy ($p = 0.68$) (Fig. 1a).

Orbital imaging analysis:

Fifteen patients (30 orbits) included in the study had pre and post-treatment imaging and were therefore included for volumetric analysis. All patients who had CT scans within 6 months prior to therapy and 6 weeks post therapy were included.

Extraocular muscle volume

The mean (SD) muscle volume within the study orbit prior to therapy was 6508 mm^3 (3716). Post-therapy, mean (SD) muscle volume significantly reduced to 4287 mm^3 (2228) ($p < 0.01$). For the fellow eye, prior to therapy, mean (SD) muscle volume was 6244 mm^3 (3578), while the mean (SD) volume post therapy was 4625 mm^3 (2227) ($p < 0.01$). Mean (SD) reduction of muscle tissue was 2011 mm^3 (1847) in the study orbit and 1620 mm^3 (1759) in the fellow orbit.

Orbital fat volume

The mean (SD) for volume within a single study orbit prior to therapy was 15,241 mm^3 (5041). Post-therapy, mean (SD) fat volume significantly reduced to 13,142 mm^3 (5286) ($p < 0.01$) (Fig. 2). For the fellow eye, the mean (SD) fat volume was 14,873 mm^3 (4686) prior to therapy and 13,002 mm^3 (4276) post therapy ($p < 0.01$). Mean (SD) reduction of fat volume was 2101 mm^3 (1681) in the study orbit and 1370 mm^3 (1181) in the fellow orbit.

Reliability of measurements

Interobserver variability revealed a strong correlation between two observers for measurement of muscle volume (0.99) and fat volume (0.98).

Descriptive case—case 30

A 60-year-old black male with a 5 year history of Graves' orbitopathy presented with progressively worsening proptosis and diplopia/ptosis. He had previously been treated with steroids, bilateral orbital radiation, bilateral orbital decompression and

Table 1. Clinical characteristics of patients pre and post therapy.

Case	VA OD pre	VA OD post	VA OS pre	VA OS post	CAS OD pre	CAS OD post	CAS OS pre	CAS OS post	Hertel OS pre	Hertel OD post	Hertel OD pre	Hertel OS post	Gorman score pre	Gorman score Pre	Gorman score post	CAS clinical activity score
1	20/30	20/30	20/30	20/30	3	1	3	1	19	20	18	19	2	4	2	1
2	20/50	20/30	20/30	20/30	3	1	3	1	22	20	22	20	0	0	0	1
3	20/25	20/25	20/30	20/25	3	1	3	1	20	20	20	20	4	4	2	1
4	20/20	20/20	20/30	20/30	3	0	3	0	20	17	20	16	0	1	0	0
5	20/30	20/30	20/30	20/30	3	0	3	0	20	17	20	16	0	1	0	0
6	20/25	20/25	20/25	20/25	3	0	3	0	21	20	21	20	0	0	0	0
7	20/20	20/20	20/20	20/20	3	0	3	0	19	18	19	18	0	0	0	0
8	20/20	20/20	20/20	20/20	3	0	3	0	19	18	19	18	0	0	0	0
9	20/20	20/20	20/20	20/20	3	0	3	0	22	22	22	22	0	0	0	0
10	20/70	20/20	20/30	20/20	3	0	3	0	19	19	19	19	0	0	0	0
11	20/50	20/20	20/30	20/20	3	0	3	0	19	18	19	18	0	0	0	0
12	20/20	20/20	20/20	20/20	3	0	3	0	19	18	19	18	0	0	0	0
13	20/20	20/20	20/20	20/20	3	0	3	0	20	20	20	20	0	0	0	0
14	20/25	20/20	20/40	20/30	3	0	3	0	23	23	23	23	0	0	0	0
15	20/30	20/30	20/30	20/30	3	0	3	0	19	17	18	17	0	0	0	0
16	20/50	20/30	20/30	20/25	3	0	3	0	20	17	20	17	0	0	0	0
17	20/20	20/20	20/30	20/20	3	0	3	0	20	17	20	17	0	0	0	0
18	20/20	20/20	20/30	20/25	3	0	3	0	20	17	20	17	0	0	0	0
19	20/20	20/20	20/30	20/30	3	0	3	0	20	17	20	17	0	0	0	0
20	20/20	20/20	20/30	20/30	3	0	3	0	20	17	20	17	0	0	0	0
21	20/25	20/20	20/40	20/40	3	0	3	0	20	17	20	17	0	0	0	0
22	CF	20/400	CF	20/400	3	0	3	0	20	17	20	17	0	0	0	0
23	HM	CF	HM	CF	3	0	3	0	20	17	20	17	0	0	0	0
24	20/20	20/20	20/20	20/20	3	0	3	0	20	17	20	17	0	0	0	0
25	20/25	20/20	20/30	20/20	3	0	3	0	20	17	20	17	0	0	0	0
26	20/30	20/20	20/30	20/20	3	0	3	0	20	17	20	17	0	0	0	0
27	20/40	20/20	20/30	20/20	3	0	3	0	20	17	20	17	0	0	0	0
28	20/30	20/20	20/30	20/20	3	0	3	0	20	17	20	17	0	0	0	0
29	20/40	20/20	20/40	20/30	3	0	3	0	20	17	20	17	0	0	0	0
30	20/30	20/20	20/30	20/20	3	0	3	0	20	17	20	17	0	0	0	0
31	20/25	20/25	20/25	20/25	3	0	3	0	20	17	20	17	0	0	0	0

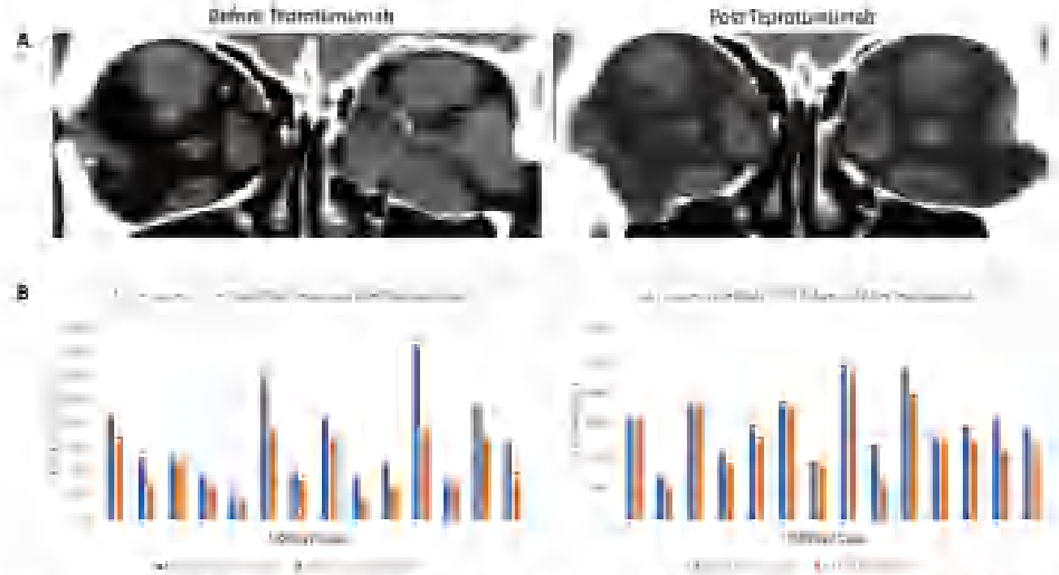

Fig. 2 Changes to orbital soft tissue before and after Teprotumumab therapy. a CT scan showing the extraocular muscles before and after completion of teprotumumab therapy in the same patient. b Extraocular muscle and orbital fat volume in each patient before and after Teprotumumab therapy.

Before Teprotumumab Post Teprotumumab

Fig. 1 Clinical case. Photograph at baseline and following treatment with teprotumumab.

strabismus surgery. On presentation, his visual acuity was 20/30 OU. He had no signs of optic neuropathy. His colour vision was normally tested and found to be normal. Hertel exophthalmometry measurements were 32 mm OD and 32.5 mm OS. His CAS was 3 OU. He diplopia score was 2 with gaze restriction involving the right eye (−1 looking right and −2 looking left). Following treatment with Teprotumumab (8 infusions), his proptosis reduced to 26 mm OD and 28 mm OS. His diplopia score reduced to 0 and gaze restriction improved. His CAS reduced to 0 in both eyes (Fig. 2).

DISCUSSION

In two placebo controlled randomised clinical trials, teprotumumab has been shown to be a promising and well tolerated first line treatment for TED [21, 22]. However, the previous studies have been limited to patients with ocular involvement for <9 months to capture the "active" inflammatory phase of the disease. In recent work, we showed that the IGF-1R is overexpressed on OFs in patients with active and chronic TED [15]. A key effector in the pathogenesis of TED is the OF. Activation of the IGF-1R initiates intracellular signalling along the Akt signalling pathway, a stimulator of cell growth and proliferation, and a potent inhibitor of programmed cell death [23]. In GD, OFs that are stimulated by IGF-1 have an increased propensity toward HA production and proliferation of extracellular matrix proteins, contributing significantly to the anabolic effects seen in TED (Fig. 4) [24]. Hydration of hyaluronan within orbital tissue leads to swelling and soft tissue expansion within a rigid bony cavity, causing proptosis.

Based on this data, our hypothesis is teprotumumab may be effective in patients with chronic TED. Aside from a case description [25] there have been no clinical series providing clinical evidence to support a potential role for teprotumumab in the treatment of chronic TED.

The present study describes the experience of 31 consecutive patients with chronic TED, treated with teprotumumab. These patients presented, on average, 7 years after being diagnosed with TED and demonstrated a marked improvement in proptosis, CAS and diplopia. Ninety percent of study orbits had a clinically significant improvement (≥2 mm) in proptosis, while 84% of fellow orbits also had a clinically significant improvement. Further, there was a significant reduction in fat and muscle volume following treatment, which may explain some of the reduction in proptosis. Sixty-seven percent of patients experienced a clinically significant improvement in diplopia while 40% had complete resolution following therapy.

Given the IGF-1R controls the constitutive metabolic turnover of macromolecules in the extracellular matrix by OFs [26] the recent finding of overexpression of the IGF-1R in longstanding disease becomes more meaningful in the context of teprotumumab [27]. Despite the dominant appearance of chronic TED, OFs continually turnover HA and other ECM macromolecules once a week to maintain tissue integrity [28]. Therefore, interrupting the IGF-1R pathway may reduce the downstream signaling that leads to tissue expansion in chronic TED (Fig. 4).

In blocking the IGF-1R, teprotumumab may reduce the activity of this pathway, causing a reduction in soft tissue volume within the orbit. This notion gains support from a previous study in which patients with active TED were treated with teprotumumab, leading to a marked reduction in extraocular muscle volume [29].

The results of the present study raise key questions regarding the potential for widening access to teprotumumab for patients with chronic TED, most pertinently, in countries with a state sponsored healthcare system. A previous report on the economic and public health impact of TED revealed that on average, 22% of patients were registered as temporarily disabled, while 9% were registered as permanently disabled [30]. This study was conducted in Germany, an economy with a predominantly state funded healthcare system, much like the UK. The total indirect economic burden of TED was calculated at $3,475,325,640. When adjusted for inflation since 2013, this figure rises to $3,951,518,218 (£3,502,868,944) in 2021 [24].

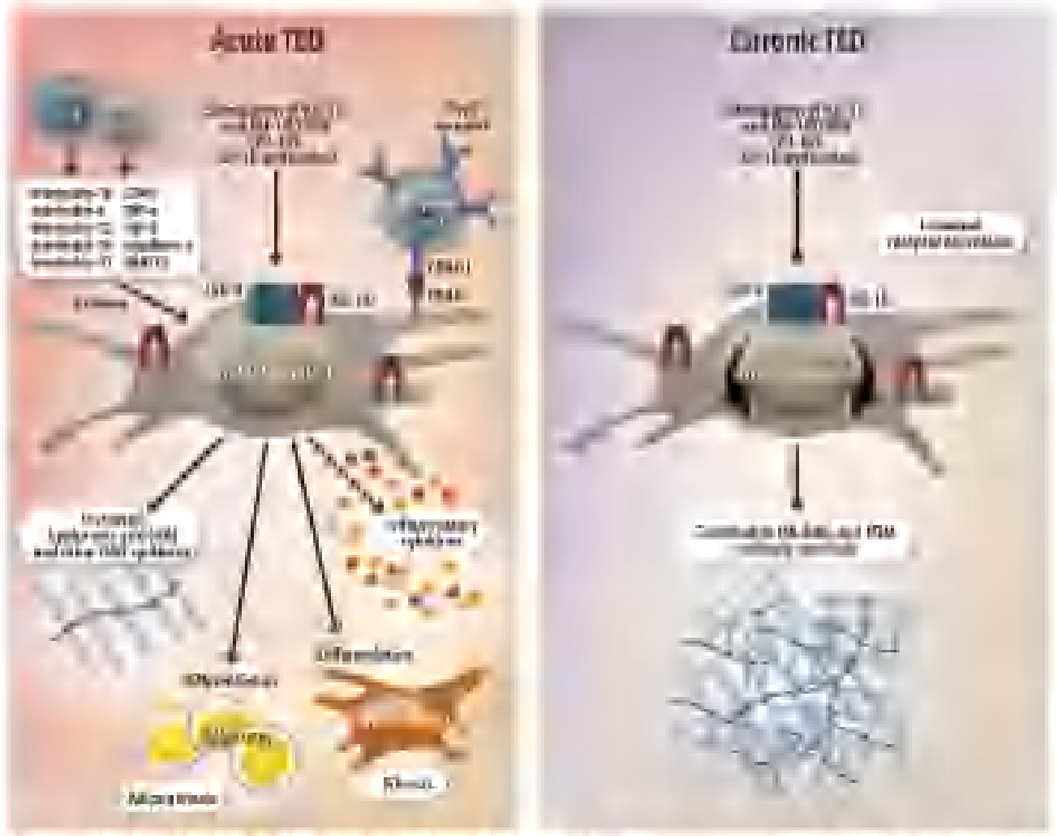

Fig. 4 The role of orbital fibroblasts (OFs) in acute and chronic TED. The IGF-1R is overexpressed on OFs in the acute and chronic phase. In the acute phase, activation of the IGF-1R/TSHR pathway leads to proliferation of inflammatory cytokines, production of hyaluronan and other extracellular matrix proteins and differentiation into adipocytes or myofibroblasts resulting in tissue expansion. In the chronic phase, the overexpression of IGF-1R on OFs persists and maintains tissue expansion. RANTES regulated upon activation, normal T cell expressed, and secreted, also known as CCL5. HA hyaluronic acid, GAGs Glycosaminoglycans.

The burden on the quality of life of patients with TED is also significant. Ponto and colleagues also reported that from a pool of 250 outpatients in a TED clinic 49% complained of restrictions in their daily activities, 38% reported impaired self-perception, 21% underwent psychotherapy and 38% were on sick leave because of their TED [30].

Given the significant impact of TED on the economy and quality of life, an extensive cost benefit analysis for the use of teprotumumab in patients with chronic disease is encouraged.

The limitations of the present study pertain to the inclusion of patients with a heterogenous history of TED. Some patients had surgical intervention, while others had only medical therapy prior to inclusion. Although this study focused on the worst affected orbit (proptosis), this may have implications for the magnitude of the effect of teprotumumab in our group of patients. On the other hand, a key strength of the study was its longitudinal design, allowing for a robust comparison within patients. Long term follow-up to review longevity of treatment impact was not available for this study and is the subject of ongoing work at our institutions.

There is a growing body of evidence, which suggests that chronic TED may not be as inactive as previously thought. The present study adds to that and prompts a discussion regarding potentially widening the group of patients who are deemed to potentially benefit from teprotumumab.

Summary
What was known before:

- Teprotumumab clinically improves thickness and symptoms of Thyroid eye disease in patients with active disease of recent onset (<9 years).

What this study adds:

- Teprotumumab also has a statistically significant impact on patients with stable chronic (>2 years), significantly reducing proptosis, diplopia, inflammation and tiredness.

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AUTHOR CONTRIBUTIONS

All authors were involved in the conception of the study, data collection, analysis and drafting of the manuscript.

PATIENT CONSENT

Patient consent obtained for the publication of Fig. 1.

CONFLICT OF INTEREST

[illegible]

ADDITIONAL INFORMATION

Supplementary information [illegible]

Reprints and permission information [illegible]

Publisher's note [illegible]

Open Access [illegible]

CLINICAL SCIENCES

Experimental and Clinical Evidence for Brimonidine as an Optic Nerve and Retinal Neuroprotective Agent

An Evidence-Based Review

Meredith Salinger, BA; Linda G. McGuire, PhD; Andrew R. Harrison, MD; Michael S. Lee, MD

Objective: To review the available evidence for the neuroprotective qualities of brimonidine tartrate in optic nerve and retinal injury.

Methods: References for this study were obtained by running a search of the PubMed database using keywords *brimonidine*, *neuroprotection*, *ischemic optic neuropathy*, and *α2-adrenergic agonists*. References focusing on ocular hypertension were excluded.

Results: Forty-eight studies addressing 1 of 4 criteria for neuroprotection were included. The literature confirms that brimonidine therapy meets the first 3 criteria for neuroprotection: receptors on its target tissues, adequate penetration into the vitreous and retina at pharmacologic levels, and inhibition of intracellular changes that enhance neuronal resistance to insults or interrupt apoptosis in animal models. Brimonidine did not meet the final neuroprotective criterion of success in humans.

Conclusions: Experimental evidence has demonstrated that brimonidine is a potential neuroprotective agent. However, various clinical trials have failed to substantiate similar efficacy in humans.

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THE MAIN OBJECTIVE OF NEUROPROTECTIVE treatments for optic neuropathies is to increase retinal ganglion cell (RGC) survival.[1] To be deemed neuroprotective, an agent must meet the following 3 criteria: (1) receptors on its target tissues, such as the optic nerve and retina; (2) adequate penetration into the vitreous and retina at pharmacologic levels; (3) inhibition of intracellular changes that enhance neuronal resistance to insult or interrupt programmed cell death mechanisms (apoptosis) in animal models; and (4) demonstration of similar efficacy in clinical trials.[1,2]

Brimonidine tartrate (Alphagan; Allergan, Inc, Irvine, California) is a highly selective α2-adrenergic agonist that was introduced in 1996. During the past decade, brimonidine has gained attention for its role in reducing intraocular pressure in the initial and long-term treatment of ocular hypertension and glaucoma.[3] Although several clinical studies[4-7] document its safety and efficacy in lowering intraocular pressure, more recent experimental animal models suggest a neuroprotective effect of brimonidine. These investigations indicate that it might have therapeutic effects if used clinically to treat optic neuropathies in humans.

In this article, we evaluate the experimental evidence for the neuroprotective role of brimonidine in optic nerve injury. We also discuss the inability thus far to translate this into clinical use.

METHOD OF LITERATURE SEARCH

References for this study were obtained by running a search of the PubMed database using the keywords *brimonidine*, *neuroprotection*, *ischemic optic neuropathy*, and *α2-adrenergic agonists*. Approximately 35 references were originally identified. References that addressed at least 1 of 4 criteria for neuroprotection were included in this article. We did not include references focusing on glaucoma or ocular hypertension–induced injury, as it is difficult to distinguish the neuroprotective effects of brimonidine independent of its role in reducing intraocular pressure.

RECEPTORS ON TARGET TISSUES

Without specific receptors on retinal ganglion cells, a neuroprotective agent cannot bind to its target tissue. Brimonidine is a highly selective α2-adrenergic agonist with weak α1 activity.[8] Several animal studies[9-13] demonstrated the presence of α2 receptors in the retina or optic nerve head, laying the foundation for the potential neuroprotective role of brimonidine. Immunohistochemical techniques localized α2 receptors mainly within the ganglion cell layer and, primarily within the inner nuclear layer and amacrine cells in rats,[9] rabbits,[10] and primates[11] (including humans).[12] Radioligand binding studies also localized the existence of α2 receptors in primates[11] and in humans.[12] However, studies have yet to prove the presence of these receptors in the human optic nerve head.

When α2 receptor agonists (clonidine and apraclonidine) are administered, they specifically activate the activation of the corticofugal α2-mediated pathway to Müller cells in the retina[14] and inhibit cyclic adenosine monophosphate production.[15] Endogenous ligands include dopamine-containing neurons in the retina via these α2 receptors.[16] Findings from Hoffmann et al[17] and other evidence thus far suggest that these α2 receptors are able to bind endogenous ligands and specific α2 receptor agonists and antagonists and that this binding leads to measurable effects in the treated retinas.

Treating the eyes with α2-adrenergic agonists results in the attenuation of the blood-compound action potential after optic nerve injury.[18] Other experiments demonstrated that α2 antagonists such as rauwolscine and yohimbine hydrochloride (but not prazosin, an α1 antagonist) block the neuroprotective effects of α2 agonists in models of optic nerve and photoreceptor injury, respectively.[19,20] This finding suggests that the receptors are present within the retina and that the activation of such receptors alters several signaling pathways in the retina. In addition, the activation of these receptors seems to have a role in mediating endogenous neuroprotective mechanisms.

ADEQUATE PENETRATION INTO THE VITREOUS AND RETINA AT PHARMACOLOGIC LEVELS

Brimonidine must adequately penetrate through the various structural barriers of the eye, including the cornea, conjunctiva, and sclera, to reach the posterior retina and retina at pharmacologic doses. Preclinical investigations revealed a minimum concentration of 0.001 μmol/L to produce a maximal response, which equates to 0.38 ng/mL.[21] Animal findings demonstrated that the ocular concentrations of brimonidine in albino and pigmented rabbits after topical administration ranged between 0.03 and 2.2 ng/mL during a 6-hour period after topical administration.[22] After single and multiple dosing, topically applied brimonidine distributes to the posterior segment of monkey eyes and binds to melanin-containing melanosomes to activate α2 receptors. Specifically, after multiple topical administrations of brimonidine tartrate (0.2% [2 mg/mL]) in monkeys and rabbit eyes, the drug's maximal concentrations in the vitreous were 82 nM and 172 nM, respectively. In experimental models of brimonidine tartrate (0.5 mg/kg) in rats treated at peak levels, peak retinal tissue concentrations were 33 nM, and peak neuroretinal concentrations reached 140 nM.[23] Each of these concentrations exceeds the 1 nM concentration required for α2-receptor activation within the target tissues.

Similarly, findings in humans showed that topical instillation of brimonidine tartrate (0.2%) 2 to 3 times daily for 4 to 14 days to fellow eyes of healthy volunteers undergoing cataract surgery resulted in aqueous concentrations in the vitreous well above the level necessary to activate α2 receptors in the retina.[24] Twelve hours after the last dosing, the mean (SD) brimonidine concentration among 5 patients in the pseudophakic eye was 0.11 (0.11) nM. The overall mean brimonidine concentration in the study was 0.85 nM.[24] Results of animal studies suggest that brimonidine binds to melanin[25] and accumulates to peak concentrations in the ciliary body for 6 hours after a single dose.[26] This may explain the significant retinal concentrations detected in 30 to 11 hours after the last dose in humans.[24] These findings indicate that topically applied brimonidine reaches adequate intraocular concentrations for neuroprotection to be possible.

BALANCE MUST BE STRUCK BETWEEN RESISTANCE TO INSULT AND INTERRUPTION OF APOPTOSIS

Experimental models suggest that brimonidine confers neuroprotection in several types of ocular injury, including pharmacologic-induced injury,[27-29] optic nerve compression or transection,[30-32] glutamate-induced degeneration,[33] and ocular hypertension and glaucoma.[34-36] We will exclude discussion of glaucomatous ocular hypertension–induced injury, as it is difficult to distinguish the neuroprotective effects of brimonidine independent of its role in reducing intraocular pressure.

Several experimental animal models have demonstrated the neuroprotective effects of topically and systemically administered brimonidine in reducing the effects of optic nerve injury, as measured by decreased apoptosis in the inner retinal ganglion cell (RGC) layer. Topical application of brimonidine 1 hour before partial optic nerve crush or ischemic optic nerve injury in rats is effective in decreasing apoptosis in retinal ganglion cells, as indicated by a large decrease in terminal deoxynucleotidyl transferase–mediated biotin–deoxyuridine triphosphate nick end labeling (TUNEL) staining.[27,28] After ischemic injury caused by ligation of the ophthalmic artery, systemic administration of brimonidine reduced RGC loss by 33% of the ganglion cell population, while topical administration prevented up to 95% of retinal ganglion cell loss, affecting almost 100% survival of the retinal ganglion cells.[28] The effect of brimonidine treatment was shown to be dose dependent and α2-receptor specific.[27,28]

Using rat ophthalmic vessel ligation as a model of optic nerve ischemia, brimonidine was administered in rats 1 hour before or 30 minutes before ligation.[27] This single dose of topical or systemic brimonidine rescued 42% of retinal ganglion cells 7 days after the induction of ischemia. This neuroprotective effect persisted at 21 days, suggesting that brimonidine treatment could be neuroprotective during the delayed phase of apoptosis seen in these types of optic nerve injury.[27] These findings were confirmed and extended in another study,[28] topical pretreatment with brimonidine 1 hour before transient ischemia of the ophthalmic vessel in rats significantly protected against ischemia-induced damage. The same authors studied brimonidine's dose-response relationship and found that 3 doses of brimonidine (0.2%) administered at 1-hour intervals before ischemia provided the most protection. In addition, the brimonidine treatment prevented decreases of retinal ganglion

cent of the volume of ischemic cell proliferation was preserved in the brimonidine-treated rats compared with 30% in the rats that received saline after nerve injury and all drug treatment.[40]

The long-term neuroprotective activity of brimonidine was examined when topically administered before and after ischemia could produce a photoreceptor rescue.[41] These data support that pretreatment topically with brimonidine 7 days before photocoagulation-induced optic nerve ischemia in rats can prevent long-term (1 month) neuronal and axonal loss. A limited and variable degree of ganglion cell protection resulted from treatment with topical brimonidine for 14 days, starting after the ischemic insult. This conclusion finding by Lafuente et al[42] who found that intraperitoneal brimonidine administered 4, 24, or 72 hours after the onset of transient ischemia and reperfusion had no effect on retinal ganglion cell survival. Differences in these 2 studies could be because of differing methods of producing ischemia, nerve routes of brimonidine administration, varying time between reperfusion and the initiation of treatment, or differences in the duration of treatment after injury.

In a model of endothelin 1 (ET-1)–induced chronic ischemic optic neuropathy in the rabbit, a primary effect on vasoconstriction and decreased ocular blood flow.[43] Endothelin 1 acts via the ET_A and ET_B receptors, which are present in the retina, optic nerve, and optic nerve head of rabbits and humans.[44] Therefore, there is ample evidence that after optic nerve injury produced by several methods brimonidine has the ability to be neuroprotective in the injured ganglion cells.

The exact mechanism of the role of brimonidine in postischemic optic neuropathy remains unclear. Several authors proposed possible mechanisms for the ability of the drug to prolong cellular survival and function and attenuate apoptosis. For example, degeneration of optic nerves in rats leads to elevated extracellular levels of excitatory amino acids, including aspartate and glutamate.[45] Administration of brimonidine can protect ganglion cells from excitotoxic injury by glutamate-induced levels of intravitreal glutamate or aspartate in the rat.[46] Several studies[47–49] demonstrated that intraperitoneal administration of brimonidine in rats results in elevated levels of neurotrophic factors, including brain-derived neurotrophic factor and fibroblast growth factor. In vitro and after intravitreal injection, these factors are important in preserving retinal ganglion cells after various forms of injury.[50] Activation of specific cellular apoptotic pathways from ischemic injury has been shown to upregulate antiapoptotic cell survival signaling pathways and antiapoptotic genes such as Bcl-2 and Bcl-x.[51] The neuroprotective properties of brimonidine are likely multifactorial.

EFFICACY OF NEUROPROTECTION IN CLINICAL TRIALS

Despite the accumulation of medical literature regarding the various aspects of nonarteritic anterior ischemic optic neuropathy (NAION) and other human optic neuropathies in humans, little is understood about how diseases NAION has no effective treatment; therefore, the potential of brimonidine for treatment of this neurodegenerative disease is promising. Even in the absence of controlled clinical trials, physicians practicing brimonidine as a treatment for NAION. This perhaps premature because similar experimental evidence demonstrating the efficacy of brimonidine as a neuroprotective agent in animal models of ischemia. However, the results of clinical investigations suggest that brimonidine treatment before or after the ischemic event (hours rather than days or weeks) might significantly increase its potential therapeutic effect. Another dosing regimen or use of a different preparation of brimonidine may represent other avenues for enhancing the effectiveness of treatment.

Another explanation for discrepancies may relate to differences between species. For example, there are multiple types of α_2-adrenergic receptors. Rabbit eyes possess all 3 subtypes (α_{2A}, α_{2B}, and α_{2C}) of α_2-adrenergic receptors. But immunofluorescence labeling only identifies the presence of the α_{2A} receptor on cells in the ganglion cell layer and nerve fiber layer.[52] However, all 3 subtypes have been cloned from humans. In fact, radioligand-binding investigations reveal that the α_{2A} adrenergic receptors are the most prominent subtype in the iris, ciliary body, retina, human ciliary body, and retinal pigment epithelium-choriocapillaris.[53] Nevertheless, α_2-adrenergic receptors in animals and humans have different molecular and functional characteristics. Variations in the coexpression of the receptors on the target tissues (animals vs humans) also exist. Furthermore, there are differences between species in the microcirculation of the optic nerve head in animals and humans.[54] Each of these differences serves as a challenge when attempting to translate animal model successes into effective clinical applications.

CONCLUSIONS

The literature contains that brimonidine meets the following 3 criteria for neuroprotection: (1) it protects retinal ganglion cells in the optic nerve crush model, (2) it penetrates into the vitreous and retina at pharmacologic levels, and (3) exploration of intracellular changes that enhance neuronal resistance to ischemia-induced programmed cell death mechanisms (apoptosis) in animal models. However, the ischemic events in animal models regarding the neuroprotective effects of brimonidine (activating ischemic optic nerve injury) have not translated into effective clinical applications. The fourth criterion, demonstration of similar efficacy in human trials, has yet to be met.

Ultimately, these differences may put the role of efficacy in clinical applications with animal models. Potential factors for these studies include the differences in the cellular and molecular differences between ischemia-induced optic nerve injury in animals vs humans, the specific cellular and molecular mechanisms underlying the neuroprotective activity of brimonidine, a discussion on the time between disease onset and treatment, and perhaps new modes of delivery of neuroprotective agents and neurotrophic factors.

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Bilateral orbital inflammation in a pediatric patient with eosinophilic granulomatosis with polyangiitis

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CASE REPORT

Bilateral orbital inflammation in a pediatric patient with eosinophilic granulomatosis with polyangiitis

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ABSTRACT

A 3-year-old female presented to the ophthalmology clinic with one month of left upper eyelid ptosis and three months of intermittent wheezing and coughing. MRI of the brain and orbits revealed infiltrative enhancement involving both orbits including the intraconal fat, medial rectus muscles, superior wing of the sphenoid, and possibly the left cavernous sinus. She experienced acute respiratory decompensation in the setting of granulomatous and eosinophil-rich nodular pulmonary opacifications. Laboratory workup revealed anemia, thrombocytosis, and elevated inflammatory markers. An orbitotomy with biopsy demonstrated an eosinophil-rich granulomatous infiltrate consistent with eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome. The patient was placed on high-dose steroids and mepolizumab. To our knowledge, this patient represents the youngest case of EGPA with orbital involvement. Further, this case illustrates the importance of prompt orbital biopsy to provide a timely, unified diagnosis, enabling specialists to initiate appropriate disease management to reduce morbidity and mortality.

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KEYWORDS
Eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome; orbit

Eosinophilic granulomatosis with polyangiitis (EGPA) is a necrotizing vasculitis affecting small- and medium-sized blood vessels. It can be distinguished from other vasculitides by the presence of asthma, rhinosinusitis, and peripheral eosinophilia. Orbital involvement represents a rare manifestation of EGPA, particularly in the pediatric population. Herein, we describe a case of bilateral orbital inflammation among the constellation of EGPA manifestations in a young pediatric patient. Prompt ophthalmology with biopsy facilitated the identification of a unifying diagnosis, allowing for timely multidisciplinary management. Consent for clinical photographs was obtained and is on file. This report is compliant with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA).

Case presentation

A 3-year-old female with no significant past medical history presented to the ophthalmology clinic with left upper eyelid ptosis of one month duration as well as intermittent wheezing and coughing of three months duration. Of note, a course of oral prednisone prescribed for the patient's respiratory symptoms in the interim had led to near-complete transient resolution of her ptosis.

On examination, the patient's visual acuity was 20/20 in both eyes, and she had a normal pupil exam and intraocular pressures. Sensorimotor exam showed a left intermittent monocular esotropia and a mild supraduction deficit of the left globe. External examination was notable for fullness and near-complete ptosis of the left upper eyelid, which was found to be firm and nontender to palpation, and a faint, red-brown discoloration of the periorbital skin (Figure 1(a)). Slit lamp and fundic examinations were otherwise unremarkable.

Magnetic resonance imaging (MRI) of the orbits under sedation was obtained, which demonstrated mass-like infiltrative enhancement involving both extraconal orbits (left greater than right) and pan-mucosal thickening (Figure 2). Of note, the patient experienced acute respiratory failure following sedation, necessitating admission to the intensive care unit and management with positive pressure ventilation and multimodal

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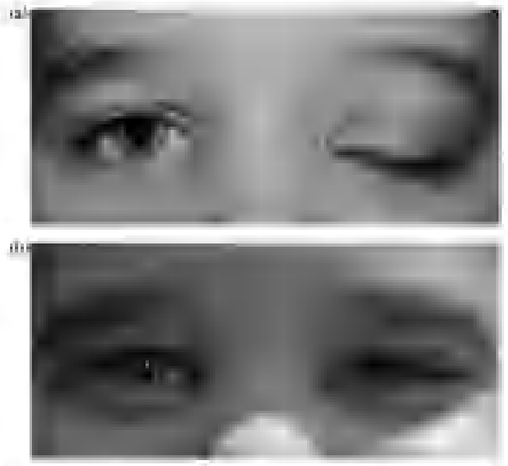

Figure 1. (a) An external photograph of the patient at presentation, showing fullness and near-complete ptosis of the left upper eyelid and a faint, red-brown discoloration of the periorbital skin. Consent was obtained and is on file. (b) A post-operative photograph of the patient, showing significant improvement in the fullness, left upper eyelid ptosis, and discoloration. Consent was obtained and is on file.

respiratory therapies. Computed tomography (CT) imaging was emergently obtained, which revealed tree-in-bud nodular opacifications in both lung apices. Laboratory workup, which showed anemia, thrombocytosis, and elevated inflammatory markers, was concerning for an underlying systemic inflammatory etiology. Rheumatologic workup was negative for anti-neutrophil cytoplasmic antibody (ANCA) and positive for anti-myeloperoxidase (anti-MPO) antibodies. Infectious workup was positive for rhinovirus.

An anterior orbitotomy with biopsy, via an upper eyelid skin crease approach, was performed. Histopathology revealed orbital soft tissue dense inflammatory infiltrate consisting largely of epithelioid histiocytes and eosinophils with scattered small mature lymphocytes and plasma cells (Figure 3). The inflammation was associated with small foci of necrosis. Immunohistochemical stains were performed to better characterize the lesion. Staining for CD68 highlighted the increased number of histiocytes. CD3 and CD20 demonstrate a polyclonal population of lymphocytes. CD138 and IgG were positive in plasma cells. There was not an increased proportion of IgG4-positive to IgG-positive plasma cells. CD31 and CD34 were obtained to identify vascular endothelial cells. No frank vasculitis was identified. CD56 and CD1a were negative. Infectious stains including GMS stain for fungus and Fite stain for acid fast bacilli were negative for these organisms. EBV RNA in situ hybridization (EBER-ish) was also negative.

In the context of sinopulmonary disease, anemia, and elevated inflammatory markers, the eosinophil-rich granulomatous inflammation of the orbital soft tissue was consistent with a unifying diagnosis of eosinophilic granulomatosis with polyangiitis. During her admission, her ocular and respiratory symptoms improved on high-dose systemic and inhaled corticosteroid therapy. She was discharged on these measures with plans to initiate mepolizumab, a new FDA-approved IL-5 inhibitor for EGPA, on an outpatient basis.

Two months after her initial presentation, the patient was doing well. She had completed her first infusion of mepolizumab and was gradually tapering off her steroids. Her ptosis and bilateral periocular swelling had improved significantly (Figure 1(b)).

Figure 2. Magnetic resonance imaging of the orbits with and without contrast was obtained, demonstrating mass-like, infiltrative enhancement involving both extraconal orbits (left greater than right).

Figure 3. Histopathology revealed adipose tissue and collagenous soft tissue densely infiltrated by a mixed inflammatory infiltrate and an occasional small foci of necrosis. The inflammatory cells consist of epithelioid histiocytes and prominent eosinophils with scattered small mature lymphocytes and plasma cells.

Discussion

Eosinophilic granulomatosis with polyangiitis, previously known as Churg-Strauss Syndrome, is an ANCA-associated necrotizing vasculitis affecting small- and medium sized blood vessels.[1] Other ANCA-associated vasculitides include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).[1] EGPA is the least common of these variants and it can be distinguished by the presence of asthma, eosinophilia and peripheral eosinophilia. The exact pathophysiology of this disorder has not been elucidated, but it is known to involve helper T-cell immune responses.

With a mean age at diagnosis of 40 years, EGPA is extremely rare in children.[1,2] Fewer than 50 cases of pediatric EGPA, including those with ocular manifestations, have been reported in the literature.[2–4] Prior to the patient described in our report, the youngest patient found in literature with EGPA was 16 years old at the time of diagnosis.[2] Albeit less common among children, EGPA is more frequently associated with pulmonary and cardiac manifestations in this population, resulting in an increased mortality among pediatric patients as compared to adult patients, while our patient experienced severe otorhinolaryngeal manifestations but cardiac workup was negative. The higher average age distribution, in combination with the atypical symptoms of pediatric EGPA, can lead to difficulty and delays in diagnosis in pediatric patients, further contributing to a poor prognosis.[2]

There have been very few reports of orbital involvement in EGPA, especially in the pediatric population.[2,3,5] Ocular signs of EGPA can be largely classified into two distinct presentations: idiopathic orbital inflammatory-like disease and ischemic vasculitis.[5] In decreasing order of frequency, the former subtype is associated with conjunctival nodules (40% of patients), orbital myositis (25%), orbital inflammatory syndrome (20%), dacryoadenitis (10%), and cranial nerve palsy (10%).[5] When considering ophthalmic EGPA, differential diagnoses include hypereosinophilic syndrome, granulomatosis with polyangiitis, microscopic polyangiitis, infectious, and neoplastic etiologies.[2]

While EGPA is considered an ANCA-associated vasculitis, only about 40% of adult patients and 25% of pediatric patients are ANCA positive.[2] Patients with ANCA positivity tend to develop a "vasculitic phenotype," which is commonly associated with myalgias, weight loss, mononeuritis multiplex, migrating polyarthralgia and renal involvement. Patients who are ANCA negative more often develop an "eosinophilic phenotype" which is commonly associated with myocarditis. Our patient's laboratory workup demonstrated ANCA negativity and weak anti-myeloperoxidase antibody positivity.[1] The most reliable lab findings to suggest EGPA are peripheral blood eosinophilia and elevated serum IgE.[1] The remainder of labs, including ESR and CRP, are largely nonspecific.

Early disease recognition and management is critical to improve prognosis.[2] Management involves systemic high-dose corticosteroids most commonly 0.5–1.0 mg/kg/day of prednisone for 8–12 weeks or until disease remission is achieved.[2] Mepolizumab is a monoclonal antibody that inhibits IL-5, a cytokine that contributes to eosinophil maturation and survival.[1,6] In 2017, mepolizumab was approved by the Food and Drug Administration (FDA) for use in severe eosinophilic asthma and hypereosinophilic syndrome.[1,6] In 2020, it was approved for use in EGPA. Mepolizumab at both 100 mg every 4 weeks and 300 mg every 4 weeks has been shown to improve the respiratory symptoms of EGPA and facilitate more effective disease control.[1,6] Alternative options for the treatment of EGPA are dependent on organ involvement. For instance, plasmapheresis has been shown to be useful in renal-associated disease and intravenous immunoglobulin is beneficial in neuropathy- and cardiomyopathy-associated disease.[1] Lastly, in patients with EGPA, a multidisciplinary assessment of cardiac, renal, and neurologic function is critical, as multi-organ failure is possible.

Herein, we present a rare case of bilateral orbital involvement of EGPA in a pediatric patient. To our knowledge, this is the youngest patient reported to demonstrate ophthalmic signs of this disorder. This case highlights the importance of considering ANCA-associated vasculitides in pediatric patients presenting with orbital inflammation in conjunction with systemic manifestations. Further, this case illustrates the utility of orbitotomy with tissue biopsy in providing a timely, unifying diagnosis and enabling specialists to initiate appropriate disease management.

Disclosure statement

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Chemodenervation for facial dystonias and wrinkles

Andrew R. Harrison

Purpose of review

Chemodenervation has evolved greatly over the past 30 years since botulinum toxin was first introduced as a therapeutic injection for managing strabismus.

Recent findings

Botulinum toxins are now accepted as a lifelong treatment for patients suffering from spasms secondary to facial dystonias. These treatments are extremely effective and well tolerated by most patients. New agents including abobotulinum toxin A and non-mp405 are rapidly developed to create a longer-lasting treatment option for patients with facial dystonias. Recently the use of chemodenervation for managing facial wrinkles has extended the use of these agents. The botulinum toxins have been found to be extremely efficacious in managing facial wrinkles, especially in the upper half of the face. The federal drug administration approved the use of Botox (Allergan, Irvine CA) for glabellar furrows. Periocular crow's feet lines and horizontal forehead lines are also amenable to treatment with the botulinum toxins. Further uses including chemical browlift as well as lower face and neck line treatments have also been described.

Summary

The use of the botulinum toxins had revolutionised the treatment of a broad array of diseases from benign essential blepharospasm to facial wrinkles.

Keywords:

chemodenervation, botulinum toxins, facial spasms, facial wrinkles

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Abbreviations

BTX	botulinum toxin
SNARE	soluble N-ethylmaleimide-sensitive factor attachment protein receptor

Introduction

Alan Scott first described the use of the botulinum toxin (BTX) type A as a therapeutic option in the 1970s by injection into the extraocular muscles as a treatment for strabismus [1,2]. In the 1980s the use of BTX in many benign essential blepharospasm and hemifacial spasm became a standard therapy [3–11]. The use of the BTX for other dystonias and spastic conditions has continued to grow over the ensuing 20 years. During the past 15 years facial thirds treatment has been predominated by the use of BTX as a passive procedure as in all joints or other procedures [12–16]. The FDA approved the use of Botox for managing glabellar wrinkles on April 15, 2002. Subsequently the use of these toxins is skyrocketing.

Botulinum toxins

Clostridium botulinum toxin, which was once termed as the "most poisonous poison" [17], is one of the most frequently used medicaments in ophthalmic physiotherapy. The bacteria produces seven distinct toxins (A, B, C1, D, E, F and G) of which type A is the strongest, followed by types B and F. Each botulinum toxin is synthesized as a single chain polypeptide, which is inactive until it is cleaved by bacterially produced proteases into a dimer consisting of two chains that remain joined to one another via a disulfide bond [18].

The toxins paralyse muscle by inhibiting the release of acetylcholine from vesicles at the presynaptic nerve terminal at the neuromuscular junction. The different serotypes bind to different sites on the motor nerve terminal and within the nerve axon. The heavy chain binds to both a channel and chaperone to bring the light chain across the endosomal membrane and then into the cytosol of the presynaptic neuron. The light chain cleaves the cytosolic synaptosomal associated protein receptor protein (SNARE) to block the release of the vesicle-bound neurotransmitter acetylcholine from nicotinic and muscarinic nerve endings [19]. Muscle weakness may become evident for 2 to 3 days due to the unopposed action of acetylcholine from vesicles that have not been blocked by the toxin. Resolution of muscle activity typically begins 3 to 4 months after treatment and is thought to occur due to the regeneration of new end plate axons.

Preparations

Three preparations of botulinum toxin are commercially available. Botox (Allergan, Irvine, CA) and Dysport (Ipsen, Maidenhead, UK) are botulinum toxin type A. Myobloc (Elan, San Francisco, CA) is a botulinum toxin type B. Dysport is available in Europe and has not received FDA approval for use in the US. Myobloc is licensed by the FDA for use in cervical dystonia. Myobloc (like B-adinum Twin Vial B Package insert) The reported benefits of Myobloc include a shelf life of up to 36 months refrigerated and 9 months at room temperature. It is supplied as a ready-to-use injectable solution. Botox is to be used within 4 hours of reconstitution although several reports suggest that keeping the vial in the refrigerator may be reasonable for up to 1 week [8,20].

Toxicity

The potency of the botulinum toxins is expressed as the weight of toxin required to kill 50% of a group of Swiss-Webster mice weighing 16 to 20 g after intraperitoneal injection [22]. This weight is equal to 1 unit of that particular toxin. The units do vary between the different toxin preparations so it is important to recognize the conceptual basis of the product being used in any medical recommendation. The reported equivalences have been reviewed in the literature as 1 unit Botox is equal to 3 to 4 units Dysport, whilst 1 unit Botox is equal to 50 to 100 units Myobloc. The lethal dose of Botox is estimated in the human at 2500 and 4000 units for a 70 kg person [24].

Side effects

Most side effects of the injection occur at the site of injection. Mild swelling and soreness at the site is not uncommon. Skin swelling before injection and the use of topical anesthetic creams has been shown to reduce the incidence of injection site pain [25••,26••]. Ultrasound into the periocular area may lead to blepharospasm, ptosis, and lower eyelid malposition including ectropion and entropion. Most importantly, BTX injection can lead to a permanent hyperlacrimation in 10% of patients with punctate keratopathy developing in up to 50% [25]. An effective method to prevent lacrimal hyperlacrimation is the use of post-injection pressure. Rare distant side effects include systemic paralysis, and flu like symptoms have been reported after injections [25].

Other agents

Wirsching *et al.* [27•] have developed the use of the chemotherapy drug doxorubicin as a chemoneurolytic agent for the treatment of patients with intractable essential blepharospasm and hemifacial spasm. The drug was chosen due to its cytotoxic effect on striated muscle when injected directly into the orbicularis oculi. The results in the initial treated group has been encouraging over the 8 weeks studied. Recent discussion on the primary route used [28•] was large (Wirsching, IO, personal communication). The main drawback of doxorubicin injections are the local side effects including skin erythema and edema, but ulceration. One month after initial treatment of patients discontinued their treatments because of the unpleasant skin changes.

Third Septum Pharmaceuticals (Menlo Park, CA) are developing a peptide from all dystrophin. Studies have shown that the chemoneurotoxic effect of Dystrophin is similar to that of doxorubicin in animals [27]. The benefit of the dystrophin peptide is that it is the reduced incidence of skin injury. Patients will have the clinical evidence of the induced lids for up to 6 weeks following injection, but this has resolved in all treated patients to date [28]. A multicenter trial is now underway to determine the optimal dose for treating patients with eyelid spasms.

Recent work has shown the possible clinical utility of the toxin subunit V35 as an immunosuppressive agent [29••–32]. This agent has been extensively studied in the experimental models with excellent results. Rivest *et al.* [29••] have shown that the intramuscular injection of a monoclonal antibody for receptor ligand before receptors. The toxin has been shown to paralyse the extraocular muscles (i.e. in human muscle with no histologic damage to the muscles [29••]. We are currently studying the effect of this toxin — the pharmacokinetics in the animal model (both primate and rodent (Nicholas J.R., personal communication).

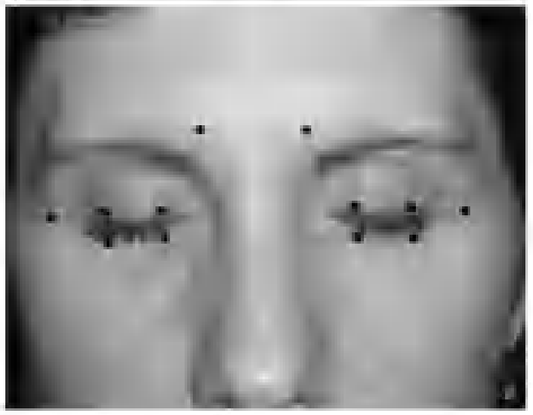
Clinical use of chemodenervation agents

Facial dystonias

The botulinum toxins have significantly improved the treatment of patients with benign essential blepharospasm, hemifacial spasm, and the other facial dystonias. The success rate has been reported to be greater than 90% [19]. Patient acceptance of the injections is high as well [8]. Patients with blepharospasm are typically injected every 3 to 4 months while those with hemifacial spasm may require every 6 to 8 months. Patients should be evaluated 2 to 3 weeks after their initial treatment to assess the efficacy. Further injections can be given at this time and may be made to treat new areas in the more than one side previously.

Subcutaneous injections of BTX are given into the orbital margin of the upper and lower lids and the periorbital injection muscle of the eyebrows. The sites are injected only by subcutaneous and submuscular injection are modified based on the patient's response to treatment. I most commonly use 4 units Allergan, Botox (2.5 units per 0.1 ml) in each side and 1 unit Botox diluted with 1 ml of unpreserved saline (2.5 units per 0.1 ml). The toxin is then drawn into tuberculine syringes and injected with a 30-gauge needle. Typically 2.5 to 5 units are injected into the pretarsal orbicularis of the upper and lower eyelids medially and laterally and into the lateral canthus and corrugator muscles and 2.5 to 7.5 units are injected into the procerus muscle. Injections into the procerus muscle have been shown to produce a significant

Figure 1. External photograph demonstrating placement of injections



Anatomic drawing and corresponding placement of injections into the glabella, procerus, corrugator, and depressor supercilii muscles. Each mark represents a subcutaneous injection of 2.5 to 5 units of Botox (Allergan, Irvine, CA).

fadeout response and longer duration in both blepharospasm and hemifacial spasm patients [56]. Injections of this toxin have been shown to be efficacious and safe over a 10-year time period in one study [54••].

Facial wrinkles

Facial wrinkles or rhytides may be categorized as static or dynamic. Thinning of the dermis with age causes static wrinkles. Dynamic wrinkles are typically deeper depressions or lines and are a result of hyperactivity of the underlying muscles. These dynamic wrinkles are most commonly over the upper third of the face (brow and periorbital regions) and are amenable to management with the chemodenervation agents [14–16]. Other facial rejuvenation techniques including peels, laser resurfacing, and fillers do not target the underlying muscular etiology of the dynamic wrinkle [16].

The use of botulinum toxin A injections as a potential treatment for dynamic wrinkles in the glabella was first studied and reported by Carruthers *et al.* [15] in 1992. The use of Botox and the other toxins have matured dramatically in the past year due to the FDA approval of Botox for managing glabellar wrinkles. The use has expanded to the midface, perioral and neck areas as well. BTX has also been used to augment other procedures including peels, laser resurfacing, brow lift, and fillers [15,16].

Glabellar furrows

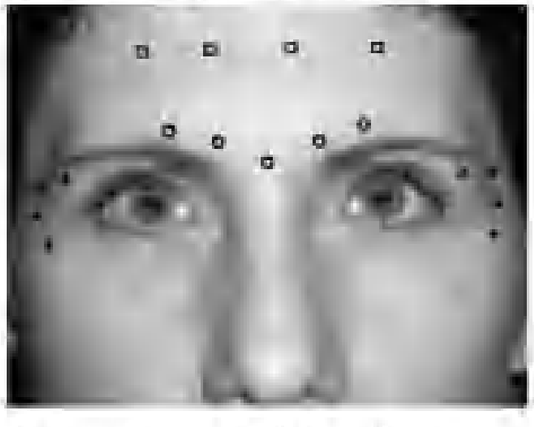
The glabellar wrinkles are unusual primarily because of the unique corrugator-procerus depressor supercilii anatomy. The mechanism of BTX in these areas has been shown to cause a temporary paralysis that begins 24 to 48 hours after injection and lasts for up to 6 months. Injections of 2.5 to 5 units of Botox are given in 5 to 7 sites into both corrugators and into the procerus (Fig. 2). A intraplane injection technique into the deep and superficial muscle planes has been reported to be efficacious by some authors [55]. A multicenter double-blind, randomized placebo-controlled study revealed a significant reduction in the glabellar line severity with BTX [36]. The effect was maintained for up to 120 days. They reported a 5.4% incidence of blepharoptosis. The efficacy of botulinum toxin injections has also been quantified by digital image analysis [37]. They showed a 71% decrease in brow lateral mobility and a 57% decrease in lateral mobility of the browsat 12 weeks post injection.

Recent papers have shown the merit of Botulinum in managing glabellar wrinkles [38–40]. One study using sex injections of 500 units [36] showed the injections to be efficacious with rapid onset and a mean duration of effect being 8 weeks. Subjective and the physician assessment scores were high. The main drawback discussed for the methods is the shorter duration when compared with the botulinum toxin A agents.

Periocular crow's feet

The contraction of the lateral orbicularis oculi as well as the zygomaticus and platysma muscles give rise to the wrinkles in the lateral canthus area referred to as the crow's feet. Injection of BTX into this area may soften and diminish these lines. There is less experience (2.5 to 5 units of BTX A are typically given into the lateral orbicularis near the zygoma. Care should be given to avoid

Figure 2. External photograph demonstrating placement of injections managing upper facial wrinkles and lines



Each site is injected subcutaneously with 2.5–5.0 units of Botox (Allergan, Irvine, CA). Open circles are placed approximately 1 cm above the orbital rim. Closed circles are placed approximately 1 cm below the orbital rim. The injections are often placed more superficially in the forehead.

affecting the zygomaticus major muscle which may lead to an ipsilateral lip ptosis [14]. A study comparing the efficacy of injecting 0, 12, or 48 units into the periocular area found no significant difference in the various amounts of toxin injected [47••]. This study also found that the benefits of the injections are more sustained with repeat treatments. Adding a 2-mm injection of BTX A into the central lower eyelid 3 to 4 mm below the lash line was found to significantly increase the palpebral aperture and improve infraorbital wrinkles [15].

Horizontal forehead wrinkles

The action of the frontalis muscle may lead to the development of horizontal forehead lines in repose. Injections of BTX in 4- to 8-sites spaced equally over the forehead may relax the muscle and soften these lines [14–16]. The injections are typically given 2 to 3 cm above the eyelid rim using 2.5 to 5 units per injection site (Fig. 3). Injecting less than 2 cm above the brow may lead to ptosis in some patients.

Chemical brow lift

Several authors have examined the use of BTX to create a temporary chemical brow lift by selectively paralyzing the depressors of the eyebrow [44, 45]. Injections of BTX are given into the glabellar area for detailed procedure) and the lateral orbital orbicularis muscle (Fig. 2). The main complications of the injections is upper-eyelid ptosis which may be avoided by aiming the needle up and horizontal to the injected orbicularis muscle [44].

Lower face and neck

Several recent articles have reviewed the use of BTX for the facial wrinkles in the perioral and neck regions [14–16••]. These authors have injected the orbicularis oris muscle, portion of the platysma muscles, as well as the other muscles of the neck. These muscles function in eating, swallowing, and breathing. It is important in the physician to be familiar with the anatomy and physiology of these muscles before treatment with pharmacologic agents is performed. A patient has been reported who developed severe dysphagia requiring nasogastric tube placement for 6 weeks following neck injections [15]. Small dose dilution injections are necessary in these areas to prevent displacement of the drug. Experience with injections in these areas have been limited. Experienced physicians

Conclusion

The use of the botulinum toxins has revolutionized the treatment of a broad group of diseases from hyperkinetic facial dystonias to cosmetic facial wrinkles. The botulinum toxins have now come of age in the office now for the first time in the history of medicine, a drug has allowed physicians to treat patients with a temporary chemical paralysis of muscles. With time we will likely see the development of new generation toxins with increasing differences in duration of effect.

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Clinical & Experimental Ophthalmology RANZCO

childhood, an exceedingly rare occurrence. A 42-year-old [illegible] presented with a [illegible] history of painless central vision loss in his right eye. [illegible] Chickenpox, confirmed by VZV [illegible] (IgM) titres, had started 5 days prior. He claimed to have had chickenpox as a child, and VZV immunoglobulin G was also detected. Unaided visual acuity (VA) was [illegible] OD, and 6/6 OS. Colour vision and pupillary reflexes were normal in both eyes. On general examination, he had characteristic pox-like skin lesions, and on ocular examination he had blurred disc margins with subretinal fluid in the right eye, but no other signs of intraocular inflammation [illegible]. The left eye was unremarkable. Subretinal fluid was confirmed on optical coherence tomography and fluorescein angiography (FA; Fig. 1). [illegible] several areas of late pinpoint leakage [illegible] to the disc and possibly to the area of the subretinal fluid (Fig. 1). After the exclusion of other [illegible] such as syphilis and [illegible], a diagnosis of unilateral neuroretinitis secondary to VZV was made. As there was no evidence of [illegible] and the patient's general physician did not recommend systemic treatment for his chickenpox [illegible], we chose to observe this patient.

A month later the vision had gradually improved as the subretinal fluid resolved without any notable lipid [illegible]. At the same time, a large nerve fibre layer (NFL) haemorrhage [illegible] the disc margin appeared in the area of late pinpoint leakage present on FA at baseline (Fig. 1a–i). Six months later, the NFL haemorrhage resolved leaving an atrophic [illegible] (Fig. 1) and VA in the right eye improved to [illegible].

Despite the dramatic initial appearance, the patient recovered with minimal loss of [illegible] without any signs of intraocular inflammation. As [illegible] chickenpox is very rare in adults, the occurrence of an associated neuroretinitis is even rarer and is [illegible]. [illegible]

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Placement of an eyelid weight as an upper lid spacer for lagophthalmos

For over 50 years, upper lid loading has been accepted treatment for lagophthalmos and exposure keratopathy.[1] Numerous modifications have been described. [illegible] the dimensions of the weight used and secured it to the septum. Pretarsal placement with fixation to tarsus was described by [illegible] in 1989. In 1996, [illegible] and [illegible] described [illegible]. In 2004, [illegible] the weight to [illegible]. In the same year Caesar et al. [illegible] supratarsal location [illegible]. [illegible], while pretarsal [illegible].

We describe another modification: [illegible] weight implantation [illegible], optimizing lid closure while minimizing the required weight, and preventing the visible contour associated with pretarsal placement.

A retrospective review of consecutive patients undergoing gold or platinum weight placement [illegible] from March 2006 through February 2008 was performed. Internal Review Board (IRB) and Health Insurance Portability and Accountability Act (HIPAA) authorization was obtained. The review adhered to tenets of the Declaration of Helsinki. Preoperative and postoperative lagophthalmos, marginal reflex distance (MRD1) measurements and corneal changes were compared. Postoperative complications were noted. Corneal changes were rated as: 0 = no keratopathy, 1 = mild punctate epithelial keratopathy, 2 = moderate epithelial keratopathy, but no epithelial defect, 3 = severe epithelial keratopathy with epithelial defects or corneal thinning. [illegible] MRD1 and corneal status were compared using [illegible]. Wilcoxon signed rank test. Statistical analysis was performed using JMP 7.0.1 (SAS Institute, Cary, NC).

The weight implanted was the minimal preoperative [illegible] weight to achieve passive closure, plus 0.2 gm to account for differences in [illegible] between

[illegible]

the taped weight and intraoperative position. Andrew R. Harrison performed all procedures.

The upper lid crease is marked and injected with 2% lidocaine with epinephrine. A crease incision is made and superior third of tarsus exposed. Levator aponeurosis is separated from septal and tarsal attachments. Levator is dissected from Müller's muscle and recessed 3–4 mm. The weight is placed on Müller's muscle, and sutured to the superior edge of tarsus (anteriorly, and to the recessed levator aponeurosis superiorly) with a 5/0 Mersilene (Ethicon, Somerville, NJ, USA). Orbicularis muscle is closed with 6-0 Vicryl (Ethicon, Somerville, NJ, USA) and skin 6-0 plain gut (Fig 1).

Sixteen eyelids of 14 patients met criteria. Average age was 61 years (range 18–93 years). Average follow-up was 16.3 months (SD 5 months; range 6–22 months). Facial paralysis was secondary to tumour resection (12 eyelids), trauma (three eyelids) and Bell's palsy (two eyelids).

Average preoperative lagophthalmos was 5 mm (SD 2.8) and preoperative MRD1 was 3.9 mm (SD 1.5). Mean postoperative lagophthalmos was 1.5 mm (SD 1.7), and MRD1 was 2.7 (SD 1.8). Eight eyes had no lagophthalmos postoperatively. Mean weight was 1.5 gm (SD 0.3 gm). Average change in lagophthalmos was −3.7 mm (SD 1.8, P-value < 0.0001). Average change in MRD1 was −1.2 mm (SD 1.1, P-value = 0.002). Only one eyelid required revision: a patient with 10 mm of lagophthalmos, improved to 3.5 mm after surgery, then underwent permanent lateral tarsorrhaphy (Fig 2).

Preoperatively, four eyes had severe epithelial keratopathy, six moderate keratopathy and seven mild keratopathy. Average preoperative corneal score was 1.8 (SD 0.9), and postoperative score was 0.7 (SD 0.7). Average change in corneal score was −1.1 (SD 0.9, P-value = 0.0011). Five eyes experienced complete resolution of keratopathy and 11 had mild residual symptoms.

Both patients had subconjunctival granulomas formed by implanting 4 mm discs on the eyelid, deep below the tarsus (three eyelids) and overlying tarsus (two eyelids). The 0.8 mm increase in MRD1 (mean 1.2 mm (+/− 1.2) with weight only and −1.1 mm (+/− 1.4) in weight plus anchor procedure (P-value = 0.72). The change in lagophthalmos was 2.6 mm (+/− 1.5) with weight only and 4.5 mm (+/− 1.9) with weight plus eyelid procedure (P-value = 0.07). Average preoperative lagophthalmos was 4 mm (+/− 2.8) in the weight only cohort and 5 mm (+/− 2.8) in the weight plus eyelid procedure group.

Three experienced infection, migration or extrusion. There were no complaints regarding cosmetic result.

The technique combines elements of the levator aponeurosis with superficial weight implantation. The implant becomes a 'spacer' between the recessed levator aponeurosis and tarsus to alleviate both lagophthalmos and eyelid retraction caused by weakened orbicularis tone. Additionally, it addresses the eyelid and palpebral vessels without compromising function.

This study is limited by small size and retrospective nature. Strengths include the use of a single surgeon (AH) and patients with relatively stable facial nerve function. Future studies will separately analyse and evaluate underlying ocular procedures in addition to weight placement. Bauer and Bailey's manuscript is the only study that quantified change in lagophthalmos.

All patients experienced significant improvement in lagophthalmos and corneal status. The average reduction of 3.5 mm in lagophthalmos was similar to 3.2 mm reported by Bauer and Bailey although we used an average 0.9 gm compared to their standardised 2.2 gm. We observed upper lid retraction of 1.2 mm, which was cosmetically significant. We believe this should be considered in addition to other lid retractive forces weakened individuals bear.

Comparison based on Gilbertson et al. [1] check, all had significantly more reduction of lagophthalmos than weight placement alone. This seems intuitive as both lower lid retraction and upper lid ptosis contribute to lagophthalmos. Those with other procedures in addition to weight placement had more lagophthalmos preoperatively.

No patients had implant migration or extrusion, with an average of 11.5 months follow up. Proper exposure of the weight remains a concern as only sutures and conjunctiva separate the weight from the surface of the globe and the corneal tear film can be disturbed.

This study is limited by small size and retrospective nature of a single surgeon (AH). These do not negate the efficacy of the modification of a widely accepted procedure. This modification is simple, effective and economically acceptable. It can be added to the surgical armamentarium for treating exposure keratopathy due to lagophthalmos.

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Treatment efficacy and safety of canaloplasty for open-angle glaucoma after 5 years

Canaloplasty is one of the newer advances in non-penetrating glaucoma surgery. Published data demonstrate good efficacy and safety of canaloplasty in the short- and mid-term.[1] However, anatomical changes in the juxtacanalicular meshwork and the subsequent space might cause failure in the long term or even in the course of less penetrating deep sclerectomy in principle. We aim to investigate, if there is a decline of efficacy of canaloplasty in the treatment of adult patients with open-angle glaucoma (OAG) in the long term.

Comparison of Pain Scores With 30-Gauge and 32-Gauge Needles for Periocular Botulinum Toxin Type A Injections

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Purpose: To determine whether a 32-gauge needle can reduce the pain associated with periocular injections of botulinum toxin type A compared with 30-gauge needles.

Method: In this prospective, randomized, masked study, 30 patients received periocular injections of botulinum toxin type A for benign essential blepharospasm. For each patient, a 30-gauge needle was used in one side of the face, and a 32-gauge needle was used in the other side. Equal numbers of injections and equal amounts of botulinum toxin type A at each injection site were administered on each side of the face. Patients were then asked to rate their pain level on each side of the face, using a standardized verbal visual analog pain scale.

Results: The average pain score was 3.36 ± 1.82 for 30-gauge needles and 3.91 ± 1.83 for 32-gauge needles. Statistical analysis via Mann-Whitney U test confirmed the null hypothesis that no statistical difference in pain level existed between the 2 needle sizes.

Conclusions: There is no difference in perceived pain when comparing periocular botulinum toxin type A injections with 30- and 32-gauge needles. In addition, smaller-gauge needles require special order and result in greater cost. The authors recommend continued use of 30-gauge needles for botulinum toxin injection in the office setting.

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The efficacy of botulinum toxin was first described in the German romance novel and only found limited success in the early 1980s.[1] Since then, the medical uses of this toxin have greatly increased. Today, botulinum toxin type A (BTA; Botox®, Allergan Inc., Irvine, CA, U.S.A.) is commonly used for a variety of disorders including blepharospasm, hemifacial spasm, and hyperhidrosis. Ophthalmologists commonly use BTA injections for the treatment of strabismus, blepharospasm, and benign essential blepharospasm and for cosmetic purposes.[2] Although this treatment is quite effective, the pain induced by these injections is significant for many patients.

Many physicians recommend that pain be considered a "fifth vital sign."[3–5] In the practice of surgery and other procedures, such as botulinum toxin injections, however, pain results in undesirable complications. Most techniques to alleviate the pain associated with injections should be simple, fast, and require little preparation.[6] Recent studies have described application of ice, use of several needles, and EMLA cream (Lidocaine 2.5% and prilocaine 2.5%) to relieve pain associated with injections.[7–9] Investigators have commonly suggested that injections with smaller-gauge needles may reduce patient pain. The aim of this study was to determine whether the pain associated with BTA injections may be reduced using a 32-gauge needle when compared with the standard 30-gauge needle used by most practitioners.

METHODS

A total of 30 patients (10 women, 11 men) receiving BTA injections for blepharospasm were enrolled. The average age of patients was 66.6 ± 10.76 years. Subjects' pain scores, recorded with 30-gauge needles, ranged from 1 to 7. The average pain score associated with 30-gauge needle injection was 3.38 ± 1.80 (median = 3). Statistical analysis via Mann-Whitney U test showed a standard deviation of 1.82 and a mean of 3.36 ± 1.82 for 30-gauge needles and 3.91 ± 1.83 for 32-gauge needles (Table). The average number of injections per side of the face using 30-gauge and 32-gauge needles was 3.4 and 3.5, respectively. Statistical analysis via Mann-Whitney U test showed a standard deviation of 0.68 and a mean of 3.4 ± 0.68 for 30-gauge needles and 3.5 ± 0.68 for 32-gauge needles. There were no significant differences in pain level between the 2 needle sizes.

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Summary of number of botulinum toxin type A injections, number of units used, and pain score of patients with 30- and 32-gauge needles

	30-Gauge injections	30-Gauge units	30-Gauge pain score	32-Gauge injections	32-Gauge units	32-Gauge pain score
Sum	102	1061	101.5	101	1052.5	101.5
Average	3.4	35.33	3.38	3.37	35.08	3.98
Median	3	35	4	3	35	4
Standard deviation	1.80	11.23	2.02	2.04	10.43	1.83

DISCUSSION

BTA injections are used to treat a wide variety of orofacial and ocoupetic conditions.[2] Because patients usually require numerous injections during treatment, pain control is an important aspect to consider. Methods such as using anesthetic creams, 30% lidocaine tape, and skin cooling have been performed, but to our knowledge, this is the first study to compare pain with different needle sizes for BTA injections.[7–9] Our statistical analysis confirmed the null hypothesis that the amount of pain that patients experience is the same whether a 30-gauge or 32-gauge needle is used. In a 2000 study by Flanagan et al.,[10] 800 injections on 800 patients, using 25-gauge and 27-gauge needles for alveolar blocks and 25-, 27-, and 30-gauge needles for buccal infiltration or palatal injection, were administered. Similar to our study, they found that needle size does not significantly alter the amount of injection pain experienced by patients.

In addition, smaller-gauge needles are more expensive in the clinic setting and require special order. The cost of 100 30-gauge needles (Becton, Dickinson and Company) is $36.95 from Research Supply Inc., whereas 32-gauge needles (TSK Laboratory) cost $43.50 from the same supplier, resulting in a 18% cost increase per needle. Questions remain about whether there is any difference in efficacy of the botulinum toxin when injected with 32-gauge needles. However, in our experience, there is no difference. Because we excluded patients in whom topical anesthesia was used, we cannot comment on the difference in pain perception in these patients. Given the increased cost and lack of any published benefit, we continue to use and teach the use of 30-gauge needles for botulinum toxin injection in the office setting.

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Case Reports in Ophthalmology

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Case Report

Periorbital Necrobiotic Xanthogranuloma Successfully Treated with Intravenous Immunoglobulin

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Keywords
Necrobiotic xanthogranuloma · Non-Langerhans histiocytosis · Intravenous immunoglobulin

Abstract
Background: Necrobiotic xanthogranuloma (NXG) is a rare non-Langerhans histiocytosis with cutaneous manifestations most commonly of the periorbital skin and is often associated with hematologic disorders such as monoclonal gammopathy. Treatment of NXG is notoriously difficult, and fraught with recurrence and progression. ***Case Presentation:*** The authors describe a case of NXG with periorbital involvement in a patient with a complex autoimmune and hematologic medical history. The biopsy of this rare lesion prompted subsequent evaluation for an underlying disorder, which led to the diagnosis of multiple myeloma. Her NXG lesions demonstrated remarkable clinical improvement after treatment with intravenous immunoglobulin (IVIG). ***Conclusions:*** This case demonstrates the ophthalmologist's critical role in the diagnosis and management of NXG, as early detection cannot only prevent ophthalmic consequences such as ocular perforation and blindness but also prompt further investigation that may reveal an underlying disorder or systemic involvement, including hematologic malignancy as in this case. NXG has been effectively treated with IVIG in a handful

Background

Necrobiotic xanthogranuloma (NXG) is a rare chronic granulomatous disease first described by Kossmann and Winkelmann in 1965 [1, 2]. It typically affects adults in their 60s, with no gender preference [3]. All patients exhibit cutaneous involvement, most commonly of the periorbital skin. Half of the patients will have ophthalmic complications that may mimic uveitis or scleritis [4, 5]. Orbital signs can include proptosis, blepharoptosis, and restricted extraocular motility [6].

An important association of NXG is that most patients have or will be diagnosed with an underlying paraproteinemia, particularly IgG kappa light-chain monoclonal gammopathy, which may progress to multiple myeloma [7]. As in our patient, other biological markers associated with NXG include leukopenia in one third to one-half of patients and cryoglobulinemia [3, 4, 7–9]. The pathogenesis of NXG and its link to paraproteinemias has yet to be elucidated, though many hypotheses have been proposed. NXG has been reported to affect a wide variety of organs, including cardiac, pulmonary, splenic, renal, and facial nerve tissues [7]. Hematologic disorders may precede or follow NXG, and given the high association, patients with NXG require regular follow-up to screen for disease development. No characteristics of NXG have been found to predict disease course or severity. Therefore, with any new diagnosis of NXG, it is recommended to undergo evaluation for systemic involvement. As was the case in our patient, diagnosis of NXG may be critical to early detection of occult malignancy.

Treatment of NXG is challenging due to its rarity and resultant limited data. No controlled trials have been conducted to evaluate efficacy. Many different treatment options have been attempted, with no clear standard treatment established. Thus, choice of treatment is largely decided by patient factors such as disease extent, comorbidities, and tolerability. In patients with NXG associated with an underlying malignancy, treatment should be directed at treatment of that malignancy [10]. Otherwise, common agents used are alkylating agents and systemic glucocorticoids [8]. Other reported modalities include intralesional corticosteroids, interferon alpha, plasmapheresis, extracorporeal photopheresis, laser therapy, radiotherapy, and psoralen plus ultraviolet A photochemotherapy [7–9]. Surgical debulking has been discouraged due to the high rate of recurrence [10].

High-dose intravenous immunoglobulin (IVIG) has diverse immunoregulatory effects and multiple mechanisms of action. It is beneficial in a variety of autoimmune and inflammatory disorders, due to its anti-inflammatory and immunosuppressive effects via modulation of IgG levels, production of cytokines, effects on lymphocyte function, inhibition of complement deposition, and removal of pathogenic IgG [10]. Though expensive, IVIG has shown rapid clinical results with near-complete remission and few side effects in a handful of reported cases [11–15].

Case Presentation

[illegible] 3 swelling. Examination revealed yellow, non-pigmented nodules involving the upper eyelid, bilateral ophthalmoplegia with surrounding proptosis, and bilateral periorbital edema (Fig. 1). Similar extensions were noted on the right temple, left chin, and dorsal right forearm. Magnetic resonance imaging with gadolinium of the orbit revealed no enhancement or mass within the orbits. Visual acuity, pupils, and extraocular motility were normal. Biopsy of the right lower eyelid and right temple demonstrated a dermal histiocytic infiltrate surrounding areas of collagen degeneration (Fig. 2). Numerous Touton and foreign body type multinucleated giant cells were present, consistent with NXG (Fig. 3).

At the time of diagnosis, the patient was being regularly followed by hematology and oncology for a 7 year history of persistent leukopenia thought to be secondary to an unclassified multisystemic disorder, as well as history of monoclonal gammopathy of undetermined significance, dysgammaglobulinemia, and hypopigmentation. Diagnosis of NXG prompted bone marrow biopsy and aspirate, and CT/PET scan of the chest, abdomen, and pelvis to rule out development of myeloma or ocular lymphoma. Serum protein electrophoresis revealed an IgG kappa monoclonal protein spike. Serum hemoglobin was 9.1 g/dL, felt to be related to the underlying plasma cell disorder. She was normocalcemic and had normal renal function. Her skeletal survey showed no osteolytic lesions. CT scan showed splenomegaly. Finally, bone marrow biopsy revealed 20–30% IgG kappa monotypic plasma cells on biopsy and trephine biopsy. Diagnosis of multiple myeloma was then made and she was treated with CyBorD (cyclophosphamide, bortezomib, and dexamethasone) with subcutaneous bortezomib.

After completing and tolerating 7 cycles of CyBorD without complication, therapy was re-evaluated. The plasma cell myeloma had responded to chemotherapy with a diminution in serum protein and improved cytopenias of myeloma; however, an abnormal B cell clonality was still evident. It was decided to complete cycle 8 of CyBorD and only treat further if there was significant acceleration or evolution of her disease, as CyBorD appeared to have reached the major therapeutic benefit, and because of her low marrow cellularity and other medical comorbidities. There was also concern that continuing CyBorD may promote toxicity. After completing cycle 8 of CyBorD, bone marrow aspirate/biopsy and bone survey was unchanged. Because there were no significant changes, and IgG kappa monoclonal protein remained stable at 0.4 g/dL, it was opted to withhold treatment of the asymptomatic myeloma.

During the years of aggressive CyBorD chemotherapy regimen for treatment of myeloma, she had progression of her periocular NXG. Alternative treatment of her NXG eyelid lesions was then considered, and IVIG was selected due to reports of its success in treating this disfiguring and painful disorder associated with myeloma. No local therapy was tried. She was started on IVIG 0.5 gm/kg/day for 4 consecutive days administered every 4 weeks with the intention to complete at least 3 cycles of IVIG, and more if it appeared helpful (Fig. 4). After 3 cycles of IVIG, the patient noticed improvement in periorbital discoloration and pain.

After 6 cycles, there was dramatic improvement in the appearance of the soft tissue around her eyes. By cycle 10, all previously noted lesions were resolved. She continues to receive monthly injections of IVIG with favorable results at 4 years of follow-up (Fig. 5). Since completion of the initial 8 cycles of CyBorD, her multiple myeloma has been minimally monitored and there has been no significant change in the objective markers of myeloma off chemotherapy.

[illegible]

Discussion and Conclusions

NXG is a progressive, systemic disease that often presents with ocular complaints. This case demonstrates the clinical significance of early diagnosis and management of NXG, as detection cannot only prevent ophthalmic consequences such as ocular perforation and blindness, but also prompt the detection of systemic effects, including hematologic malignancy. The lack of ophthalmic literature on NXG may signify that NXG is underrecognized by the ophthalmologic community. Despite this, the ophthalmologist plays a critical role in the diagnosis, as NXG most commonly presents on the periorbital skin. This case documents periorbital NXG that promoted the detection of an underlying asymptomatic malignancy, as well as successful treatment with IVIG, a promising, yet underutilized approach. To the best of our knowledge, this represents the first case of periorbital NXG successfully treated with IVIG in the ophthalmic literature, with two prior cases of eyelid involvement in the dermatology literature [11, 15].

Statement of Ethics

We have obtained informed consent from the participant to report individual patient data, including images.

Disclosure Statement

None of the authors have any competing interests.

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Author Contributions

R.M.O. prepared the first draft of the paper based on input from A.M. A.R.H. oversaw the writing process and was involved in revision. A.M. performed the ocular pathologic analysis and was involved in manuscript revision. A.M. oversaw the paper from the first draft to submission and assisted in multiple revisions.

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Fig. 1. Pretreatment clinical findings of periorbital necrobiotic xanthogranuloma demonstrating multiple yellow, firm papules coalescing into plaques and resulting in cicatricial lagophthalmos.

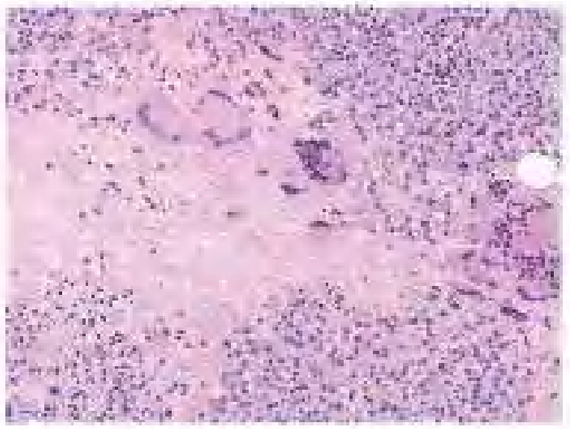

Fig. 2. Skin biopsy of necrobiotic xanthogranuloma lesions revealing a diffuse dermal infiltrate of histiocytes with multinucleated giant cells along with cholesterol clefts, Touton forms, and geographic necrobiosis. Hematoxylin and eosin, ×100.

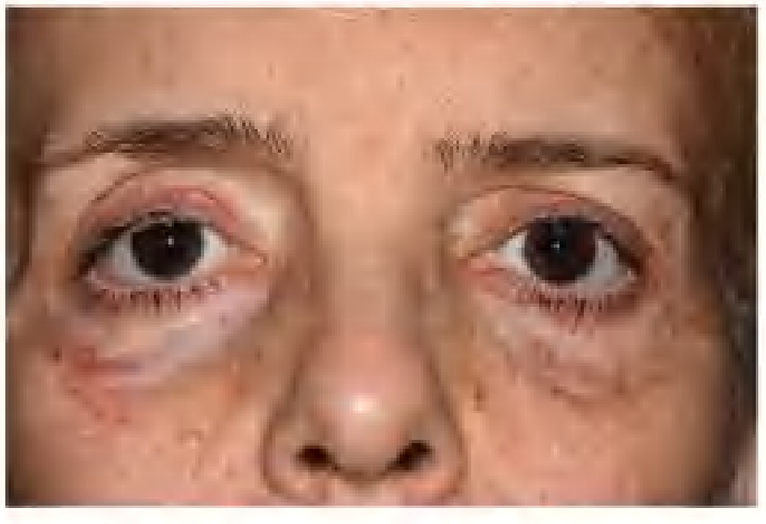

Fig. 3. Treatment outcome of periorbital lesions of necrobiotic xanthogranuloma after 16 cycles of intravenous immunoglobulin.

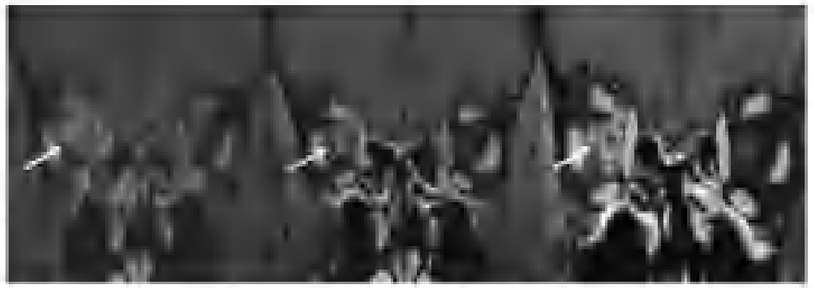

FIG. 1. Axial contrast-enhanced MRI of the orbits revealed right optic nerve sheath enhancement and thickening with a well-defined circular mass measuring 6 mm in diameter (arrow). Note the normal appearance of the left optic nerve sheath (arrowhead).

ABSTRACT: A 55-year-old male presented with headaches and painless episodes of unilateral vision loss. He had a history of renal cell carcinoma in remission following surgery and immunotherapy with ipilimumab and nivolumab. Seventy-two days and 3 months before presentation, respectively, MRI revealed an optic nerve sheath mass and perineuritis. After 1 month of corticosteroid therapy, there was a robust clinical and radiographic response, which relapsed three months following cessation. An optic nerve sheath biopsy showed chronic mild inflammation, and extensive workup for alternative etiologies of orbital inflammation was negative, following a prolonged taper of corticosteroids. He demonstrated complete response to the resolution of ocular inflammation, ophthalmic immune-related adverse events (irAEs) are rare, serious manifestations. While no treatment for irAEs are well-characterized, posttreatment irAEs have become increasingly recognized across multiple organ systems. We report a case of a delayed-onset inflammatory optic nerve sheath mass and perineuritis after cessation of immunotherapy.

Ipilimumab and nivolumab are combined checkpoint inhibitors approved for the treatment of systemic immunosensitive neoplasms (irAE). To the authors' knowledge, only one previously published report linked the use of these medications to the development of orbital inflammation. While uncommon, irAEs can be characterized as delayed-onset, immune-mediated side effects that may occur months to years after cessation of therapy. As the use of these medications becomes increasingly widespread across multiple organ systems, delayed-onset irAEs may become more frequently encountered. Although the pathophysiology remains poorly understood, it is thought that the immune system may remain primed to attack tumor antigens even after cessation of therapy. We present a case of delayed-onset inflammatory optic nerve sheath mass and perineuritis after cessation of immunotherapy.

CASE PRESENTATION

A 55-year-old male with a history of clear cell renal cell carcinoma status post nephrectomy in 2016 was referred to the neuro-ophthalmology clinic for evaluation of episodic vision loss. The patient's ocular history was notable for chronic conjunctivitis and dry eye syndrome, which began after the initiation of ipilimumab and nivolumab therapy. His medical history was also significant for hypertension, hyperlipidemia, and coronary artery disease. His medications included aspirin, atorvastatin, and metoprolol. He had no known drug allergies. He had a 30-pack-year history of tobacco use but quit 7 years prior to presentation. He denied any recreational drug use. He had no family history of ocular or neurologic disease.

Approximately 2 months before presentation, the patient developed a sudden, painless, transient, and complete loss of vision in the right eye that lasted for approximately 1 minute. He described the vision loss as a "curtain coming down" over his right eye. He denied any associated headache, jaw claudication, or polymyalgia rheumatica symptoms. He had no history of migraines or transient visual obscurations. He had no other neurologic symptoms. He had no history of similar episodes in the past. He had no other ocular symptoms, including pain, redness, or diplopia. He had no recent illnesses, fevers, or chills. He had no recent travel history. He had no sick contacts. He had no recent vaccinations. He had no recent trauma to the head or eyes. He had no recent changes in medications. He had no recent changes in his diet. He had no recent changes in his exercise routine. He had no recent changes in his sleep habits. He had no recent changes in his stress levels. He had no recent changes in his alcohol consumption. He had no recent changes in his caffeine consumption. He had no recent changes in his smoking habits. He had no recent changes in his drug use. He had no recent changes in his sexual activity. He had no recent changes in his urinary habits. He had no recent changes in his bowel habits. He had no recent changes in his weight. He had no recent changes in his appetite. He had no recent changes in his energy levels. He had no recent changes in his mood. He had no recent changes in his sleep patterns. He had no recent changes in his cognitive function. He had no recent changes in his memory. He had no recent changes in his concentration. He had no recent changes in his ability to perform activities of daily living. He had no recent changes in his ability to work. He had no recent changes in his ability to drive. He had no recent changes in his ability to read. He had no recent changes in his ability to write. He had no recent changes in his ability to speak. He had no recent changes in his ability to understand language. He had no recent changes in his ability to recognize faces. He had no recent changes in his ability to recognize objects. He had no recent changes in his ability to recognize colors. He had no recent changes in his ability to recognize numbers. He had no recent changes in his ability to recognize letters. He had no recent changes in his ability to recognize words. He had no recent changes in his ability to recognize sentences. He had no recent changes in his ability to recognize paragraphs. He had no recent changes in his ability to recognize pictures. He had no recent changes in his ability to recognize faces. He had no recent changes in his ability to recognize objects. He had no recent changes in his ability to recognize colors. He had no recent changes in his ability to recognize numbers. He had no recent changes in his ability to recognize letters. He had no recent changes in his ability to recognize words. He had no recent changes in his ability to recognize sentences. He had no recent changes in his ability to recognize paragraphs. He had no recent changes in his ability to recognize pictures.

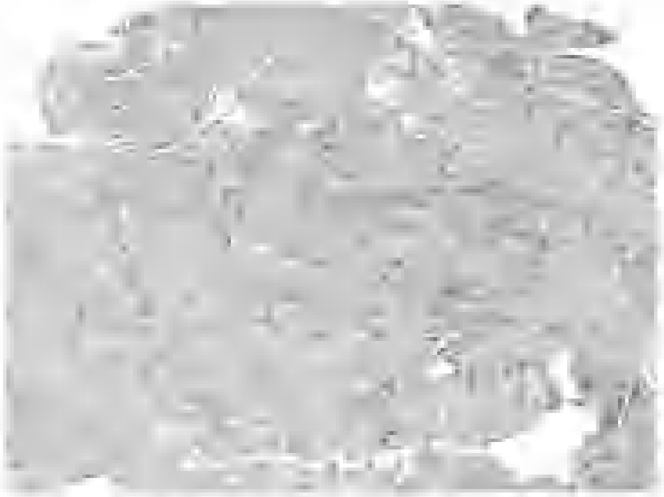

FIG. 2. Histopathology from the patient's optic nerve sheath biopsy [illegible], without evidence of malignancy (hematoxylin and eosin stain).

Recurrent Retrobulbar Hemorrhage Associated With CPAP Use After Orbital Fracture Repair

Abstract: We present a patient who underwent orbital fracture repair complicated by retrobulbar hemorrhages twice within the first postoperative week. The suspected cause is continuous positive airway pressure (CPAP) use with inappropriate patient modified settings. The most likely mechanism of action was venous congestion from the extrinsic positive pressure, similar to Valsalva maneuvers increasing orbital vasculature pressure. In our patient, because his orbital tissue vessels had recently been cauterized, they were too fragile to handle the engorgement and likely leading to a retrobulbar hemorrhage. It is possible that at a lower CPAP setting, the vascular congestion would not have been as severe and caused bleeding. We recommend routinely asking patients about CPAP use before orbital surgeries and instructing patients to stop CPAP usage for 1 week after any orbital surgeries if medically cleared.

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CASE PRESENTATION

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CURRENT EYE RESEARCH

Effects of Repeated Eyelid Injections with Botulinum Toxin A on Innervation of Treated Muscles in Patients with Blepharospasm

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ABSTRACT

Purpose: To learn changes in innervation and muscle morphology after repeated botulinum toxin A injections in subjects with benign essential blepharospasm.

Methods: Surgical waste specimens were processed for histologic examination of nerve fibers, neuromuscular junction, fiber size, and central nucleation and compared to age-matched control orbicularis oculi muscles from subjects with blepharospasm that had not received botulinum toxin A injections.

Results: There was a significant increase in amount of nerve fibers and numbers of neuromuscular junctions in the orbicularis oculi muscles from subjects with blepharospasm treated repetitively with botulinum toxin A. In addition there was a significant decrease in mean muscle fiber cross sectional area and an increase in central nucleation. The specimens from the subjects with only blepharospasm had the same density of nerves but had intermediate levels of neuromuscular junctions.

Conclusions: These data suggest that repeated injections of botulinum toxin A has an effect on nerve and neuromuscular junction numbers. Which we have termed re-innervation, from muscle from subjects with blepharospasm only. These studies suggest the potential for molecular level changes in order to extend the duration of effectiveness of botulinum toxin.

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Botulinum toxin A; orbicularis oculi muscle; blepharospasm; peripheral nerve; neuromuscular junction

Introduction

Benign essential blepharospasm is a form of focal dystonia[1] with an incidence rate of 1.2 persons per 100,000 per year[2] and prevalence rates from 20 to 133 per million in multiple studies.[3] Prevalence estimates for all forms of primary dystonia range from 2 to 30 cases per million of the population for early onset dystonia[4] and 40–720[5] cases per million for late onset dystonia.[6] Botulinum toxin A, which blocks the release of acetylcholine at the neuromuscular junction, resulting in paralysis was originally developed as a potential treatment for strabismus.[7] Its utility in the management of blepharospasm was realized shortly thereafter.[8] After these initial studies, the intramuscular injection of botulinum toxin A has safely relieved dystonia symptoms for thousands of patients of all ages as well as significantly improved their quality of life.[9]

Research into the mechanism of action revealed the botulinum toxin A acts specifically on the presynaptic terminal where it cleaves the protein SNAP25.[10] The effect of botulinum toxin persists for several months as the cleaved SNAP25 is retained at the neuromuscular junction, preventing the assembly of new SNAP25 into the nerve terminal.[11] However, functional studies of botulinum toxin-induced muscle paralysis. A number of studies have demonstrated nerve terminal and axonal sprouting in the rat levator nerves as early as 2 days after botulinum toxin injection.[12] Evidence of axon sprouting after botulinum toxin A injections was seen specifically in human orbicularis oculi muscle from blepharospasm subjects at the single neuromuscular junction level.[13,14] This axon sprouting was postulated to be responsible for the formation of de novo neuromuscular junctions over the extrafusal orbicularis oculi muscle fibers, increasing the speed of the return of muscle function. Using rabbits, an injection of botulinum toxin A resulted in a significant increase in neuromuscular junctions throughout the paralyzed orbicularis oculi muscles[15] with a similar finding seen after injection of botulinum toxin A into rabbit extraocular muscles.[16]

Individuals with benign essential blepharospasm and other focal dystonias will receive many series of botulinum toxin A injections. The potential effects of repeated injections on the orbicularis oculi muscle and its innervation are not known. In a study of long-term efficacy there was a significant increase in botulinum toxin A dose between the first year and last year of treatment (with a range of 10–20 years of treatment), but no significant difference in the duration of effect.[17] The current study focused on the potential effects of repeated botulinum toxin A injections on muscle and nerve despite using surgical waste specimens from subjects who underwent an orbicularis oculi myectomy. These were compared to naïve orbicularis oculi specimens removed during blepharoplasty to the observe of focal dystonia in these subjects.

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Methods

[illegible] were approved by the Institutional Review Board of the University of Minnesota. Specimens [illegible] were [illegible] processed without knowledge of the presence or type of specimen. [illegible] gives the age, sex and number of botulinum toxin A injections per treatment and dose, the age of the two specimens from a subject with benign essential blepharospasm (BEB) who never received an injection of botulinum toxin and who was matched several individuals who underwent an upper eye blepharoplasty for the absence of facial dystonia or other neuromuscular disorder. At the time of surgery, orbicularis oculi preseptum specimens (performed by ARM or AAR) the pretarsal and preseptal muscles were excised separately and were placed in cryopreservant immediately. Within 1 h, they were embedded in tragacanth gum and frozen in 2-methylbutane chilled in liquid nitrogen. The tissue blocks were stored in a −80°C freezer until sectioned.

Ten muscle specimens were sectioned at 12 μm using a cryostat. Representative sections through the tissue thickness were stained using hematoxylin and eosin by standard methods. A series of six [illegible] were immunostained using an antibody to neurofilament protein (anti-H; 1:10000; Biolegend, San Diego, CA, USA) for identification of nerve fibers. Sections were incubated in normal serum at 10% in 1M phosphate buffered saline (PBS) containing [illegible] (antibody diluent), incubated in antibody [illegible] overnight at 4°C in humid chambers, rinsed in PBS, and then incubated in secondary antibody using the Vectastain Elite kit (Vector Laboratories, Burlingame, CA, USA) following [illegible] instructions. The sections were then rinsed in PBS, and stained with diaminobenzidine and 0.1% hydrogen peroxide using heavy metals to intensify the reaction. Tissues were stored in PBS, dehydrated in graded alcohols, and counterstained with Permount (Fisher Scientific, Pittsburgh, PA, USA). Several series of three slides per tissue block were stained for the visualization of neuromuscular junctions. Slides were stored in PBS, and mounted with α-Bungarotoxin conjugated to Alexa Fluor-488 overnight at a dilution of 1:40 at 4°C. Following a PBS rinse, the sections were counterstained using fluorescent mounting medium (Vector Labs).

Morphometric analysis was performed. Mean muscle, [illegible] areas and percent of myofibers with central nuclei, indicative of degeneration/regeneration or denervation/reinnervation, were measured manually using Bioquant Nova Prime software (Bioquant, Nashville, TN). A minimum of 3 slides were analyzed, and a minimum of 200 fibers were examined per muscle. For any given subject, the right and left sides of the same region (e.g. pretarsal) were averaged, and the averages were used to determine the means for the botulinum toxin A treated muscles from subjects with benign essential blepharospasm and for the naive control muscles. For the two subjects with benign essential blepharospasm who were never treated with botulinum toxin A, the average of the left and right sides of each region were calculated, and the means from the two muscles were then averaged. For nerve fiber analysis, a minimum of three slides were analyzed from each muscle region from both right and left eyelids. For each muscle from each eyelid area (pretarsal and preseptal), all the anti-H-positive nerve fibers within any given microscopic field of view were manually circled as was the total area of the field. The entire section was measured, and percent area containing nerve fibers was determined and compared to muscle area and compared to tissue area (muscle plus connective tissue). Similarly, every neuromuscular junction encountered in each of the three muscle sections, and the entire tissue section area was measured, to determine number of neuromuscular junctions relative to tissue area. As the three sections/specimens from the same muscles from each individual were averaged to determine the overall averages.

The means ± SEM were reported. Data analyses of the blepharospasm and botulinum toxin treated measurements compared to naive controls used an unpaired Student's *t*-test and JMP-In software (Graphpad, San Diego, CA, USA). Statistical significance was defined as $P < 0.05$.

Results

The mean age of the control subjects was 64.9 (range: 49–80), the mean age of the subjects with blepharospasm who were treated with repeated botulinum toxin injections was 67 (range: 55–82) and the mean age of the subjects with blepharospasm only was 59.5 years (Table 1). Thus the collected specimens were closely age-matched. Table 1 gives the amount of botulinum toxin injections and doses (if known) for each of the treated subjects, with a mean of 16.8 injections (range 3–28) per botulinum toxin treated subject.

When the amount of nerve fibers was calculated based on percent of total cross-section (Figure 1a) or percent of muscle tissue area (Figure 1b), the blepharospasm and botulinum toxin A–treated specimens had significantly more nerve fibers than naive control muscles, showing differences of 46.1% and 47.9%, respectively. While statistical analysis could not include the muscle specimens from the two subjects with blepharospasm who had not been injected with botulinum toxin A, these specimens had 54.7% more nerves as a percent of total tissue cross-section and 143% more nerve as a percent of muscle tissue cross-section. These values are 14.2% and 36.7% less than the nerve densities from the blepharospasm and botulinum toxin A–treated specimens.

This analysis was extended to analyze each muscle region separately. In the pretarsal region, there was significantly more nerve tissue both as a percent of all tissue and as a percent of muscle tissue, 87.8% and 103.2%, respectively (Figure 2). In the preseptal region, the blepharospasm and botulinum toxin treated muscles had 44.5% and 31.1% more nerve fibers than the naive control tissues, but only the nerve per total cross-section was statistically different. It is interesting to note that in both the pretarsal and preseptal regions of the orbicularis oculi muscle from the subjects with blepharospasm but without botulinum toxin A injections, the nerve density as a percent of either total cross-section or muscle cross-section was similar to the muscles from the subjects with both blepharospasm and botulinum toxin A treatment.

In order to assess changes on the postsynaptic side, neuromuscular junctions were localized using α-bungarotoxin staining and quantified morphometrically (Figure 3). There were significant increases in neuromuscular junctions per mm^2 in both the pretarsal and preseptal regions of the muscles from subjects that had blepharospasm and botulinum toxin A treatment compared to the age-matched control muscles from the same muscle regions, with a 5-fold and a 4-fold difference respectively. In contrast to the nerve density measurements, the pretarsal muscles from the blepharospasm subjects untreated with botulinum toxin A showed a level of neuromuscular density approximately equal to that of the control muscles, but 4-fold fewer than that of the blepharospasm muscles treated with repetitive botulinum toxin A injections. In the preseptal region, there were relatively similar levels of neuromuscular junctions in the control and blepharospasm only muscles, however there was a 114.7% difference between the controls and the botulinum toxin A treated muscles and an 81.5% difference between the treated and blepharospasm only muscles. This suggests that neuromuscular junction changes are increased with repetitive botulinum toxin A injections. It should also be noted that while there were many more neuromuscular junctions in the muscles from the botulinum toxin A–treated blepharospasm subjects, they tended to be smaller and thinner (Figure 3a, b).

The mean cross-sectional area of the pretarsal region of the muscle specimens from the subjects with benign essential

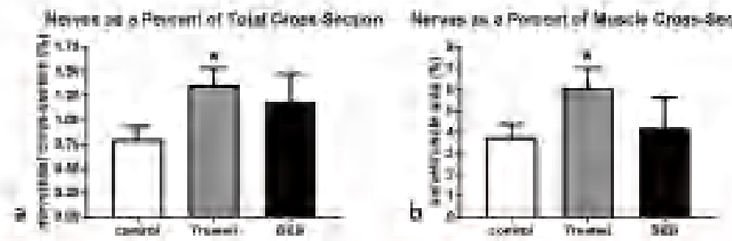

Figure 1. Morphometric analysis of nerve fibers in surgically excised orbicularis oculi muscle as a percent of total tissue cross-section (a) or muscle cross-section (b). * indicates significant difference from control. Control: naive control orbicularis oculi muscles. Treated: muscles from subjects with blepharospasm who had been treated with multiple botulinum toxin A injections. BEB: muscles from subjects with blepharospasm who never had an injection of botulinum toxin A.

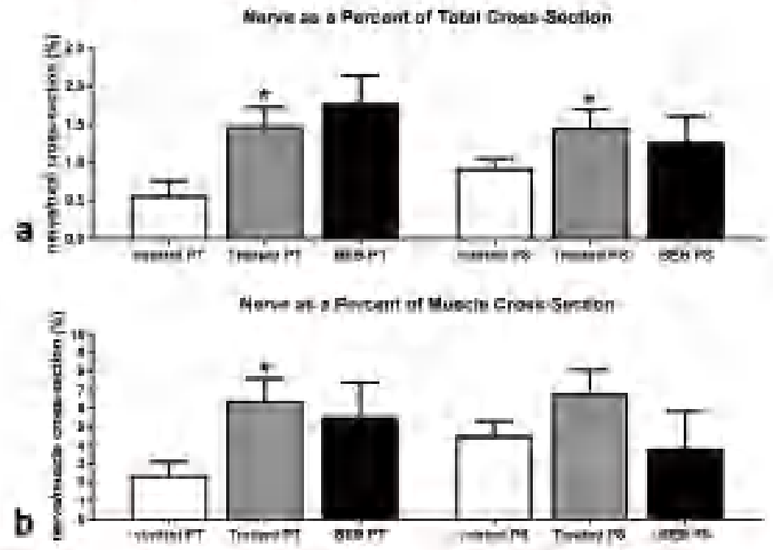

Figure 2. Morphometric analysis of nerve fibers in the pretarsal (PT) region and preseptal (PS) region of the orbicularis oculi muscle as a percent of total tissue cross-section (a) or muscle cross-section (b). * indicates significant difference from control. Control: naive control orbicularis oculi muscles. Treated: muscles from subjects with blepharospasm who had been treated with multiple botulinum toxin A injections. BEB: muscles from subjects with blepharospasm who never had an injection of botulinum toxin A.

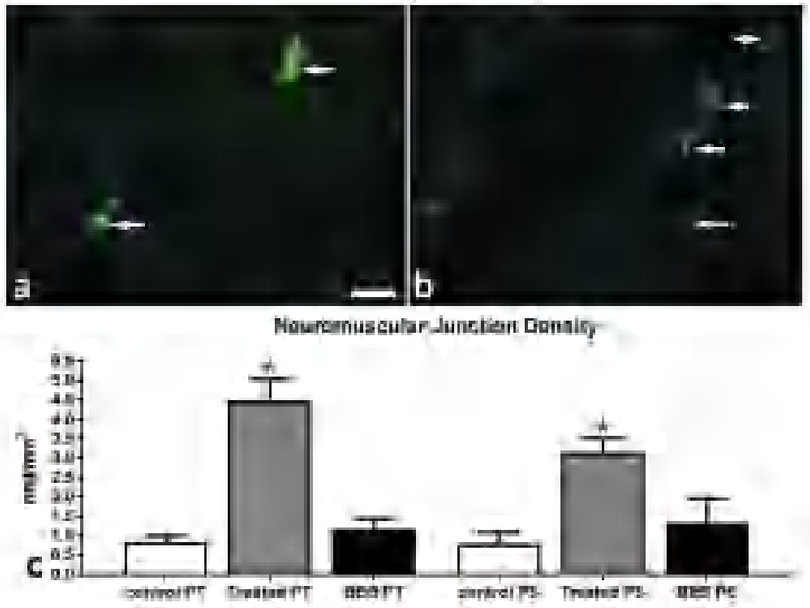

Figure 3. Photomontage of neuromuscular junctions (green) stained after transgression conjugate to Alexa fluor 488 in (a) naive rectus retractus oculi muscle and in (b) orbicularis oculi muscle from a subject with blepharospasm who had multiple botulinum toxin injections prior to surgical myectomy. (c) Neuromuscular junction density was significantly greater in the preseptal (PT) and preseptal (PS) regions of the orbicularis oculi muscle from control, botulinum toxin treated muscles from blepharospasm subjects, and subjects with blepharospasm only. Bar = 50 μm. * Indicates significant difference from control.

blepharospasm treated with multiple injections of botulinum toxin A were significantly smaller than the untreated control muscles, with a difference of 24.8% (Figure 4b–d). The myofibers in the preseptal region were also significantly smaller, with a difference of 52.4% in the botulinum toxin A–treated muscles from blepharospasm subjects compared to controls (Figure 4). It is also interesting to note that the muscles from the subjects with only blepharospasm had similar areas to the control muscles, with a 7% and 6.5% difference, respectively. Central nucleation is a hallmark sign of degeneration/regeneration or denervation/reinnervation. In both the preseptal and preseptal regions, there was a significant increase in percent of myofibers with central nucleation in the botulinum toxin A–treated muscles from subjects with blepharospasm, with a 6-fold (129.8%) and a 2-fold (131%) increase, respectively (Figure 4(e,f)). The muscles from the subjects with only blepharospasm had intermediate central nucleation levels, 72.5% and 71.6% greater, respectively.

Discussion

Previous studies examining individual neuromuscular junctions in subjects with blepharospasm and repeated botulinum toxin A injections showed limited evidence of terminal sprouting in the excised orbicularis oculi muscles.[7,11] In the present study, we showed that multiple injections of botulinum toxin A over time resulted in a number of widespread changes in the orbicularis oculi muscles of these subjects with blepharospasm. Botulinum toxin A injections caused a muscle wide increase in both nerve fiber and neuromuscular junction density compared to naive control orbicularis oculi muscles. While statistics cannot be reliably performed on four specimens from two subjects with blepharospasm and no botulinum toxin A treatments, it is interesting that only the nerve densities were similar to the botulinum toxin A treated orbicularis oculi muscles, with neuromuscular junction levels the same as the control muscles. This suggests that the increased number of nerve fibers per tissue area may be specifically related to the blepharospasm and not due to up-regulation by the repeated botulinum toxin injections. As there are only orbicularis muscles from two untreated blepharospasm subjects, the data must be interpreted carefully, it is, however, quite interesting given a condition whose primary etiology is not understood. This does not negate the literature which clearly has demonstrated that botulinum toxin A–induced nerve paralysis results in nerve sprouting in the area of the chemically denervated muscle fibers.[7,11] This is important to note that this sprouting occurs in the absence of physical damage to the nerve fibers, as physical damage is known to induce significant nerve fiber sprouting from the end of the injured nerve.[11]

The increase of de novo neuromuscular junctions as a response to muscle paralysis with botulinum toxin has been described in a number of muscles,[7,10,11,14] and specifically in the orbicularis oculi muscles.[7,11] These extrajunctional acetylcholine receptors also form in response to nerve sectioning.[15] As we demonstrated after botulinum toxin injections into the extraocular muscles, the induced muscle paralysis results in significant increases in neuromuscular junctions throughout the length of the muscles.[16] There are strong

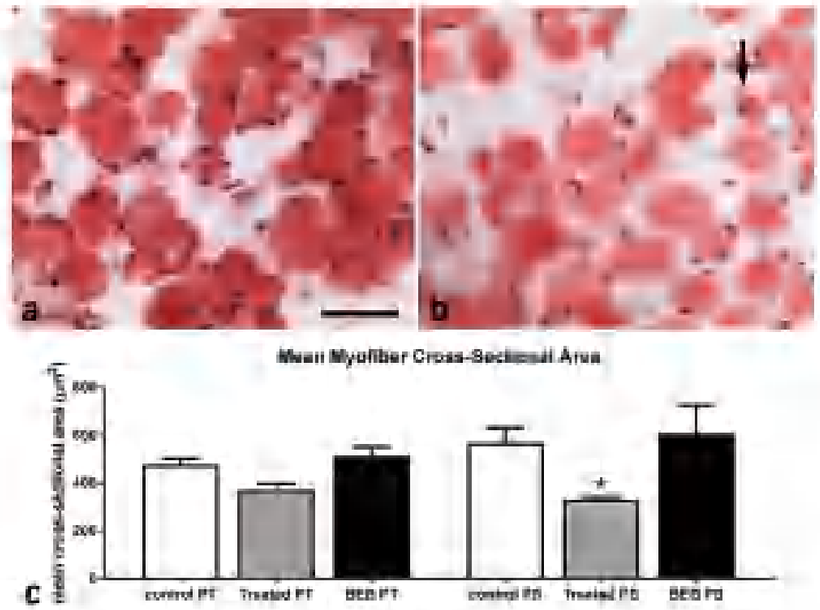

Figure 4. Photomontage of (a) naive control orbicularis oculi muscle and (b) orbicularis oculi muscle from a subject with blepharospasm who had multiple botulinum toxin injections prior to surgical myectomy. Arrow indicates a centrally located myonucleus. (c) Mean myofiber cross-sectional areas and (d) percent of myofibers with central nucleation in the preseptal (PT) and preseptal (PS) regions of the orbicularis oculi muscle from control, botulinum toxin treated muscle from blepharospasm subjects, and subjects with blepharospasm only. Bar = 50 μm. * Indicates significant difference from control.

similarities between the response to botulinum toxin A injection in the orbicularis oculi muscles and extraocular muscles. Both sets of muscles have short myofibers that do not span the length of the muscles,[17–19] have more than one neuromuscular junction on single muscle fibers,[18,20] and have small mean cross-sectional areas compared to limb skeletal muscles.[21–23] It is interesting that there was not as large an increase in neuromuscular junction density in the specimens with blepharospasm only. While one must be careful not to over-interpret data from two subjects (4 muscles), these data suggest that while denervation causes a large increase in neuromuscular junction number across each specimen, a good proportion of this response is due specifically to the botulinum toxin treatment. This observation, and the elevation in the number of nerves in the specimens with blepharospasm only, makes it tempting to speculate that at least part of the peripheral manifestation of blepharospasm might be due to some level of denervation and subsequent reinnervation. These specimens are quite rare, as the general standard of care for blepharospasm is botulinum toxin injections. Examination of additional specimens of orbicularis oculi muscle from blepharospasm patients who have not undergone treatment with botulinum toxins will allow us to better understand the pathophysiology of this disorder.

In peripheral skeletal muscles, the almost universal response to botulinum toxin injection is temporary muscle atrophy.[24–27] This was even seen in leg muscles after the large doses of botulinum toxin A needed for the treatment of cervical dystonia.[28] Botulinum toxin A also produced muscle atrophy in the masseter,[29] and has been used to reduce masseter muscle hypertrophy in human subjects.[30] Similar types of muscle fiber atrophic changes were described in experimental studies of the effects of botulinum toxin A into orbicularis oculi including human subjects.[31,32] In a previous study using human surgical waste tissues from blepharospasm subjects treated with botulinum injections, extreme variability in myofiber cross-sectional

areas was noted.[31] Relative to some studies we saw a significantly decreased mean myofiber cross-sectional area only in the preseptal portion of the treated orbicularis oculi muscle compared to saline control. However, it is important to note that the muscle specimens from the subjects with blepharospasm only did not show a decrease in mean fiber cross-sectional area. Thus one can speculate that these changes are likely due to the repeated exposure to botulinum toxin A.

The studies thus far have shown that the innervation to and structure of mammalian neuromuscular junctions have a fair bit of plasticity,[32,33] and these features are altered by long duration after botulinum toxin injection. This plasticity has the potential to be modified by other treatments as well. A number of studies have shown that the terminal nerve sprouting in denervated skeletal muscle can be altered in multiple ways, for example by changing neurotrophic factor levels, such as insulin-like growth factor (IGF-1),[34] by modifying levels of other molecules such as corticotropin releasing factor (CRF),[35] and by injection of blocking antibodies for neural cell adhesion molecule (NCAM),[36,37] tenascin,[38] or TGF-β.[39] These studies suggest the potential for these types of approaches to extend the duration of effectiveness of botulinum toxin. The orbicularis oculi muscle specimens from the subjects with previously untreated blepharospasm also had increased amounts of peripheral nerve within the muscles compared to naïve age-matched[8] control muscles suggesting that these peripheral changes may be part of the disease process. If borne out by future studies, these data suggest that reduction of nerve and neuromuscular junction numbers by use of CRF or blocking peptides or antibodies has the potential to be a primary treatment for blepharospasm.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Etiology of Immune Stromal (Interstitial) Keratitis

Gary S. Schwartz, M.D., Andrew R. Harrison, M.D., and
Edward J. Holland, M.D.

Purpose. We compared the etiologies of immune stromal keratitis (ISK) (also known as interstitial keratitis (IK)) in a referral group of patients with active and inactive ISK. **Methods.** We reviewed the charts of 97 patients seen in the uveitis clinic at the University of Minnesota from 1985 through 1994. Fifty-five patients were observed to have active ISK, defined by stromal inflammation without ulceration within 1 year of presentation. Forty-two patients were identified as having inactive ISK, defined by evidence of past stromal inflammation (scarring, stromal thinning, ghost vessels, and dehiscence of Descemet's membrane) without active inflammation for the 1 year before presentation. We determined the etiology of the ISK by careful review of the patient's ocular examination as well as medical and laboratory workup. Patients were labeled with the diagnosis of idiopathic ISK if no identifiable etiology was found. **Results.** Herpes simplex virus (HSV) accounted for 31.4% of unilateral active ISK. Idiopathic accounted for 13.9% and varicella-zoster virus accounted for 8.6% in this group. HSV was the etiologic factor in 70.0% of inactive unilateral cases, whereas 33.3% were idiopathic. Sixty percent of cases of bilateral active ISK were from idiopathic causes. Syphilis was the cause of all 5% of bilateral inactive cases. In this group, 39.3% were from idiopathic causes. **Conclusion.** Although syphilis has been recognized for many years as the cause of 90% of cases of ISK, this is no longer true. We demonstrated that active ISK is most commonly caused by HSV or is idiopathic and that, although syphilis is the leading cause of inactive bilateral ISK, it is responsible for only 18.0% of total cases.

Key Words: Immune stromal keratitis—Interstitial keratitis—Syphilis—Herpes simplex virus.

Immune stromal keratitis (ISK), also known as interstitial keratitis (IK), is a noninfectious inflammatory reaction of the corneal stroma. It may be seen as small, white, stromal opacities that most likely represent antigen-antibody complexes, or it may be seen as a dense, white cellular infiltrate. Some cases can have an accompanying stromal ring. The chronicity of this reaction may lead to neovascularization of the stroma, which may occur several days or weeks after the onset of inflammation. The inflammation may be seen at any level of the cornea. It may be epithelial, mid, or posterior stroma, or pre-Descemet's membrane. It may involve many levels of the cornea or be full thickness. In addition, the inflammation may be central, paracentral, or peripheral, sectoral or diffuse.

A variety of causes of ISK have been elucidated. Infectious agents include spirochetes, viruses, mycobacteria, parasites, and fungi/mycoplasma (1–8). Collagen vascular disease (9–11) has been implicated, and contact lens wear also has been associated with ISK (12).

In the literature, syphilis accounts for 90% of cases of ISK (1–3). This figure was reported by Duke-Elder (3) years ago and has been propagated in the literature since. The purpose of this study is to evaluate the etiology of ISK in our clinic over a 10-year period.

METHODS

A retrospective review of all cases of ISK in the Cornea and External Disease service at the University of Minnesota Hospitals and Clinics between January 1, 1985, and December 31, 1994, was performed. All cases of ulcerative keratitis and keratoconjunctivitis were excluded. Ninety-seven cases of ISK were identified. The etiology of each case was determined by review of the patient's history and review of systems, ophthalmic examination, and laboratory tests.

The diagnosis of active ISK was made if ongoing, immune-mediated stromal inflammation was present in the face of intact corneal epithelium (Fig. 1). Clinical findings associated with active ISK include stromal infiltration, edema, neovascularization, and an immune ring within 1 year before presentation.

Patients were classified as having inactive ISK with history of immune-mediated stromal inflammation with intact epithelium, without any evidence of active inflammation within the year before presentation. HSV was the most common etiologic factor, accounting for 27 cases. Seventeen cases were idiopathic, and four cases were contact-lens associated. Three cases were the result of VZV, and one case each was attributable to Lyme disease and EBV. Only two of the 55 cases of active ISK were thought be caused by syphilis.

Forty-two cases of ISK were considered inactive, as defined by history of immune-mediated stromal inflammation with ocular pathology, without any evidence of acute inflammation within the year before presentation. Syphilis was the leading cause of inactive ISK, accounting for 16 (38%) of the 42 cases. Fourteen cases were idiopathic and seven were the result of HSV. Three cases were caused by tuberculosis, and one each was caused by collagen vascular disease and measles.

Evaluation of bilaterality and unilaterality was also undertaken. A total of 47 patients had unilateral disease. HSV was the most common etiologic factor accounting for 21 (68%) cases. Nine unilateral cases were idiopathic, and three cases were the result of VZV. Two cases were caused by tuberculosis, and one each was the result of syphilis and contact lens use.

Fifty patients had bilateral ISK. Twenty-two (44%) of these patients had idiopathic ISK, making it the most common etiology within the group. Seventeen patients had ISK resulting from syphilis, and three each had ISK after BSO and contact lens use. One each had ISK from tuberculosis, measles, collagen vascular disease, Lyme disease, and EBV.

TABLE 1. Etiologies of immune stromal keratitis*

	Inactive		Active		
	Unilateral	Bilateral	Unilateral	Bilateral	Total
HSV†	9 (21.4)	1 (1.4)	20 (36.4)	2 (4.1)	34 (27.1)
Idiopathic	5 (11.9)	10 (23.8)	5 (9.1)	12 (24.4)	32 (25.6)
Syphilis	0	16 (38.1)	1 (1.8)	1 (2.0)	18 (14.4)
Contact lens	0	3	1 (1.8)	3 (6.1)	7 (5.6)
VZV	0	0	3 (5.5)	0	3 (2.4)
Tuberculosis	2 (4.8)	1 (1.4)	0	0	3 (2.4)
Measles	0	1 (2.4)	0	0	1 (0.8)
SLE	0	1 (2.4)	0	0	1 (0.8)
Lyme	0	0	0	1 (2.0)	1 (0.8)
EBV	0	0	0	1 (2.0)	1 (0.8)
Total	16 (12.8)	33 (26.4)	30 (24.0)	20 (16.0)	126 (100.0)

*Percentages are in parentheses.
†HSV, herpes simplex virus; VZV, varicella-zoster virus; BSO, bilateral salpingo-oophorectomy; EBV, Epstein-Barr virus.

The etiology of ISK was determined by careful medical and ophthalmic history, review of systems, and laboratory testing. Herpes simplex stromal keratitis was determined by either ghost vessels or a dendritic ulcer with decreased corneal sensation, corneal edema, or history of a prior dendritic ulcer. Varicella-zoster virus (VZV) keratitis was determined by either culture or scrapings with a history of varicella-zoster skin lesions in the distribution of the trigeminal nerve. Measles was determined by history. Epstein-Barr virus (EBV) was determined by viral titers. Syphilis was determined by VDRL or FTA-ABS testing or both. Lyme disease was determined by serologic testing. Tuberculosis was determined by chest radiograph and Mantoux skin test with controls. Collagen vascular disease was determined by serologic testing for autoantibodies, antibodies, and rheumatoid factor. Patients with negative history and laboratory workup for a specific disease etiology were labeled idiopathic.

RESULTS

Ninety-seven patients were seen with ISK between 1985 and 1994 (Table 1). Thirty-four had evidence of HSV eye disease, making this the most common etiologic factor. For 31 cases, no etiologic factor could be found, and these cases were labeled idiopathic. Eighteen cases were caused by syphilis. The remaining etiologies accounted for only 15% of the total cases. Four cases resulted from contact lens wear. There were three cases each attributable to VZV and tuberculosis, and one case each from Lyme disease, EBV, collagen vascular disease, and measles.

Fifty-five cases of ISK were considered active by the presence of ongoing, immune-mediated stromal inflammation within the year before presentation. HSV was the most common etiologic factor, accounting for 27 cases. Seventeen cases were idiopathic, and four cases were contact-lens associated. Three cases were the result of VZV, and one case each was attributable to Lyme disease and EBV. Only two of the 55 cases of active ISK were thought be caused by syphilis.

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Evaluation of bilaterality and unilaterality was also undertaken. A total of 47 patients had unilateral disease. HSV was the most common etiologic factor accounting for 27 (68%) cases. Nine unilateral cases were idiopathic, and three cases were the result of VZV. Two cases were caused by tuberculosis, and one each was the result of syphilis and contact lens use.

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DISCUSSION

ISK is one of the most common causes of chronic corneal inflammation. It may lead to significant corneal scarring and visual loss. Several terms have been used to describe the immunologic reaction of the stroma. These include: IK, nonulcerative bacterial keratitis, ISK, and disciform keratitis. Confusion exists regarding the usage of the term IK. Some authors use IK to refer to stromal neovascularization even inflammatory. Others reserve the term for posterior neovascularization only. Still others limit this term to the description of syphilitic keratitis. We recommend that the term IK be used to refer to any inflammatory reaction of the stroma that has an immunologic etiology and should not be connected by the presence or absence of neovascularization, the depth of stromal inflammation, or the etiology of the inflammation. We believe that the terms IK and ISK are synonymous. We prefer the term ISK because the majority of stromal findings are related to an immunologic reaction within the stroma, and therefore we used the term ISK throughout this study.

Syphilis has been recognized for many years as the

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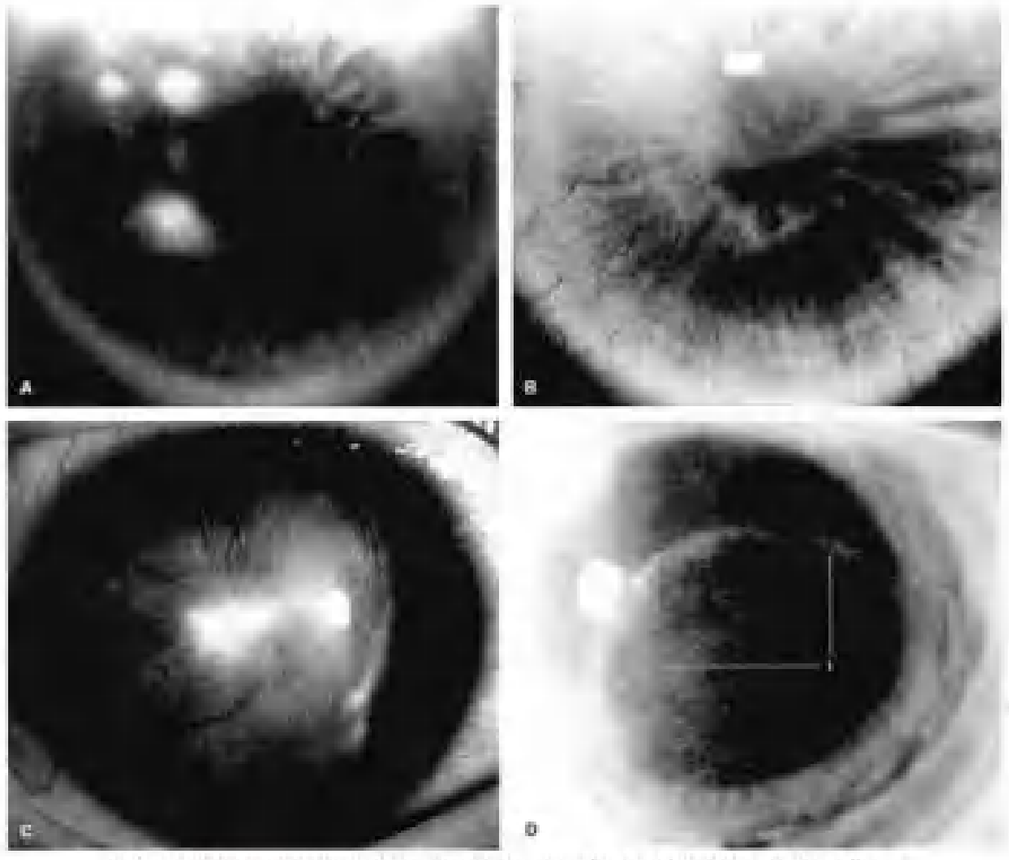

FIG. 1. Slit-lamp photographs of a patient with active ISK. Note the signs of active inflammation. A: Stromal infiltrate. B: Neovascularization. C: Lysis. D: Immune ring (1).

overwhelmingly most common cause of ISK. Studies have consistently stated that 90% of cases of ISK are caused by syphilis (1–3). It has been our clinical impression that, although syphilis may have been the most common cause of ISK years ago, that appears no longer to be true.

This study demonstrates different etiologies depending on whether the patient has active or inactive or unilateral or bilateral disease. Patients with active, unilateral, inactive disease were found to have HSV as the most common etiologic agent (50.0%). Other etiologies within this group were idiopathic (33.3%) and tuberculosis (16.7%). It is interesting to note that syphilis accounted for no patients within this group.

Patients with unilateral, active disease also had HSV as the most common etiologic agent (71.4%). Idiopathic causes were 14.3% of this group, and VZV accounted for an additional 3.6%. Syphilis accounted for <3% of cases within the unilateral, active group.

Of the patients with bilateral, active disease, the majority (60.0%) had idiopathic causes. Fifteen percent were caused by contact lens use, 10.0% HSV, and only 5.0% syphilis. Only in the bilateral, inactive group were the majority of cases (53.3%) caused by syphilis. Another 33.3% in this group were idiopathic.

HSV was found to be the most common causative agent of ISK among all patients evaluated. This was especially true in the unilateral cases, in which HSV accounted for 86.0% of cases. HSV accounted for only 8% of bilateral cases. The majority of patients in the HSV category with ISK had a history of HSV infectious epithelial keratitis. However, several patients with ISK without clinical history of HSV disease later developed HSV infectious epithelial keratitis and thus were classified as having ISK caused by HSV. Therefore, it is likely that a significant number of patients currently classified in the idiopathic group may in fact have ISK resulting from HSV and merely have not had a clinically diagnosed episode of HSV infectious epithelial keratitis.

It is interesting to note the small number of cases in our clinic with ISK resulting from syphilis. Although the literature has stated for decades that syphilis is the leading cause of ISK, accounting for >90% of cases, we have not observed this to be true in our clinic. Of the 97 patients in this study, only 16 (16.6%) had ISK caused by syphilis. Only in the bilateral, inactive group did syphilis account for >5% of cases. In this group it accounted for the majority of cases, but at 53% was still far below the 90% quoted in the literature. It is possible that before the antibiotic era, syphilis was more prevalent and therefore accounted for many more cases of ISK. Our data, however, show that other causes of ISK have supplanted syphilis as the leading etiologic factor. Our approach to the diagnosis and treatment of ISK in the modern age must reflect these changes.

Although this study demonstrates that systemic causes of ISK are not as common as previously described in the literature, we still believe it is valuable systemically to evaluate patients on initial presentation. Careful physical examination and review of systems are also important to help detect symptoms and signs associated with infectious agents and collagen vascular disease. If the patient has unilateral disease on the same side as a prior episode of either HSV infectious epithelial keratitis, or VZV involving distribution of the ophthalmic nerve, and the review of systems is unremarkable, we believe no further workup needs to be performed. In all other patients, systemic workup should be carried out. This workup should include FTA-ABS to rule out syphilis, PPD and chest radiograph to rule out tuberculosis, and Lyme titer to rule out Lyme disease. Collagen vascular disease should be evaluated by rheumatoid factor and antinuclear antibodies. We recommend EBV titers if patient's symptoms are consistent with EBV infection.

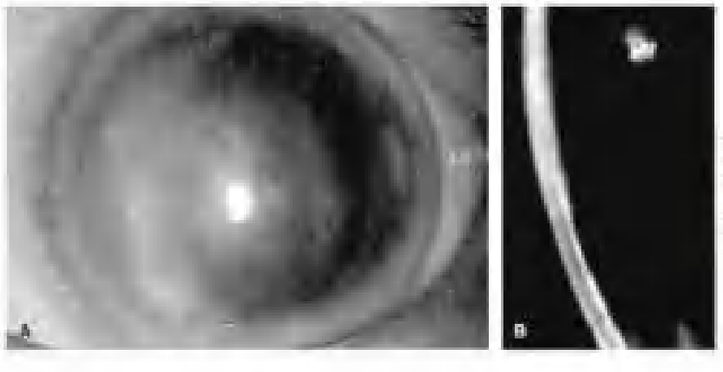

FIG. 2. Slit-lamp photographs of a patient with inactive ISK. A: Diffuse illumination reveals stromal scarring and ghost vessels. B: A thin slit beam shows stromal thinning.

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CME

Eye Injuries in the Young Athlete: A Case-Based Approach

Andrew Harrison, MD, and David G. Telander, MD, PhD

Eye injuries are the leading cause of blindness in children in the United States and more of these occurring in school-aged children are sports related. Many percent of these injuries can be prevented with protective eyewear. Despite certain preventive measures, the incidence of sports-related eye trauma has increased during the past decade.[1]

Three-quarters of all sports injuries involve individuals younger than 25 years, with most occurring in boys between 10 and 19 years old. The sports most commonly associated with eye injuries are baseball, basketball, soccer, football, and hockey.[2] Baseball causes the most eye injuries in children between 5 and 15 years of age (19%), whereas basketball causes most eye injuries in older children and young adults (15 to 24 years old).[3] Sports using small balls (eg, squash) tend to cause injuries with higher ocular morbidity,[4] and sports that have mandatory eye protection have greatly reduced the incidence of ocular injury.

LEARNING OBJECTIVES

1. Review the basic anatomy of the growing eye and special considerations these unique facts have imply for children with eye injuries.
2. Discuss the features of the basic eye trauma examination.
3. Determine the most appropriate evaluation and management for the common sports-related eye injuries in children.

SPECIAL CONSIDERATIONS FOR CHILDREN

Children are predisposed to eye injuries for many reasons. First, their developing coordination and often daring manner of play render them vulnerable to accidental trauma of all types. Moreover, the eye itself is more prominent and less protected by the eyebrow, the cheekbones, and the nose in children. Consequently, balls and objects striking the face are much more likely to result in ocular injury in children than in adults. Children are also less capable of identifying their injury. Specifically, they are less likely to notice or report a change in vision loss. Young children often rely on vision from their better-seeing eye and ignore visual changes in the other eye. It is not uncommon for a child to come to the physician's office with profound difference in visual acuity between eyes without reporting any symptoms.

For example, a mother recently brought her 7-year-old boy into our ophthalmology clinic because she had noticed that one of his eyes was "lazy" during the previous 6 months. She also reported that the change seemed reflex he was hit in the eye by his sister's jump rope. The boy denied any symptoms. On examination, his vision was 20/20 in the right eye and 20/200 in the left eye. Fundoscopic examination revealed a macular hole in the left retina, which was most likely due to the jump rope injury.

Early treatment is important. Appropriate treatment not only improves the structural healing of

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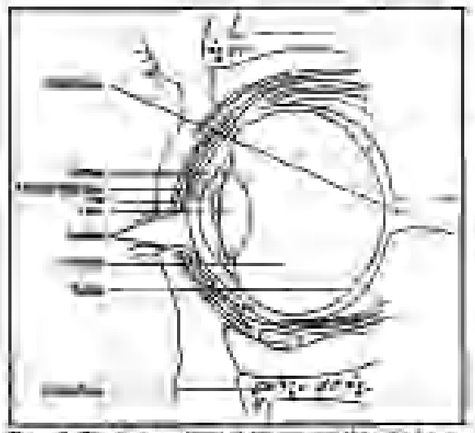

Figure 1. The basic anatomy of the eye and the orbit from a sagittal view.

the injured eye, but also prevents loss of vision necessary to amblyopia, especially in younger children. Loss of vision for any reason in the developing child younger than 10 years can result in abnormal development of central vision (amblyopia), which is irreversible.

BASIC ANATOMY OF THE EYE (Fig. 1)

The eyelids are two movable folds that protect, lubricate, and allow tear drainage from the ocular surface. Within each lid, the tarsal plates provide structural support and contain the lubricating meibomian glands. Their medial aspect contains the puncta and the canaliculi of the nasolacrimal drainage system. The conjunctiva is a continuous thin mucous membrane covering the inner aspect of the lids (palpebral conjunctiva) and the sclera (bulbar conjunctiva) up to the corneal limbus. The sclera is the white outer layer of the eyeball. It is normally white with few vessels. The cornea is the transparent window of the eye. It is sclera is the major refractive surface.

Within the eye, the anterior chamber is the space between the iris and the inner aspect of the cornea that contains a clear fluid termed aqueous humor. Its pressure determines the intraocular pressure. The iris is the transparent muscular tissue that gives the eye and the pupil that allows accommodation and some refracting power for the eye. The vitreous cavity is the large space behind the lens filled with a jelly-like material called vitreous humor. The retina is the neural tissue lining the vitreous cavity to which the photoreceptors reside. The macula is the center of the retina and is responsible for central, fine vision. The choroid is the vascular pigmented layer that provides support and nourishment to the retina. The optic disc is the part of the optic nerve that is visible through the eye.

There are six separate extraocular muscles that move the globe. The muscles innervated by cranial nerve III include the inferior rectus (inferior gaze), the medial rectus (medial gaze), the superior rectus (superior gaze), and the inferior oblique (elevation and incyclotorsion). Cranial nerve IV innervates the superior oblique muscle that controls depression and incyclotorsion of the globe. Cranial nerve VI innervates the lateral rectus muscle that permits lateral gaze.

There are four orbital walls. The medial wall is composed of the sphenoid, ethmoid, lacrimal, and maxillary bones. The lateral wall is made up of the zygoma and the greater wing of the sphenoid. The roof has the frontal and lesser wing of the sphenoid, and the floor is composed of the maxillary, zygoma, and palatine bones. The thinnest bone within the orbit is the lamina papyracea of the ethmoid along the medial wall. However, the most commonly fractured bone in the orbital complex is the orbital floor.

BASIC EXAMINATION FOR EYE TRAUMA

During the examination of the eye and the orbit after trauma, pressure should not be placed on the globe in case it has ruptured. Pressure on a ruptured globe can cause displacement of the intraocular contents, causing further hemorrhage, retinal detachment, lens displacement, and permanent visual loss. Beyond this, the basic eye examination can be done in large part with basic skills and without extensive equipment.

First, any documentation of visual acuity is of enormous help in assessing the severity of an ocular injury. Many children are able to identify numbers or letters. The vision in each eye should be checked separately. Next, it is important to determine whether pupil responses are intact by examining direct and consensual reactions. In addition to using the swinging flashlight test, the physician should be able to determine the comparative function of the optic nerves. With this test, the light is

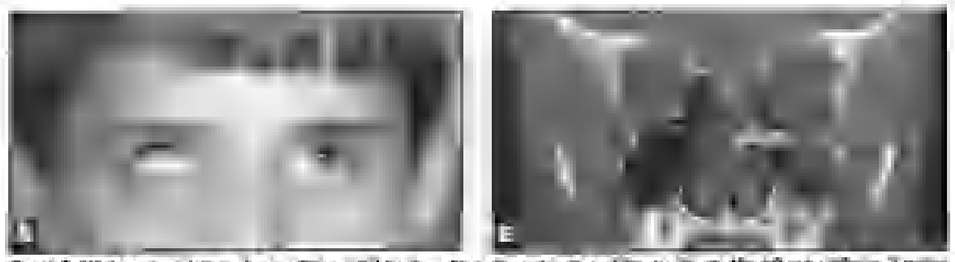

Figure 2. (A) An external view of a positive-optic fracture. Note the patient's inability to elevate the left eye while it tries to look up. (B) A computed tomography scan (axial bone window filter) revealing the significant orbital floor fracture (arrow) with mucosal thickening of the inferior sinus.

limit shown in one eye) and minimal constriction is allowed. Then the light is quickly shifted to the other pupil and back again. Normally, the other pupil should respond equally to the same amount of light. A dilated unresponsive pupil indicates injury to the afferent limb of the pupillary reflex. With acute head injury, this most often indicates compression of the third cranial nerve by herniation of the temporal lobe. This is a neurosurgical emergency. A pupil that dilates in response to light with the swinging flashlight test (a Marcus-Gunn pupil) indicates injury between the optic chiasm and the front of the eye. This is the most common clue to an optic nerve injury.

Next, a penlight should be used to examine the eyelids and the orbits. The orbital rims should be palpated to assess for point tenderness and possible stepoff fractures. The sensation of the face should also be assessed to check for possible nerve injury. Injury to the infraorbital or supraorbital nerves is often associated with orbital rim fractures and causes numbness of the skin around the eye. The child should then be asked to open the injured eye. This may need to be done in a darkened room for comfort. If at any point during the examination it becomes obvious that the eye is ruptured, it should immediately be covered with a metal shield and the child referred for urgent surgical repair. If the child is able to open the eye, he or she should look in each direction to assess ocular motility.

Next, with a penlight or at the slit lamp, it is imperative to take a close look at the conjunctiva, the sclera, the cornea, the anterior chamber and the iris. Fluorescein dye should be instilled into the eye and staining of the cornea and conjunctiva noted. The physician should look closely for subconjunctival hemorrhage (obvious blood in the anterior chamber (hyphema), or corneal injury or foreign body. The depth of the anterior chamber and its clarity should be inspected. With the direct ophthalmoscope, the lens should be assessed for clarity and the fundus, the optic disc, the vessels and the macula inspected. Finally, the lids should be inspected for any lacerations, especially that involving the lid margin or near the medial canthus.

TYPES OF OCULAR INJURIES IN SPORTS

The types of ocular injuries in sports can vary. For example, one study of 78 such cases found that 40% of the patients had hyphema and 12% had traumatic cataract. Remarkably, 18% remained legally blind in the injured eye.[2]

Orbital Fractures

A 10-year-old boy was hit in the left orbit by an elbow while playing basketball. He described double vision in addition to pain. On examination, his vision was 20/20 bilaterally, and his pupils reacted equally without evidence of an afferent pupillary defect. An examination of extraocular motility revealed an inability to elevate the left eye above midline (Fig. 2A). The left cheek was numb in the V2 distribution, but no stepoff fracture was palpated on the inferior rim. The left eye appeared to be sunken into the orbit. A computerized tomography (CT) scan revealed a significant fracture of the left orbital floor with orbital fat herniating into the maxillary sinus and impinging the inferior rectus (Fig. 2B).

Approximately one-third of orbital rim fractures and orbital wall fractures are secondary to sport injuries. Orbital rim fractures usually result from a blow below, whereas orbital wall fractures are generally caused by trauma to the globe. In sports, the latter most often results when a small ball or an elbow directly compresses the globe. This causes increased hydraulic pressure in the orbital tissues that translates to pressure on the orbital walls and floor. The posteromedial floor is the thinnest part of the orbital floor and is thus most frequently involved by these injuries. Soft tissues, including the inferior rectus muscle, may herniate into the maxillary and the maxillary sinus. Symptoms are usually pain, double vision, numbness of the cheek, and nausea. On examination, restricted eye movements (especially on up and down gaze), enophthalmos (with larger fractures), hypoesthesia in the V2 distribution, or orbital emphysema may be present. Nonspecific signs include eyelid edema, periorbital ecchymosis, and subconjunctival hemorrhage.

The workup for these patients should include a complete examination that includes looking for diplopia and eye motility and a dilated fundus examination. It is important to rule out a ruptured globe. CT is the imaging modality of choice and axial and direct coronal views of the orbits should always be ordered. Patients with suspected blowout fractures should undergo imaging promptly and be referred.

The treatment of blowout fractures remains controversial. Indications for early surgical intervention (less than 1 week) include entrapment of the globe, enophthalmos, a large fracture, or muscle entrapment.[3] Surgical repair is generally recommended within 1 to 2 weeks of injury. Initial treatment should include oral antibiotics, nasal decongestants, and ice compresses. The patient should be told to not blow his or her nose. Oral corticosteroids can be used to moderate swelling of edema. Surgery often leads to satisfactory results. Hawkins, Sherman, et al. found that 37% of 54 patients had some persistent diplopia.[4]

Eyelid Laceration

A 9-year-old boy was playing baseball when struck in the left eye by his brother's finger. He immediately had significant bleeding and pain and complained of pain vision. His vision was 20/20 in the right eye and 20/50 in the left eye. His pupils and extraocular motility were normal. He had a full-thickness marginal laceration of the left eyelid (Fig. 3A). There was mild injection of the conjunctiva and no fluorescein staining of the cornea. After repair in the operating room, he had a good cosmetic and functional result (Fig. 3B).

Eyelids have important functions that include protecting the eye, defining the limits of the visual fields and axes, and producing components of the tear film. Moreover, the eyelids play a predominant role in the cosmesis of the face. They also dictate tear flow. The proximal tear duct begins within the medial aspect of the upper and lower eyelids, and the eyelid actively participates in the movement of tears toward the tear duct. Injury to the eyelids can affect any or all of these functions. Blunt or sharp injuries from virtually any object can lead to an eyelid laceration.

The accuracy of the eyelid and the harmony of the injury dictate appropriate treatment. The eyelids contain a rich vasculature that resists necrosis, allowing cosmetic debridement. The abundant blood supply allows delay in repair until an experienced surgeon and surgical supplies are available. The tarsal plate within the eyelids is an struc-

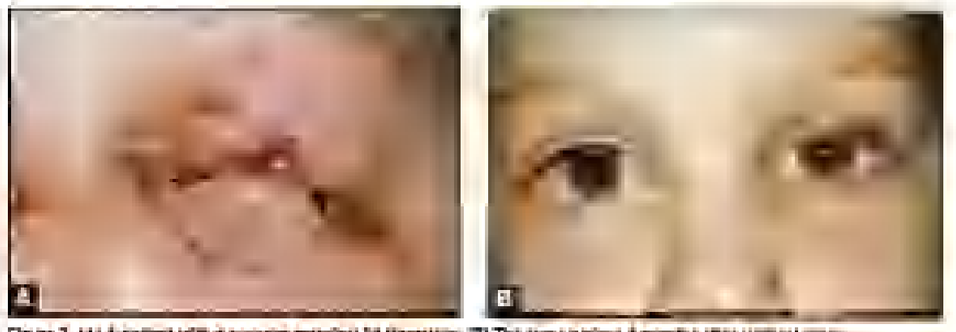

Figure 3. (A) A patient with a posterior maxillary lid laceration. (B) The same patient 6 months after surgical repair.

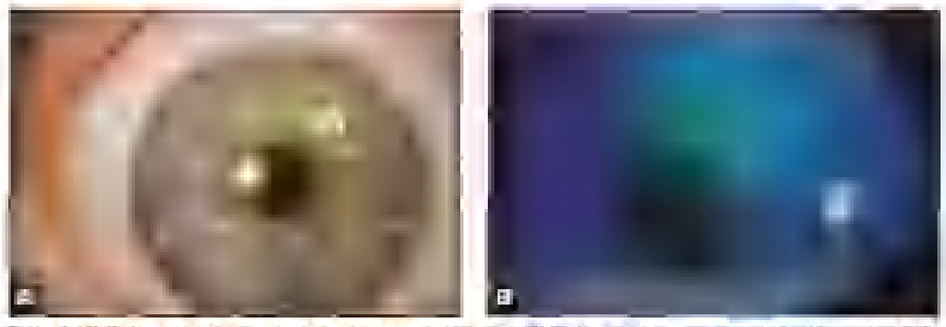

Figure 4. (A) Slit-lamp examination demonstrating a ruptured globe. (B) Slit-lamp examination showing total hyphema on the right eye. (Courtesy of Thomas Lloyd, MD.)

need support. Therefore, it is critical that the small globe be realigned properly. Improper realignment can result in a notched fat margin, increased vascularization of the epidermis, and corneal irregularities.

Lacerations that extend medially often result in damage to the nasolacrimal system. These injuries need careful examination and consideration with stenting of the nasolacrimal system. Without careful repair, patients can have chronic tearing and irritation. The finding of prolapsed orbital fat indicates a deep, penetrating laceration that may have injured the globe. These patients need to be examined carefully to rule out a ruptured globe.

The appropriate workup should include a complete ocular examination to rule out any other trauma. Expectant treatment should include topical ophthalmic antibiotic ointment, oral cephalexin, and referral to an ophthalmologist for definitive repair.

Corneal Abrasion

A 15-year-old wrestler was injured in the right eye with a finger during a match. He came to the clinic with increasing pain and blurred vision. *His vision was* 20/80 *in the right eye and* 20/20 *in the left eye. His pupils were normal and extraocular motility was full. Results of the external examination were within normal limits. Fluorescein (Fig. 3) showed a corneal abrasion of the cornea stained with fluorescein dye (Fig. 4). With appropriate treatment, the eye healed completely within 24 hours.*

Children with corneal abrasions present with significant pain, decreased vision, and photophobia. These injuries can occur in any sport, but are more common in sports such as basketball where players put their hands in their opponent's face to block a shot or pass. On examination, damage to the corneal epithelium will stain with fluorescein, highlighting the extent of the injury. In addition, the conjunctiva will be injected and the eyelids may be swollen. The anterior chamber often contains white blood cells in response to the injury.

The necessary workup includes a slit-lamp examination with fluorescein dye and measurements of the size of the abrasion for follow-up examinations. Treatment should include topical antibiotic coverage to prevent secondary infection and corneal ulceration. We prefer bacitracin or erythromycin ophthalmic ointment four times a day. Cycloplegic drops are provide comfort if there is significant inflammation in the anterior chamber. Pressure patching of the eye can be considered, especially for large abrasions. *A pressure patch should never be used for contact lens wearers* because this practice is associated with an increased risk for developing corneal infections. The patient should see an ophthalmologist the next day for close monitoring. In addition, these injuries can place the patient at risk for future corneal problems such as recurrent erosion, which may require further treatment. A patient should never be sent home with a topical anesthetic (eg, proparacaine). Topical anesthetics can inhibit normal healing and have led to corneal ulcers and perforations.

Hyphema

An 11-year-old girl was hit in the right eye with a soccer ball. She complained of pain and decreased vision in the eye. Her vision was 20/60 *in the right eye and* 20/20 *in the left eye. Her pupils were normal and her ocular motility was full. There was minimal conjunctival*

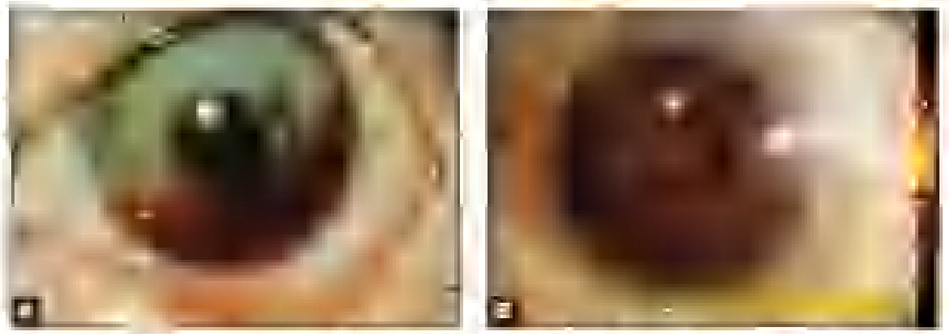

Figure 5. (A) Slit-lamp examination showing the layering of blood in the anterior chamber (hyphema). (B) Slit-lamp examination showing five clear lines may be seen directly on the test of the eye in a patient who remains in a reclined position.

of the left eye. The right eye appeared normal. The left eye had a clear cornea with blood in the anterior chamber that covered the inferior one-third (Fig. 5).

Hyphema or internal eye injury is blood within the anterior chamber of the eye. This typically occurs after blunt trauma such as being hit by a ball. Children may complain of pain and blurred vision. The hyphema can be seen using the entire anterior chamber with blood (an "8-ball" hyphema). These injuries need immediate treatment. A hyphema can also be microscopic, in that red blood cells can be seen only with a slit-lamp microscope. Significant bleeding can lead to dramatic elevations in intraocular pressure. In turn, this can lead to glaucoma with irreversible damage to the optic nerve. In addition, especially with prolonged elevation of intraocular pressure, blood in the anterior chamber can stain the cornea and reduce vision even after it has cleared. If this occurs, the child may need a corneal transplant to restore vision.

The appropriate workup for the child with a hyphema includes a complete eye examination with a dilated fundus examination when possible. If blood obscures the view of the fundus, an ultrasound examination may be performed at an ophthalmologist's office to rule out damage to the retina. It is important to rule out the possibility of a ruptured globe by examination, and a CT scan should be considered if orbital fractures are suspected. It is also reasonable to consider a sickle cell prep test for the African American patient.

Immediate management should include placing a metal shield over the eye. This is to prevent further injury, which can cause extending of fragile healing vessels. Shielding should be followed by prompt referral to an ophthalmologist. The patient may require hospitalization and medical or surgical treatment to regulate intraocular pressure, sedation, the eye, and provide pain control.

Ruptured Globe

A 17-year-old boy was struck with the blunt side of a baseball during a fight in the car. He had loss of vision and significant pain. His vision was counting fingers in the right eye and 20/20 *in the left eye. The pupil in the right eye was irregular and consistent. He was unable to do examination for extraocular motility. The slit-lamp examination revealed a prolapse of the iris through the cornea with loss of normal globe form and significant chemosis and subconjunctival bleed (Fig. 6).*

Children with a ruptured globe will naturally present with pain and decreased vision. The signs of injury include subconjunctival hemorrhage, hyphema, peaked pupil, shallow anterior chamber, low intraocular pressure, or intraocular contents outside of the globe.

The workup is limited to examination by slit-lamp or penlight with no additional pressure being placed on the globe or the eyelids. Once a diagnosis of ruptured globe is made, a metal shield should be placed over the eye and further examination should be deferred until the patient is under anesthesia in the operating room. If an intraocular foreign body or orbital fractures are suspected, CT scans should be performed. The patient should be prepared for surgery (ie, no food or drink). Tetanus shots should be given if needed, and systemic antibiotics started. Tonometric and an amino-

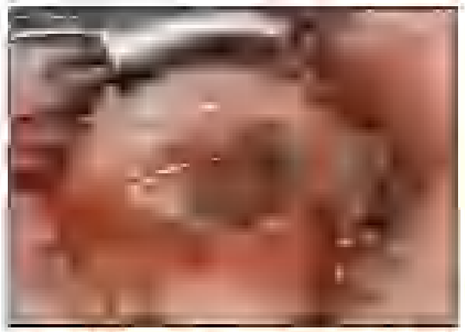

Figure 6. Extensive loss of the inferonasal retina, which can be demonstrated by many confrontational techniques.

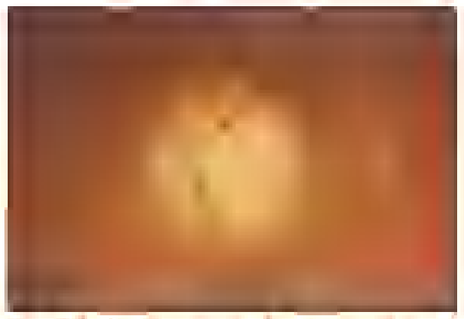

Figure 7. Fundus examination revealing optic pallor of an eye, nearly several weeks after blunt-ball, optic neuropathy.

glycoside in third-generation cephalosporin provide good antibiotic coverage. Antiemetics should be given when needed to prevent increased intraocular pressure secondary to nausea.

Definitive treatment is surgical repair. Corneal or scleral laceration eye wound is often obtained prior to surgery in case the damage is more extensive than anticipated or unrepairable. Patients with penetrating eye trauma are at risk for an immunologic rejection of the uninjured eye known as sympathetic ophthalmia. This risk can be minimized with enucleation of the irreparable eye (if there is no light perception) within the first 10 to 14 days following the trauma.

Optic Nerve Trauma

A 14-year-old girl in her local soccer league was hit in the left eye by a soccer ball during a gymnastics performance. She complained of complete loss of vision in the left eye after regaining consciousness. Her vision was 20/20 in the right eye and no light perception in the left eye. Results of the examination of her pupils were remarkable for normal reactivity in the right and a relative afferent pupillary defect in the left. Her ocular motility was full. The results of examination of the cornea and the anterior segment were within normal limits bilaterally. A dilated fundus examination revealed a normal optic disc and retina. Follow-up examination of the nerve revealed later characteristic waxy pallor of the optic disc (Fig. 7).

Optic nerve injury can be divided into direct and indirect types. Direct injuries are secondary to penetrating trauma and can result in optic nerve lacerations, optic nerve avulsion, or optic canal injury. Indirect optic nerve trauma, termed traumatic optic neuropathy, is usually accompanied by a closed head injury with an incidence of 0.5% to 5%.[7] Diagnosis and treatment require the teamwork of both a trauma physician and an ophthalmologist. Although motor vehicle accidents are often responsible for these types of injuries, they can also be associated with more minor blows to the head or the eye. Patients with optic nerve injury may experience vision loss from near normal to no light perception. Ocular signs include pupil color intervisual field defects and a new afferent pupillary defect (Marcus–Gunn pupil). Associated findings in the optic nerve may be edematous and have surrounding hemorrhages. However, there are often no optic disc changes. Over time, optic atrophy can develop after significant injury.

The workup of these injuries should include a complete eye examination with careful attention to the pupillary responses and the optic nerve. CT scans of the orbits (axial and coronal slices 1 to 2 mm sections) and the brain are essential. Occasionally, electromyography and the visual evoked response may be helpful, especially when the view of the fundus is poor.

Management of these types of injuries is controversial. Medical treatment involves high-dose intravenous corticosteroids. Alternatively, surgical decompression of the optic canal may be attempted with or without corticosteroids. The efficacy of these treatments remains unproven.[7] Despite treatment, recovery from these injuries is variable. 30% typically have 20/200 vision or worse and 30% have 20/40 vision or better. The more severe the initial visual loss, the worse the prognosis for recovery.

other fracture and the field for fracture.

Trauma can cause injury to any and all parts of the eye. Other common injuries include corneal lacerations, lens injuries, traumatic retinopathy, glaucoma, retinal edema, vitreous hemorrhage, traumatic cataract, traumatic uveitis, choroidal rupture, traumatic macular hole, and retinal detachments. Even asymptomatic patients can have injuries. Wedrich et al. found that 20% of asymptomatic bowel had angiographic retinal tears or holes, placing them at increased risk for retinal detachments.[8]

In general, patients with the following signs and symptoms should be referred to an ophthalmologist for further evaluation:

1. Change in visual acuity. When available, Snellen chart measurements are most helpful for detecting this. In young children, any evidence of the vision of each eye individually (eg, fixes and follows an object) can be helpful.
2. Diplopia (double vision) for any duration.
3. Eyelid swelling that prevents a thorough ocular examination or limits vision.
4. Hyphema (blood in the anterior chamber) of any amount.
5. Change in the size or shape of the pupil or sudden severe eyeball elevation.
6. Persistent discomfort including pain within the eye or pain with eye movement.

PREVENTING INJURY WITH PROTECTIVE EYEWEAR

The importance of prevention cannot be stressed enough. Access to hockey and water hockey are the only sports that mandate full-face protection. Ophthalmology played an important role in instituting the requirement for face and eye protection in Canadian ice hockey in the 1970s.[9] The mandate decreased the incidence of serious eye injuries by 65%.[9]

Protective goggles or polycarbonate lens visors are essential in all sports with high risk of eye injury.[10] Injury can occur from the ball (ie, baseball, racquet sports or soccer) and small balls (and in other cases) injuries. Sports with body contact or close aggressive play (eg, wrestling or basketball) have a high risk for direct blows or scratches. Most high-risk sports have available eye protection. However, some (eg, boxing and "all contact martial arts") do not, which may result in disastrous eye injuries. Normal impact-resistant eyeglasses (nonprescription, plastic lenses), open sport eye guards and contact lenses are not adequate eye protection. At the least, participants should wear a one-piece molded polycarbonate eye protector that passes the American Society for Testing and Materials standard for the particular sport. It is essential that pediatricians counsel patients about risk reduction and preventive measures that can avoid disastrous results.

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Emerging therapies in the medical management of thyroid eye disease

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Introduction: Thyroid eye disease (TED) is an immune-mediated disorder associated with a heterogeneous array of manifestations that may unfavorably impact vision and quality of life. As understanding of the entity's complex pathogenesis has evolved, so have therapies with novel molecular targets offering promise for improved patient outcomes.

Results: Emerging immunologic therapies for the management of thyroid eye disease have diverse mechanisms of actions and routes of administration. Different conventional and biological immunosuppressive agents have been studied as mediators of the autoimmune and autoinflammatory pathways in thyroid eye disease. Teprotumumab – an anti-IGF-1R monoclonal antibody that has recently emerged as a first line therapy for active, moderate-to-severe TED – has demonstrated statistically significant improvements in proptosis, diplopia, clinical activity score, and quality of life compared to placebo. Currently under investigation are several other agents, with varying administration modalities, that aim to inhibit IGF-1R: VRDN-001 (intravenous), VRDN-002 or VRDN-003 (subcutaneous), tongulumab (subcutaneous), and linsitinib (oral). Tocilizumab, a monoclonal antibody of interleukin 6, has played a role in the management of multiple autoimmune and inflammatory conditions and may offer promise in TED. Another incipient biologic target for TED management is the neonatal Fc receptor, inhibition of which has potential to decrease recycling of immunoglobulin and antibody levels; agents addressing this target including monoclonal antibodies as well as antibody fragments. Finally, hypokalemic agents may play a role as mediators of TED-associated inflammation.

Conclusion: Among the agents under investigation that aim to decrease ocular morbidity associated with TED are agents that IGF-1R, interleukin 6, and the neonatal Fc receptor. The management of TED continues to expand with novel immunologic approaches for disease therapy.

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Introduction

Thyroid eye disease (TED) is a multifactorial autoimmune disorder with an annual incidence of 16-19 cases per 100,000 individuals [1]. While this entity most commonly occurs among individuals with Graves' hyperthyroidism, it may manifest patients with Hashimoto thyroiditis (immune-mediated hypothyroidism) as well as those with normal thyroid function. In addition, genetic, immune status and environmental factors such as smoking and stress play a role in disease pathogenesis.

Thyroid eye disease is associated with a heterogeneous array of clinical findings secondary to orbital fibroblast activation and subsequent connective tissue remodeling, orbital fat expansion, and extraocular muscle enlargement. The most frequently reported sign of TED is upper eyelid retraction, while additional clinical features include proptosis, hypothyroidism, eyelid edema, diplopia, surface keratopathy, and optic nerve dysfunction [2]. Appropriate evaluation of these diverse clinical phenotypes may require a multidisciplinary team consisting of endocrinology, neuro-ophthalmology, adult strabismus, and oculoplastic surgery.

Management of thyroid eye disease

Management of endocrine disease may require antithyroid medications, radioactive iodine ablation or thyroidectomy. Albeit resolution of thyroid function is preferable among TED patients, the course and severity of ocular manifestations are relatively unresponsive to state of the comorbid endocrine dysfunction.

Management of TED is multifaceted, and is determined based on clinical severity, progression, and associated morbidity. In addition to supportive measures (i.e., lubrication, prism therapy, selenium supplementation, and smoking cessation), the historical mainstays of non-surgical therapy for active orbital inflammation were high-dose glucocorticoids and orbital radiation. Surgical management plays an integral role in addressing associated clinical morbidity and vision pathology, but is beyond the scope of this review.

Emerging immunologic therapies for the management of thyroid eye disease have diverse mechanisms of actions and routes of administration [3–5]. Different conventional and biological immunosuppressive agents, such as cyclosporine, mycophenolate mofetil, rituximab, and others, have been studied as mediators of the autoimmune and autoinflammatory pathways in thyroid eye disease. An understanding of the complex pathogenesis of TED has enabled the use of novel medical therapies with novel molecular targets offering promise for improved patient outcomes.

Targets of emerging therapies

Thyroid stimulating hormone receptor and insulin-like growth factor 1 receptor

Thyroid stimulating hormone receptor (TSHR) – a glucose [illegible] receptor – is an autoantigen shared by the thyroid gland and the orbit [6, 7]. In TED, activation of T cells sensitized to this receptor [illegible] TSHR autoantibodies, which mediate secretion of excess thyroid hormone by the thyroid gland and bind to TSHR expressed by fibroblasts in the orbit. Activation of the TSHR and insulin-like growth factor 1 receptor (IGF-1R) – a transmembrane receptor kinase-containing receptor complex in which fibroblasts and fibrocytes cross-talk between these two entities trigger an inflammatory cascade culminating in cytokine and chemokine release, lymphocyte recruitment, and adipogenesis [8].

Teprotumumab

Teprotumumab – a fully human monoclonal antibody that binds to the extracellular alpha subunit of IGF-1R – was developed originally as an antineoplastic agent for solid and hematologic tumors and subsequently investigated as a target for the management of TED. This IGF-1R antagonist decreases IGF-1R and TSHR display on fibrocytes in vitro via phosphorylation and inhibits the induction of pro-inflammatory cytokines [9]. The [illegible] by teprotumumab of pathways crucial to muscle cell and adipocyte integrity leads to downstream impacts on extraocular muscle as well as orbital fat volume and volume.

Two consecutive, multicenter, randomized, double-masked, placebo-controlled clinical trials (OPTIC and OPTIC-S; NCT03461809 and NCT03298451, also known as OPTIC) among patients with active, recent-onset, moderate-to-severe TED demonstrated statistically significant, sustained improvements in proptosis, clinical activity score, diplopia, and quality of life with teprotumumab therapy as compared to placebo [10, 11]. On the basis of these investigations, teprotumumab was approved by the United States Food and Drug Administration in January 2020 for the management of adults with TED. An open-label clinical extension study (NCT03461419, or OPTIC-X) analyzed the role of teprotumumab therapy among patients who were previously treated in the aforementioned efficacy trials and demonstrated similar efficacy with regards to primary and secondary outcome measures as compared to the placebo wash-in [12]. The results from OPTIC-X demonstrated that while relapse rate following teprotumumab therapy are non-negligible, patients with a history of treatment response to this antibody from additional therapies (duration of TED) may not serve as a significant predictive indicator for response to teprotumumab therapy. Among patients with chronic, stable TED, teprotumumab has also shown promise for reduction in proptosis, diplopia, and extraocular muscle and orbital fat volume [13–15].

Teprotumumab is typically administered over 90 minutes as a total of 8 intravenous infusions, completed every three weeks [16]. The standard medication dose is 10 mg/kg of body weight for the first infusion followed by 20 mg/kg of body weight for subsequent infusions. The most frequent adverse effects associated with teprotumumab are muscle spasms (25%), nausea (17%), alopecia (15%), diarrhea (12%), fatigue (12%), hyperglycemia (10%), and hearing impairment (10%) [17]. Pre-infusion screening of all patients should include complete medical and ophthalmic examinations, baseline laboratory tests (i.e., complete

blood count, fasting blood glucose, hemoglobin A1c, liver function tests, and baseline electrocardiogram. As a result of rare but known supporting irreversible autoimmune toxicity has linked to cytomegalovirus therapy, many centers advocate for vaccination testing pre-initiation and post-therapy, particularly among individuals with a history of hearing loss (19–21). In addition, contraindications to therapy include current pregnancy, nursing status, prepubertal age and concomitant biologics or recent glucocorticoid use, poorly controlled diabetes and inflammatory bowel disease, requirement use of certain radiographic management with endocrinology and gastroenterology, respectively (22).

VRDN-001

VRDN-001, a full antagonist antibody of IGF-1R, was the subject of investigation for a phase 2a randomized, double-masked clinical trial (NCT03970486). According to authors, VRDN-001 inhibited ligand binding and IGF-1 induced IGF-1R but did not phosphorylation more completely than teprotumumab in the dose range tested. Among patients with chronic TED, an assessment was completed of dosage with either 15 mg/kg or 3 mg/kg of body weight of VRDN-001 for two intravenous infusions, three weeks apart, as compared to placebo. In this study, the infusions led to substantial reductions in proptosis and clinical activity scores. The patients treated with VRDN-001 achieved exceptional evaluation of diplopia as well as. Moreover, there were no reported serious adverse events, including hearing impairment and hyperglycemia. A phase 3 trial (TRIUMPH) aims to further evaluate the efficacy and safety of VRDN-001 (23, 24).

Other agents

Currently in the pipeline are several other agents with varying administration modalities that aim to inhibit IGF-1R. VRDN-002 and -003 are monoclonal antibodies to IGF-1R with half-life extension technology (25–27). Surprised by encouraging data from the 3 mg/kg dose cohort of the VRDN-001 study, VRDN-002 and -003 were developed as low volume monthly administered anti-inflammatory agents that may be subjects of further clinical investigation. Teprotumumab is in a phase IV, prolonged, double-masked clinical trial (NCT05848466) as another subcutaneous therapy. Finally, linsitinib is the subject of a phase 3b randomized double-masked study (NCT02284503) as twice daily, oral medication for TED (28). An alternative subject of investigation to IGF-1R is TSHR, which serves as the target of human monoclonal immunoglobulin M 7K administration of the agent via intramuscular and intravenous routes has been assessed in a phase 1 clinical trial (Integrated Research Application System Identifier: 199697) (29).

Interleukin 6

Interleukin-6 increases expression of TSHR in orbital fibroblasts, augmenting TSHR autoantibody-elevated stimulation of the fibroblasts (30). Tocilizumab – a humanized recombinant monoclonal antibody of interleukin-6 – has played in the role of the management of multiple autoimmune and inflammatory conditions such as rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis. In a randomized, double-masked clinical trial assessing the efficacy of intravenous tocilizumab at a dose of 8 mg/kg of body weight, compared to placebo, in patients with steroid-resistant active, moderate-to-severe TED demonstrated meaningful improvements in clinical activity scores and proptosis (31). Adverse effects linked to this agent include hypercholesterolemia, neutropenia, and transaminitis. Though reports of associated adverse effects in TED have been fewer than those in other autoimmune conditions (31). A randomized, multicenter clinical trial (NCT04731233) is underway to compare treatments with tocilizumab or methylprednisolone for patients with severe, moderate-to-severe TED.

Neonatal fragment crystallizable receptor

The neonatal fragment crystallizable receptor (FcRn) plays a role immunoglobulin G transport across barriers and in its protection from lysosomal degradation (32, 33). Rozanolixizumab – a monoclonal antibody of FcRn – reduced the FcRn-mediated recycling of immunoglobulin G and may promote degradation of pathogenic antibodies against TSHR and IGF-1R in a phase 2a, multi-center, open-label trial (NCT03943537) of ADCEND-GO (i.e. seven subjects with active moderate-to-severe TED received subcutaneous injections of rozanolixizumab 480 mg for two weeks followed by 340 mg for four weeks (34)). Among these patients, levels of serum immunoglobulin G and anti-TSHR antibodies decreased by 54.8% and 70.7%, respectively. Subsequently, rozanolixizumab was assessed for safety and efficacy in severe TED in a phase 3b, randomized, placebo-controlled study (NCT05168748) as ADCEND-GO 2), which was terminated secondary to decreases in serum cholesterol levels among study participants (35). Multiple other anti-FcRn agents, including monoclonal antibodies and antibody fragments, are currently under investigation for a variety of immunoglobulin G-mediated autoimmune conditions, and may be explored as therapeutic targets for TED in the future.

Hydroxymethylglutaryl–coenzyme A reductase

Statins, also known as hydroxymethylglutaryl-coenzyme A reductase inhibitors are a class of lipid-lowering drugs that have been reported in recent years to also exhibit pleiotropic anti-inflammatory, fibrotic, and immunomodulatory behavior (36). In orbital fibroblasts in therapeutic effect has been attributed to suppression of transforming growth factor beta-induced fibrotic markers, inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and downregulation of adipogenesis (37–39). In a recent report, statin users were found to be less likely to develop TED, with a full adjusted hazard ratio (aHR) between statin and CAS for current statin lipid-lowering medications that are demonstrate a comparable protective effect (40). In a phase 2, open label, single center, randomized clinical trial (NCT03122600; or STATO) statins as oral adjuvants to an intravenous glucocorticoid regimen for patients with hypercholesterolemia and active, moderate-to-severe TED demonstrated improvements in orbitopathy outcomes (41). Additional lipophilic statins that have shown early signs of promise as anti-inflammatory vehicles in TED include lipophilic hypoglycemic drugs and antibiotic agents previously connected with chemoresistance (42, 43).

Additional agents

Immunomodulatory agents under study for potential use in the management of TED include Sirolimus, a monoclonal anti-cancer B cell circulating mayor antibody used in the treatment of systemic lupus erythematosus (44) Clinical Trials identifier: IndraCT 2015-002127-39), ravulizumab, a monoclonal anti-interleukin 17A antibody approved for the management of severe plaque psoriasis, psoriatic arthritis, and axial spondyloarthritis (NCT04927871) and nilotinib, a soluble decoy receptor for both vascular endothelial growth factor A and B and placental growth factor (NCT04161586). A diversity of additional anti-inflammatory targets is currently in the exploratory pipeline for TED therapy, including bromodomain inhibitors, interferon receptors, histaminergic, and dopaminergic (45).

Discussion

Thyroid eye disease is a complex, immune-mediated disorder characterized by inflammatory dysregulation and remodeling of the periorbital and orbital. Over the last few decades, significant developments in the understanding of disease pathophysiology have allowed researchers and clinicians to identify and leverage novel molecular targets for therapy. Emerging immunologic therapies for the management of thyroid eye disease have diverse mechanisms of actions and routes of administration. Among the agents under investigation that aim to decrease ocular morbidity associated with TED are agents that IGF-1R, interleukin 6, and the neonatal Fc receptor. These novel immunologic approaches for disease therapy show promise for enhanced function, cosmesis, and quality of life among patients with TED.

Further discovery efforts for TED must identify and characterize candidate drugs that optimize both clinical efficacy and patient safety. In order to achieve this well-balanced profile are adaptive endpoints, timing, dose, quantity, frequency, and route are paramount. Moreover, detailed reporting of drug associated pharmacokinetics and studies aiming to prevent, minimize, or treat adverse effects of the associated therapies is crucial. Ultimately, clinic-specific algorithms may be developed that simply connect patient demographics, comorbidities, and risk factors with disease activity and severity to refine therapeutic recommendations effectiveness and safety.

Author contributions

AS: Conceptualization, Writing – original draft, Writing – review & editing. AH: Writing – review & editing. AM: Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gender Differences in Benign Essential Blepharospasm

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Purpose: Discussion of differences in disease characteristics between male and female patients with benign essential blepharospasm (BEB).

Methods: We retrospectively reviewed charts of 52 male and 61 female BEB patients comparing the time to initial botulinum treatment with botulinum toxin A. We prospectively compared BEB-related questionnaire results between 36 female and 19 male patients.

Results: The mean interval between symptom onset and botulinum toxin A treatment was 7.51 years for women and 4.58 years for men ($p = 0.04$). The questionnaire results showed a higher degree of symptom severity and frequency in female patients ($p < 0.05$). But similar responses to botulinum toxin treatment and follow-up in daily activities.

Conclusions: Aside from greater symptom severity and frequency among women, we found no significant differences between male and female patients with BEB.

Benign essential blepharospasm (BEB), a focal cranial dystonia, results in involuntary sustained eyelid closure. The current first-line treatment is botulinum toxin injections, which temporarily weaken the eyelid pretarsal orbicularis muscles. Although surgical myectomy and myectomy with levator aponeurosis disinsertion are options for patients with BEB who are refractory to botulinum toxin injections, surgery is usually reserved for patients who have failed medical therapy.[1–3]

Blepharospasm may result in significant disability and reduced quality of life.[4] Although various questionnaires have been developed to assess the impact of BEB symptoms on patients' daily activities, to date, only a few studies have addressed the psychosocial functioning and quality of life.[5–7] One study found the degree of disability to be comparable to that of major age-related eye diseases, such as the exudative form of age-related macular degeneration.[5]

Among various treatment modalities for this disease, botulinum toxin type A has been shown to be particularly effective. Jankovic et al.[8] demonstrated that compared with placebo, botulinum toxin type A administration resulted in a significant improvement in the severity of BEB symptoms, with a mean duration of 12.9 weeks. Other studies have found the duration of the effect to range from 1 to 5 months.[9,10]

Epidemiologic studies of BEB suggest that the prevalence of the disease is 16 to 133 patients per million. The onset is typically in the fifth or sixth decade, and a female-to-male preponderance may be noted. One review of the literature found that 61 of 71 studies reviewed, the ratio of female to male patients was 2:1 and 10:1.[11]

To our knowledge, no study has previously compared the disease characteristics of BEB between male and female patients. Our study intends to highlight any differences between male and female patients with BEB with regard to the frequency of treatment with botulinum toxin type A and self-reported severity of symptoms and associated disabilities.

METHODS

Chart Review: A retrospective chart review was performed for all patients with a diagnosis of blepharospasm (ICD-9 = 333.81), who were seen and evaluated through the neuro-ophthalmology service at the University of Minnesota from January 1996 to May 2003. Patients with secondary causes of blepharospasm were excluded. Secondary causes of blepharospasm include drug-induced dyskinesia, tardive dyskinesia, parkinsonism, and other movement disorders. Patients with these types of movement disorders were excluded from the study.

Questionnaire-Based Study: Consecutive patients presenting with BEB were also interviewed to obtain a history of botulinum toxin A injections. Patients were asked to complete a questionnaire that included the Jankovic Rating Scale (JRS) and the Blepharospasm Disability Index (BSDI) before the injection of botulinum toxin A. The JRS assesses the severity and frequency of the BEB symptoms (maximum severity = 4 and maximum frequency = 4). The BSDI measures disability as a result of BEB. At the time of each botulinum toxin injection, patients were questioned by the same physician (MSL) to complete the questionnaire. The questionnaire results were compared by using the *t* test. Differences in response were considered statistically significant if $p < 0.05$. Data were collected and analyzed using the same method that was used to analyze the results of the previous study.[12]

RESULTS

We compared [illegible] patients who underwent [illegible] BEB. [illegible] patients and [illegible]

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[illegible]

Results of the IBS and BSDI questionnaires

Item response*	45 weeks (SD)	96 weeks (SD)	p Value
Intestinal symptoms			
IBS			
Symptom severity			
Symptom frequency			
Quality of life			
BSDI†			
Burning			
Redness			
Watering			
Stinging			
Irritation			
Pain			

*Based on patient response to questionnaire, scored 0–10.

for the comparative statistical analysis. Because the distribution of the patient ages was not normal, the Mann-Whitney U test was used to perform the comparison between the two groups. Fisher's exact test was performed to determine the significance of the association between gender and the presence of BEB. Statistical significance was defined as $p < 0.05$. We used the same statistical methods to compare the duration between type A treatments in the BEB group and in the HFS group. Results are presented as mean ± standard deviation (SD) unless otherwise noted.

For the prospective questionnaire study, 39 female and 17 male patients were included, with a mean age of 67 years (range, 55 to 86 years; median, 68 years) and 67 years (range, 49 to 82 years; median, 69 years), respectively. Three of the female patients had blepharospasm. Each patient reported a mean of 3.1 (± 1.6) symptoms. The most common symptoms were irritation (84%), tearing (82%), and pain (79%). The IBS subscale questionnaire showed that the BEB patients had a significantly greater mean score (mean ± SD, 4.2 ± 1.6) than the HFS patients (mean ± SD, 2.1 ± 1.8) ($p < 0.001$). The BSDI subscale questionnaire showed that female patients with BEB had a significantly greater mean score (mean ± SD, 3.2 ± 1.4) than female patients with HFS (mean ± SD, 1.8 ± 1.2) ($p < 0.001$). The BSDI subscale questionnaire showed that male patients with BEB had a significantly greater mean score (mean ± SD, 2.9 ± 1.3) than male patients with HFS (mean ± SD, 1.5 ± 1.1) ($p < 0.001$). There was no significant difference between female patients with BEB and male patients with BEB ($p = 0.17$). There was no significant difference between female patients with HFS and male patients with HFS ($p = 0.13$). Female patients with BEB had a significantly greater mean score than female patients with HFS ($p < 0.001$). Male patients with BEB had a significantly greater mean score than male patients with HFS ($p < 0.001$). There was no significant difference between female patients with BEB and male patients with HFS ($p = 0.08$). There was no significant difference between female patients with HFS and male patients with BEB ($p = 0.08$).

DISCUSSION

Studies in other areas of medicine have shown a gender difference for disease ranging from cardiovascular to cardiac risks. Although prior studies have performed on the epidemiology of BEB patients, no study has specifically compared the clinical characteristics between female and male patients. This comparison, in our view, could be useful in counseling both newly diagnosed and long-standing BEB patients.

The results of our study suggest that BEB manifests itself similarly between male and female patients for the specific disease aspects studied. No statistically significant difference was noted between these 2 groups of patients for the mean interval between treatments. The average number of weeks between treatments for both groups is consistent with results of prior studies, showing the average duration of relief for botulinum toxin A to be 12 to 14 weeks for BEB patients.[1–3] No statistically significant difference in activities of daily living was seen, as measured by the IBSQ based on gender. However, the results of the IBS subscale show that female patients presenting for botulinum toxin A treatment may have more frequent and severe disease-related symptoms of BEB than presenting for treatment.

The emergence of subjective questionnaires of an orbital disease as objective scales to calculate fluctuations of clinical fulfillment from A to BEB patients assumes that all patients continued for all injections of botulinum toxin A. Clearly a prospective survey of BEB patients as they present for treatment would improve accuracy. However, we tried to account for this by excluding those patients who received only 2 injections and those with large intervals between injections. Additionally our sample size of 56 patients for the questionnaire-based study may not be large enough to generalize to all BEB patients.

Despite these limitations, we believe that our results are valid. Gender differences were noted in duration of botulinum toxin type A efficacy and disability do not appear to exist. Women seem to have greater symptom severity and frequency than men at the time of scheduling botulinum toxin type A injection follow-up. In the future, further prospective studies with a larger cohort of patients may be of interest to identify any differences between disease characteristics of early and chronic BEB patients.

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Late Presentation of Enlarging Lower Eyelid Mass and Muscle Degeneration Secondary to Hyaluronic Acid Filler

[redacted]

Abstract: A seventy-six female presented for evaluation of progressively worsening edema and palpable masses in both lower eyelids. While she denied prior filler to the lower eyelid or face trough, histopathology revealed degenerating striated muscle surrounding pools of hyaluronic acid. While cases of gradually enlarging masses associated with facial filler placement have been reported, there is no literature identifying muscle degeneration adjacent to hyaluronic acid filler.

Hyaluronic acid (HA) dermal fillers are commonly and increasingly used to improve facial aesthetics. The popularity of these injectables is due to the fact that they are widely considered

[redacted]

FIG. 1. [redacted]

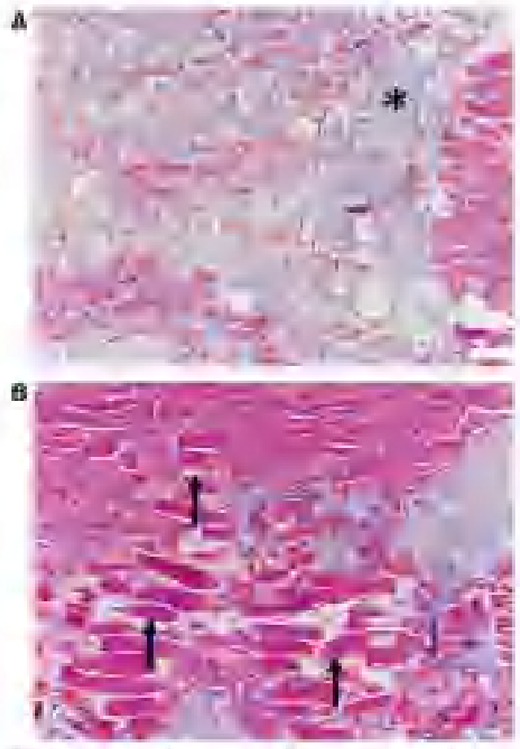

FIG. 2. [redacted]

cally reachable. The reversible chemotoxin is evaluated in the following case. Hyaluronidase (HA) is also used in the treatment of [redacted]. This report is in full compliance with the Declaration of Helsinki, and informed [redacted] was obtained.

CASE DESCRIPTION

A [redacted]

DISCUSSION

REFERENCES

Neuropathic Pain Following Poly-L-Lactic Acid (Sculptra) Injection

Joel Pech, M.D.,* Juan Alcalde, M.D., PhD,
Eric Chen, M.D., Daniel Chen, B.S.,
and Jaime Jobe, M.D., FACS

Abstract: Injectable fillers have become a prevalent means of facial rejuvenation and volume expansion. While typically well tolerated, serious complications have been reported. The authors present a case in which an otherwise healthy female with a history of multiple filler injections including poly-L-lactic acid, developed 3 weeks of neuropathic pain in the left temporal fossa following injection. To the best of the authors knowledge, neuropathic pain has not been reported as a complication following poly-L-lactic acid injection. The patient was treated with an injection of steroid and long-acting anesthetic with resolution of symptoms.

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Medical Cannabis, a Beneficial High in Treatment of Blepharospasm? An Early Observation

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ORIGINAL ARTICLE

Medical Cannabis, a Beneficial High in Treatment of Blepharospasm? An Early Observation

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ABSTRACT

The objective of this study was to observe the effect of medical cannabis in human essential blepharospasm (BEB) as an adjunct to botulinum toxin. A retrospective chart review was performed on patients certified for medical cannabis use for BEB from September 2015 to May 2016. Patient demographics and response, cannabis history, and recently follow-up were collected. Two patients were certified for medical cannabis use. One met the inclusion criteria, which was any patient with a diagnosis of BEB receiving standard botulinum toxin treatment who had started medical cannabis treatment by a registered physician within the same and was traceable to follow-up. Each patient demonstrated two. Three out of four patients (75%) reported symptomatic improvement. Medical cannabis is an accepted therapy for multiple sclerosis symptoms and chronic pain. Its use as an alternative treatment for BEB remains unknown, and further investigations would be of benefit.

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KEYWORDS
Blepharospasm; botulinum toxin; cannabis; marijuana

Introduction

Benign essential blepharospasm (BEB) is a common craniofacial movement disorder. BEB can be a disabling process, as symptoms of excessive involuntary blinking, photophobia, and uncontrolled eyelid closure can cause functional blindness.[1–3] Its prevalence is estimated to be 52.3 per 1 million. Onset generally occurs after the fourth decade, with a higher frequency in women, and it can severely impact quality of life.[1–3] BEB is most often idiopathic, however, brainstem lesions have been reported.[1,2]

The standard treatment of BEB is life-long therapy with scheduled periocular botulinum toxin injections, which reduce symptoms of facial dystonia for BEB and other facial spasm disorders (hemifacial spasm and Meige syndrome).[1–3] Although not curative, botulinum toxin provides an effective, safe, successful long-term alleviation of facial dystonia symptoms such as BEB.[1–3] With routine treatment, symptom-free periods can be maintained.

Medical cannabis, a once-taboo subject, has gained much press over the years with its potential utility as being an adjunct treatment for many diseases. Studies have shown benefit in symptomatic improvement for muscle spasms related to multiple sclerosis, and also in neurogenic symptoms, neuropathic pain, refractory pain due to human immunodeficiency virus (HIV), chemotherapy-induced nausea and vomiting, and urinary dysfunction.[4–7] Twenty-five states including Washington, DC, Puerto Rico, and Guam have passed comprehensive medical cannabis and marijuana programs to varying degrees and implementation.[8] Minnesota allows for medical cannabis to those with 10 qualifying conditions with one specifically being severe and persistent muscle spasms (including those characteristic of multiple sclerosis).[9] Qualifying conditions are determined based on public petitions for specific conditions to a seven-member panel following review of the condition, current treatments, and available research on medical cannabis.

In this study, we observed the effects of medical cannabis therapy, as an adjunctive treatment modality in conjunction with maintenance botulinum toxin therapy, in patients with BEB.

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Methods

We performed a retrospective chart and prospective data gathering review with University of Minnesota Institutional Review Board approval on all patients at the University of Minnesota Department of Ophthalmology and Visual Neurosciences who were certified for medical cannabis use for treatment of BEB from September 2015 through May 2018, and those who were contacted by telephone. The collection and evaluation of protected patient health information was Health Insurance Portability and Accountability Act (HIPAA) compliant, and in accordance with the Declaration of Helsinki. Inclusion criteria were a clinical diagnosis of BEB, receiving maximally tolerated subcutaneous botulinum toxin treatment, and medical cannabis treatment by one of two registered distributors (Leadiant Labs, LLC, and Minnesota Medical Solutions) within the state of Minnesota. Furthermore, patients were only included if they verbally agreed via telephone to discuss their history with the medical cannabis use. Patient demographics (age and gender), prescription type and dose, history of medication use, side effects, patient responses to medication, and responses to the Blepharospasm Disability Index (BSDI) and Jankovic Rating Scale (JRS), if available, were documented (Table 1). The indices were taken during the standardised botulinum toxin treatment received every 3 months, once before and once during cannabis therapy. All patients were contacted by telephone to collect responses and reactions to the medical cannabis therapy.

To receive medical cannabis, each patient was certified for the Minnesota Department of Health medical cannabis program by one of the two senior authors (M.S.L. and A.R.H.) for medical cannabis treatment for severe and persistent muscle spasms. The discussion of medical cannabis therapy was initiated by the senior authors (A.R.H. and M.S.L.) if the patients who had received long-term botulinum toxin therapy were determined to have residual symptoms and could potentially benefit from additional treatment. Following certification, the patient met with a pharmacist at one of the two distribution centres who would determine the type and quantity of medical cannabis to best provide symptom control based on past studies, pharmacist experience, and availability. There was no contact between the certifying doctors and the distribution centres. The patient would then follow up with the distribution centres for alterations to the dosage and type.

Table 1. Blepharospasm Disability Index (BSDI) and Jankovic Rating Scale (JRS).[a]

Jankovic Rating Scale (JRS)
Obtained by assessing eye closure (max. 16)
Head
Blinking
Closing eyelids
Watching television
Shopping
Eating/ drinking
Walking (on level)
Ratings:
0 = No impairment
1 = Mild impairment
2 = Moderate impairment
3 = Severe impairment
4 = Not possible due to disease severity
Blepharospasm Disability Index (BSDI)
(Originally described by Grandas et al., 2002)
Blepharospasm severity
0 = None
1 = Minimal, increased blinking, corrects with very strong external stimuli (i.e., bright light or wind)
2 = Mild, spontaneous eyelid flickering (sustained eyelid spasm). Spontaneous eye closure, severity not meeting full set of functionality guidelines.
3 = Moderate, very noticeable closure of eyelids, truly, Mildly incapacitating.
4 = Severe, incapacitating failure of eyelids and severely compromised muscles
Blepharospasm Frequency
0 = None
1 = Slightly increased frequency of blinking
2 = Eyelid spasms lasting less than 1 second at a time
3 = Eyelid spasms lasting for more than 1 second, but episodes make often less of overall time
4 = Functionally "blind" due to persistent eyelid closure, more than 50% of the waking day.

and dose of cannabis is listed in Table 1. Four patients stopped the treatment, two due to no treatment effect noted, one for cost, and one due to concern for related side effects. The most common side effects were disturbed sleep and headache, whereas one patient developed lightheadedness, which led to a thorough cardiac work-up and cessation of the medication (Table 2).

Three of the patients participated in objective measures of two severity indices utilised in the study, the Blepharospasm Severity Index and the Jankovic Rating Scale. The BSDI assesses the severity and frequency separately, with 0 being no symptoms and 4 being severe/incapacitating. In addition, the JRS measures the disease severity regarding six different activities, with 0 being no impairment and 4 being too severe to perform (the total score is additive and can measure from no impairment to severe impairment, or 0 to 24). The duration of use of cannabis for those patients were 8, 12, and 12 weeks, respectively. Of note, there was a decrease in both indices when comparing the pre and post averages of the three patients (Table 3).

All the participants receiving medical cannabis therapy were contacted by telephone. Of those contacted, one patient declined to comment about his experience with the medical cannabis, as he only used the medication 2 weeks before stopping. He reported minimal residual symptoms following his standard botulinum toxin injection treatment, and he stopped the cannabis shortly after starting, as he felt there were no improvement in the symptoms after initially starting the treatment. He therefore felt his participation would not provide valid data and declined providing further commentary on history of use. Three of the other patients reported a subjective improvement in clinical symptoms. Lastly, three of the patients had other significant disabling diseases (craniomandibular and cervical dystonia, post-herpetic neuralgia, and Meige syndrome). All three described a further reduction in symptoms related to these diseases in addition to the blepharospasm (Table 4).

Table 2. Patient and medication history.

Patient	Age	Sex	Prescription	Number of botulinum injections (prior to cannabis)	Recumbent dose	Duration of cannabis use (weeks)	Treatment stopped (Yes/No)	Reason for stop	Side effects
1	69	Female	2.5 mg THC: 47.5 mg CBD capsule	>4	1 capsule bid	8	Yes	Cost	None
2	54	Male	5 mg THC: 5 mg CBD /1 mL tincture	04	1 mL bid	2	Yes	No treatment effect noted	Disturbed sleep*
3	61	Female	PM sublet: 25 mg THC: 25 mg CBD /1 mL tincture 2nd sublet: 20 mg THC: 3 mg CBD /1 mL tincture	>5	1/10 mL bid	12	Yes	N/A	Disturbed sleep*
4	72	Male	PM sublet: 2.5 mg THC capsule 2nd sublet: 5 mg THC: 1 mg CBD capsule	03	1 capsule bid	12	Yes	No treatment effect noted	Headache, lightheaded
5	69	Female	5 mg THC: 5 mg CBD /1 mL tincture	22	Up to 2 mL bid	8	Yes	Side effect**	Lightheaded

*Normal PM medication taken at night.
**Admitted twice times to emergency department for evaluation of lightheadedness.

Table 3. Pre/post-cannabis therapy blepharospasm scale results.

	Patient 1		Patient 3		Patient 4			
Blepharospasm scale	Pre	Post	Pre	Post	Pre	Post	Pre patient average (SD)	Post patient average (SD)
BSDI Severity (0–8)	3	2	4	3	3	4	3.33 (0.58)	2.67 (1.15)
BSDI Frequency (0–8)	2	1	4	3	4	4	3.33 (1.15)	2.67 (1.53)
JRS (0–24)	10	6	14	11	11	7	11.67 (2.08)	8.00 (2.65)

Note: BSDI = Blepharospasm Disability Index; JRS = Jankovic Rating Scale.

Table 4. Subjective patient responses to cannabis therapy.

Patient	Benefit to symptom (Yes/No)	Other diseases with noted cannabis improvement	Would participate in crossover study (Yes/No)
1	Yes	Dysmenorrhoea and cervical dystonia	Yes
2	Unclear*	None	Yes
3	Yes	Post-herpetic neuralgia	Yes
4	No	None	No
5	Yes	Meige syndrome	Yes

*Patient stopped after 2 weeks as by clinician's time response rate to complete symptomatic relief by botulinum therapy. He declined and did not feel he could adequately respond to the questions.

Discussion

Use of marijuana, medical or otherwise, remains an offense under federal law, and due to its classification as a schedule I substance by the Food and Drug Administration (FDA), it continues to be a challenge to research its therapeutic properties.[7,8] The principal cause of marijuana's psychoactive effects was found to be attributed to the cannabinoid Δ^9-tetrahydrocannabinol (THC); however, other important cannabinoids have been isolated in cannabis.[9] For example, cannabidiol (CBD) is one of the main non-psychotropic components in cannabis. There is continued uncertainty to its actual effect, although it has been postulated to be a potential important inverse agonist; however, its use in Nabiximols (THC:CBD extract) has been well studied for treatment of multiple sclerosis-related muscle spasms.[9] It has been thought that the interplay between these two cannabinoids can be a helpful anti-spastic therapy. Furthermore, reports have found medical cannabis well tolerated, with only mild to moderate adverse effects. However, due to the vast different concentrations of cannabinoids in each product, and the various patient responses to medical cannabis, the adverse effect profiles vary considerably.[10]

Focusing on neurologic conditions, medical marijuana has been found efficacious and safe for specific disorders; however, for others, minimal effect was reported. Cannabis was found effective for reducing patient-centred measures for spasticity, central pain and painful spasm, and urinary dysfunction [1]. However, has little effect as a treatment modality for tremor and conditions such as levodopa-induced dyskinesias in Parkinson's disease patients. Further research needs to be performed in regards to cannabis treatment for Huntington's disease. Recently, cannabis has been found to be beneficial in Tourette syndrome, cervical dystonia, and epilepsy, as current efficacy remains unknown.[11]

Our review focused on the outcomes of medical cannabis use in five patients with BEB treated with standard scheduled botulinum toxin therapy who had residual symptoms. Through the collective experiences of these five patients, interesting observations apply. (1) The medical cannabis was tolerated by a majority of the participants, with only one having to stop treatment due to cessation of an adverse event. (2) Objective and subjective measures did not clearly comport. Objectively, the standardized blepharospasm scales showed only 1 of the 5 patients with reduction in all three scales. Subjectively, in those able to respond, a majority of patients reported improvement in symptoms, the belief that medical cannabis could extend the duration of standard botulinum toxin therapy, and symptomatic relief from other co-morbidities. Contrastingly, patient 4 had a notable decrease in the JRS but did not report any symptomatic improvement. Potential reasons behind this disconnect could be the limited sample size collected, the variation of patient treatment plan, approach, and performance when taking the blepharospasm scales, limited patient understanding of disease severity in relation to reported symptoms, or a placebo effect. The potential use of medical cannabis use remains unknown, and further prospective studies are warranted.

There were several important limitations to our observations, with one being the retrospective design. In addition, the follow-up time was too short to determine true potential of adding cannabis to botulinum toxin therapy; there was an inability to control treatment design, as each participant in the medical cannabis program had unique experiences, treatment plans, and doses. Lastly, the sample size was small. We certified 10 patients, but only 50% proceeded with therapy. Patients in this age group expressed reservations about using "medical marijuana." The cost of medical cannabis, which is several hundred dollars a month, can also be prohibitive.

Medical cannabis has made great strides as a treatment modality for symptom relief for many disease processes, including muscle spasms related to multiple sclerosis. As a muscle spasm disorder, the effect of cannabis on BEB remains uncertain. We believe that this observational case series provides a backdrop to exploring prospective, double-masked studies to determine the therapeutic effect of cannabis for patients suffering from BEB.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Effects of Repeated Eyelid Injections with Botulinum Toxin A on Innervation of Treated Muscles in Patients with Blepharospasm

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Abstract

Purpose: To assess changes in innervation and muscle morphology after repeated botulinum toxin A injections in subjects with benign essential blepharospasm.

Methods: Surgical waste specimens were processed for histologic examination of nerve fibers, neuromuscular junctions, fiber size, and central nucleation and compared to age matched controls and to two subjects with blepharospasm that had not received botulinum toxin A injections.

Results: There was a significant increase in amount of nerve fibers and numbers of neuromuscular junctions in the orbicularis oculi muscles from subjects with blepharospasm treated repetitively with botulinum toxin A. In addition there was a significant decrease in main muscle fiber cross-sectional area and an increase in central nucleation. The specimens from the subjects with only blepharospasm had the same density of nerves but had intermediate levels of neuromuscular junctions.

Conclusions: These data suggest that repeated injections of botulinum toxin A has an effect on nerve and neuromuscular junction numbers, which are partly mirrored in orbicularis oculi muscle from subjects with blepharospasm only. These studies suggest the potential for modulating these changes in order to extend the duration of effectiveness of botulinum toxin.

Précis:

Repeated botulinum toxin A injections in blepharospasm subjects' orbicularis oculi resulted in smaller muscle fibers, central nucleation, and increased nerve and neuromuscular junctions.

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Keywords

botulinum toxin A; orbicularis oculi muscle; blepharospasm; peripheral nerves; neuromuscular junctions

INTRODUCTION

Benign essential blepharospasm is a form of focal dystonia,[1] with an incidence rate of 1.2 persons per 100,000 per year[2] and prevalence rates from 16-133 per million in multiple studies.[3] Prevalence estimates for all forms of primary dystonia range from 2-50 cases per million of the population for early onset and 30-7320 cases per million for late-onset dystonia.[4] Botulinum toxin A, which blocks the release of acetylcholine at the neuromuscular junction, resulting in paralysis, was originally developed as a potential treatment for strabismus.[5] Its utility in the management of blepharospasm was realized shortly thereafter.[6] Since these initial studies, the intramuscular injection of botulinum toxin A has safely relieved dystonia symptoms for thousands of patients of all ages[7] as well as significantly improved their quality of life.[8,9]

Research into the mechanism of action revealed the botulinum toxin A acts specifically on the presynaptic terminal, where it cleaves the protein SNAP25.[10] The effect of botulinum toxin persists for several months as the cleaved SNAP25 is retained at the neuromuscular junction, preventing the insertion of new SNAP25 into the nerve terminal.[11] However, function slowly returns after botulinum toxin-induced muscle paralysis. A number of studies have demonstrated nerve terminal and nodal sprouting in the paralyzed nerves as early as two days after botulinum toxin injection.[12,13] Evidence of axon sprouting after botulinum toxin A injections was seen specifically in human orbicularis oculi muscle from blepharospasm subjects at the single neuromuscular junction level.[14,15] This axon sprouting was postulated to be responsible for the formation of de novo neuromuscular junctions over the orbicularis oculi muscle surface, increasing the speed of the return of muscle function. Using rabbits, an injection of botulinum toxin A resulted in a significant increase in neuromuscular junctions throughout the paralyzed orbicularis oculi muscles,[16] with a similar finding seen after injection of botulinum toxin A into rabbit extraocular muscles.[17]

Individuals with benign essential blepharospasm and other focal dystonias will receive many series of botulinum toxin A injections. The potential effects of repeated injections on the orbicularis oculi muscle and its innervation are not known. In a study of long term efficacy, there was a significant increase in botulinum toxin A dose between the first year and last year of treatment (with a range of 10-20 years of treatment), but no significant difference in the duration of effect.[18] The current study focused on the potential effects of repeated botulinum toxin A injections on muscle and nerve density using surgical waste specimens from subjects who underwent an orbicularis oculi myectomy. These were compared to naïve orbicularis oculi specimens removed during blepharoplasty in the absence of focal dystonia in these subjects.

METHODS

All studies were approved by the Institutional Review Board at the University of Minnesota, de-identified, and subsequently processed without knowledge of the source or type of specimen. Table 1 gives the age, sex, and number of botulinum toxin A injections per individual and dose, the age of the two specimens from a subject with benign essential blepharospasm who never received an injection of botulinum toxin, and five age-matched control individuals who underwent an upper lid blepharoplasty in the absence of focal dystonia or other neuromuscular disorder. At the time of regularly scheduled orbicularis oculi myectomy surgery (performed by ARH or AM), the pretarsal and preseptal muscles were excised separately and were placed in physiological saline on ice. Within 1-3 hours, they were embedded in tragacanth gum and frozen in 2-methylbutane, chilled on liquid nitrogen. The tissue blocks were stored in a −80°C freezer until sectioned.

The muscle specimens were sectioned at 12 μm using a cryostat. Representative sections through the entire thickness were stained using hematoxylin and eosin by standard methods. A series of at least 3 sections were immunostained using an antibody to neurofilament protein (smi-31; 1:30,000; BioLegend, San Diego, CA) to identify nerve fibers. Sections were incubated in normal serum at 10% in 1M phosphate buffered saline (PBS) containing 0.01% Triton X-100 (antibody buffer), incubated in antibody buffer overnight at 4°C in humid chambers, rinses in PBS, and then incubated in secondary antibody using the Vectastain Elite kit (Vector Laboratories, Burlingame, CA) following package instructions. The sections were then rinsed in PBS and reacted with diaminobenzidine and 0.1% hydrogen peroxide, using heavy metals to intensify the reaction. Slides were rinsed in PBS, dehydrated in graded alcohols, and coverslipped with Permount (Fisher Scientific, Pittsburgh, PA). A second series of three slides per tissue block were stained for the visualization of neuromuscular junctions. Slides were rinsed in PBS, and incubated with α-bungarotoxin conjugated to Alexa Fluor 488 overnight in a humid chamber at 4°C. Following a PBS rinse, the sections were coverslipped using Vectashield mounting medium (Vector Labs).

Morphometric analyses were performed. Mean cross-sectional areas and percent of myofibers with central nuclei, indicative of degeneration/regeneration or denervation/reinnervation, were measured manually using Bioquant Nova Prime software (Bioquant, Nashville, TN). A minimum of 3 slides were analyzed, and a minimum of 200 fibers were examined per muscle. For any given subject, the right and left sides of the same region (e.g. pretarsal) were averaged, and the averages were used to determine the means for the botulinum toxin A treated muscles from subjects with benign essential blepharospasm and for the naïve control muscles. For the two subjects with benign essential blepharospasm who were never treated with botulinum toxin A, the average of the left and right sides in each region were calculated, and the means from the 2 muscles were then averaged. For nerve fiber analysis, a minimum of 3 slides were analyzed from each muscle region from both right and left eyelids. For each muscle from each eyelid area (pretarsal and preseptal), all the smi-31-positive nerve fibers within any given microscopic field of view were manually circled as was the total area of the field. The entire section was measured, and percent area containing nerve fibers was determined and compared to muscle area and compared to tissue

area (muscle plus connective tissue). Similarly, every neuromuscular junction was counted in each of the three muscle sections, and the entire tissue section area was measured to determine number of neuromuscular junctions relative to tissue area. As for the fiber areas, specimens from the same muscles from each individual were averaged to determine the overall averages.

The mean ± SEM were reported. Data analyses of the blepharospasm and botulinum toxin treated measurements compared to naive controls used an unpaired Students' t-test and Prism software (GraphpadSan Diego, CA). Statistical significance was defined as $P<0.05$.

RESULTS

The mean age of the control subjects was 64.8 (range: 59-69), the mean age of the subjects with blepharospasm who were treated with repeated botulinum toxin injections was 61.5 (range: 55-68), and the mean age of the subjects with blepharospasm only was 59.5 years (Table 1). Thus the collected specimens were closely age-matched. Table 1 gives the number of botulinum toxin injections and doses (if known) for each of the treated subjects, with a mean of 16.8 injections (range 3-28) per botulinum toxin treated subject.

When the amount of nerve fibers is calculated based on percent of total cross-section (Figure 1A) or percent of muscle cross-sectional area (Figure 1B), the blepharospasm and botulinum toxin A- treated specimens had significantly more nerve fibers than naïve control muscles, showing differences of 48.1% and 47.3%, respectively. While statistical analysis could not include the muscle specimens from the two subjects with blepharospasm who had not been injected with botulinum toxin A, these specimens had 34.7% more nerve as a percent of total tissue in cross-section and 11.1% more nerve as a percent of muscle tissue in cross-section. These values are 14.2% and 36.7% less than the nerve densities from the blepharospasm and botulinum toxin A- treated specimens.

This analysis was extended to analyze each muscle region separately. In the pretarsal region there was significantly more nerve tissue both as a percent of all tissue and as a percent of muscle tissue, 87.8% and 102.2% respectively (Figure 2). In the preseptal region, the blepharospasm and botulinum toxin treated muscles had 44.5% and 71.1% more nerve fibers than the naïve control tissues, but only the nerve per total cross-section was statistically different. It is interesting to note that in both the pretarsal and preseptal regions of the orbicularis oculi muscle from the subjects with blepharospasm but without botulinum toxin A injections, the nerve density as a percent of either total cross-section or muscle cross-section was similar to the muscles from the subjects with both blepharospasm and botulinum toxin A treatment.

In order to assess changes on the postsynaptic side, neuromuscular junctions were localized using α-bungarotoxin staining and quantified morphometrically (Figure 3). There were significant increases in neuromuscular junctions per mm^2 in both the pretarsal and preseptal regions of the muscles from subjects that had blepharospasm and botulinum toxin A treatment compared to the age-matched control muscles from the same muscle regions, with a 5-fold and a 4-fold difference respectively. In contrast to the nerve density measurements,

the pretarsal muscles from the blepharospasm subjects untreated with botulinum toxin A showed a level of neuromuscular density approximately equal to that of the control muscles- but 4-fold lower than that of the blepharospasm muscles treated with repetitive botulinum toxin A injections. In the preseptal region, there were relatively similar levels of neuromuscular junctions in the control and blepharospasm only muscles; however there was a 114.7% difference between the controls and the botulinum toxin A treated muscles and an 81.5% difference between the treated and blepharospasm only muscles. This suggests that neuromuscular junction changes are associated with repetitive botulinum toxin A injections. It should also be noted that while there were many more neuromuscular junctions in the muscles from the botulinum toxin A-treated blepharospasm subjects, they tended to be smaller and thinner (Figure 3A, B).

The mean cross-sectional area of the pretarsal region of the muscle specimens from the subjects with benign essential blepharospasm treated with multiple injections of botulinum toxin A were significantly smaller than the untreated control muscles, with a difference of 24.8% (Figure 4A,C). The myofibers in the preseptal region were also significantly smaller with a difference of 52.8% in the botulinum toxin A-treated muscles from blepharospasm subjects compared to controls (Figure 4). It is also interesting to note that the muscles from the subjects with only blepharospasm had similar areas to the control muscles, with a 7% and 5.5% difference respectively. Central nucleation is a hallmark sign of degeneration/regeneration or denervation/reinnervation. In both the pretarsal and preseptal regions, there was a significant increase in percent of myofibers with central nucleation in the botulinum toxin A-treated muscles from subjects with blepharospasm, with a 6-fold (129.8%) and a 2-fold (111%) increase respectively (Figure 4A,B,D). The muscles from the subjects with only blepharospasm had intermediate central nucleation levels, 72.5%- and 71.6%- greater respectively.

DISCUSSION

Previous studies examining individual neuromuscular junctions in subjects with blepharospasm and repeated botulinum toxin A injections showed marked evidence of terminal sprouting in the excised orbicularis oculi muscles.[14,15] In the present study, we showed that multiple injections of botulinum toxin A over time resulted in a number of widespread changes in the orbicularis oculi muscles of these subjects with blepharospasm. Botulinum toxin A injections caused a muscle wide increase in both nerve fiber and neuromuscular junction density compared to naïve control orbicularis oculi muscles. While staining cannot be reliably performed on four specimens from two subjects with blepharospasm and no botulinum toxin A treatment, it is interesting that only the nerve densities were similar to the botulinum toxin A treated orbicularis oculi muscles with neuromuscular junction levels the same as the control muscles. This suggests that the increased number of nerve fibers per tissue area may be specifically related to the blepharospasm and not due to up-regulation by the repeated botulinum toxin injections. As there are only orbicularis muscles from two selected blepharospasm subjects, the data must be interpreted carefully; It is, however, quite interesting given a condition whose primary etiology is not understood. This does not negate the literature which clearly has shown that botulinum toxin A-induced nerve terminal sprouting is

the area of the chemically denervated muscle fibers.[13,19] This is important to note that this sprouting occurs in the absence of physical damage to the nerve fibers, as physical damage is known to induce significant nerve fiber sprouting from the end of the injured nerve.[20]

The increase of *de novo* neuromuscular junctions as a response to muscle paralysis with botulinum toxin has been described in a number of muscles,[17,21–23] and specifically to the orbicularis oculi muscles.[15,16] These extrajunctional acetylcholine receptors also form in response to nerve section.[24] As we demonstrated after botulinum toxin injection into the extraocular muscles, the induced muscle paralysis results in significant increases in neuromuscular junctions throughout the length of the muscles.[17] There are strong similarities between the response to botulinum toxin A injection in the orbicularis oculi muscles and extraocular muscles. Both sets of muscles have slow myofibers that do not span the length of the muscles,[17,24,25] have more than one neuromuscular junction on single muscle fibers,[24,26] and have small mean cross-sectional areas compared to limb skeletal muscles.[27–29] It is interesting that there was not as large an increase in neuromuscular junction density in the specimens with blepharospasm only. While one must be careful not to over-interpret data from two subjects (4 muscles), these data suggest that while chemodenervation causes a large increase in neuromuscular junction number across each specimen, a good proportion of this response is due specifically to the botulinum toxin treatment. This observation, and the elevation in the number of nerves in the specimens with blepharospasm only, makes it tempting to speculate that at least part of the peripheral manifestation of blepharospasm might be due to some level of denervation and subsequent reinnervation. These specimens are quite rare, as the general standard of care for blepharospasm is botulinum toxin injections. Examination of additional specimens of orbicularis oculi muscle from blepharospasm patients who have not undergone treatment with botulinum toxins will allow us to better understand the pathophysiology of this disorder.

In peripheral skeletal muscles, the almost universal response to botulinum toxin injection is temporary muscle atrophy.[30–32] This was even seen in big muscles after the larger doses of botulinum toxin A needed for the treatment of cervical dystonia.[33] Botulinum toxin A also produced muscle atrophy in the masseter,[34] and has been used to reduce masseter muscle hypertrophy in human subjects.[35] Similar types of muscle fiber atrophic changes were described in experimental studies of the effects of botulinum toxin A into orbicularis oculi including human subjects.[36,37] In a previous study using human surgical waste tissues from blepharospasm subjects treated with botulinum injections, extreme variability in myofiber cross-sectional areas was noted.[9] Relative to these studies, we saw a significantly decreased mean myofiber cross-sectional area only in the preseptal portion of the treated orbicularis oculi muscle compared to naïve control. However, it is important to note that the muscle specimens from the subjects with blepharospasm only did not show a decrease in myofiber cross-sectional area. Thus one can speculate that these changes are likely due to the repeated exposure to botulinum toxin A.

The studies thus far have shown that the innervation zone and structure of mammalian neuromuscular junctions have a fair bit of plasticity,[13,17,19,21–23,38] and these features are altered for long durations after botulinum toxin injection. This plasticity has the potential to be modified by other treatments as well. A number of studies have shown that the terminal nerve sprouting in denervated skeletal muscle can be altered in multiple ways, for example by changing neurotrophic factor levels, such as insulin-like growth factor (IGF-1),[39] by modifying levels of other molecules such as corticotropin releasing factor (CRF),[16] and by injection of blocking antibodies for neural cell adhesion molecule (NCAM),[41,42] tenascin,[43] or BDNF.[44] These studies suggest the potential for these types of approaches to extend the duration of effectiveness of botulinum toxin. The orbicularis oculi muscle specimens from the subjects with previously untreated blepharospasm also had increased amounts of peripheral nerve within the muscles compared to naïve, age-matched control muscles, suggesting that these peripheral changes may be part of the disease process. If borne out by future studies, these data suggest that reduction of nerve and neuromuscular junction numbers by use of CRF or blocking peptides or antibodies has the potential to be a primary treatment for blepharospasm.

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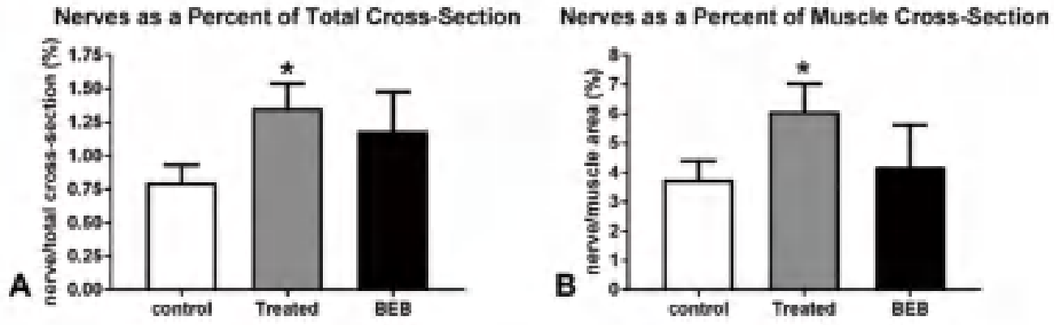
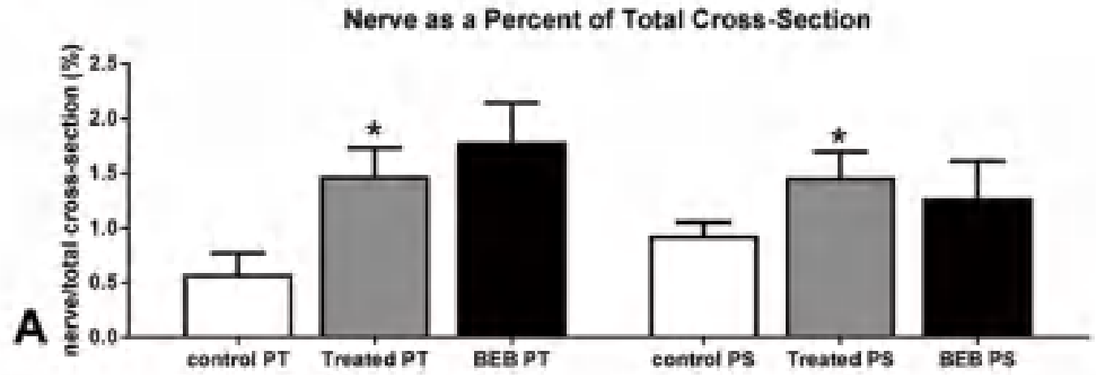


Figure 1:
Morphometric analysis of nerve fibers in surgically excised orbicularis oculi muscle as a percent of total tissue cross-section (A) or muscle cross-section (B). * indicates significant difference from control. Control: naïve control orbicularis oculi muscles; Treated: muscles from subjects with blepharospasm who had been treated with multiple botulinum toxin A injections; BEB: muscles from subjects with blepharospasm who never had an injection of botulinum toxin A.



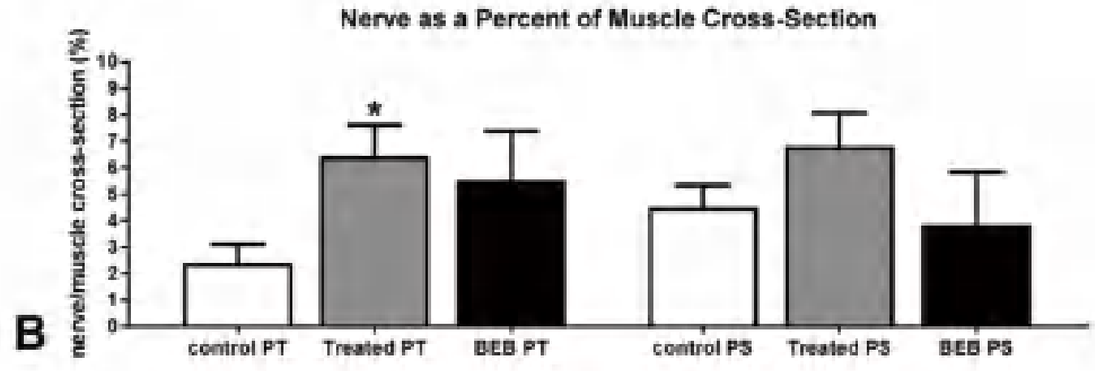
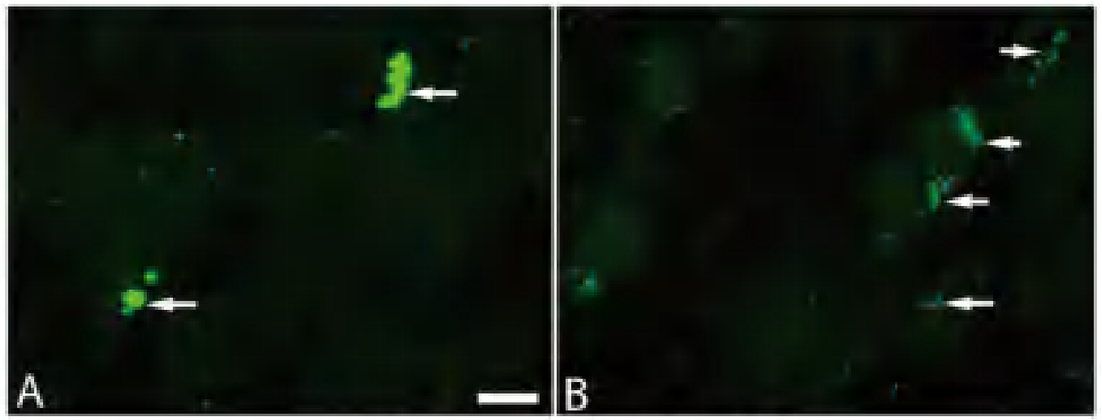


Figure 2:
Morphometric analysis of nerve fibers in the preseptal (PT) region and preseptal (PS) region of the orbicularis oculi muscle as a percent of total tissue cross-section (A) or muscle cross-section (B). * indicates significant difference from control. Control: naïve control orbicularis oculi muscles; Treated: muscles from subjects with blepharospasm who had been treated with multiple botulinum toxin A injections; BEB: muscles from subjects with blepharospasm who never had an injection of botulinum toxin A.



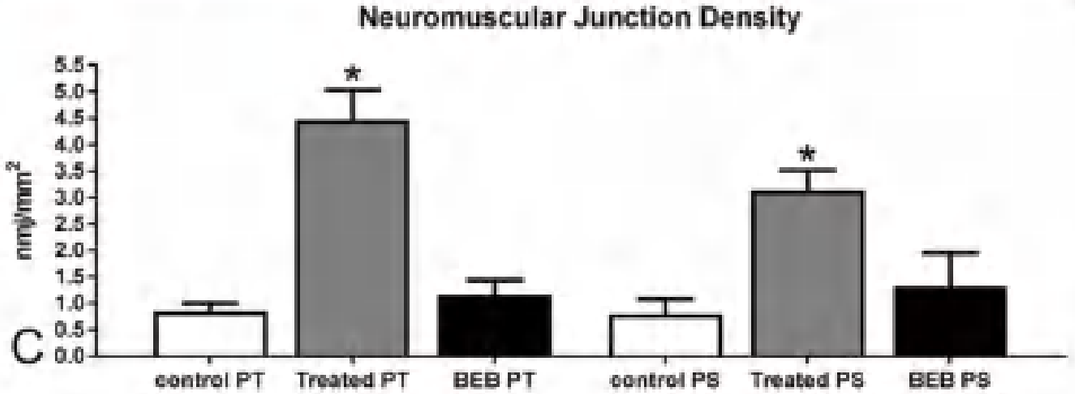
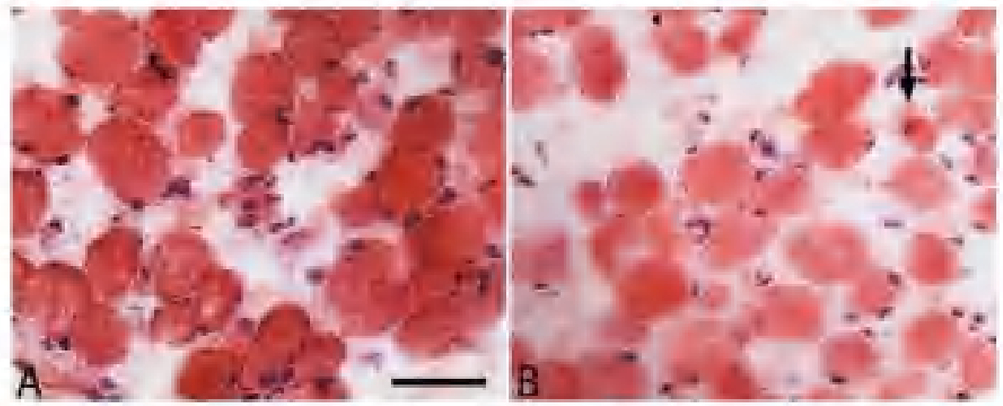
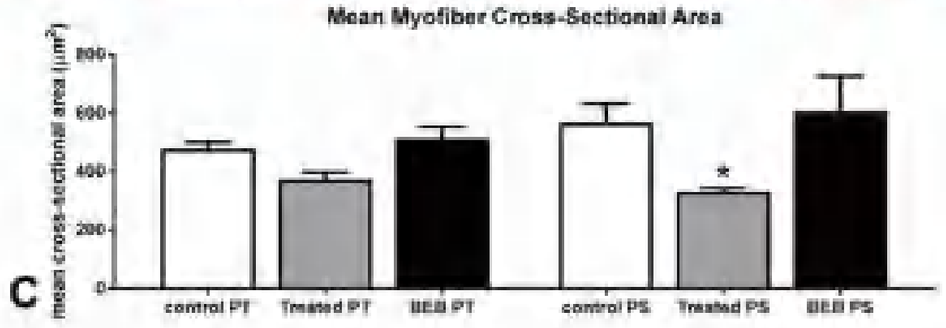


Figure 3:
Photomicrograph of neuromuscular junctions (green) stained with a-bungarotoxin conjugated to AlexaFluor 488 in (A) naïve control orbicularis oculi muscle and in (B) orbicularis oculi muscle from a subject with blepharospasm who had multiple botulinum toxin injections prior to surgical myectomy. (C) Morphometric analysis of neuromuscular junction density was a percent of mm^2 of tissue in the pretarsal (PT) and preseptal (PS) regions of the orbicularis oculi muscle from control, botulinum toxin treated muscles from blepharospasm subjects, and subjects with blepharospasm only. Bar is 30 μm. * indicates significant difference from control.





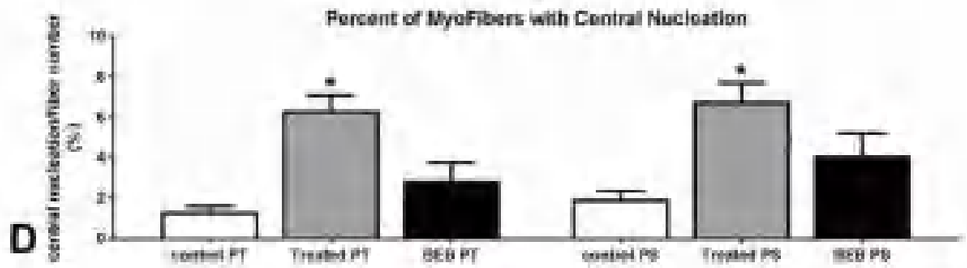


Figure 4:
Photomicrograph of (A) naïve control orbicularis oculi muscle and (B) orbicularis oculi muscle from a subject with blepharospasm who had multiple botulinum toxin injections prior to surgical myectomy. Arrow indicates a centrally located myonucleus. (C) Mean myofiber cross-sectional areas and (D) percent of myofibers with central nucleation in the pretarsal (PT) and preseptal (PS) regions of the orbicularis oculi muscle from control,

botulinum toxin treated muscles from blepharospasm subjects, and subjects with blepharospasm only. Bar is 50 μm. * indicates significant difference from control.

Table 1:

Subject Information

	Subject Age	Subject Sex	Number of Botulinum Toxin A Injections	Dose/Visit
BEB and Botox				
1	55	F	20	72.5-80 units
2	59	F	20	60 units
3	55	F	6	50 units
4	68	F	24	60/80 units
5	64	F	28	80 units
6	61	F	3	variable
BEB only				
1	59	F	None	
2	60	F	None	
Normal Controls				
1	69	F	None	
2	64	F	None	
3	64	F	None	
4	68	F	None	
5	59	M	None	

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Teprotumumab-Related Adverse Events in Thyroid Eye Disease: A Multi-Center Study

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Disclosure of interests
Dr. Andrea Kossler is a Consultant/Advisor for Horizon Therapeutics, Immunovant Inc., Amgen, Kriya Therapeutics, Viridian Rx, and Argenx and performs research with Sling Therapeutics, Viridian Therapeutics, Lucerne Therapeutics, and ViroBeta. Dr. Raymond Douglas is the Chief Executive Officer of Sling and is a Consultant/Advisor for Horizon Therapeutics, Immunovant, Corporation, and Viridian Corporation. Dr. Sara Wester is a Consultant/Advisor for Horizon Therapeutics, Immunovant, and Shire. Dr. César Briceño is a Consultant/Advisor for Horizon Therapeutics. Dr. Madhura Tamhankar is a Consultant/Advisor for Horizon Therapeutics. Dr. Chrysoula Dosiou is a member of Sling Therapeutics Scientific Advisory Board and has received an Unrestricted Gift Third Rock Ventures and The Orphan Group. Dr. Kimberly Cockerham is a Consultant/Advisor for Horizon Therapeutics and Viridian Pharmaceuticals. Dr. Andrea Harrison is a Consultant/Speaker for Horizon therapeutics and BVI pharmaceuticals. Dr. Julia Kang is a speaker for Horizon Therapeutics. Shreya Shah, Dr. Linus Amarikwa, Dr. Connie Sears, Dr. Kevin Clouse, and Dr. Raneem Rajjoub have no disclosures.

Conflict of Interest
All authors have completed and submitted the ICMJE disclosures form. Author MB has no financial interests to disclose or conflicts of interest in the submitted work.

Meeting presentation: This study was presented as a paper presentation at the American Academy of Ophthalmology Annual Meeting, 2023 in November 13, 2023 in New Orleans.

Online Materials: This study contains additional materials. The following should appear online-only: Supplemental Table 1, Table 2, Figure 1, and Figure 2.

Abstract

Purpose: To assess the duration, incidence, reversibility, and severity of adverse events (AEs) in patients with thyroid eye disease (TED) treated with teprotumumab.

Design: Multi-center retrospective observational cohort study.

Participants: Patients with TED of all stages and activity levels treated with at least 4 infusions of teprotumumab.

Methods: Patients were treated with teprotumumab between February 2020 and December 2022 at 6 tertiary centers. AE method were collected and recorded at each visit. AEs were grouped according to the United States FDA Adverse Event Reporting System.

Main Outcome Measures: Primary outcome measures: AE incidence and onset. Secondary outcome measures: AE severity, reversibility, duration, proptosis response, clinical activity score (CAS) reduction, and Gorman diplopia score (GDS) improvement.

Results: The study evaluated 131 patients. Proptosis improved by 2mm or more in 27% (109/131) of patients with 3.0±2.1mm average proptosis improvement and 3.2 points average CAS reduction. GDS improved by at least one point for 50% (36/72) of patients with baseline diplopia. AEs occurred in 81.7% (107/131) of patients. Patients had a median of 4 AEs. Most patients' AEs were mild (74.0%, 97/131), 28.2% (37/131) moderate, and 8.4% (11/131) severe. Mean interval AE onset was 7.9 weeks after the first infusion. Resolved AEs had a mean duration of 17.6 weeks. Forty-six percent (60/131) of patients had at least 1 persistent AE at last follow-up. Patients had a mean follow-up of 70.7±38.5 weeks after the first infusion. The most common type of AEs was musculoskeletal (58.0%, 76/131), followed by gastrointestinal (48.2%, 63/131), skin (38.2%, 50/131), ear and labyrinth (30.5%, 40/131), nervous system (20.6%, 27/131), metabolic (15.3%, 20/131), and reproductive system (12.2%, 16/131). Sixteen patients (12.2%) discontinued therapy due to AEs including hearing loss (n=4), inflammatory bowel disease flare (n=2), hyperglycemia (n=2), muscle spasms (n=1), and multiple AEs (n=8).

Conclusions: AEs are commonly reported while receiving teprotumumab treatment. Most are mild and reversible; however, serious AEs can occur and may warrant treatment cessation. Treating physicians should inform patients about the AE-risk, properly screen patients prior to treatment, monitor patients closely throughout therapy, and understand how to manage AEs should they develop.

Keywords:
teprotumumab; thyroid eye disease; Graves' ophthalmopathy; adverse events; insulin-like growth factor 1 receptor (IGF-1R); aspirin

Insulin-like growth factor 1 (IGF-1) and its receptor, IGF-1R, play a key role in regulating tissue formation and remodeling in many different tissues throughout the body.[1,2] This interaction triggers a complex signaling cascade within the cell, ultimately leading to increased cell proliferation, differentiation, and survival. The overactivation of the IGF-1 signaling pathway has been implicated in the development and progression of various

diseases, including thyroid eye disease (TED).[3] TED is a potentially sight-threatening and disfiguring autoimmune condition that affects up to 50% of patients with Graves' disease (GD) and 2% of patients with Hashimoto's thyroiditis.[4–6] The insulin-like growth factor 1 receptor (IGF-1R) and the thyrotropin receptor (TSHR), which co-localize and are overexpressed by orbital fibroblasts in TED patients, are thought to be the auto-antigens involved in the pathophysiology of the disease.[3,6]

Inhibition of IGF-1R has long been a target of pharmacologic interest, with phase 1 clinical trials initially investigating its inhibition in sarcomas, non-small cell lung cancer, and diabetic macular edema.[7–12] In 2020, teprotumumab became the first human anti-IGF-1R monoclonal antibody to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of TED based on 2 randomized, placebo-controlled trials (RCTs).[6,13] These studies demonstrated a significant improvement in proptosis (≥ 2mm), clinical activity score (CAS, ≥ 2 points), and Gorman diplopia score (GDS, ≥ 1 level) of improvement in patients with baseline diplopia following treatment with teprotumumab when compared with placebo.[6,13]

The IGF-1R is involved in multiple physiologic processes. IGF-1 has neurotrophic effects on cochlear hair cells and supports synapses.[3,14] It is also key in the development of the cochlear/vestibular ganglion (CVG) as evidenced by sensorineural hearing loss seen in patients with congenital syndromes causing low IGF-1 levels.[15–17] In the gastrointestinal (GI) tract IGF-1 appears to play a crucial role in promoting the growth of the GI mucosa, preventing apoptosis, supporting the barrier function of the GI mucosa, and reducing inflammation.[18] In glucose metabolism, IGF-1 mediates insulin signaling, promotes the uptake of glucose in peripheral tissues, and inhibits gluconeogenesis via growth hormone inhibition.[19] IGF-1 also plays an anabolic and catabolic role in skeletal muscle, and the suppression of IGF-1R has been linked to muscle atrophy which can then lead to muscle wasting and sarcopenia.[20] As IGF-1R is ubiquitous throughout the body, off-target effects of teprotumumab have been an ongoing concern.

The FDA has reported muscle spasms, hearing loss, hyperglycemia, nausea, alopecia, diarrhea, dry skin, dysgeusia, headache, and fatigue as systemic AEs associated with teprotumumab.[3,6] The pooled analysis of AEs from the phase 2 and 3 clinical trials demonstrated that 80% of patients experienced AEs, though only 36% were determined to be teprotumumab-related adverse events (TAEs).[13] The majority of AEs were mild or moderate and most resolved after discontinuation of teprotumumab.[13] Serious AEs (SAEs) were noted in 3% (7/84) of the treatment group, with 4% (3/84) attributed to teprotumumab (inflammatory bowel disease (IBD), infusion reaction, and Hashimoto's encephalopathy).

The RCTs, however, had limited inclusion criteria. The trials excluded patients less than 18 and greater than 75 and 80 years of age in the phase 2 and 3 trials, respectively. Those who had inactive disease (CAS < 4), long-standing disease (>9 months), compressive optic neuropathy in the preceding 6 months, uncontrolled diabetes, a history of orbital radiotherapy, orbital radiation, a cumulative dose of 4g or higher of methylprednisolone, and any treatment with rituximab or tocilizumab were also excluded.[6,8] Patients were required to have good thyroid and glycemic control. Additional exclusion criteria were a

history of a bleeding disorder, history of a malignant condition in the past year, drug or alcohol use disorder in the past 2 years, or an ophthalmic condition that could compromise study results.[6,8] Given the narrow inclusion criteria, the clinical trial data may not be generalizable to the entire population of patients with TED who may be at a higher risk of developing AEs. Lastly, the RCTs provided limited data regarding the assessment, duration, and management of AEs.

This study provides a comprehensive assessment of the real-world incidence of TAEs by assessing TAE duration, severity, and reversibility and providing recommendations for proper patient selection, screening, and monitoring throughout therapy.

Methods

This was a multicenter, retrospective observational cohort study of 153 consecutive patients with TED treated with teprotumumab between February 2020 and October 2022 at six tertiary centers. Sems Clinic treated and followed 45 patients, Bascom Palmer Eye Institute 9, Scheie Eye Institute 14, the University of Minnesota Department of Ophthalmology and Visual Neurosciences 25, Cedars-Sinai Medical Center 41, and Byers Eye Clinic 27. Intravenous teprotumumab infusions, dosed at 10 mg/kg for the initial infusion and 20 mg/kg for subsequent infusions, were given every 3 weeks for a planned total of 8 infusions. Patients were seen at baseline, throughout therapy, and at regular intervals after therapy. A detailed exam, including an evaluation of all current and past AEs, was performed at the discretion of the treating provider. Patients were excluded from the analysis if they completed fewer than 4 infusions or if a detailed AE evaluation was not performed. Each institution varied in its approach to collecting AEs: 15 patients reported AEs via a questionnaire, 68 patients were prompted about AEs, and 69 patients volunteered information. Providers were responsible for assessing if AEs were related to teprotumumab treatment; only TAEs were analyzed in this study.

Charts were queried for demographic data, including age, gender, ethnicity, and past medical history, including concurrent medical issues and medications, smoking history, prior treatment for GD, thyroid status, and prior TED treatment. Thyroid status was classified according to the free T4 (FT4) and total T3 (TT3) into three categories: normal FT4 and TT3, elevated FT4 or TT3, or low FT4. Three measures were used to evaluate treatment outcomes: CAS, proptosis (Hertel exophthalmometry), and GDS.

Primary outcome measures included the incidence and time of onset of each AE. Secondary outcome measures included AE severity, reversibility, and duration. Reduction in CAS, proptosis response, and GDS improvement were also recorded. AEs were defined as any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of teprotumumab. TAEs that occurred after the first infusion and no later than 90 days after the last infusion were evaluated. AEs were grouped according to the United States FDA Adverse Event Reporting System.[21–23] These categories and several of the symptoms that fall within each can be seen in Table 1.

AE severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE).[29] Grade 1 or mild AEs were minimal and did not require intervention. Grade 2 or moderate AEs required minimal, local, or noninvasive intervention. Grade 3 or severe AEs were either disabling or required hospitalization. Hearing impairment was defined as any patient self-reporting partial or complete hearing loss, muffled hearing, or decreased word recognition. The presence of hearing impairment was assessed subjectively and graded using the CTCAE. Hearing impairment was considered severe if a patient required hearing aids and/or the hearing changes were disabling or limited activities of daily living.

Onset and resolution of each AE were recorded as the time in weeks after the first infusion. The AE outcome was recorded as a) resolved, b) persistent or worsening, or c) unknown. Unknown resolution status was defined as outcomes that were either unascertained or when patients were lost to follow-up. Persistent symptoms were defined as those that had not resolved before the end of patient follow-up. Management alterations (no change, concomitant treatment, dose interruption, and drug discontinuation) were also documented. Treatment discontinuation was reported only if patients experienced intolerable AEs.

The study adhered to the tenets of the Declaration of Helsinki. It was performed in accordance with the Health Insurance Portability and Accountability Act and was approved by each site's institutional review board.

Statistics

Statistical analysis and calculation of descriptive statistics were done using SPSS and MATLAB. Descriptive statistics were used to describe demographic data, time intervals, and the number of AEs; the most appropriate summary statistic was chosen given the variable type and distribution of the data. Categorical variables were summarized with percentages. If patients had multiple symptoms within one category, the average onset of those AEs were used in category-specific calculations.

Results

Patient Summary

A total of 131 TED patients with a mean age of 56.3 years (range 15–93 years) were included. Seventy-seven percent (101/131) of patients were female and 22.9% (30/131) were male. Caucasians accounted for 39.7% (52/131) of the study population, followed by Asian and Hispanic patients at 9.9% (13/131) each, and African Americans at 6.1% (8/131). Twenty-five percent (33/131) of patients reported a history of smoking (9 current). At baseline, 52.7% (69/131) of patients were euthyroid, 31.3% (41/131) were hyperthyroid, 6.9% (9/131) were hypothyroid, and 9.1% (12/131) did not report thyroid status. Most patients (91.6%, 120/131) had prior therapy for GD (radioactive iodine, anti-thyroid medications, thyroidectomy) and more than half (52.7%, 71/131) had a history of recalcitrant TED and were previously treated with steroids (30.6%, 40/131), orbital radiation (10.7%, 14/131), orbital decompression (18.3%, 24/131), or biologic therapy (4.6%, 6/131). The most prevalent past medical conditions were diabetes mellitus type 2 (20.6%, 27/131), hypertension (28.2%, 37/131), and malignancy (13%, 17/131). There were no significant

differences in the demographic and clinical characteristics of patients with or without AEs except for hyperthyroidism, which was more prevalent in patients with AEs (Supplemental Table 2).

Treatment outcomes

Over a 33-month period, 131 study patients were treated with teprotumumab. Patients received an average of 7.4 infusions (range 4–8). A total of 101 (77.1%) patients completed the entire course of eight infusions. The mean baseline CAS was 4.1±1.5 (range 1–7) and reduction was 3.2±1.6 and 77% (101/131) of patients had a proptosis response of 2 mm or more in the treatment eye, with a mean reduction of 3.0±2.1 mm. GDS was available for 91 patients, with 79% (72/91) experiencing diplopia at baseline. Of the 72 patients with baseline diplopia, 58% (36/72) experienced an improvement of 1 point or more in GDS. CAS reduction, proptosis, and GDS were all measured at an average follow-up of 38.2±13.6 weeks after the first infusion. AEs were followed for a mean of 70.2±98.5 weeks after the first infusion.

Adverse Events Overview

Of the 131 patients, 81.7% (107/131) experienced at least one TAE. The cohort experienced a combined total of 867 AEs, with each patient experiencing a median number of 4 (1–19) AEs. Eighteen percent (24/131) of patients did not report any AEs, 9.9% (13/131) of patients had only one AE, and 71.8% (94/131) of patients had multiple AEs. The mean interval of AE-onset was 7.9 weeks after the first infusion, with a mean AE-duration of 17.6±17 weeks for the AEs that had resolution during the study period. Most patients experienced mild AEs (74.0%, 97/131), while a smaller proportion experienced moderate (20.2%, 37/131) or severe symptoms (5.4%, 11/131). Thirty-five percent (308/864) of all reported AEs did not resolve in this cohort. Forty-six percent (60/131) of patients (48 women and 12 men) had at least 1 persistent AE at average time of last follow-up after the first infusion (60.0±99.5 weeks). Twelve percent (16/131) discontinued treatment due to AEs and 10.7% (14/131) of patients were lost to follow-up.

AEs reported by more than 5% of patients are listed in Table 1; those experienced by less than 5% are listed in Supplemental Table 3. AE incidence was notably greater in this study compared to the pooled clinical trials (Table 4).[17] Muscle spasms, fatigue, diarrhea, alopecia, nausea, hearing loss, and hyperglycemia were the most prevalent AEs in this cohort, but the probability of remaining AE-free after starting teprotumumab varies slightly between different classes of symptoms. Patients with diarrhea and nausea were the most likely to fully recover, and their symptoms were mostly mild. While hearing loss and hyperglycemia happened more infrequently, those patients were more likely to have severe symptoms (Figure 3). Mild musculoskeletal, gastrointestinal, and skin and subcutaneous AEs affected the most patients (Supplemental Figure 2).

Musculoskeletal (MSK) and Connective Tissue Disorders

Muscle spasms affected 58.0% (76/131) of patients (mean age 55.7 years) during treatment. Forty-six percent (60/131) of patients experienced mild muscle spasms, 11.5% (15/131) had moderate spasms, and 0.8% (1/131) had a severe manifestation. Seventeen

patients received treatment, including vitamin/mineral supplementation (n=4), magnesium (n=2), intravenal fluids (n=1), massage (n=3), muscle relaxants (n=1) and non-steroidal anti-inflammatory drugs (NSAIDs) (n=3). Symptom onset was 7 d weeks after the first infusion. Spasms resolved in 55% (42/76) of patients. In patients with resolution, the mean duration of symptoms was 23.7 weeks. Forty percent (30/76) of patients had persistent spasms at average follow-up of 55.5±41.6 weeks after the first infusion. Resolution status was unknown for 5.3% (4/76) of patients. Six patients discontinued in part due to musculoskeletal AEs.

Gastrointestinal (GI) Disorders

GI disorders affected 38.2% (50/131) of patients (mean age 52.6 years). Diarrhea (27.5%, 36/131) and nausea (13.7%, 18/131) were the two most common GI AEs. Less common symptoms included constipation (3.8%, 5/131), abdominal cramps (0.8%, 1/131), vomiting (1.5%, 2/131), and bloody stools (2.3%, 3/131). Thirty-three percent (45/131) had mild symptoms and 2.3% (3/131) moderate. Two persons (2/131) had severe symptoms, one with nausea and vomiting and another with an IBD flare. Three additional patients received anti-diarrheal medications and 1 also utilized a moisturizer cream for painful bowel movements. The mean symptom onset was 6.1 weeks and 74% (37/50) of these patients reported symptom resolution. Resolved AEs had a mean duration of 16.2 weeks. Twenty-two percent (11/50) had persistent symptoms at average follow-up of 44.6±42.6 weeks. Resolution status was unknown for 4.0% (2/50) of patients. Four patients discontinued leproturumab, at least in part, due to leproturumab-related GI AEs, 2 of whom experienced IBD flares. Of note, 1 additional patient with a history of IBD did not experience GI symptoms during treatment.

Skin and Subcutaneous Tissue Disorders

Thirty-nine percent (50/131) of patients (mean age 55.9 years) experienced at least one or more skin disorders. Twenty-seven percent (35/131) had alopecia, 8.4% (11/131) dry skin, 7.6% (10/131) onycholysis, and 7.6% (10/131) skin rash. Thirty-five percent (46/131) of patients experienced mild skin AEs and 3.1% (4/131) moderate AEs. Four patients were treated with topical creams (n=2), hydrocortisone + diphenhydramine cream (n=1), and diphenhydramine (n=1). The mean onset was 10.7 weeks after the first infusion and 45% (22/51) of these patients had complete resolution. Resolved AEs had a mean duration of 23.0 weeks. Fifty-two percent (26/50) had persistent findings at average follow-up of 70.5±42.1 weeks. Resolution status was unknown for 4.0% (2/50) of patients.

Ear and Labyrinth Disorders

Thirty-one percent (40/131) of patients (mean age 56.2 years) experienced at least one otologic AE. Ten of these patients had a prior history of subjective hearing impairment; of the 12 patients with baseline audiograms, 7 demonstrated baseline hearing impairment. Nineteen had a recent history of ototoxic drug use, including NSAIDs (n=11), serotonin and norepinephrine reuptake inhibitors (n=2), vancomycin (n=1), diuretics (n=5) and aspirin (n=1). During treatment, 13.7% (18/131) of patients reported new or worsening hearing impairment, of which 8 were confirmed by audiogram. Thirteen percent (17/131) also experienced ear fullness, 12.2% (16/131) tinnitus, 6.9% (9/131) autophony, and 3.8% (5/131) otalgia. Twenty-three percent of (30/131) of symptoms were mild, 0.8% (1/131) moderate, and 0.8% (1/131) severe. Hearing aids were recommended for 8 patients with severe hearing impairment at the discretion of the audiologist. Two patients were treated with a topical vitamin supplement ear drop for ear plugging and 1 with systemic steroids for hearing impairment. The mean symptom onset was 9.1 weeks and 53% (21/40) of patients had complete resolution of otologic symptoms. Resolved AEs had a mean duration of 23.5 weeks. Forty percent (16/40) had persistent otologic symptoms at average time of last follow-up (60.8±61.3 weeks). Resolution status was unknown for 3 (2.3%). When specifically evaluating subjective hearing impairment, 59% (9/18) of patients had persistent symptoms at average follow-up of 81.1±58.4 weeks, including 4 of the 6 patients that discontinued treatment, at least in part due to otologic AEs. Two patients interrupted treatment due to hearing impairment but later completed the full course. Of note, 2 additional patients with baseline hearing impairment confirmed via audiogram did not experience hearing changes with leproturumab.

Nervous System Disorders

Neurologic disorders occurred in 20.6% (27/131) of patients (mean age 53.5 years). Eleven percent (15/131) of patients experienced headaches and 8.4% (11/131) dysgeusia. Most nervous system AEs were mild (19.1%, 25/131) and 0.8% (1/131) moderate. One patient (1/131) had a severe syncopal event. Most neurologic AEs (85.2%, 23/27) did not require management, and one required concomitant therapy with acetaminophen for a mild headache. The mean onset of nervous system AEs was 9.1 weeks and resolved in 66.7% (18/27) of patients. Resolved AEs had a mean duration of 15.3 weeks. Neurological AEs were persistent in 33.3% (9/27) of patients at average follow-up of 68.6±48.9 weeks.

Metabolism and Nutrition

Fifteen percent (20/131) of patients (mean age of 56.3 years) had metabolism or nutrition-related AEs. Hyperglycemic events were the most common (10.7%, 14/131). Ten patients had a history of type II diabetes mellitus. Decreased appetite affected 2.3% (3/131) and weight loss 2.3% (3/131) of patients. Eight percent (11/131) had mild AEs, 6.1% (8/131) moderate, and 0.8% (1/131) had a severe hyperglycemic event. The mean onset of metabolic AEs was 5.2 weeks and 65% (13/20) of patients had AE resolution. Resolved AEs had a mean duration of 22.7 weeks. Thirty-five percent (7/20) had persistent AEs at average follow-up of 74.9±48.0 weeks. Five patients discontinued in part due to metabolic AEs.

Reproductive System Disorders

Reproductive AEs occurred in 12.2% (16/131) of patients (15 females and 1 male) with a mean age of 39.6 years. Eleven percent (14/131) of patients reported amenorrhea, 0.8% (1/131) vaginal dryness, and 0.8% (1/131) erectile dysfunction. All cases of menstrual irregularity were mild (10.0%, 13/131) or moderate (0.8%, 1/131). Most patients did not require management; only 1 with amenorrhea was treated with concomitant oral contraceptives and the 1 case of erectile dysfunction was treated with tadalafil. The mean onset of reproductive AEs was 9.8 weeks after first infusion and resolved in 57.5% (9/16) of patients. Resolved AEs lasted on average for 25.3 weeks. Reproductive AEs remained persistent in 62.5% (10/16) at average follow-up of 55.6±50.2 weeks.

Adverse Event-Related Teprotumumab Discontinuation

Sixteen (12.2%) patients (13 women and 3 men), mean age of 60 years (45–93), permanently discontinued teprotumumab infusions due to AEs. This subgroup completed a mean number of 5.2 infusions (range 4–7) and an average baseline CAS of 3.6 with an average reduction of 2.8. Of these patients, 4 had isolated ear and labyrinth AEs, 2 isolated GI AEs, 1 an isolated metabolic AE, 1 an isolated musculoskeletal AE, and 8 a combination of AEs. Seven patients experienced severe AEs, 7 experienced moderate AEs, and 2 mild AEs.

Six patients, all female, discontinued teprotumumab due to otologic AEs (including hearing impairment, autophony, ear plugging, and tinnitus): 4 (ages 64, 65, 78, and 82) solely due to these symptoms and 2 (ages 68 and 84) due to hearing impairment and several other AEs. Three of these 6 patients had a history of otologic pathology (age-related hearing impairment, amiodarone, and ototoxicity) and 1 had a history of smoking.[37] Five of these 6 patients had baseline audiometry testing: 2 had severe baseline hearing impairment (1 had hearing loss secondary to trauma and Meniere disease), 2 had mild baseline hearing impairment in a single ear, and 1 had normal hearing. Five patients demonstrated sensorineural hearing loss on post-treatment audiometry testing; 2 of these patients also developed patulous eustachian tube dysfunction. Five stopped teprotumumab after failure to recover hearing despite a pause in treatment, and the sixth primarily due to her concurrent AEs. Three patients began using hearing aids, one returned hearing aids, one was monitored closely by audiology without treatment. Hearing impairment persisted at last follow-up for 4 of these 6 patients. 1 patient self-reported that her hearing returned to baseline after discontinuation and 1 demonstrated return to baseline hearing status per an audiogram 31 weeks after her last infusion.

Two female patients, ages 45 and 76, discontinued due to new-onset IBD flares. Neither patient had a history of smoking, recent hormone therapy, infectious gastroenteritis, or a history of GI disorders. The 45-year-old patient had a family history of IBD in one first degree and one second-degree relative. She was hospitalized for bloody diarrhea and fecal urgency after her fifth infusion. She was diagnosed with ulcerative colitis and treated with infliximab, prednisone, methotrexate, mesalamine, pantoprazole, and budesonide. She discontinued teprotumumab after the 7th infusion due to worsening symptoms.[38,39] The 76-year-old patient presented with a moderate IBD flare after her first teprotumumab infusion. She was co-managed with a GI specialist and treated with hydroxamic and budesonide. She discontinued treatment after the 7th infusion due to her AEs and lack of a robust response; her GI symptoms resolved slowly after.

Five patients, 1 with a history of pre-diabetes and 3 with Type II diabetes, discontinued treatment due to metabolic symptoms; 1 solely due to hyperglycemia and 3 due to hyperglycemia as well as other symptoms. The first patient was a 55-year-old male with a history of pre-diabetes. He developed elevated blood sugars after his first infusion, treated with metformin. He discontinued teprotumumab due to hyperglycemia and poor response to therapy. All four patients' worsening hyperglycemia resolved after discontinuation.

Four patients discontinued due to muscle spasms. A 67-year-old female discontinued teprotumumab after the fifth infusion due to mild but intolerable muscle spasms. These

subjects discontinued due to muscle spasms and other symptoms. All muscle spasm symptoms resolved after discontinuation.

Eight patients discontinued teprotumumab treatment due to multiple causes. An 84-year-old female developed hearing loss and severe hyponatremia. She also developed depression-related cognitive dysfunction and hyperglycemia leading to treatment cessation after the fourth infusion. A 69-year-old female with mild baseline hearing loss developed hearing decline during treatment; she also developed an ear infection, dry eye, and poorly controlled hyperglycemia that led to discontinuation after the fourth infusion. A 76-year-old female with a history of Type II diabetes, hypertension, and hyperlipidemia developed hyperglycemia, hair loss, fatigue, hypertension, and pruritus that led to discontinuation after 6 infusions. A 56-year-old male with Type II diabetes mellitus developed poorly controlled hyperglycemia, urinary insufficiency, muscle spasms, fatigue, and mild changes. He discontinued after the fourth infusion and symptoms resolved shortly thereafter. A 77-year-old female presented to the ED after the fifth infusion for severe vomiting, nausea, anxiety, and worsening of already severe muscle spasms. She was treated with calcium citrate 950 mg BID for the spasms but discontinued teprotumumab after the sixth infusion. All symptoms resolved after teprotumumab was discontinued. A 54-year-old male developed moderate muscle spasms, diarrhea, and nausea treated with ondansetron. Though CAS decreased by 2, he had no objective improvement in proptosis and there was no change in diplopia. His AEs, coupled with a poor response to treatment, led to discontinuation of teprotumumab after the fifth infusion. A 70-year-old female with baseline anxiety developed severe panic attacks that required treatment with alprazolam after two infusions. Though she also experienced mild muscle spasms, her psychiatric symptoms were the main cause for discontinuation after the fourth infusion. Her anxiety improved after stopping treatment. Finally, a 97-year-old female found her mild muscle spasms and fatigue intolerable and discontinued after the fourth infusion.

Discussion

Targeted therapies, including teprotumumab, have changed the treatment landscape for many ocular and orbital inflammatory diseases. This trend is expected to increase as several investigational drugs are being studied for the treatment of TED.[7] Therefore, it is important to familiarize ourselves with the AE profile of targeted therapies to safely treat patients. Two pivotal RCTs reported TAEs in 47 of 84 patients treated with teprotumumab; however, these studies reflect data from a carefully selected population that may not be representative of the patients receiving teprotumumab in clinical practice.[9,10,13] Recent case reports and case series have highlighted AAEs with teprotumumab use; however, reports thus far include small numbers with limited follow-up.[38–42] Large studies reflecting data after the FDA's approval of teprotumumab are lacking. This study is the first field analysis of AEs in the largest cohort of teprotumumab-treated patients to date.

This study population included patients treated with teprotumumab for TED without exclusion due to disease activity, chronicity, severity, past medical history, prior therapies, glycemic status, or thyroid function status. Additionally, the follow-up timepoints, patient compliance, and AE reporting were representative of typical practice and differed

significantly from the carefully designed RCT setting. Yet, the treatment outcomes demonstrated similar reductions in progress and the CAS when compared to the clinical trials. This is consistent with post-approval studies demonstrating that tepromumumab is effective for the treatment of both active and chronic moderate-to-severe disease.[33,34]

In this study, over 80% of patients treated with tepromumumab for TED experienced at least one TAE, and the majority of patients experienced 4 or more TAEs. While most AEs were mild, 28.2% were moderate and 8.4% were severe. Almost half of these patients were reported to have at least one persistent AE at average follow up of 70.2±18.5 weeks after the first infusion. Of the 463 AEs collectively experienced by this cohort, muscle spasms, alopecia, fatigue, and hearing loss make up most of the 169 persistent AEs. Twelve percent of patients discontinued tepromumumab treatment due to AEs, mainly related to hearing loss, IBD and hyperglycemia.

When comparing this cohort's AE profile to the clinical trials, we found more TAEs (81.7% vs. 56%), more tepromumumab-related SAE's (7.6% vs. 4%), and more individual AEs in each AE category. These results also demonstrate more persistent AEs at 90-week follow-up (45.8% vs. 20%) compared to a 72-week follow up study of the pooled AE's from the clinical trials.[11] Notably, this study did not include a placebo arm, however, the clinical trials demonstrated that 20% of patients in the placebo arm experienced AEs and 1% experienced a SAE.[11] The increased frequency of AEs in this study can be explained by the differences in the patient populations being studied and differences in AE data gathering and reporting. Yet, this cohort represents 6 tertiary centers across the US, therefore, these results may be more generalizable to providers treating patients with TED.

This study found similar rates of IBD flares and hyperglycemia in tepromumumab-treated patients compared to the clinical trials, however, the clinical trials found that both AEs were associated with a history of pre-existing IBD and diabetes, respectively. The FDA warning label cautions against exacerbation of preexisting IBD; however, 2 patients in this cohort experienced new-onset IBD symptoms during treatment with tepromumumab and both discontinued therapy.[35] Neither patient had a history of IBD, demonstrating that patients without preexisting IBD are also at risk. Of note, the single patient in this cohort with a noted history of IBD did not develop an IBD flare throughout treatment. Similarly, at least one of the patients that developed hyperglycemia and then diabetes during tepromumumab therapy did not have a history of diabetes. Eleven percent of patients in this study experienced hyperglycemia and 3% had persistent hyperglycemia at last follow-up. However, the incidence of hyperglycemia was likely underestimated in this study as hyperglycemia was primarily assessed via a review of HbA1c and blood glucose levels which were not uniformly assessed in all patients. Only 46 patients received a pretreatment HbA1c. One observational study evaluated hyperglycemic changes in a cohort of 40 patients treated with tepromumumab and found that 52% of patients experienced clinically significant hyperglycemia, this included patients with normoglycemia, prediabetes, and diabetes.[17] This underscores the importance of baseline glycemic status testing and monitoring throughout therapy in all patients.

One third of patients in this cohort experienced audiologic symptoms or hearing impairment, higher than the 20% seen in the RCTs (Table 4). Half of the patients with hearing impairment (partial or complete hearing loss, muffled hearing, or decreased word recognition) had persistent subjective hearing loss at last follow-up, and a third of patients with hearing impairment discontinued treatment at least in part due to hearing loss. The differences in audiologic findings may be, in part, explained by demographic differences like age. The mean age of patients with hearing impairment was 65.3 years in this study versus 50.5 years in the treatment arm of the RCTs. Other notable risk factors such as pre-existing hearing loss and prior ototoxic medication use were not reported in the RCTs. Additionally, the variation in AE assessment likely influenced reporting. A prospective observational study of 27 patients found that 81.5% of patients treated with tepromumumab complained of at least one audiologic symptom when questioned, and 40.7% experienced hearing impairment.[32] The study found that patients with a history of baseline hearing loss are at higher risk for hearing loss with tepromumumab and recommends baseline audiometric testing in all patients before starting tepromumumab treatment with repeat testing during and after treatment.[32] Risk of ototoxic, and possibly permanent, hearing impairment was added to the FDA warning label in July 2023.[35]

This study has several limitations. First, the method of assessment, follow-up timepoints, data collection, and outside medical record evaluation varied at each institution. While this may have led to variability in AE reporting, this study is reflective of the diversity in disease presentation, monitoring, and treatment across the country. Second, the AEs may be over- or under-reported. The clinical trials reported the most common AEs which, if prompted by the treating physician or known by the patient, could have resulted in over-reporting of such AEs. There is also no placebo arm in this study and the determination of a TAE was often subjective and at the discretion of the treating provider, potentially leading to TAE over-reporting. AE under-reporting could have occurred due to several reasons. Patients who received less than four infusions of tepromumumab were excluded from this study; they may have discontinued therapy early due to AEs. AEs may have been missed due to the retrospective nature of the study and the method of review of systems data collection by ophthalmologists. If a patient reported an AE to an outside ER, physician, or hospital and did not report it to the treating ophthalmologist then the AE may not have been included in this study. Furthermore, not all patients underwent the same screening tests. For example, audiograms were not ordered for each patient, therefore, some may not have noticed or reported hearing loss symptoms. Third, the timing of AEs was not precise and often an estimate as dates depended on patient memory, leading to recall bias. Finally, there was no consensus on the screening, monitoring, and management of TAEs; therefore, the rates and duration of AEs may differ between groups.

The authors recommend providers utilize a standardized questionnaire (Supplemental Figure 3) to better understand and report TAEs. Further investigation into TAEs is warranted to improve patient safety. While our study predominantly observed AEs experienced by over 5% of participants, less common AEs, such as psychiatric symptoms, require investigation. Additionally, the potential additive effect of tepromumumab overtreatment in steroid patients is still unknown. Finally, studies are needed to risk stratify based on subgroups, such as age, gender, comorbidities, and treatment duration.

Prescribing physicians should work closely with patients' PCP or endocrinologist during teprotumumab therapy to monitor thyroid function tests every 4–6 weeks and adjust thyroid related medications to maintain euthyroidism, as dysthyroidism is a known risk factor for TED progression.[35–37] Furthermore, patients with hyperthyroidism had an increased likelihood of developing AEs in this study. Importantly, all patients should be screened for hearing loss, IBD, and glycemic status prior to therapy. If risk factors are present, patients should be co-managed with the appropriate specialists. To mitigate AE risk, all patients should undergo the following baseline screening tests: thyroid function tests, HbA1C, and audiometric testing. Additional testing may be warranted based on each patient's unique past medical history. The authors recommend pregnancy testing (when applicable) and blood sugar testing prior to each infusion, repeat HbA1C every 12 weeks during treatment, and repeat audiometry testing should cochlear symptoms develop or for at risk patients. Audiometry should also be repeated after treatment cessation. Any patient who develops bloody stools or intractable diarrhea should be referred to gastroenterology for co-management of GI AEs. Treatment delay or cessation may be necessary for work-up or concern of a potential SAE. Finally, teprotumumab should be strictly avoided in pregnant women and should not be used in growing children. Patients of child-bearing potential should be counseled on use appropriate forms of contraception prior to teprotumumab therapy, during treatment, and for 6 months following therapy, and they should be advised of the risk of prolonged amenorrhea with teprotumumab therapy. Studies confirm that IGF-1 has a role in growth hormone signaling and can alter fetal development resulting in intrauterine growth restriction and other congenital disabilities.[38–40]

In conclusion, our results confirm that teprotumumab is effective for the treatment of moderate-to-severe TED; however, AEs are common and, rarely, can be serious. To safely manage patients, prescribing physicians should properly educate patients regarding the risks of therapy, carefully screen and select patients for therapy, monitor patients closely, and understand how to manage AEs in collaboration with a multi-disciplinary team. Should significant AEs occur, providers should consider holding teprotumumab to allow for proper management. SAEs may warrant discontinuation of therapy. Additional studies are needed to better understand which patients are at risk for serious TAEs, the reversibility of TAEs, and the risk benefit ratio for patients with mild or chronic forms of TED.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms:

AE	Adverse event
TED	Thyroid eye disease
IBD	Inflammatory bowel disease
GD	Graves' disease
IGF-1	Insulin-like growth factor I
IGF-1R	Insulin-like growth factor I receptor
FDA	U.S. Food and Drug Administration
RCTs	Randomized controlled trials
CAS	Clinical activity score
GDS	Gorman diplopia score
CTCAE	Common Terminology Criteria for Adverse Events
CVG	Cochleovestibular ganglion
GI	Gastrointestinal
TAE	Teprotumumab-related adverse event
SAE	Serious adverse event
FT4	Free T4
TT3	Total T3
dB HL	Decibels hearing level
NSAIDs	Non-steroidal anti-inflammatory drugs
UC	Ulcerative colitis
PCP	Primary care physician

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A multicenter study of 131 teprotumumab-treated patients found over 80% of experienced teprotumumab-related adverse events, with 12% discontinuing treatment mainly due to hearing loss, inflammatory bowel disease, and hyperglycemia. Understanding teprotumumab's safety profile is critical.

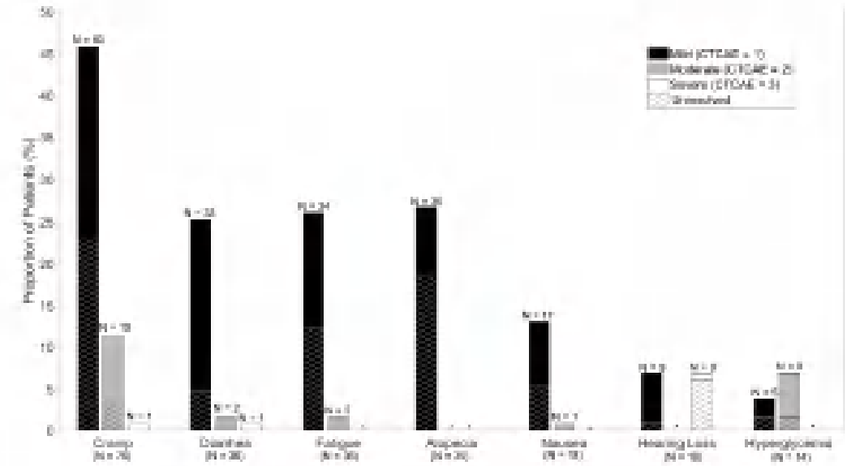

Figure 1:
Resolution status of the most common adverse events were stratified by severity. The incidence of each adverse event is reported as a number under each adverse event on the x-axis. The solid bar indicates the proportion of adverse events in each category that were resolved, and the slashed bar indicates adverse events that were persistent. The black, gray, and white shades indicate adverse events that were graded as mild, moderate, and severe according to the Common Terminology Criteria for Adverse Events.

Table 1:

Adverse events that occurred in more than 5% of patients

		Number of Patients (%)	Mean Onset after 1st Infusion (weeks)	Mean Duration of Resolved AEs (weeks)	Percent Resolved
Musculoskeletal	Muscle Cramps	78 (28)	7	23.7	55.30%
Gastrointestinal	Diarrhea	36 (25.4)			80.50%
	Nausea	18 (13.7)			55.50%
	All GI Disorders	**89 (48.2)**	**6.1**	**19.2**	**74.00%**
Ear And Labyrinth	Hearing Impairment	18 (13.7)			50.00%
	Tinnitus	16 (12.2)			68.80%
	Amophony	9 (6.9)			55.50%
	Ear Fullness	17 (13)			41.20%
	All Ear Disorders	**40 (30.8)**	**9.1**	**23.5**	**52.50%**
Skin	Alopecia	38 (26.7)			26.60%
	Onycholysis	10 (7.6)			20.00%
	Dry Skin	11 (18.4)			54.50%
	Skin Rash	10 (7.6)			100.00%
	All Skin Disorders	**50 (36.2)**	**10.7**	**23.9**	**44.00%**
General	Fatigue	36 (30.5)	38	14.5	55.60%
Reproductive System and Breast	Menstrual Irregularity	16 12.2)	6.8	25.3	37.50%
Nervous System	Headache	15 (11.5)			73.30%
	Dysgeusia	11 (8.4)			36.30%
	All Nervous System Disorders	**27 (20.6)**	**8.1**	**18.3**	**66.70%**
Metabolism And Nutrition	Hyperglycemia	14 (10.6)	1.8	23.6	71.40%

Table 4:

A comparison of the incidence of AEs in the RCTs with AEs in this study.

	Our Data		Clinical Trial Data: Teprotumumab-Related[a,b]	
Adverse Event	**Affected Patients**	**Percent**	**Affected Patients**	**Percent**
Any AE	107	82%	47	56%
Muscle Spasm	26	20%	16	19%
Fatigue	36	27%	3	4%
Diarrhea	36	27%	7	8%
Alopecia	38	27%	8	10%
Nausea	18	14%	8	10%
Nails	24	18%	37	44%
Hearing Change	40	31%	4	5%
Headache	15	11%	5	6%
Menstrual	14	11%	4	10%[c]
Dysgeusia	11	8%	4	5%
Hyperglycemia	14	11%	7	8%
Skin Rash	10	8%	3	4%
Dry Skin	11	8%	4	5%
Onycholysis	10	8%	4	5%
AEs resulting in discontinuation of treatment[d]	16	12.2%	3	4%

[a]Probably or possibly related to teprotumumab as assessed by investigator.

[b]Source: Kahaly et. Al. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. Lancet Diabetes Endocrinol. 2021.

[c]Only reported in Phase II clinical trial, 4/32 patients with reproductive AEs.

[d]Hearing impairment, IBD, hyperglycemia, and severe muscle cramps and nausea led to discontinuation in our study cohort. IBD, infusion reaction, and Hashimoto's encephalopathy led to discontinuation in the clinical trials.

REVIEW

Profile of Xeomin® (incobotulinumtoxinA) for the treatment of blepharospasm

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Abstract: Even though conventional botulinum neurotoxin (BoNT) products have shown successful treatment results in patients with benign blepharospasm (BEB), up to date, potential long-term side effect of BoNT such as the development of immunologic resistance due to the production of neutralizing antibody to the neurotoxin after repeated injections. Xeomin® (incobotulinumtoxinA), a purified botulinum neurotoxin type A (BoNT/A) drug free from complexing proteins otherwise contained in all conventional BoNT/A drugs, was recently approved by US Food and Drug Administration for the treatment of cervical dystonia or blepharospasm in adults. The newly approved BoNT/A drug may overcome the limitation of previous conventional products since it contains pure neurotoxin (150 kDa) through a manufacturing process that separates it from complexing proteins such as hemagglutinins possessing immunogenicity. Clinical efficacy between Xeomin® and conventional BoNT/A drugs are assumed to confirm the new immunogenicity of Xeomin®.

Keywords: blepharospasm, botulinum neurotoxin type A, Xeomin®, incobotulinumtoxinA, complexing proteins, immunology, antibodies

Introduction

Blepharospasm is a localized form of dystonia consisting of involuntary tonic and spasmodic contractions of the orbicularis oculi, corrugator supercilii, and procerus muscles, leading to partial or complete closure of the eyelids. These contractions may be intense and last from several seconds to a few minutes.[1]

It is a bilateral condition with time rather than clonic spasms, which develops typically between 50 and 70 years of age. Women appear to be more affected than men. The exact cause remains unknown, but may result from damage to areas of the basal ganglia including the superior colliculus, pars reticularis of the substantia nigra, and nucleus raphe magnus. The most common form is called benign essential blepharospasm (BEB), which is restricted to the orbicipetal area.[2] Botulinum toxin (BoNT) treatments were first used to treat strabismus in 1977 by Alan Scott, a pediatric ophthalmologist,[3] and subsequently used to treat blepharospasm in the early 1980s by Elston et al[4] and Scott et al.[5] BoNT is highly effective and well tolerated in the symptomatic treatment of a very broad range of conditions involving either muscle hyperactivity such as blepharospasm or cervical dystonia, or cholinergic hyperactivity

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such as hyperhidrosis or hypersalivation.[6] Recently, BoNT has been approved for the treatment of glabellar rhytids and migraine headaches.[7]

BoNTs act on the peripheral nervous system where they inhibit acetylcholine exocytosis at the motor endplate within the neuromuscular junction by inhibition or proteolytic cleavage of different proteins of the acetylcholine release apparatus. Specific N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) proteins. Botulinum toxin type A (BoNT/A) hydrolyzes SNAP-25 (synaptosomal-associated protein 25) which is located on the presynaptic cell membrane whereas type B (BoNT/B) acts on synaptobrevin or VAMP (vesicle-associated membrane protein) which is embedded in the acetylcholine vesicle membrane. By cleaving these target proteins, BoNT prevents the fusion of the synaptic vesicle with the presynaptic membrane thereby blocking the release of acetylcholine in the synaptic cleft. Between 4 hours' (about 1700 kDa) and 6 hours' (about 900 kDa) maximum, only the light chain is responsible for the pharmacological action of BoNT.[8]

Botulinum toxin A (botulinum neurotoxin A) is among seven immunologically distinct serotypes of botulinum toxin, all of which are pharmacologically active in that it binds to receptors and gangliosides on the presynaptic cholinergic nerve terminal, is internalized, and cleaves one of three proteins involved in docking, fusion, and release of acetylcholine from vesicles in the presynaptic cholinergic nerve terminal. Botulinum toxin type A and type B

In August 2010 the US Food and Drug Administration (FDA) approved Xeomin® (incobotulinumtoxinA; Merz Pharmaceuticals GmbH, Frankfurt, Germany) for the treatment of cervical dystonia or blepharospasm in adults (Table 1). New Xeomin® is the fourth BoNT product available for the US market, following Botox® (onabotulinumtoxinA;

Figure 1 Xeomin® (incobotulinumtoxinA) 50 U and 100 U vials.

Allergan Inc, Irvine, CA), Dysport® (abobotulinumtoxinA; Ipsen Ltd, Slough, Berks, UK), and Myobloc® (rimabotulinumtoxinB; Solstice Neurosciences Inc, Malvern, PA).[9] With this recent entry, 3 type A and 1 type B brands of botulinum neurotoxin are available – that is, 4 in total (Table 1).

The most long-term side effect of BoNT use is the development of immunologic resistance due to the production of neutralizing antibody to the neurotoxin after repeated injections. The frequency of this complication reported by several authors is around 3% to 10%.[10] The newly approved BoNT/A drug may overcome this limitation of the other 7 previous products since Xeomin® contains only the pure neurotoxin (150 kDa) through a manufacturing process that separates it from complexing proteins such as hemagglutinins (HA) and other proteins of the hemagglutinin complex produced by fermentation of *C. botulinum*.[11]

Xeomin®: BoNT/A preparation free of complexing proteins

Xeomin® was first introduced in Germany in early 2005.[12] It received approval for the treatment of blepharospasm and cervical dystonia in a number of European countries and then Argentina and Canada. For the treatment of blepharospasm, cervical dystonia, and poststroke upper-limb spasticity, and now in the US for cervical dystonia and blepharospasm. The FDA's approval of Xeomin® for the treatment of blepharospasm marked the drug as adult patients previously treated with Botox®. Therapy with the newer BoNT/A product should be based on the previous dose, number, and location of Botox® treatments. Regardless of whether the patient has cervical dystonia or blepharospasm, the treatment intervals should occur no more frequently than every 12 weeks. Xeomin® is supplied in single use vials containing 50 or 100 units of lyophilized incobotulinumtoxinA, which do not require refrigeration before use.[13]

In all clinically available serotypes of botulinum toxin (types A–G), the active neurotoxin (150 kDa; 150 kDa of a heavy chain and 50 kDa of a light chain) is noncovalently associated with a set of nontoxic and nontoxic complexing proteins (hemagglutinins (HA) and nonhemagglutinins (NHA)) and thus forms high molecular mass complexes.[8,9,14] The molecular weight of the toxin complex ranges between 296 and 900 kDa, depending on the serotype.[15] All serotypes of BoNT drugs, including Botox® and Dysport®, contain these nontoxic and nontoxic complexing proteins in addition to the neurotoxin (Figure 2).[16] This new preparation, Xeomin®, is derived from a wild type strain of *C. botulinum* type A

Table 1 Properties of different botulinum toxin preparations

Brand name	Botox®	Dysport®	Xeomin®	Myobloc® (Neurobloc™)
Generic name	OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA	RimabotulinumtoxinB
Manufacturer	Allergan, Inc. (USA)	Ipsen Ltd. (UK)	Merz Pharmaceuticals GmbH (Germany)	Solstice Neurosciences Inc. (USA)
Serotype	A	A	A1	B
Target SNARE	SNAP-25	SNAP-25	SNAP-25	VAMP (synaptobrevin)
Packaging (units/vial)	100	500	50, 100	2500 (0.5 mL), 5000 (1 mL), 10,000 (2 mL)
Pharmaceutical preparation	Powder	Powder	Powder	Ready-to-use solution (5000 U/mL)
Stabilization	Vacuum dried	Freeze dried	Vacuum dried	pH stabilization
Complexing proteins (kDa)	900	300–900	150	700
Complexing proteins	O	O	X	O
Excipients (per vial)	0.5 mg human serum albumin, 0.9 mg NaCl	125 μg human serum albumin, 2.5 mg lactose	100 μg human serum albumin, 1 mg sucrose (saccharose)	1.65 mg human serum albumin, 0.31 mg NaCl, 0.1 M H_2O, hydrochloric acid
Biological activity (units in pharm.)*	1	1/3	1	1/40
Specific activity (units/ng)	20	40	167	75–125
Storage of packaged product	2 °C–8 °C	2 °C–8 °C	Room temperature	2 °C–8 °C
Shelf life	36 months	24 months	18–48 months	24 months
Half of commercialized preparations	7.4	7.4	1.4	5.8
Storage once reconstituted	2 °C–8 °C for 24 hours	2 °C–8 °C for several hours – 4 hours if stored at room temperature	2 °C–8 °C for 24 hours	For 6 hrs (max.)

Notes: *Myobloc® is not a brand name in Canada, the United States, and Korea. Neurobloc® is the brand name in the European Union, Norway, and Iceland.
Abbreviations: HSA, human serum albumin; VAMP, vesicle associated membrane protein.

(ATCC 3502) which is the same strain from which Botox® is derived and thus has similar biologic activity to Botox®.[1,2,10] Unlike Botox® it contains only the active neurotoxin molecule with complexing proteins removed through a manufacturing process for removal of all clostridial contaminants.[11,12]

Clinical functions of complexing proteins

The function of the nontoxic portions of the protein complexes in BoNT/A preparations has been studied. It was initially thought that these proteins protected the native neurotoxin from destruction in the gastrointestinal tract with oral ingestion (its natural route of entry).[13,14] This was subsequently confirmed in biochemical analysis (protease resistance) of different toxin serotypes.[15] Others have suggested that complexing proteins may have a role in the uptake and transcytosis of botulinum toxin through the intestinal epithelium to reach and affect muscle.[16,17] Xeomin® does not have complexing proteins to protect it from the low pH and gastric enzymes and therefore should pose one hypothesis for safety and toxicity.[18] However, in the therapeutic setting these proteins are not relevant to clinical efficacy.

Another consideration is that complexing proteins may in fact limit botulinum toxin diffusion from the injection site and thereby minimize adverse events, due to the large size of the toxin complex.[19,20] The smaller size of Xeomin® might more rapidly and easily diffuse away from the target tissue into adjacent tissues and produce an adverse effect profile different from other BoNT/A drugs. However, an in vivo study using Botox®, Dysport®, and a purified preparation of BoNT/A (150 kDa) showed that diffusion from the injection site does not differ between the 3 preparations.[21] Another study using ^{125}I-labeled botulinum toxin type A showed no difference in the diffusion of the toxin complexed form of BoNT/A after injection into the muscle, even when using high doses.[22] Comparing the adverse effect profile of conventional BoNT/A drugs and complexing proteins-free BoNT/A drug, Xeomin® did not reveal any of these differences.[23,24,25] These findings can be explained by a dissociation of the complex consisting of neurotoxin and complexing proteins immediately after injection.[26] At physiologic pH values the active 150 kDa neurotoxin is efficiently released in less than 1 minute from the 900 kDa complex.[26] This is in contrast with the earlier time of its therapeutic effect, which is mea-

Figure 2 Components of botulinum toxin preparations.
Abbreviations: HA, hemagglutinin; NHA, non-hemagglutinin.

sured in days. Therefore, complexing proteins do not seem to be essential for safety or efficacy of the 900 kDa toxin complex at physiologic pH or for limiting diffusion of the 150 kDa neurotoxin after injection of conventional BoNT/A preparations.[27]

Another possible function of complexing proteins in a therapeutic setting could be to enhance the stability of the botulinum toxin drug during storage before use. However, a series of in vitro studies (often experiments of Xeomin® do not support this hypothesis. The stability of Xeomin® was evaluated in both long-term storage studies and in short-term temperature-stress studies. The studies evaluated the toxic biological (neurotoxin) and nontoxic ingredients (sucrose and human serum albumin [HSA]) of vials containing Xeomin® stored at 5 °C or 25 °C, as well as the biologic activity of the neurotoxin without nontoxic ingredients (LD$_{50}$) after 36 months of storage at a temperature of 5 °C (a common temperature, 25 °C), no significant changes in botulinum toxin A or HSA content or toxic potency (biologic activity) were observed in the Xeomin®. Furthermore, storage studies showed that Xeomin® was stable for at least 18 months at 30 °C and for at least 6 months at 45 °C. Also, a stress-strain temperature-abuse cluster study was neither loss of activity nor degradation detectable after 14 days at 60 °C and at 80 °C the reduction of biologic activity occurred within 3 days although proteolytic activity had not fallen to lower than half of the initial value after 7 days, with a decline over time considerably slower than for biologic activity.[28] Overall, these results demonstrate that complexing proteins are not required to maintain the stability of BoNT/A preparations during storage.[29] The manufacturer states that Xeomin® is stable at room temperature for 3 years and was also demonstrate stability for 4 years at room temperature.[30,31]

Complexing proteins may have the disadvantage of immunostimulation since HA, which belong to the complexing proteins, are known to be potent stimulators of immunity in the case of repeated vaccination experiments in mice with botulinum toxoid type B (type B).[32] The amount of neutralizing antibodies increased when the neurotoxoid was combined with HA complexes and the neurotoxoid complexed with NHA, in which the neurotoxoid was administered alone. Further analysis showed that among the 4 subcomponents of HA designated HA1, HA2, HA3a, and HA3b, HA1 and HA3b were responsible for the adjuvant activity. The mechanism of increased immune response to HA1 and HA3b appeared to be mediated by an increase in interleukin-6 leading to increase in CD19+ cells. Further experiments showed that in vitro enzyme-linked immunosorbent assay analysis of antibody binding to BoNT/A light chain complex showed that HA1 was responsible for most of the immunogenic response.[33] Some have commented that this study was flawed and does not reflect a therapeutic situation. The dose of toxin used was about 1000 times greater than in typical clinical use. The antigen concentration in the mice was actually undetectable even though they were injected with formaldehyde, which in itself causes the conformation to become antigenic (toxic) proteins.[34] However, these undesirable antimicrobial HA1 and HA3b appear to increase the immunogenic potential.[35]

Hence the presence of complexing proteins in commercially available BoNT/A preparations may influence immunogenic reactions and the development of neutralizing antibodies against the active neurotoxin leading to partial or complete clinical unresponsiveness, treatment failure in BoNT/A-naïve patients, incidence of antibody development following treatment with Botox® has been significantly reduced since the original formulation was changed to reduce complexing proteins and minimize contamination.[36] Furthermore, removing the complexing proteins in the manufacture of Xeomin® may reduce the risk markedly. Preliminary experiments with Xeomin® also suggest that the absence of complexing proteins is indeed associated with reduced immunogenicity. In a study of guinea pigs with [illegible] monkeys, repeated injections with 4.4 ng (= 1.6 U) Xeomin® or treated with no exposure to the development of neutralizing antibodies in each group, despite a clear dose-dependent biologic activity of the preparation, particularly in the highest dose groups.[37] The immunogenicity of Xeomin® was compared with that of Botox® and Dysport® in New Zealand white rabbits. After repeated injections, Xeomin® did not induce the formation of [illegible] antibodies, unlike the other preparations.[38]

Similar results were shown in a human study of up to five weeks in patients with [illegible] spasticity who received

multiple injections of Xeomin® and potential development of neutralizing antibodies throughout the study.[1] Although in the clinical development program of Xeomin® in the US, 12 of 1090 subjects developed antibodies against the neurotoxin, each of these patients was previously treated with a conventional BoNT/A product which contained complexing proteins. They may have already been primed by the previous treatment.[41]

No new risk factors of this sensitization were identified.[1,41] Injection of over 100 units of Botox® or 400 units of Dysport® per session, interval of less than 3 months between 2 injections, booster technique where another dose is injected 2 to 3 weeks after the first injection, and use of a BoNT drug with a low stimulating activity. Cumulative dose, number of treatment sessions have been evaluated as risk factors. Antibody-induced therapy failure usually develops within the first 2 to 3 years of BoNT therapy.[41]

Among the above risk factors, the immunogenicity of BoNT drugs is defined as the number of units per treatment session (amount of clostridial protein) for each injection of Botox®, the sensitization potential might be greater when using a BoNT with a low stimulating activity. The toxin's antigenic potential is probably related to the total protein concentration (product protein load) that was evaluated by Poewe et al.[42] this may be a more relevant parameter in the development of a resistance than the number of units.

Indeed, in patients with cervical dystonia, the original formulation of Botox® (100 U/2.5 ng protein) was 6 times more likely to trigger the production of neutralizing antibodies than the newer formulation of Botox® (100 U/5 ng protein), which contains fewer complexing proteins and reduced immunogenicity.[43] The authors concluded that the low risk of antibody formation after newer Botox® treatment is related to lower protein load.[43]

Xeomin® contains only 0.5 ng of clostridial protein per vial (100 U/0.5 ng protein), whereas the other products contain much more protein: 5 ng in Myobloc®, 2.5 ng in Botox® (100 U/2.5 ng protein), and 12.5 ng in Dysport® (500 U/12.5 ng protein).

Despite a conversion factor of 1 Botox®/Xeomin® unit to 3–5 Dysport® units,[44–46] 100 units of Botox® or Xeomin® are not equivalent to 500 units of Dysport®. In this comparison, the protein load of the preparations is important. In the case of Xeomin®, the patient receives a much lower amount of clostridial proteins including complexing proteins: 5 ng of TTN for Botox®, 12.5 ng for Dysport®, and 0.5 ng for Xeomin®. Xeomin® contains the lowest amount of BoNT/A with respect to units. Thus it has the highest specific potency, and with Xeomin® the patient gets the lowest amount of foreign protein,[47] so that the risk of development of any immunogenicity may be reduced.

The long-term trials in cervical dystonia comparing Xeomin® with conventional BoNT/A drugs are required to confirm the low immunogenicity of Xeomin®.

Efficacy and safety profile of Xeomin®

Based on the fact that Xeomin® is obtained from the same strain of *C. botulinum* as Botox® and its preclinical efficacy, the manufacturer first assumed Xeomin® had the same potency as Botox®. Subsequently, the registration studies using a cross-over design were based on identical potency labeling. The result of equivalence experiments in which LD_{50} of 3 different batches of Xeomin® and Botox® were compared in a blinded fashion demonstrated that there was no difference in the potency between the 2 preparations.[48] Results from both registration studies[1,49] together with a European head-to-head potency testing using a mouse lethality (LD_{50}) assay[47] unambiguously established equivalence between Xeomin® and Botox®. The conclusion of a European study also showed that Xeomin® and the former Botox® (before 2009), which contain 5 ng of protein, have the same potency.[47] Thus 1 unit of Xeomin® is equivalent to 1 unit of Botox®. Brenner® further confirmed the identical potency labeling by a study comparing Botox® in a diluted fashion to Xeomin® using a 1:1 conversion rate. Therefore, clinically Xeomin®

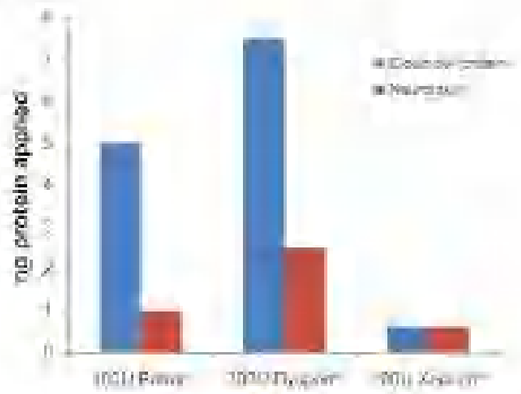

Figure 1 Amount of clostridial protein applied in a therapeutic treatment session of [illegible] (BoNT/A) drugs. Comparison between Botox® 100 units of Botox® and Dysport®.

and Botox® can be exchanged easily using a simplified conversion rate.[50]

The efficacy and safety of Xeomin® in the treatment of blepharospasm has been confirmed by a prospective, controlled, placebo-controlled, randomized, multicenter study.[51] In this study involving 109 patients, mean total dose of Xeomin® per treatment visit was 94.8 units; the Jankovic Rating Scale (JRS) severity score was significantly reduced compared with placebo ($P < 0.001$). And the most commonly reported adverse effects related to Xeomin® vs placebo were eyelid ptosis (18.0% vs 8.8%) and dry eye (10.2% vs 1.8%).

Several large clinical studies to compare the efficacy of Botox® and Xeomin® have been reported. In comparative clinical trials, the efficacy and tolerability of Xeomin® were equivalent to that of conventional BoNT/A drugs.[1,49] The efficacy of Xeomin® was compared with that of Botox® in a 24-week, double-blind, multicenter, randomized study (non-inferiority trial) in 463 patients with cervical dystonia. Both treatments significantly improved the Tsui Modified Toronto Western Spasmodic Torticollis Rating Scale severity score compared with baseline, and homogeneity of Xeomin® vs Botox® was demonstrated.[1] Similarly, a randomized, double-blind study of Xeomin® and Botox® in 100 patients with blepharospasm found that both treatments significantly reduced JRS severity scores, indicating equivalency of Xeomin®.[52] There were no differences in the time course of the 2 treatments demonstrated in the Kaplan–Meier plot. There were also clinically relevant differences between Xeomin® and Botox® in safety parameters: 40 of 148 patients (27.0%) treated with Xeomin® reported adverse events vs 45 of 155 patients (29.0%) treated with Botox®. The most common adverse event was ptosis (6.1% Xeomin® and 4.5% Botox®).

In a meta-analysis, the clinical evidence to date suggested that Xeomin® is a safe treatment for blepharospasm, which does not differ from Botox® in terms of its potency, duration of effect or adverse reaction profile.[1] The same efficacy and safety profile could be explained by the immunological observation, which would lead to the prediction of the same dose again in the 150 kDa toxin components, eliciting the same diffusion characteristics and therapeutic effects.

Dosing of Xeomin® should be based on previous Botox® treatment. If the previous information is not available, the recommended starting dose is 2.5 to 5.0 units/pa, each injection site in blepharospasm.[1] There is currently evidence of a dose-response relationship for efficacy and its duration, in which the greatest benefits for Xeomin® were observed with the highest dose and the lowest rate of adverse reactions and maximum therapeutic dose up to 80 units of Xeomin® as well as Botox® in a variety of muscle hyperactivity disorders without previously clinically detectable systemic adverse effects. However, few patients with blepharospasm received a total dose of greater than [illegible] units for cervical dystonia and spasticity. Therefore, a total dose of 200 units (35 U/kg) is recommended for initial administration.[1]

Based on safety data, Xeomin® is the only preparation that remains active for up to 3 or 4 years of intermittent treatment, in contrast, other botulinum neurotoxins require retreatment sooner.[1,53,54] After reconstitution, Xeomin® should be stored for only 24 hours at 4°C because excessive sterility problems, such as bacterial contamination, could occur.[1]

Conclusion

Xeomin® was originally developed to reduce drug antigenicity, which can lead to partial or complete treatment failure. It recently became the fourth FDA-approved botulinum toxin drug in the US. A lack of complexing proteins distinguishes Xeomin® from the other BoNT preparations. Many studies have also shown that Xeomin® has the same efficacy and safety profile as conventional BoNT/A products such as Botox® and is interchangeable with Botox® using a simple 1:1 conversion rate. Xeomin® represents a new treatment option for the relevant treatment of patients with the given indication in that it only contains the neurotoxin component and is free of complexing proteins. Thus, the risk of antibody formation after Xeomin® treatment is reduced. Long-term trials in patients comparing Xeomin® with conventional BoNT/A drugs are required to confirm the low immunogenicity of Xeomin®.

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Disclosure

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Pain Relief in Patients Receiving Periocular Botulinum Toxin A

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Purpose: We hypothesized that patients with benign essential blepharospasm and hemifacial spasm experience relief of headache and eye pain after botulinum toxin injections.

Methods: A retrospective chart review of 95 patients who had received botulinum toxin type A for the treatment of benign essential blepharospasm and hemifacial spasm was conducted. A prospective, longitudinal questionnaire was used to quantify details regarding improvement of headache and eye pain.

Results: Of the 95 patients (34 men, 61 women), 20 patients (21.5%) had headache, and 25 (26.3%) had eye pain. Two of 20 (10.0%) formerly positive patients and 21 of 24 patients (87.5%) with eye pain had reduction in their pain after botulinum toxin injection.

Conclusion: The findings of this study appear the use of botulinum toxin for headache and eye pain relief in patients with benign essential blepharospasm and hemifacial spasm. In addition, with the expanding use of botulinum toxin, we provide support to antinociceptive effects. Further investigation should examine the mechanism of botulinum toxin's effects on pain.

Botulinum toxin (BTX) is a neurotoxin that blocks acetylcholine release from the presynaptic terminal by cleaving synaptosomal-associated proteins. The toxin is produced by the bacteria, *Clostridium botulinum*, a Gram positive anaerobe. There are 7 neurotoxin subtypes produced by the bacteria (A, B, C1, D, E, F, and G). Type A is the most potent with oral by B and F.[1] The use of BTX has grown considerably since the late 1970s when Alan Scott demonstrated its use in the treatment of strabismus by injection in extraocular muscles.[2] During the 1980s, the use of BTX became a standard therapy for benign essential blepharospasm (BEB) and hemifacial spasm (HFS)[3-5] and received FDA approval for these indications in 1989. Since that time, BTX injections have shown a response rate of 80% to 90% with minimal systemic side effects.[6-10] In 1989, BTX was approved for treatment of glabellar wrinkles and has demonstrated a similar safety profile.[11-13] Investigation in its use for pain relief began when Carruthers et al[14] observed decreased migraine-type headaches in patients receiving cosmetic BTX injections.[15]

Headache and facial pain in patients with dystonias have been documented in the literature.[16-18] Furthermore, BTX injections have demonstrated relief of headache and facial pain.[19-21] However, the data on the relief of headache pain by BTX are conflicting. Some studies have shown little to no improvement after BTX injections[22-24] whereas other patient cohorts report partial or total relief of symptoms.[25-27] In addition, the type of headache, site of injection, and type of BTX used are important variables in determining the efficacy of BTX in pain relief.

The purpose of this study was to determine the efficacy of BTX injections in the relief of eye pain and headache in patients with BEB and HFS. We are unaware of previous reports of concurrent relief of headache and eye pain with BTX injections for BEB and HFS in a patient cohort of this size. We hypothesized that the injections of BTX would relieve both headache and eye pain due to mechanisms that are not fully elucidated.

METHODS

A total of 95 patients consented to sign an Authorization of Release of Information to receive BTX injections for BEB (57 patients), HFS (33 patients), or both (5 patients) at the University of Minnesota (UMN). On Institutional Review Board approval, a telephone survey was conducted that consisted of a brief series of questions relating to the presence of headache and eye pain with their quantification. Other data, such as amount of BTX injected, injection interval, and frequency of BTX use, obtained from the medical records. Three attempts were made to contact patients, with an hour between the first 2 attempts and 1 week between the second and third attempts. Patients were considered unreachable if no contact was made after the fourth attempt. Reasons for inability to contact patients included incorrect phone number and no answer or voicemail. Four additional patients declined the invitation to participate.

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Distribution of Each Group and Number of Responders in Each Category

Group (Total No.)	Better*	Same	Worse
BEB only (61)	4 (3.67 ± 1.26)	0	0
Both (also previously HFS) (18)	14 (3.43 ± 0.76)	3	1
HFS only (13)	7 (3.71 ± 1.11)	4	2
Persistent pain (13)	10 (4.00 ± 1.55)	1	0

*Average and standard deviation are provided in the "Better" column.

RESULTS

The average patient age was 69.5 years (range, 41–90 years). The average amount of BTX injected at each visit was 57.4 units (range, 15–100 units). The average total quantity of BTX injected was 1356.1 units (range, 45–5745 units) with the most common sites being the lower eyelid and upper eyelid, injected in 97.6% and 95.2% of patients, respectively. The average frequency between injections was 19.5 weeks, with a range of only 1 lifetime injection to an injection every 8 weeks. The average frequency for injections in patients with BEB was 16.2 weeks, with a range of 1 lifetime injection to injections every 36 weeks. HFS patients received injections on average every 25.8 weeks, ranging from 12 weeks to 48 weeks. The average frequency for injections for the 2 patients who had both BEB and HFS was 19 weeks.

Relief of Headache and Periocular Pain in Patients Receiving Periocular Botulinum Toxin A Injections: A Retrospective Study

Information

Age_____ Gender(circle) M F

Region of Botox Injection(circle) glabella brow crows feet

upper eyelid lower eyelid lower face Other _____

Amount of Botox Injected Total:_____ Glabella_____

Frequency of Botox (in weeks)_____

Dx(circle) Blepharospasm/BEB/Hemifacial Spasm/Headaches/Cosmesis/Other:

Questionnaire

1. **Do you have headaches? Y / N**
2. **Do you have eye pain? Y / N**
3. **Do you take medication for headaches or eye pain? Y / N**
4. **If yes, what medications do you take?**

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

5. **After Botox, are the headaches(circle) Better Same Worse**
6. **Degree of Improvement (0=none, 5=total relief) 0—1—2—3—4—5**
7. **After Botox, is the eye pain (circle) Better Same Worse**
8. **Degree of Improvement (0=none, 5=total relief) 0—1—2—3—4—5**

Study questionnaire.

Of the 65 patients with pericranial tenderness, 20 patients (30.8%) had their headache and 20 (34.4%) had eye pain. Mean pretreatment tenderness (20.04 ± 6.0) and eye pain (Table) were significantly reduced following BTX injections, with an average drop of 7.50 (20.1 ± 3.8) on a 40-point scale ($P < 0.001$, paired t test). Twenty-three of 39 patients (59%) with pericranial pain had complete relief of their pain after BTX injections, with an average relief of 6.2 ± 2.5 (range, 2–10) on the same scale.

Twenty patients had tenderness and pain in other parts of the body. The most common pericranial pain relief was seen in the temporal area (mean ± SD, 6.2 ± 2.5), followed by the occipital area (5.8 ± 2.3), the forehead (5.5 ± 2.3), and the vertex (3.8 ± 2.3). Twenty-three of 39 patients (59%) with pericranial pain had complete relief of their pain after BTX injections, which may have resulted from the additive effects of the injections.

The known and newly described BTX injection sites were highly tender, from the neck and pain in hyperkyphosis.[12] Patients with BEB and HFS who had a decrease in pain with BTX injections may represent a unique subgroup of people who have a more favorable response to BTX's antinociceptive effects. Therefore, we advocate that more research on the antinociceptive mechanism of BTX is needed to determine if several mechanisms are responsible for pain perception, from the muscle to the peripheral and central nervous systems.[13–15]

We recognize the inherent limitations of a retrospective study as well as ours. In addition, the subjective nature of pain and difficulty in verbalizing association with facial aches or eye pain make the analysis of the data more challenging. Also, the small number of the improvement scale (0–3) makes it easier for patients to answer the questions but may have hampered the ability to find a significant difference between the groups. Furthermore, the evaluation of the headache such as type and duration was not obtained. Despite these limitations, we believe that our results are valid. We achieved a high percentage of participation (85 of a possible 120 patients, 71 ± 1) for this type of study and a large cohort for the investigation of BEB and HFS. We used a standardized questionnaire using simple language and concepts focused on a single objective.

These results confirm the high prevalence of pain in patients with facial dystonias. For some of these patients, the use of BTX injections for muscle spasm had the added benefit of improving their pain and headache.

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Patients With Homonymous Hemianopia Become Visually Qualified to Drive Using Novel Monocular Sector Prisms

Adam M. Moss, MD, MBA, Andrew R. Harrison, MD, Michael S. Lee, MD

Abstract: Patients with homonymous hemianopia (HH) often fail to meet visual field (VF) requirements for a driver's license. We describe 2 patients with complete HH, who met the minimum VF requirements for driving using a novel, lightweight, monocular sector prism system. Baseline VFs were assessed using automated and kinetic perimetry. Patients were fitted with glasses and prescribed 57-PD prism and monocular sector prisms placed on the lens posteriorly to the VF defect above and below the visual axis with prisms oriented obliquely. Kinetic perimetry was reassessed both monocularly and binocularly, with and without prisms. The 2 patients had 95° and 69° angle of contralateral, horizontal, hemianopic VF. With the use of the prism system, the hemianopic VF increased to 115° and 112° angles. Both patients regained improvement in quality of life and each received a valid driver's license and has successfully operated a motor vehicle without any modifications or restrictions. These findings suggest that the addition of oblique 57-PD prisms to the peripheral spectacle lens above and below the visual axis for patients with complete HH can significantly increase their binocular VF, which may help an individual become visually qualified to obtain a driver's license.

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Homonymous hemianopia (HH) occurs after damage to the contralateral retrochiasmal visual pathways. Despite adapting to the visual field (VF) deficit, patients experience compromised independence from automobile travel during daily activities. Although the specific VF requirements to obtain a driver's license can be state-dependent, most states require that there should have at least 120° angle of binocular VF (1). In an attempt to expand the VF in patients with HH, a number of optical therapies have proposed a variety of mirrors, telescopes, and prisms. A novel approach utilizing monocular sector prisms limited to the peripheral field has been described by Peli (2). The prism is placed across the entire width of the lens above and below the visual axis, thus creating peripheral monopia. Peli proposed that this would effectively expand the VF in all lateral positions of gaze, while maintaining binocular alignment and eliminating diplopia.

Recently, Bowers et al (3) described a modified technique using obliquely oriented prisms. They found greater 48-PD prism exposure (3M Press-On Optics) were placed, transmit, at the upper and lower part of the spectacle lens ipsilateral to the VF defect with its central edge at the level of the limbus, spanning the entire width of the lens (Fig. 1). The horizontal prism segments were oriented obliquely at ~15° angle from the horizontal axis, 7–8 mm apart. At the conclusion of the trial period, prisms were permanently ground and fixed into the lenses (Chadwick Optical, White Bear Lake, MN). Patients were instructed to gaze through the inferior, prism-free area of the lens, rather than looking directly through the prism. No additional formal training was administered.

In this report, we describe successful use of the prism system for the treatment of 2 patients with HH, which expanded VFs to allow each to meet minimum acuity and field requirements for driver licensure in the state of Minnesota. The study was approved by the Institutional Review Board at the University of Minnesota.

CASE REPORT

Case 1

A 24-year-old man sustained a right occipital lobe stroke in April 2011. He was hemianopic with a visual acuity of 20/20 at distance in both eyes. Visual field testing revealed a complete left HH, which remained stable for more than 9 months. The rest of his neuro-ophthalmic examination was unremarkable.

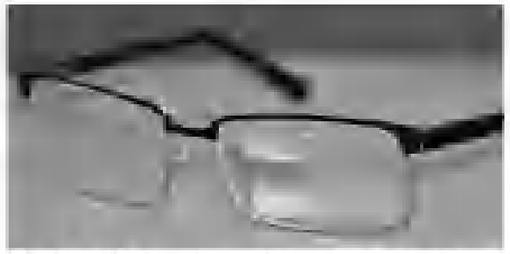

FIG. 1. Two 57-PD prism segments placed at the upper and lower part of the eyeglass lens (posterior) to the visual field loss, with the central edges at the level of the limbus, spanning the entire width of the lens. The individual prism segments are placed obliquely at 45° angle to the horizontal with the upper prism oriented base out and down and the lower prism oriented base out and up.

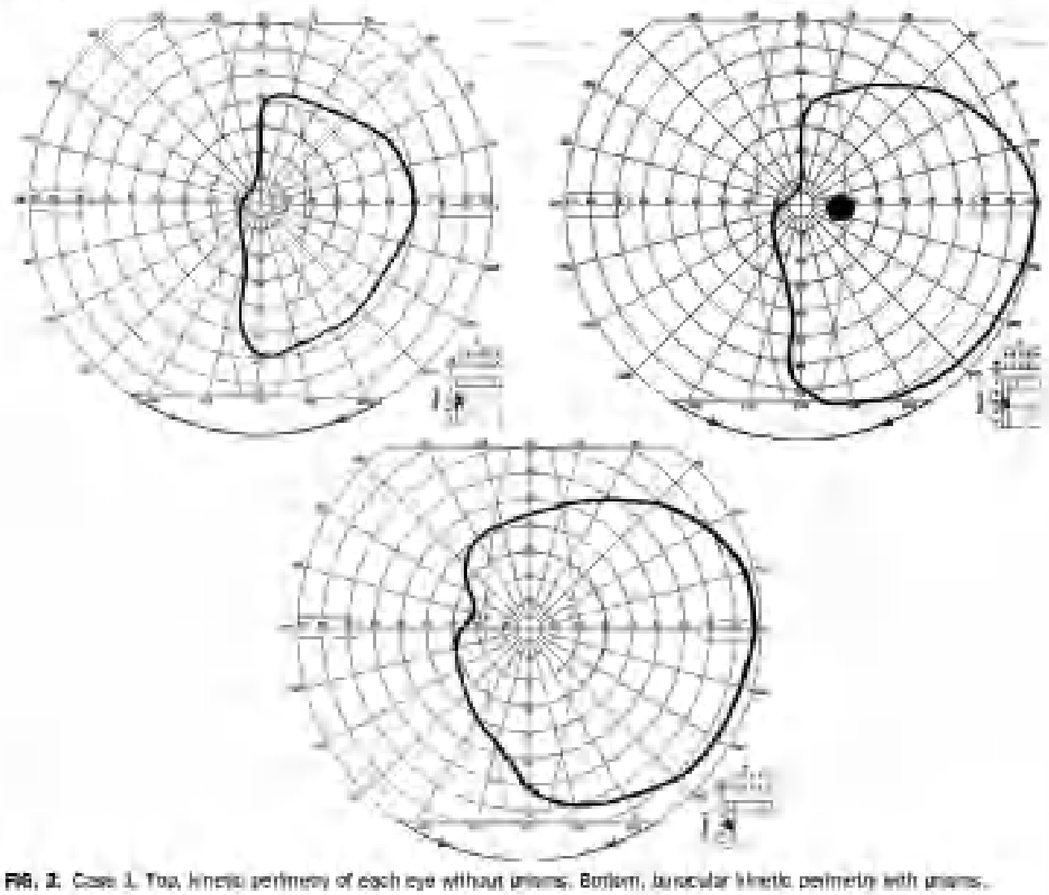

FIG. 2. Case 1. Top, kinetic perimetry of each eye without prisms. Bottom, binocular kinetic perimetry with prisms.

Case 2

A 31-year-old man underwent resection of a right parieto-occipital oligoastrocytoma measuring 5 × 5 × 5 cm in 2006. Postoperatively, he sustained a right posterior cerebral artery stroke. Visual acuity was 20/20 in both eyes and visual fields demonstrated a complete left HH. The rest of his neuro-ophthalmic examination showed normal results. Both patients were otherwise intact neurologically without evidence of neglect or cognitive impairment.

In both cases, VFs were assessed monocularly using Humphrey visual field 24-2 SITA Fast with a size-III stimulus. Binocular perimetry was performed using dynamic mapping and static perimetry, probing with a size-III stimulus. Visual fields were reassessed at multiple time points to confirm stability of the HH. Kinetic perimetry was assessed both monocularly and binocularly with and without the prisms. Fixation was monitored closely for any saccades into the blind hemifield.

Case 1 had a left HH with 95° and 69° angle of remaining horizontal VF in the right and left eyes, respectively, and

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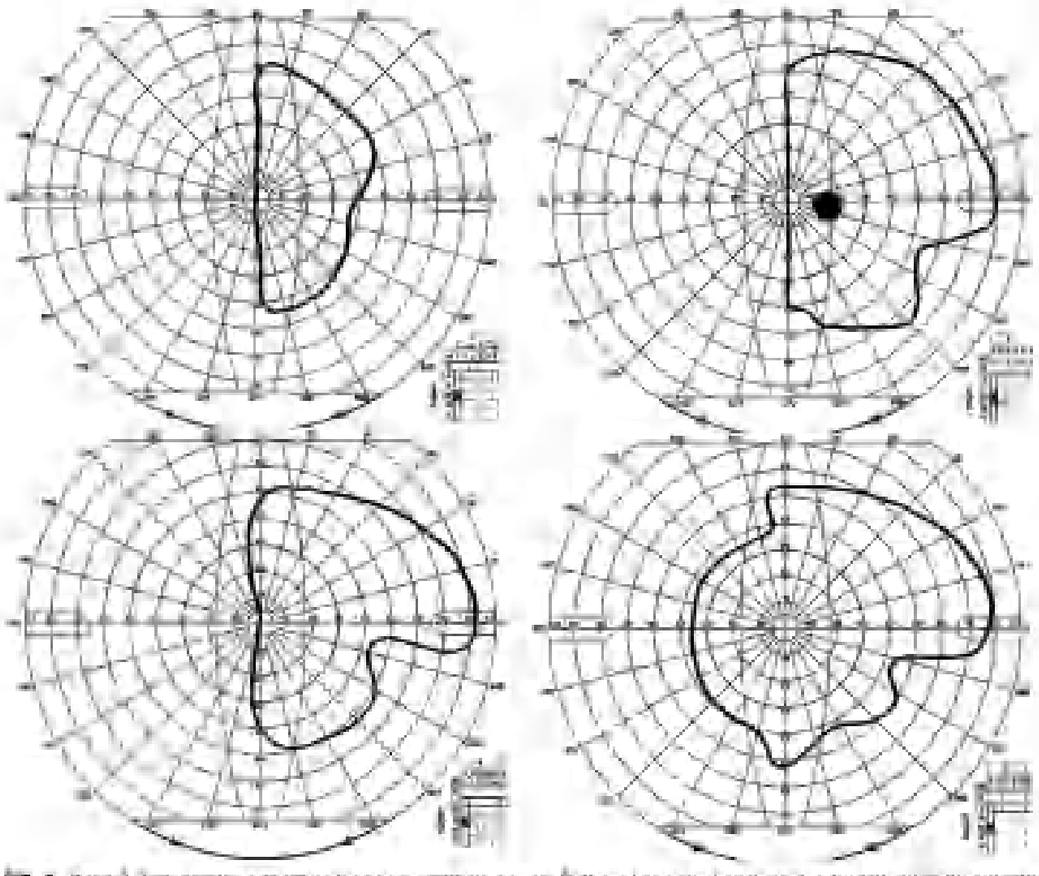

FIG. 3. Case 2. Top: kinetic perimetry of each eye without prisms. Bottom: binocular kinetic perimetry without (left) and with (right) prisms.

8° right temporally. With the 10Δ/8Δ prism system, the binocular VF increased to 114° angle of continuous horizontal VF (Fig. 3). Case 2 had a left EEI with 7° and 18° angle of remaining VF in the right and left eyes, respectively, and 82° angle from ellipsoid. With the use of the prism system, the binocular VF increased to 112° angle of continuous horizontal VF (Fig. 3). Both patients reported an immediate improvement in their VF and spatial awareness and overall safety in the prism and overall results.

Although no standardized questionnaires or formal assessments were conducted, both patients noted significant improvement in quality of life. They denied diplopia and visual confusion and reported confidence with their prism glasses. Case 1 passed an on-road driver evaluation administered by a driving rehabilitation specialist after several weeks of adapting to the prisms. Case 2 began driving after adapting to the prisms for approximately 6 months. Each holds a valid driver's license in the state of Minnesota and has successfully operated a motor vehicle without any incidents or violations for 1 and 5 years, respectively.

DISCUSSION

Optical devices can provide field-of-view expansion for patients. Reducing ample skills the purpose of the minimum binocular scan prism, which is expensive and usually allows the patient to maintain a larger amount of the maintenance of any given numeric binocular peripheral prism). The peripheral placement of the prism inside displays that could occur with prisms in the visual axis. The oblique orientation of the prisms creates overlapping fields along the horizontal meridian which may produce superior augmentation of compromise horizontal VF (Fig. 4) as required by many driver licensing agencies. These findings have led to a multicenter, randomized, controlled trial of spectacle lenses in patients with EEI (4).

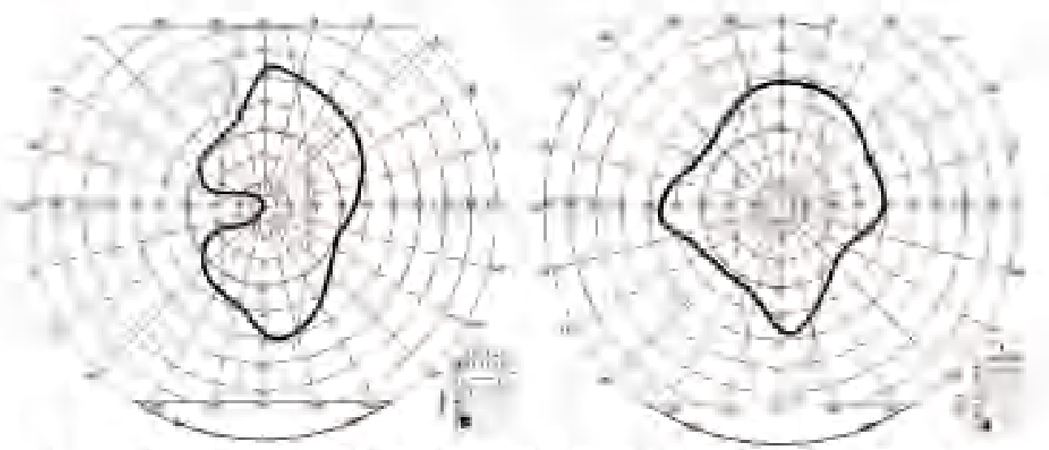

FIG. 4. Case 2. Kinetic perimetry of the left eye using peripheral prism segments placed above and below the visual axis with the prisms oriented horizontally (left) and obliquely (right). The oblique orientation results in greater augmentation of combined horizontal visual field.

Augmentation of VF in a patient with a EEI using monocular scan prisms is not surprising, but we have shown that our patients achieved the 105° VF requirement from the Department of Motor Vehicles in Minnesota.

There is conflicting data regarding quantifying the impact of VF loss on driving ability or capacity to operate a motor vehicle. In patients with glaucoma, it has been documented through the use of driving simulators and real-world self-reported data that having a binocular VF of 100° angle or less is associated with a significantly higher risk of accidents (5). In patients with EEI, Bowers et al (6), using a driving simulator, showed a decreased blind-side detection of obstacles with Nightstalker and 17° peripheral visual slightly to demonstrate reduction in visual motor control. However, Wood et al (8,9), using on-road driving performance, have reported that some individuals with homonymous VF deficits may be safe to drive. Further study is required to better define the relationship of driving simulator or on-road performance and to determine the minimum VF required to drive safely.

The state of Minnesota requires the individuals have at least 105° angle of horizontal VF to obtain a license to operate a motor vehicle (10). Both of our patients were able to meet these requirements with the use of the prism system and subsequently have been driving accident free. To the best of our knowledge, the oblique orientation of the peripheral prism segments to meet the driver license requirements has not been reported. It should be emphasized that patients with EEI may benefit from a training and adaptation period during which they learn to safely utilize their prism system before driving on the open road (10).

We acknowledge the limitations of our report. We only evaluated 2 patients with EEI. Both were young males with no neurological deficits. Our findings may not be generalizable to all patients with a EEI, particularly older patients or those with cognitive impairment or deficit. Nevertheless, clinicians should consider using the prismatic system in patients with EEI as a potential aid in obtaining a driver's license to operate a motor vehicle.

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Pegylated Interferon Alpha–Associated Optic Neuropathy

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Abstract: A 52-year-old man with chronic hepatitis C presented with painless, bilateral, simultaneous non-arteritic anterior ischemic optic neuropathy (NAION) and peripheral neuropathy. Symptoms began 16 weeks after starting pegylated interferon alpha-2a. The peripheral neuropathy and vision of the right eye improved, but the vision of the left eye worsened after stopping interferon. We identified 23 additional cases of NAION during interferon alpha therapy. At least 32 of these patients suffered bilateral NAION. Patients had vision 1–40 weeks after initiating therapy. Of 23 cases that had documented initial and follow-up acuities, 8 improved, 3 worsened, and the rest remained stable. One patient had a painful peripheral neuropathy. Treatment with interferon alpha may result in NAION. Discontinuation of therapy deserves consideration after weighing individual risks and benefits.

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Interferon alpha is a complex glycoprotein with antiproliferative, antiviral, and immunomodulatory activity (1). Pegylated interferons have a covalently attached 40 kD branched chain polyethylene glycol moiety, which improves drug absorption and prolongs the half-life from 8 to 22–80 hours (2), allowing for less frequent injections and improved patient compliance. The 2 forms of pegylated interferon alpha currently approved for the treatment of chronic hepatitis C (CHC) are peginterferon alpha-2a and peginterferon alpha-2b. While peginterferon alpha-2b has a larger volume of distribution and more effective renal clearance than peginterferon alpha-2a (3), studies have found no difference in either the standard virological response or adverse event incidence between the 2 medications in the treatment of CHC (4).

The most common adverse events associated with interferon alpha therapy are flu-like symptoms, fatigue, gastrointestinal symptoms, depression, and thyroid disorders (5). Cases of peripheral neuropathy have also been documented (6–10). Several progressive cranial nerve losses during interferon alpha therapy with a high incidence of retinopathy, demonstrated by the presence of cotton wool spots and hemorrhages (11–19), although these changes are often asymptomatic (12,16). Other documented ocular complications of interferon alpha therapy include transient blurred vision (20), increased intraocular pressure (21), exacerbation of glaucoma (22), retinal detachment (5), and orbital and intraocular hemorrhage leading to enucleation (23,24). Nonarteritic anterior ischemic optic neuropathy (NAION) is a relatively rarely reported complication of interferon alpha therapy (15,24–40).

We present a case of NAION following treatment of CHC with peginterferon alpha-2a and review the literature for other documented cases of NAION following interferon alpha therapy.

CASE REPORT

A 52-year-old man with a history of CHC developed painless progressive vision loss in his right eye. He did not detect visual loss in the left eye. He also noted new onset numbness and tingling in both hands and feet. The dental symptoms suggestive of giant cell arteritis. His medical history included migraine headache, cervical radiculopathy, depression, anxiety disorder, and insomnia. Nineteen weeks prior to ophthalmic evaluation, he began treatment for CHC with peginterferon alpha-2a 180 μg/week and ribavirin 1000 mg/day. Other medications included fluoxetine, albuterol, clenbuterol hydrochloride, lorazepam, phentermine, fluticasone and salmeterol, bupropion, clonazepam, omeprazole, zolpidem, pseudoephedrine, and ranitidine.

Two days later, examination revealed vision of 20/25 in each eye. Pupils were 3 mm bilaterally with a right relative afferent pupillary defect (RAPD). The patient correctly identified all of the Ishihara color plates with each eye. Fundus examination demonstrated bilateral optic disc edema (Fig. 1) with a normal appearance to each optic fundus photograph from 2003 revealed a cup-to-disc ratio of 0.1 OU. Visual field testing demonstrated inferior field loss in the right eye and an altitudinal loss in the left eye (Fig. 2).

Contrast-enhanced MRI of the brain and orbits showed no optic nerve or intracranial abnormalities. Lumbar puncture demonstrated a normal opening pressure, with normal protein and glucose levels, no white blood cells and 2[2] red blood cells. Homogram showed mild pancytopenia with a white blood cell count of 3400 cells per microliter, platelet count of 110 000 cells per microliter, and hemoglobin of 13 g/dL. A complete rheumatologic panel showed no abnormalities. Antineutrophil cytoplasmic-antibody-converting enzyme, rapid plasma regain, and neuromyelitis optica (NMO) IgG testing were all negative.

Both peginterferon alpha-2a and ribavirin were discontinued. The patient received intravenous solumedrol 500 mg followed by oral prednisone 40 mg, which was tapered over the next 8 days. When examined 4 weeks later, he reported a 4-day decline in vision in his previously asymptomatic left eye and some improvement in his right eye. Visual acuity was 20/20 in the right eye and 20/60 in the left eye. He saw 8/8 Ishihara color plates with the right eye and 3/8 with the left eye, and there was no evidence of a RAPD. The right optic nerve showed early segmental atrophy while the left optic nerve swelling had worsened. Visual field testing demonstrated slight progression of the inferior arcuate scotoma in the right eye and a new defect in the left eye (Fig. 3). The patient noted almost complete resolution of his paresthesias.

DISCUSSION

One patient suffered bilateral simultaneous NAION in the setting of peginterferon alpha-2a treatment. Spontaneous, bilateral, simultaneous NAION is uncommon and typically suggests a systemic disorder or toxicity. While it is conceivable that the interferon therapy was unrelated, this seems unlikely since the case has similar findings to previous reports. In addition, our patient had bilateral paresthesia of the hands and feet, a known side effect of peginterferon alpha. With discontinuation of therapy, he noted near total resolution of this symptom, strongly suggestive of a systemic toxic effect of his interferon therapy.

We are aware of 23 additional cases of NAION in the setting of interferon alpha therapy (Table 1). Eleven patients experienced bilateral NAION. One probable case of NAION following interferon alpha-2b therapy for CHC (45) and one following interferon alpha-2a therapy for severe hepatitis C (47) were omitted from this compilation because the abstracts were not available in English. All other reported patients suffered visual loss between 1 and 40 weeks after initiating therapy. Thirteen were treated with ribavirin and interferon alpha. Of these 13 patients, 6 experienced bilateral visual loss. Four patients suffered NAION while taking interferon alpha-2a and 7 while taking interferon alpha-2b. Eleven reports only described treatment as "interferon alpha" therapy. Of these 11 patients, 4 experienced bilateral optic nerve involvement. There was one documented case of NAION following therapy with consensus (interferon alpha. Of the 17 cases that provided follow-up information, 9 described improvement in signs and symptoms following cessation of interferon alpha, and one showed symptomatic improvement without the withdrawal of therapy. One patient developed painful polyneuropathy in addition to NAION (37).

How interferon causes NAION is currently unknown. Sugano *et al* (48) studied patients who developed retinopathy while taking interferon alpha (49). They observed abnormally high levels of circulating activated plasma coagulation

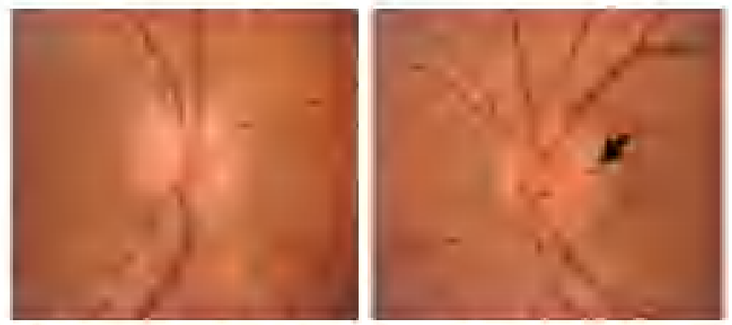

FIG. 2. Bilateral optic disc edema is present with a mild hemorrhage (arrow) on the left eye.

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FIG. 2. Initial visual field test results show an inferior nasal defect in the right eye and a normal result in the left eye.

...a clinic was an evidence of systemic vasculitis. While one patient did have thrombocythemia, Hayreh et al (13) found no association between thrombocythemia and ischemic complications in patients with GCA, pointing instead to the role of vasculitis. Additionally, development of NAION due directly to HCV infection is extremely rare, with only 2 cases documented (15,16).

Our patient had a preexisting small cup-to-disc ratio, a proposed risk factor in the development of NAION (17). One previous report of peripapillary NAION associated with peginterferon alfa-2a noted a small optic disc in the fellow eye with crowding and absence of capillaries (12). Two other cases of bilateral NAION documented absence of peripapillary capillaries in the fellow eye prior to second AION episode (18). It is conceivable that a small optic disc or crowded optic nerve head may increase the risk of NAION in patients receiving interferon therapy.

Based on the evidence from our patient, as well as from the compiled case reports, we propose that the mechanism of peginterferon alfa-2a therapy and the development of NAION is possibly based on the World Health Organization criteria for evaluating causality in adverse drug reactions (Table 2) (http://www.who-umc.org/DynPage.aspx?id=23003). The most obvious concern with

FIG. 3. Follow-up visual field test eight weeks after cessation of peginterferon alfa-2a in the right eye and an interval improvement with resolution of the nasal defect in the left eye.

TABLE 1. Previously reported cases of NAION following treatment with interferon alpha-2a, interferon alpha-2b, or natural interferon alpha

Patient Age, Gender (reference)	Underlying Disease	Medication	Unilateral vs Bilateral	Treatment Duration Prior to NAION	Visual Acuity at Presentation	Visual Acuity After IFN Cessation
54, Female (37)	CHC	IFN alpha-2a, ribavirin, and amantadine	Bilateral	6 months	Unknown	Unknown
58, Female (25)	CHC	IFN alpha-2a and ribavirin	Unilateral	3 weeks	20/50	20/30
61, Female (25)	CHC	IFN alpha-2a and ribavirin	Bilateral	8 weeks	20/100 OU	20/25 OU
71, Male (25)	CHC	IFN alpha-2a and ribavirin	Unilateral	7 months	20/400	20/30
56, Male (24)	CHC	IFN alpha and ribavirin	Unilateral	6 months	20/100	Marked improvement
Unknown (35)	Malignant melanoma	IFN alpha	Unknown	Unknown	Unknown	Unknown
40, Male (26)	RCC	IFN alpha	Bilateral	3 weeks	20/20	Unknown
61, Male (26)	Multiple myeloma	IFN alpha	Bilateral	1 week	20/20 OD; 20/30 OS	20/20 OD; 20/30 OS
70, Male (34)	RCC	IFN alpha	Unilateral	6 weeks	20/80	20/100
72, Male (34)	RCC	IFN alpha	Unilateral	10 months	Counting fingers	Did not return to baseline
Unknown (40)	CHC	IFN alpha and ribavirin	Unknown	Unknown	Unknown	Unknown
64, Male (38)	CHC	IFN alpha	Unilateral	Unknown	20/200	Improved
59, Gender not specified (31)	CHC	IFN alpha	Unknown	8 weeks	Unknown	Unknown
44, Male (18)	CHC	IFN alpha	Bilateral	10 weeks	20/100 OD; 20/200 OS	20/100 OD; 20/200 OS
61, Male (15)	Essential thrombocytosis	IFN alpha	Bilateral	3 months	20/80 OD; 20/80 OS	20/30 OU
46, Male (30)	CHC	IFN alpha-2b and ribavirin	Bilateral	3 weeks	20/400 OD; 20/100 OS	20/60 OU
51, Male (28)	CHC	IFN alpha-2b and ribavirin	Bilateral	3 months	Unknown	Unknown
54, Male (29)	CHC	IFN alpha-2b and ribavirin	Bilateral	6 weeks	Unknown	20/20 OD; 20/200 OS (both worsened)
60, Male (27)	Malignant melanoma	IFN alpha-2b	Bilateral	23 weeks	20/120 OD; 20/400 OS	20/120 OD; 20/400 OS
46, Male (33)	CHC	IFN alpha-2b and ribavirin	Unilateral	Unknown	Unknown	Improved without treatment cessation
55, Female (39)	CHC	IFN alpha-2b and ribavirin	Bilateral	8 months	20/400 OD; 20/60 OS	20/400 OD; 20/60 OS
57, Male (32)	CHC	IFN alpha-2b and ribavirin	Unilateral	8 months	20/60	20/20
40, Female (36)	CHC	Natural IFN alpha	Unilateral	2 months	20/30	20/20

CHC, chronic hepatitis C; IFN, interferon; NAION, nonarteritic anterior ischemic optic neuropathy; OD, right eye; OS, left eye; OU, both eyes; peglFN, peginterferon; RCC, renal cell carcinoma.

TABLE 2. World Health Organization causality assessment of suspected adverse drug reactions

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, which is unlikely to be attributed to concurrent disease or other drugs or chemicals. A response to withdrawal of the drug is clinically reasonable. Rechallenge information is not required to fulfill this definition.
Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.
Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction or response which requires more data or assessment of the additional possible information.
Unassessable/Unclassifiable: A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

NAION reported within 3 months after 6 months following the onset of treatment. After 6 months of other disease, underlying risk factors, or other medications.

While improvement in visual acuity was noted following discontinuation of treatment, alpha in 9 of the 28 cases reported in the European, a large randomized, prospective study of patients with NAION showed that 11% of treated eyes with mean of 20/60 or worse gained 3 lines or more of vision at 6-month follow-up (20). It is also unclear whether continuing therapy with treatment alpha results in progressive visual deterioration. The high frequency of bilateral NAION in cases found in treatment alpha therapy suggests that presentation in one eye may place the fellow eye at risk, especially in patients with small cup-to-disc ratio. Further study is warranted to identify whether discontinuing therapy diminishes the likelihood of NAION in the fellow eye.

In conclusion, occurrence with interferon alpha may lead to the development of NAION. Currently, the decision to continue or discontinue treatment alpha in patients presenting with unilateral NAION should be made on a case-by-case basis until proven therapeutic guidelines are established.

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Periocular Asymmetry in Infants With Deformational Posterior Plagiocephaly

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Abstract

Purpose: To analyze the clinical significance of the periorbital features associated with the facial asymmetry that is common in deformational posterior plagiocephaly (DPP).

Patients and methods: We identified 32 patients with DPP, photographed their faces and tops of their head, and performed a complete eye examination. Four examiners analyzed the patients' periorbital features on the photographs.

Results: Median age was 6.5 months (range 3–13 months). Pseudoptosis was identified in 30 patients and pseudo-hypertelorism in 19. Pseudoptosis was marked in 11 patients. Five patients were subsequently seen by pediatric ophthalmologists and received regular follow-ups for amblyopia until the resolution of plagiocephaly was established. All patients had normal levator function and symmetric optical axes. One patient with craniofacial and physiologic asymmetry was diagnosed with sensorineural syndrome after a negative DNA genetic test. None of the patients developed monocular or binocular amblyopia.

Conclusion: DPP is the most frequent form of skull deformation in infants. Its main features are occipital flattening and facial asymmetry. Infants with DPP may present with pseudoptosis and pseudo-hypertelorism on the ipsilateral side of the occipital flattening. The pseudoptosis in DPP is mechanically generated, therefore, ophthalmologic examination and regular follow-ups are not necessary unless other abnormalities coexist.

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Introduction

The term plagiocephaly refers to a diagonal asymmetry of the skull that is categorized into two types: synostotic plagiocephaly due to premature closure of cranial sutures, and non-synostotic, also known as deformational plagiocephaly. Non-synostotic deformational posterior plagiocephaly (DPP), or positional plagiocephaly, is the most common form of cranial misshape in infants, presenting with occipital flattening, anterior displacement of the ear, and facial asymmetry.[1–3] The occipital flattening in DPP is a result of continuous external pressure to the same spot on the back of the head, most commonly acquired when babies lie with the back of their heads in the same position for prolonged periods of time.[4] A significant increase in the incidence of DPP has been noted since 1992, when the American Academy of Pediatrics (AAP) recommended that infants sleep on their backs to reduce the risk of sudden infant death syndrome.[1,5] The prevalence of DPP is not known for certain, with reports ranging from 3% to 48% of healthy infants.[3]

In addition to sleep position, there are other contributing factors to the development of DPP, including labor/uterine positioning, difficult childbirth with assisted delivery (vacuum, forceps), premature/low muscle tone, multiple-birth babies, congenital muscular torticollis, and ocular torticollis.[1,2,6]

DPP is a benign, mostly cosmetic condition that must be distinguished from synostotic plagiocephaly, which is a serious condition that may cause increased intracranial pressure, seizures, and developmental delay if left untreated.[1,2] Unilateral Coronal synostosis (UCS) primarily affects the frontal bones, usually without the involvement of the occipital area. Unilateral lambdoid synostosis (ULS), a rare form of craniosynostosis, is the only type that would present flattening in the back of the head similar to DPP. A clinical exam is often sufficient to differentiate the two conditions, with confirmation by CT scan only if needed. In ULS, the ear and forehead on the side of the occipital flattening are displaced posteriorly, giving the head a trapezoid shape, whereas in positional plagiocephaly, the ear and forehead displacement is anterior, forming a parallelogram head shape (figure 1).[1,2,7]

Facial asymmetry is one of the cosmetic concerns in DPP. A study using three-dimensional computed

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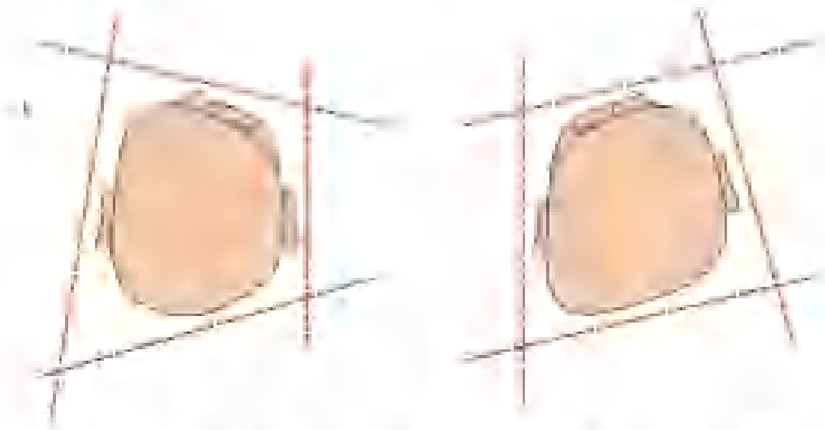

Figure 1. Vertex view showing a trapezoid head shape in ULS and parallelogram head shape in DPP.

nanography showed that the facial bones in children with DPP are distorted and the facial axis is deviated.[2,3] As a result, one side of the face becomes flat on the forehead, with smaller cheek and lower jaw, misaligned ears, and narrow fissure of the eyelid.[10,11]

Treatments for DPP include sleep repositioning and orthotic helmet.[12–19] Infants initiating helmet treatment between 4–8 month old usually achieve better outcomes.[19] A study by van Wijk et al.[17] found no difference in the improvement of the skull shape at 2 years of age in patients treated with helmet compared to patients who were not. By contrast, there are many studies showing evidence that orthotic helmet therapy is the most effective approach in correcting both cranial and facial asymmetries.[12–19]

Ocular motility abnormalities in craniosynostosis involving horizontal and vertical strabismus have been well described, showing a high incidence of V pattern exotropia with orbital ectortion causing pseudo inferior oblique overaction in syndromic craniosynostosis, and of astigmatism and exotropia in nonsyndromic types.[20–24] Gupta et al.[25] found that the prevalence of strabismus and astigmatism in DPP is equal to the general population. Considering the increase in the occurrence of DPP since the "Back to Sleep" campaign in 1992,[1] we believe that clinicians specializing in children's eye care should be able recognize the periocular features associated with this type of plagiocephaly. The primary goal of this study was to investigate if the periocular asymmetry that is common in infants with DPP, in which one eye may have a narrower eyelid fissure, is clinically relevant.

Methods

This prospective study was approved by the Institutional Review Board at the University of Minnesota and complied with the Health Insurance Portability and Accountability Act. Parents of minors provided informed consent, permitting use of information in their chart and external photographs to be used for research purposes.

Over a 24-month period, we recruited infants with DPP who presented for an eye examination at the Pediatric Ophthalmology clinic at the University of Minnesota, and who were previously diagnosed by their primary care provider or a craniofacial specialist. We excluded patients with craniosynostosis and one patient with an orbital lesion causing proptosis of the globe.

A complete eye examination was performed, including fundus exam, cycloplegic refraction, assessment of the lids' ocular position, levator function, ocular motility, and visuals, which was tested with the induced tropia test and teller acuity cards.

Photographs of the patients were obtained, including full face and top of the head so that their eyelids position and occipital flatness could be observed. The photographs were later analyzed by two orthoptists and two oculoplastic ophthalmologists for the presence of proptosis and pseudo-brow ptosis as well as their laterality in relation to the DP.

Results

We recruited a total of 32 infants with DPP, mean patient age was 6.5 months (range, 3–12 months).

Nineteen (59.4%) were male. At the time of the eye exam, 14 (43.8%) patients had never received treatment for DPP, 14 (43.8%) were under helmet therapy, two (6.3%) had completed helmet therapy, and two (6.3%) were treated with repositioning.

All examiners detected pseudoptosis in 30 (93.7%) infants, and found that two infants had symmetric periocular features. The eyelid asymmetry was marked in 17 (53%) patients. Nineteen (59.4%) patients had pseudo-brow ptosis (Figure 2). The pseudoptosis was contralateral to the occipital flatness and forehead bossing in 29 (90.6%) patients (Figure 4), and ipsilateral in one (3.1%) patient. The pseudo-brow ptosis was always contralateral to the occipital flatness.

The chief complaint reported by the parents, or the reason the patients were having an eye examination varied, including 10 (31.3%) retinopathy of prematurity, six (18.8%) ptosis, three (9.4%) strabismus, one (3.1%) amblyopia, and others such as adoption screening, cytomegalovirus, leukocoria, cornea scar, etc. There were five (15.6%) multiple-birth infants. The exam showed that all patients had a symmetrical eyelid crease, normal levator function, and no occlusion of the visual axis.

Five (15.6%) patients received the diagnosis of congenital ptosis at their first visit, and returned for amblyopia check one or two times. Follow-up care was discontinued after a diagnosis of pseudoptosis was established. Cycloplegic refraction showed that none of the infants had anisometropic astigmatism. Five patients (15.6%) were diagnosed with strabismus: accommodative esotropia (ET), infantile ET, sensory ET, esotropia, and superior oblique palsy (SOP). Three patients underwent strabismus surgery. One patient had ocular torticollis, with a right head tilt due to a left SOP, and DPP with left occipital flatness. None of the patients developed a chin-up head posture related to their eyelid position.

One infant had a narrow eyelid fissure and a miotic pupil in the left eye. Horner syndrome was suspected.

Figure 2. Left pseudo-brow ptosis.

Figure 4. The pseudoptosis (left eye) is contralateral to the occipital flatness (right).

Cocaine 10% was instilled into both eyes, and Horner syndrome was ruled-out after both pupils dilated equally (Figure 6).

Two patients returned for a one year follow-up visit, and showed improvement of eyelid position post-helmet treatment, without surgical intervention (Figure 5).

Discussion

Babies who develop occipital flatness, whether pre or post-natally, will always have pressure between the back

Figure 6. Pseudo-Horner syndrome, with physiological anisocoria (miotic pupil) and pseudoptosis in the left eye.

Figure 7. Preoperative (left) and after (right) frontal craniotomy.

of the head and the firm surface upon which the baby lies progressively flattening the occiput on that side. These deformational forces, in combination with growth-related forces, also affect the facial bones and the skull base, creating the facial and periocular asymmetry that accompanies an DPP.[10] We believe that our series of 42 patients indicate that pseudoptosis and pseudo-brow ptosis contralateral to the occipital flatness and ipsilateral to the frontal flatness is a common occurrence in infants with DPP, and their recognition may help examiners rule out unnecessary candidates involving blepharoptosis.

Some skull abnormalities have unique ocular features that, if correctly identified, may help in their differential diagnosis. For instance, in ECS, one of the eyes usually looks wider than the other because the orbit volume ipsilateral to the forehead flatness is smaller, resulting in eye proptosis.[11] In contrast, in DPP, the globe position in the orbit, and the orbital structures and volume, are normal. Babies with DPP commonly keep their face turned to the right (supine position), and consequently, that side of the face is "pushed down" by the deformational and gravitational forces, resulting in a backward displacement of the frontal, orbital, and zygomatic bones.[12,13] Consequently, this orbital recession diminishes the anterior projection of the globe and brow ridge against the eyelids and eyebrow, resulting in the pseudoptosis and brow ptosis that we describe here.

The pseudoptosis and pseudo-brow ptosis were contralateral to the occipital flatness in all patients, with only one exception. An explanation for this latter finding could be that this patient's skull deformation did not follow the DPP pattern because, according to her past medical history, other areas of the skull were affected during her complicated birth with assisted delivery.

Only one patient in our study had ocular torticollis; but, because her occipital flatness was contralateral to her head tilt, we believe that in this case, the TORT and left DPP were unrelated. The association between congenital SOP and DPP has been described in the literature, suggesting that a persistent head tilt may result in unilateral occipital deformation.[14] Although we report the clinical head posture to resolve when binocular vision is suspended upon distortion in both cases, infants with ocular torticollis often develop a sternocleidomastoid muscle tightness that forces their head to remain in the same position during sleep.[15] It is important to be aware that patients with SOP who develop DPP due to a persistent head tilt, may not have the characteristic facial features seen in DPP. A case report by Stevens et al.[16] describes an infant with SOP, right tilt, until right DPP, that had a facial asymmetry that was consistent with her head tilt, suggesting that the facial changes secondary to the gravitational forces in SOP could be dominant over the deformational forces in DPP.

Gupta et al.[17] studied the ophthalmic findings in patients with plagiocephaly and found a normal prevalence of strabismus and astigmatism in DPP. Our analysis is consistent, in part, with these findings as some of the infants developed misalignment astigmatism. Furthermore, some of the patients presented with occlusion amblyopia. There were however, five (15.9%) patients diagnosed with strabismus compared to 4% in the study by Gupta et al. The increased rate in our group is also higher than the 5% prevalence in the general population,[18] but that may represent referral bias due to the nature of our sub-specialty clinic in sampling more due to the size of my study population.

The periocular asymmetry we observed in DPP was of no clinical significance in 47% of the patients. However, five patients with marked ocular asymmetry were misdiagnosed with congenital blepharoptosis at their first examination, which is a condition that requires periodic visits for evaluation of amblyopia, astigmatism and pupillary occlusion that could lead to amblyopia.[19] They were monitored for amblyopia until the correct diagnosis of pseudoptosis related to DPP was established. Furthermore, Horner syndrome was suspected in an infant with anisocoria and narrow right eye fissure, but after a negative 10% cocaine drops test, we concluded that she had a pseudo-Horner syndrome because of her pseudoptosis secondary to DPP and physiological anisocoria. We believe these are good examples of how recognizing the true cause of ocular asymmetry in children with DPP may avoid unnecessary tests and medical visits.

Limitations of this prospective study include the relatively small number of patients enrolled, the lack of access to the patients' orthotic/helmet treatment, and that they were at various stages of therapy. In addition, we had the chance to examine only two patients before and after DPP treatment, but they allowed us to observe improvement of the cranial position after helmet treatment. Also, the two infants in which periocular asymmetry was not noticeable were near completion of their helmet treatment at the time of their eye examination. Although our study was not designed to evaluate the outcomes of therapy on periocular appearance, our findings are consistent with a study using CT scans showing significant improvement of the frontal, orbital and zygomatic bones position post-treatment,[12] allowing us to postulate that appropriate orthotic helmet therapy may improve the ocular cosmesis in patients with marked orbital asymmetry.

An advantage of our study is the use of photographs that were carefully evaluated by a team accustomed to looking at periocular features. If periocular asymmetry in an infant with DPP is noted, examiners should consider pseudoptosis related to DPP in the differential diagnosis. It is imperative however, to identify misdiagnosed DLK patients and to refer them in a timely manner to craniofacial specialists. This distinction can be made based on the side of the forehead flatness (ipsilateral to occipital flatness in DLS, and contralateral in DPP), ear displacement (posterior in DLS, and anterior in DPP), pseudoptosis (usually ear present in DLS, ipsilateral to frontal flatness and contralateral to occipital flatness in DPP), and head shape (trapezoid in DLS, and parallelogram in DPP).[20]

Upon recognition of DPP as the cause of pseudoptosis, it is important to consider that, unlike other blepharoptosis, eye pursuit on the eye examination, ophthalmology follow-up visits is not required because the eyelid asymmetry in DPP is non-amblyogenic. It is important that those involved in the care of children's eyes understand the pathogenesis and periocular features associated with DPP in order to make the correct diagnosis, support appropriate therapy, and avoid unnecessary eye exams, tests or interventions.

Conflict of interest

The authors report no conflict of interest.

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ORIGINAL ARTICLE

Risk of Glaucoma Among Patients With Benign Essential Blepharospasm

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Purpose: To study ocular disorder associated with benign essential blepharospasm (BEB) as a risk factor for glaucoma. Patients with benign essential blepharospasm (BEB) experience involuntary, often-forceful contraction of the orbicularis oculi muscles, leading to functional visual impairment and spastic eyelid closure. This article explores the development of concomitant glaucoma in the BEB population.

Methods: Medicare claims files were used to identify patients with a diagnosis of BEB from 1994 to 2006. An age-, race-, and gender-matched control group consisting of patients without BEB was created using risk-score propensity score matching. The patients with BEB and those in the control group were followed for the development of any of the following open-angle glaucoma (POAG), closed-angle glaucoma (CAG), and other glaucoma (OG) for a period of 5 years. A Cox proportional hazards model was used to estimate the risk of glaucoma associated with BEB, controlling for age, race, gender, comorbidities, and other factors.

Results: There were 1,750 patients in each group. Mean age of patients was 74 years. Of the unexposed cohort, BEB patients did not develop POAG (hazard ratio [HR], 1.143; 95% confidence interval [CI], 0.876–1.474), CAG (HR, 1.477; 95% CI, 0.711–3.068), or other glaucoma (OG, HR, 1.106; 95% CI, 0.834–1.466) more often than patients not exposed to BEB. Other risk factors for glaucoma, such as cataract, diabetes, and other eye disorders, were significantly associated with POAG (HR, 1.502; 95% CI, 1.308–1.725), CAG (HR, 1.668; 95% CI, 0.848–3.019), or other glaucoma (HR, 1.296; 95% CI, 0.981–1.573).

Conclusions: BEB is not a risk indicator for POAG, CAG, or other forms of glaucoma.

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Despite evidence that elevated intraocular pressure (IOP) consistently represents a risk factor for the development of glaucoma,[1–3] several studies have documented a number of factors other than IOP associated with progression of visual field loss among glaucoma patients, including older age, thinner IOP, and

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METHODS

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TABLE 1. Diagnostic codes

Glaucoma	
Primary open angle	H40.1x
Closed angle	H40.2x
Other	H40.3x, H40.4x, H40.5x, H40.6x, H40.8x, H40.9x, H42.x*, H43.8x, H43.9x, H44.0, H44.1, H44.2, H44.3, H44.4, H44.5, H44.6, H44.7, H44.8, H44.9, H45.x, H57.1x, Q15.0, Z86.69, Z87.640, Z87.891, Z91.041, Z91.81, Z91.89, Z92.240, Z92.241, Z92.242, Z92.243, Z92.248, Z92.249
Age-related macular degeneration	H35.3x, H35.30, H35.32, H35.33, H35.37
Diabetes or HbA1c level	E08.3x, E09.3x, E10.3x, E11.3x, E13.3x, R73.09
Cataract	H25.xx, H26.1x, H26.2x, H26.3x, H26.4x, Y83.1
Diabetic retinopathy	H36.0, H36.01, H36.02, H36.03, H36.04
Diarrhoea comorbidity (flag)	
Diarrhoea comorbidity	R19.7x, A04.x, A08.x, A09.x
Cerebrovascular disease	I60.x, I61.x, I62.x, I63.x, I64.x, I65.x, I66.x, I67.x, I68.x, I69.x
Congestive heart failure	I09.81, I50.01, I50.11, I50.21, I50.31, I50.41, I50.9, I97.13, I97.81, I97.89, I97.9, I11.0, I13.0, I13.2, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, P29.0
Dementia	F00.x, F01.x, F02.x, F03.x, G30.x, F05.1
Chronic pulmonary disease	J40.x, J41.x, J42.x, J43.x, J44.x, J45.x, J46.x, J47.x, J60.x, J61.x, J62.x, J63.x, J64.x, J65.x, J66.x, J67.x, J68.4, J70.1, J70.3, J84.1, J84.9, J96.1, J98.2, J98.3
Rheumatic disease	M05.x, M06.x, M31.5, M32.x, M33.x, M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	K25.x, K26.x
Mild liver disease	B18.x, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73.x, K74.3, K74.4, K74.5, K74.6, K76.0, Z94.4
Diabetes without chronic complication	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes with chronic complication	E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E12.2, E12.3, E12.4, E12.5, E12.6, E12.7, E12.8, E13.2, E13.3, E13.4, E13.5, E13.6, E13.7, E13.8, E14.2, E14.3, E14.4, E14.5, E14.6, E14.7, E14.8
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9
Renal disease	N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N18.x, N19.x, N25.0, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2
Malignancy	Any C code, except C44.x
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
AIDS/HIV	B20.x, B21.x, B22.x, B24.x
Metastatic solid tumour	C77.x, C78.x, C79.x, C80.x
Peripheral vascular disease	I70.0, I70.1, I70.2, I70.8, I70.9, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I73.1, I73.8, I73.9, I77.1, K55.1, K55.8, K55.9, Z95.8, Z95.9

diagnosis of BEB, we excluded any patient with a previous diagnosis of glaucoma (other than ocular hypertension) or cataract surgery recorded before the first recorded diagnosis of BEB. To ensure that we identified only incident cases of BEB, we excluded any patient with a prescription for botulinum toxin (Botox, Dysport or Xeomin) recorded before the first recorded diagnosis of BEB. Prescriptions were identified using the CPRD Gold Therapy file, which includes prescriptions issued in primary care. Diagnoses recorded during the study period in secondary care were identified using the Hospital Episode Statistics (HES) database, which includes information on all admissions to National Health Service hospitals in England. Linkage to HES was performed by the CPRD.

A control cohort of patients never diagnosed with BEB was created. To ensure that BEB patients and control patients had similar opportunities for glaucoma detection, each patient in the control cohort was required to have at least 1 year of data recorded in the CPRD before the index date (the date of diagnosis of BEB for BEB patients). Control patients were also required to have at least 1 year of data recorded after the index date. Using a random number generator, we assigned 5,000 individuals meeting the control criteria to the control pool. We then matched a control to each BEB patient based on observable characteristics of the BEB patient using propensity scores calculated as described below. After matching, the sample consisted of 3,939 BEB individuals and an equal number of controls.

Due to the transfer of health data from England to 2,190 days in 2018 recorded. Censoring controls were an individual level, linkage to HMRA mortality in the United States or left the sample. Data on country of residence were obtained generally. Any person receiving outside the United States was censored as of January 1 of the year in which they first started living outside the United States.

Propensity Score Matching. Using the BEB patient and control pool, we predicted the probability of an individual having BEB using logit regression. Covariates were basic variables for male gender, white race, practice quality of treatment, geographical region of residence, socioeconomic status (employment deprivation), duration of registration with practice, chronological age, prevalence and recorded incidence of glaucoma, diabetes, retinopathy, age-related macular degeneration, cataract, and number of GP consultations recorded in the year before the index date. All propensity scores were calculated using the Stata 16 "logit" command.

All patients who received diagnoses were selected during the study period. The Charlson comorbidity index was calculated from diagnoses recorded on Medcodes recorded during the calendar year prior to entry to the sample.

In the context of the current study, the propensity score is defined as the probability of developing BEB, conditional on observed covariates. Propensity score matching reduces selection bias between BEB patients and controls by ensuring that the distribution of observed covariates is similar between BEB patients and controls. Each BEB patient was matched to a control patient with a similar propensity score (within a specified caliper) and those without.[15,16] Using the SAS (version 9.4) digitwise Mahalanobis[17] algorithm, we performed propensity score matching. This program ranks the "best" match first, matching individuals on 5 digits of the propensity score. For example, a person with a score of 5 digits, it then matched BEB individuals to controls by 4 digits, if unmatched by 4 digits, then by 3 digits. There was then a match on 1 digit was permitted from the analysis.

Matched control individuals were subsequently considered as conditional differences for all covariates used in the logit model to ensure differences were less than 10% (the propensity score matching).

Analysis. Cox proportional hazards models were used to calculate unadjusted and adjusted rates of primary open angle glaucoma (POAG: ICD10-CM 365.06), closed angle glaucoma (CAG: ICD9-CM 365.2), and other glaucoma (Table 1) between the BEB and control patients. Covariates were the same as those used in the propensity score matching.

RESULTS

Both the BEB and control groups were 29% male and were a median age of 76 years (Table 2). A total of 38% to 41% of observations were censored in the control and 27% to 28% in the BEB group, depending on the glaucoma diagnosis codes studied. Differences in percentages of observations censored. Data on individuals diagnosed with POAG could not be censored because having a POAG diagnosis code is an end point. Only 3% of each sample already carried a diagnosis of ocular hypertension. There were no standardized differences greater than 10% making the groups well balanced.[18,19]

Primary Open Angle Glaucoma Analysis. One hundred six (7.0%) persons in the BEB group and 75 (4.7%) patients in the control group developed POAG during the study period. In unadjusted models (Table 3), persons in the BEB group were not significantly more likely to develop POAG (hazard ratio (HR): 1.46; 95% CI: 1.09–1.96) compared with controls. Adjusting for additional covariates did not affect BEB individual's probability of developing this diagnosis (HR: 1.26; 95% CI: 0.95–1.67) compared with individuals from control group.

TABLE 2. Demographic statistics at baseline

	BEB group	Control group	Std. Diff
Male	40(%)	76.947	0.005531
Age	75.9	75.9	−0.16289
Black	0.019	0.017	−0.39197
Other race	0.002	0.004	0.24269
Carlton comorbidity index	1.301	1.256	−0.11747
Age-related macular degeneration	0.155	0.148	−0.02107
Cataract	0.697	0.697	0
Diabetic retinopathy	0.027	0.018	−0.06146
Diabetes mellitus	0.197	0.209	0.030698
Observations	3939	3939	

ICD: International Classification of Diseases; Std. Diff: standardized difference; BEB: benign essential blepharospasm.

Closed Angle Glaucoma Analysis. Eighteen (1.5%) of 1,210 BEB patients developed CAG compared with 12 (0.7%) in the control group. In the unadjusted model, the BEB group was not more likely to develop CAG (hazard ratio: 2.08; 95% CI: 0.99–4.38) compared with the non-BEB control group (HR: 1.47; 95% CI: 0.61–3.56). After allowing for confounders, a diagnosis of BEB did not affect a person's probability of developing CAG (HR: 1.47; 95% CI: 0.60–3.61).

Other Glaucoma (Non-POAG and Non-CAG) Analysis. Other glaucoma was recorded in 86 (4.8%) and 50 (3.2%) persons in the BEB and control samples, respectively. In the unadjusted model, subjects with BEB were not statistically significantly more likely to develop other glaucoma (HR: 1.56; 95% CI: 1.09–2.23) compared with controls. Adjusting for additional covariates did not affect a BEB individual's probability of developing other glaucoma (HR: 1.26; 95% CI: 0.88–1.80).

DISCUSSION

We found that BEB does not increase the risk for the development of POAG among Medicare beneficiaries compared with a control group without BEB. We found CAG and other glaucoma at similar control groups, and BEB did not affect the incidence risk of these groups. Previous investigations that link BEB fluctuation results in visual field defect asymmetries among patients with glaucoma.[1–3] Meanwhile, a report from the Early Manifest Glaucoma Trial disagreed with this finding.[4] Many studies have suggested that IOP fluctuation is associated with glaucoma development, while others have not.[5–7] These studies described a modification variability of IOP of less than 10 mm Hg.[8–10]

Applanation tonometry measures the IOP. We found that the IOP increases by 5 to 10 mm Hg among normal and glaucomatous eyes when the patient consciously closes the eyelid (such as examination).[11–14] However, these eyes were not examined to close their eyelids. Mills[11] placed a pressure transducer on 10 normal subjects. He found that the IOP increased by 10 and 20 mm Hg with a normal blink and total eyelid squeeze, respectively. Kontiola and Sivonen[12] reported that blinking increased the IOP by 10 ± 2 mm Hg, and forceful eyelid closure increased the IOP to 30 mm Hg. Drake-Duke[13] visualized the facial nerve in dogs and found similar results. Coleman and Trokel measured IOP elevation by placing a 23-gauge needle connected to a pressure monitor in the anterior chamber of an eye about to undergo enucleation. Passive blinking resulted in an increase of 5 to 10 mm Hg. Forceful closure elevated an average maximum 30 mm

TABLE 3. Hazard ratios (95% confidence intervals) from cox proportional hazard analysis: time to glaucoma for persons previously diagnosed with BEB

	POAG		Closed angle glaucoma		Other glaucoma		Any glaucoma	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
BEB	1.459 (1.071–1.546)	1.262 (0.950–1.822)	2.077 (0.991–4.380)	1.469 (0.696–3.015)	1.561 (0.994–2.449)	1.258 (0.800–1.977)	1.457 (1.092–1.946)	1.199 (0.910–1.577)
Age		1.092		1.216		1.027		1.089
Male		0.981 (0.750–1.283)		0.997 (0.479–2.075)		0.980 (0.598–1.606)		0.982 (0.765–1.260)
White		1.081		0.683		0.895		1.018
Other		0.771 (0.344–1.727)		0.419 (0.055–3.211)		0.559 (0.078–4.006)		0.703 (0.304–1.625)
Carlton comorbidity index		1.102		1.112		1.018		1.076
Cataract		1.111 (0.850–1.453)		0.735 (0.339–1.593)		0.934 (0.543–1.606)		1.016 (0.787–1.312)
Diabetes mellitus		1.311		2.439		1.507		1.599
Other race		0.504 (0.069–3.681)		0.274 (0.036–2.082)		0.815 (0.114–5.847)		0.577 (0.079–4.196)
Carlton comorbidity index		0.914		1.115		0.918		0.949
Diabetic retinopathy		0.665 (0.304–1.454)		0.897 (0.319–2.519)		0.893 (0.304–2.624)		0.975 (0.495–1.919)
Age-related macular degeneration		1.091		1.317		1.167		1.103
Cataract		0.727 (0.494–1.071)		0.956 (0.452–2.022)		0.826 (0.467–1.461)		0.799 (0.586–1.089)
Diabetes mellitus		0.961		1.417		0.889		1.015
Glaucoma		0.968 (0.651–1.441)		0.830 (0.330–2.088)		0.968 (0.588–1.777)		0.970 (0.670–1.404)
Diabetic retinopathy		1.084				0.828		1.017
Diabetes mellitus		0.401 (0.111–1.451)				0.254 (0.064–1.004)		0.318 (0.110–0.919)
Glaucoma		1.044		0.276		1.348		1.027
Diabetes mellitus		0.756 (0.470–1.215)		0.466 (0.099–2.200)		0.934 (0.484–1.803)		0.746 (0.461–1.207)
Observations	2,788	2,788	2,788	2,788	2,788	2,788	2,788	2,788

Only those covariates with statistically significant coefficients are shown.

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Ocular and Orbital Pain for the Headache Specialist

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Abstract: Ocular pain is most commonly associated with redness and inflammation; however, eye pain can also occur in the absence of grossly visible pathology. Pain in the quiet eye can be the first sign of a number of threatening conditions. Many of these conditions such as intermittent angle closure glaucoma, carotid artery dissection, idiopathic intracranial hypertension, and giant cell arteritis can lead to permanent vision loss or blindness. In this review, ocular history and examination techniques are summarized. The article also reviews pertinent ocular, orbital, referred, and other causes of eye pain in the quiet eye. The neurologist and headache specialist should recognize when consultation with an ophthalmologist is necessary.

Keywords: Ocular pain · Orbital pain · Eye pain · Quiet eye · Headache · Optic Migraine · Ocular surface disease · Episcleritis · Scleritis · Intermittent angle closure glaucoma · Posterior scleritis · Primary trocular headache · Trochleitis · Carotid artery dissection · Cavernous eye pain · Supraorbital neuralgia · Trigeminal neuralgia · Trigeminal autonomic cephalgia · Cluster headache · SUNCT syndrome · Hemicrania continua · Paroxysmal hemicrania · Giant cell arteritis · Idiopathic intracranial hypertension

Introduction

Nearly every specialist has seen patients with ocular and orbital pain. Most patients with eye pain present with accompanying symptoms such as redness, injection, proptosis, cloudy cornea, or visual loss. These cases are diagnosed without much difficulty upon referral to an ophthalmologist. However, many cases exist in which the patient presents with a quiet appearing eye which can present a challenge to all providers involved. Undiagnosed, some of these conditions can result in irreversible vision loss or systemic morbidity. In this article, we will discuss appropriate historical features and examination techniques (Table 1), a quick reference guide to various etiologies and treatments of pain in the quiet eye (Table 2), and when referral to an ophthalmologist is necessary. We divide eye pain into three categories: 1) eye pain from an ocular or orbital source; 2) eye pain referred from a distant source; and 3) eye pain from other sources.

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Ocular History and Evaluation for the Headache Specialist

Because the brain here is on a grossly normal appearing eye, history is of the utmost importance to determine the diagnosis. As with any chief complaint, the history focuses on quality, timing, location, modifying features, and review of systems (Table 1). Special attention should be given to symptoms of giant cell arteritis (GCA) in the elderly or migrainous symptoms in the young adult. Medication lists may reveal anticholinergic or sympathomimetic use, which can precipitate angle closure glaucoma. A substantial number of medications exacerbate symptoms of dry eye and dry mouth. Ocular history should include known eye conditions, use of systemic or topical ocular medications, ocular surgery, ocular trauma, corrective eyewear use, and any history of vision loss.

A full neuro-ophthalmologic examination includes specialized equipment unavailable to the practicing neurologist such as slit lamp biomicroscopy, quantitative intraocular

Table 1 Focused history of isolated eye pain

Timing
Onset (when started, suddenly, slowly, mediated)?
How long does it last (seconds, minutes, hours, days)?
How often does it occur (continuous, hourly, daily, weekly)?
Location
Where does it hurt (around or in the eye [how deep], along the temple, in the face)?
Quality
What does it feel like (sharp, shooting, stabbing, throbbing, aching, burning)?
How severe is it (0–10 scale)?
Modifying factors
Alleviations (closing or rubbing eyes, ibuprofen, other OTC drugs)?
Aggravations or triggers (bright lights, reading, moving, stress, sharing, touching, sleep)?
Associated features
Autonomic features (tearing, nasal congestion, red eye, ptosis)?
Blurred vision?
Double vision?
Migrainous symptoms (nausea, photophobia, phonophobia, scintillations)?
Special considerations in history (medications, and family history)
Any medications causing dry eye or angle closure glaucoma?
Any trauma, chemical injury?
Any personal or family history of migraine?
Any symptoms of giant cell arteritis (eye complications, weight loss, jaw pain, malaise)?
Systemic autoimmune disease?

OTC over the counter

Table 2 Causes of pain in the quiet eye

Condition	Associated Symptoms	Quality	Duration	Diagnostic test	Treatment
Ocular surface disease	Tearing, foreign body sensation, photophobia	Dull ache, pressure or gritty sensation, 1 or both eyes	Often constant or fluctuating throughout day	Topical anesthetic, fluorescein dye, Schirmer testing	Artificial tears, topical corticosteroids, topical cyclosporine, punctal plugs
Anterior uveitis	Headache, blurred vision, light sensitivity	Soreness, burning, dull pain	Days with prolonged healing	Refraction, corneal testing, Goldmann tonometry	Antiinflammatories, cycloplegics
Intermittent angle-closure glaucoma	Blurred vision, rainbow-colored halos, nausea, vomiting	Deep, profound eye and orbital pain	Minutes to hours	IOP home and perimetry evaluation	Laser treatment
Periorbital cellulitis	Variable effect on vision	Tenderness, periorbital and eyelid pain, 1 eye	Continuing until treated	Orbital ultrasound, computerized tomography (CT)	NSAIDs, antimicrobials, intravenous antibiotics
Primary headache syndrome	None	Dull to throbbing, often with ocular pain, 1 eye	Chronic with paroxysmal exacerbations	Patient must meet criteria as outlined in the text, MRI	NSAIDs, triptans and preventive medications (see the text for details)
Cranial artery dissection	Ipsilateral visual symptoms	Sudden onset, variable periorbital pain	Hours to weeks	Visual impairment on MRI, MRA, CTA	Anticoagulation for 3–6 months, carotid stent
Corneoscleral eye pain	Mild dry eye symptoms, tearing	Variable, dry gritty or scratchy pain, 1 or both eyes	Chronic with intermittent exacerbations	Topical fluorescein dye, genetic corneal dystrophy testing	NSAIDs, punctal occlusion, possible corneal transplant
Superficial scleritis or episcleritis	Minimal dysfunction possible	Mild to moderate discomfort	Several days to a week for episcleritis, 2 wk to months for scleritis	Similar to peripheral ulcerative keratitis	Antihistamine eye drops, phenylephrine, oral NSAIDs
Trigeminal neuralgia	Trigger zones	Shock-like, stabbing	Seconds to a few minutes per episode, 1 side	MRI brain with MS sequences or vascular loop	Carbamazepine, oxcarbazepine, lamotrigine, gabapentin
SUNCT	TAC, ipsilateral autonomic features	Burning, stabbing, deep	5–240 s	Diagnosis	Carbamazepine, lamotrigine, topiramate, gabapentin
Cluster headache	TAC	Sharp, stabbing, throbbing, boring	30–180 min	History	Verapamil, topiramate, high-flow oxygen, triptans for prophylaxis
Paroxysmal hemicrania	TAC	Sharp, stabbing, throbbing	2–30 min	Indomethacin trial	Indomethacin
Giant cell arteritis	Jaw claudication, diffuse scalp tenderness, polymyalgia rheumatica	General fatigability in 40% of patients	Chronic	Acute-phase reactants, temporal artery biopsy	Prednisone 1 mg/kg/day
Increased intracranial hypertension	Headache, vomiting, visual loss	Mostly diffuse and bilateral, but may be unilateral in papilledema, 50% with VI nerve palsy	Chronic	MRI, MRV brain, cerebrospinal pressure, lumbar puncture	Weight loss and acetazolamide, optic nerve fenestration, ventriculoperitoneal shunting

CTA computed tomographic angiography; CRAO retinal artery occlusion; MRA magnetic resonance angiography; MRV magnetic resonance venography; NSAIDs nonsteroidal anti-inflammatory drugs; SUNCT short-lasting unilateral neuralgiform pain with conjunctival injection and tearing; TAC trigeminal autonomic cephalgia

pressure (IOP) measurement, and Hertel exophthalmometry. Currently, these can be replaced by penlight evaluation, palpation of the globes through closed eyelids, and inspection of eye protrusion from above or below. Any clinician can perform and should be familiar with the rest of the examination including visual acuity, visual fields, color vision, pupillary evaluation, extraocular motility, fundus examination, corneal and facial sensation testing, and palpation of particular structures.

MRI has been used in many settings, but its yield is debatable. One such study evaluated 127 patients with isolated eye pain and a completely normal neuro-ophthalmologic examination. All underwent neuroimaging, and although 17% had some type of abnormality observed on the MRI, only one could have related to the ocular pain (pontine lacunar infarction). The authors concluded that neuroimaging has a decisively low yield in cases of isolated eye pain [1].

Causes of Eye Pain in the Quiet Eye

Ocular or Orbital Causes

Ocular Surface Disease

The most common cause of eye pain is overwhelmingly dry eye or aqueous tear insufficiency. The cornea contains the highest density of free nerve endings throughout the human body, and inadequate tear film coverage causes these trigeminal fibers to discharge. Recent evidence indicates that inflammation of the accessory lacrimal glands of the eyelid and conjunctiva contributes much to the pathophysiology of dry eye [2].

Patients often describe a dull ache, pressure, or pulling sensation, which can radiate around the eye and behind the eye. These symptoms typically improve in the morning and worsen as the day progresses. Reading, dry or windy environment, and computer use may exacerbate symptoms. Dry eye symptoms classically include stinging, burning, foreign body sensation, photophobia, tearing, and blurred vision. Signs, if present, can include conjunctival injection, swollen or erythematous eyelid margins, and mucous filaments. However, patients with dry eye may complain of isolated ocular or behavioral eye pain without any other signs or symptoms.

The ophthalmologist may argue that the patient who does not gain relief from topical anesthetics cannot have ocular surface disease. Interestingly, in dry eye, a chronic state of ocular irritation can lead to upregulation of central pain receptors despite interruption of peripheral nociceptive input from the anesthetic. Thus, patients with chronic eye pain may still have ocular surface disease. The neurologist can request that uncommonly performed diagnostic evaluations such as tear break-up time and Schirmer testing be performed to fully evaluate these patients. Schirmer testing involves placing filter paper strips into the lower cul-de-sac and measuring the degree of wetting after 5 min. This test could also easily be performed in the neurologist's office with minimal training required. Tear break-up time measures how long it takes for the tear film to begin drying and is measured at the slit lamp.

Treatment with artificial tears and washing the eyelashes using a hot washcloth results in improvement in many patients. Other options include low-dose topical corticosteroids, topical cyclosporine, or placement of punctal plugs.

Syndrome or Asthenopia

A fairly uncommon and probably overused cause of eye pain, asthenopia is a term used to describe the sensation of ocular discomfort that accompanies prolonged near work (ie, reading). True eyestrain occurs in teenagers or young adults usually from a small misalignment of the eyes or improper spectacle correction. Patients experience sore eyes, burning, tearing, blurred vision, and light sensitivity. Persistent near work may result in frontal or bitemporal headache in rarely holocranial headache. Careful cover testing or Maddox rod evaluation may show a subtle misalignment of the eyes such as a hyperdeviation or

constriction. Although often irritating symptoms often improve with rest and in the supine. Most symptoms of cyanosis likely represent ocular surface damage and a host of unethical pain may attenuate the symptoms. If the patient's eyelids persist, then refraction and endothelial evaluation is warranted.

Intermittent Angle Closure Glaucoma

Acute elevation of ocular tension of the drainage angle of the eye results in markedly elevated IOP. Intermittent angle closure glaucoma has been misdiagnosed as migraine with aura. The two share some similarities including unilateral eye pain. Blurred vision rainbow-colored halos around lights, nausea, and vomiting. The pain may be localized or referred to the ipsilateral forehead, and it may last a few hours. Patients with either diagnosis may choose to lie down in a dark room. In migraine with aura, the visual changes usually precede the headache. The blurred vision and halos begin simultaneously with the pain in intermittent angle closure glaucoma.

Besides revealing the gross appearance of the eye and IOP are normal. Triggers for angle closure include pupillary reading, sudden changes in lighting conditions, and use of cold, allergy, or anticholinergic medications. Occasionally, one can assess the depth of the anterior chamber by holding a penlight parallel to the eye. A shadow cast on the opposite side of the eye suggests that the central iris is protected forward and that the angle is narrow. Diagnosis of an occludable angle typically requires slit lamp and gonioscopic examination by an ophthalmologist. A laser iridotomy creates a passageway through the iris to prevent future angle closure attacks. One report described 11 patients with a history of migraine who were later diagnosed with intermittent angle closure glaucoma. Laser iridotomy in seven of the patients improved or eliminated "migraine" attacks [1].

Posterior Scleritis

Anterior scleritis presents with intense conjunctival and scleral injection observable within the palpebral fissure. However, as the name suggests, posterior scleritis results in inflammation of the posterior sclera and, therefore, the front aspect of the eye appears grossly quiet. These patients complain of severe, unremitting, boring pain progressively intensifying over days. Vision is variably affected depending on macular involvement. Posterior scleritis may be idiopathic or it can be associated with systemic diseases such as systemic lupus erythematosus, Wegener's granulomatosis, or sarcoidosis.

Posterior scleritis may cause a unique retinal detachment known as bullous retinal elevation. However, the diagnosis may require an orbital ultrasound, which demonstrates thickening of Tenon's space behind the sclera. Careful review of a fat-suppressed, postcontrast MRI may also show thickening of Tenon's space and enhancement of the sclera.

Treatment requires systemic therapy with NSAIDs, glucocorticoids, or other immunosuppressive drugs. One report described 47% of patients required these high-dose glucocorticoids and another immunosuppressive agent to control the disease [2]. If the history is consistent with posterior scleritis, then consideration of a trial of oral corticosteroids for several days or referral for fluorescein examination and ocular echography can be considered. Generally the pain in scleritis resolves within 48 h of corticosteroid treatment.

Primary Trochlear Headache (Trochlear)

The trochlea is a cartilaginous structure along the superomedial orbital rim that acts as a pulley for the superior oblique tendon. Primary trochlear headache or trochlear neuralgia is inflammation of the trochlea. Patients present with dull to severe pain in the supratrochlear region that worsens with eye movement. The pain may radiate to the ipsilateral hemicranium. It affects women in 90% of cases and autonomic features of other headache syndromes are absent [3].

Palpation over the trochlea reproduces the pain. Although unnecessary, MRI may show enhancement of the trochlea. Normal findings may be the result of the radiologist missing the diagnosis, the images missing the trochlea, or the MRI protocol failing to perform fat suppression. Treatment consists of NSAIDs and/or a single injection of long-acting corticosteroids over the trochlea. Relief often occurs rapidly with injection, and the patient can be free of symptoms for months to years. Some studies have reported that intranasal may relieve associated migraine pain [4].

Referred Pain Causes

Carotid Artery Dissection

Carotid artery dissection generally produces relatively sudden onset pain in the ipsilateral head, neck (face, or jaw and occasionally) in the periorbital region. The oculosympathetic traverses along the common carotid artery. As the angle of the mandible, the ocular fibers follow the internal carotid artery and the nasal fibers travel with the external carotid artery. Therefore, an internal carotid artery dissection may result in ipsilateral Horner syndrome without affecting facial sweating. The upper eyelid in Horner syndrome usually droops approximately 1 to 2 mm. The lower eyelid is often 1 mm higher on the involved side as well. The ipsilateral pupil is smaller and the disparity is more prominent in dim illumination. The anisocoria usually be noted at a brightly lit examination room.

Historically, the confirmation of Horner syndrome required 10% topical cocaine eye drops in each eye. With cocaine testing, the involved pupil does not dilate, while the normal pupil does. Apraclonidine 0.5% drops can also help diagnose Horner syndrome because the involved pupil develops supersensitivity. After instillation, the Horner pupil will dilate and the eyelid rises. The clinician observes equalization or reversal of the anisocoria [5] (Fig. 1).

Painful Horner syndrome is a carotid dissection until proven otherwise. The test of choice remains color fat-suppressed T1 MRI images of the neck through the base of the skull looking for blood products within the wall of the internal carotid artery. Magnetic resonance angiography or computed tomographic angiography may reveal a narrowed lumen on the involved side. Carotid dissection can lead to hemisphere stroke or ipsilateral vision loss and treatment involves anticoagulation for 6 months. Resolution of the dissection does not typically eliminate the pain or anisocoria.

Cervicogenic Eye Pain

The International Headache Society defines cervicogenic headache as "... pain referred from the neck and perceived in one or more regions of the head or face with abolition of the headache from a diagnostic block." There is a subset of patients who perceive neck pain as isolated eye pain. They can point quite close to the eye [6]. The spinal tract of the trigeminal nerve receives the afferent in the C2 root within the upper spinal cord. Experimental evidence in rodents shows that mechanical stimulation of the greater occipital nerve causes increased excitability of the dural afferents of the trigeminal nerve [7]. Therefore, patients with greater occipital nerve irritation can perceive pain in and around the ipsilateral eye.

Patients with cervicogenic eye pain describe various symptoms from chronic low-grade, boring eye pain to sensitivity pain. This typically occurs unilaterally but may be bilateral. Interestingly, some patients deny the presence of neck pain, but palpation along the course of the greater occipital nerve causes localized pain and can also reproduce the ipsilateral eye pain. Initial treatment involves NSAIDs or muscle relaxants for several days. Neck physical therapy or massage therapy may also improve the pain. In our hands, greater occipital nerve block of 0.5% lidocaine without epinephrine and 40 mg of triamcinolone often induces durable relief. Botulinum toxin injections also the symptoms; injects muscle has also proven successful in some patients [8].

Trigeminal Neuralgia

Trigeminal neuralgia characteristically involves the V2 distribution; however, some patients describe the pain as ocular only. These paroxysmal episodes last seconds and feel like an electric shock. The pain occurs several times a day and is often, but not always, precipitated by mild sensory stimulation of trigger areas which may be located anywhere within the territory of the affected trigeminal nerve. Typical antecedent stimuli include touching teeth or hair, chewing, talking, washing, and applying makeup. Trigeminal neuralgia is most commonly seen in middle-aged and elderly women [9,10].

Patients with trigeminal neuralgia do not typically have facial numbness, and reduced sensation should suggest a trigeminal neuropathy. One report estimated that 2% of 5,972 patients with trigeminal neuralgia had a tumor triggering the facial pain [11]. Therefore, management of trigeminal neuralgia should include an MRI and close examination with the radiologist [12]. Facial shingles can occur with trigeminal spread. These lesions would along branches of the trigeminal nerve causing constant pain and numbness and have been commonly diagnosed as trigeminal neuralgia.

Patients generally respond well to treatment with gabapentin, carbamazepine, or lacosamide. Some patients require radiofrequency ablation or intravascular decompression for intractable symptoms.

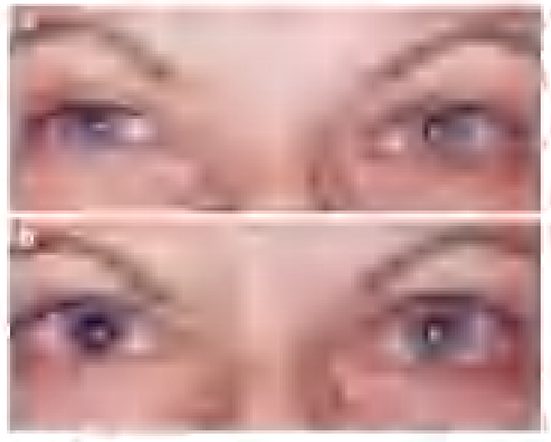

Fig. 1 a Ten years ago a deep venous syndrome, she had pain and the right peripheral vision was double. She was left to right medial to the ipsilateral vision was better than the left pupil and the suspended ptosis [corrected]

Intracranial and Supracranial Neuralgia

Supraorbital and infraorbital neuralgia, which refer to trigeminal distribution in V1 and V2, respectively, may also be referred to the eye. They are both rare clinical syndromes defined by similar diagnostic criteria including paroxysmal or constant pain and tenderness in the area supplied by the given nerve and relief by anesthetic blockade over the region. Sensory disturbances (eg, paresthesia, allodynia, and hypoesthesia) and typical autonomic symptoms such as ipsilateral precipitating mechanisms (triggers may or may not be present. Some "primary" neuralgia may be caused by chronic and subtle microtrauma [13•] such as persistent swim goggle use or tight headband wear.

Pharmacologic treatment is based on anecdotal evidence. Small studies have shown improvement with the use of gabapentin (900–2,400 mg daily), pregabalin (150–300 mg daily), or amitriptyline (25–75 mg daily). Corticosteroid injections are beneficial in the trigeminal distribution. Surgical decompression of the nerve from tissue bands or bony compression can also be considered [14].

Other Causes

Trigeminal Autonomic Cephalgias

Trigeminal autonomic cephalgias (TACs) exhibit unilateral periorbital pain with ipsilateral autonomic symptoms (eg, lacrimation, nasal congestion, conjunctival injection, lacrimation, miosis, and facial sweating). The chief complaint may be unilateral intermittent eye pain. However, on careful history and examination, patients appear normal; however, with close observation, subtle symptoms may become prominent. The TACs may be difficult to distinguish from painful Horner syndrome and these patients often undergo MRI evaluation to rule out carotid dissection.

Short-lasting unilateral neurologic pain with conjunctival injection and tearing (SUNCT) syndrome is characterized by brief stabbing unilateral pain of moderate to severe intensity periorbital pain accompanied by ipsilateral autonomic symptoms, lacrimation, and rhinorrhea. The duration of episodes may be 30 per hour, although most patients experience about 5 to 6 attacks per hour. The autonomic response is often the most prominent component (versus cluster and trigeminal neuralgia where pain is the dominant feature). The attacks may become bilateral but the most severe pain remains unilateral. SUNCT primarily affects males with a gender ratio of 1.72:1 [15]. Treatment of patients includes lamotrigine, topiramate, or lidocaine [16].

Cluster headache presents with severe unilateral orbital and temporal pain with autonomic symptoms. Patients often describe it as the most painful event in their lives [17]. The onset is extremely rapid, without the preliminary signs characteristic of migraine. Common cluster headache lasts from 30 min to 2 h or more. The headache usually occurs in clusters with multiple attacks occurring throughout the day usually for a few weeks. This condition is most commonly found in men 20 to 40 years of age. The most effective acute treatments are sumatriptan injections and high-flow oxygen. Most patients require pharmacologic prophylaxis with verapamil, lithium, or other preventives.

Paroxysmal hemicrania (PH) and hemicrania continua (HC) are other TACs. PH presents with unilateral, brief, severe attacks of pain associated with autonomic features as observed in all TACs. PH is excruciating in severity and is described as sharp, stabbing, shooting, and/or shooting pain. PH is usually unilateral and occurs without side shift in over 95% of patients [18]. Attacks are short (average, 5–30 min) and are more frequent than cluster headaches with some patients reporting PH attacks in excess of 40 per day. HC is very similar to PH; however, the pain is continuous and it varies in severity with superimposed attacks of more severe pain lasting from minutes to several days [19].

The hallmark of PH and HC is the absolute response to pain with indomethacin, which distinguishes them from the other TACs [20]. Thus, indomethacin is used both as a diagnostic test and a treatment in patients suffering from these conditions. Dosing starts with 75 mg daily in administration and increases to 150 mg if symptoms persist. A relatively high number of secondary cases of PH and HC have been reported and an MRI scan to evaluate for primary structural brain lesions is recommended [21].

Giant Cell Arteritis

GCA is the most common primary systemic vasculitis in older adults. More common in females than males, GCA causes between 50 to 85 years of age and the incidence rises with age. Permanent vision loss is the most serious complication of GCA. Early identification and subsequent treatment are vital to prevent vision loss. Headache is the most common symptom of GCA and occurs in more than 90% of patients. Rarely, this may present as isolated scalp or orbital pain. Among the many systemic symptoms (eg, malaise, scalp tenderness, polymyalgia rheumatica, fever, weight loss, appetite loss) of GCA, jaw claudication has the highest specificity. Palpation of the temporal artery may show tenderness, pulselessness, or tortuosity.

Acute-phase reactants (Westergren sedimentation rate, C-reactive protein, and platelet blood counts) may show elevated results. A general rule of thumb is the Westergren erythrocyte sedimentation rate normally is half age in men and half age +10 in women. The normal values for C-reactive protein vary by laboratory and would be interpreted without immediate urgency. Patients may present with polymyalgia rheumatica (PMR) symptoms, which is characterized by proximal muscle pain and stiffness, usually in the shoulder girdle and hip girdle. Approximately 50% of patients with GCA have PMR symptoms. Patients with PMR often present with morning stiffness lasting more than 45 min, fatigue, and depression. Laboratory findings are similar to GCA, with elevated acute-phase reactants. Although PMR is not associated with permanent vision loss, it can be extremely debilitating and may require long-term steroid therapy.

Diagnostic Assessment/Treatment

Common symptoms of idiopathic intracranial hypertension (IIH) include headaches, vomiting, tinnitus, and audible pulse synchronous bruit. Headaches are the most persistent clinical feature and present in over 90% of cases. The headache can be chronic, diffuse, and nonspecific in character or localized to one or both eyes. Many patients describe it as worse in the morning and exacerbated by Valsalva [22]. Patients with IIH often are young women of childbearing age with a body mass index of greater than 30 kg/m^2. Patients in this demographic can suffer from a bias regarding this diagnosis.

There are a few points of emphasis. It is extremely rare for a patient with IIH to have normal appearing optic nerves without edema. Fundoscopic examination should include evaluation for spontaneous venous pulsations (SVPs). The presence of SVPs signals that the intracranial pressure is normal at the time of examination. Keep in mind that 10% to 20% of normal individuals do not have SVPs as their absence does not indicate increased pressure. More commonly, ophthalmologists are relying on fluorescein-guided applanation tonometry to measure opening pressure. These are often performed in the prone position. Normal values are given for pressures measured in the lateral decubitus position, but not the prone position. There is no good evidence that pressures measured in the prone position correlate well with pressures measured in the lateral decubitus position. Additionally, variation in the level of the IJV sinus which requires the radiologist to add the length of the needle (typically ~9 cm) to the manometer reading if the patient is in the prone position. Unfortunately this is not uniformly performed and the radiologist often does not dictate how he measured the pressure.

Initial management involves weight loss and consideration of the safety of metabolic renal loss, optic nerve sheath fenestration or ventriculoperitoneal shunting may be required.

Conclusions

Isolated eye pain rarely answers from a primary ocular cause or an inflamed greater occipital nerve. Cluster can range from benign conditions such as dry eye syndrome to potentially disabling disorders such as GCA. A thorough knowledge of presenting signs and symptoms and possible pharmacologic findings will aid in proper diagnosis, management, and ophthalmologic referral.

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Neuro-ophthalmology and the eye (JP Sloan, Section Editor)

Treatment of Vision Loss in Giant Cell Arteritis

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Opinion statement

If giant cell arteritis is suspected as a cause of visual loss, emergent management is necessary. Clinical suspicion should prompt the practitioner to obtain laboratory studies and initiate treatment prior to establishing the diagnosis. The evaluation includes immediate erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count (CBC). Treatment begins with high-dose intravenous corticosteroids. We recommend intravenous methylprednisolone (250 mg every 6 h) for 3 to 5 days. During that time, a temporal artery biopsy should be performed for pathologic diagnosis. We also begin daily aspirin orally. After the initial bolus of intravenous corticosteroids, therapy transitions to oral prednisone administered at 1 mg/kg per day until the activity of the disease process attenuates, as demonstrated by improvement in systemic symptoms and normalization of both ESR and CRP. This change usually occurs in the first 3 to 4 weeks. The patient should be followed closely, with therapy tapered as guided by systemic symptoms, ESR, and CRP. To maximize the use of remaining vision, appropriate patients should be referred to specialists for help with low-vision therapies, assistive devices, and precautions to protect the better-seeing eye.

Introduction

Giant cell arteritis (GCA), vasculitis of medium and large vessels, affects individuals over 50 years of age, with a mean age of 74 years. It occurs in women two to three times more often than in men and is most common among individuals of northern European descent.

The most devastating complications of GCA are ischemic events. Occurring in 20% to 50% of patients with GCA, these events include vision loss or, less commonly, cerebrovascular accident (CVA). The pathophysiology of the disease involves vessel inflammation with myointimal thickening and stenosis. The stenosis results in either complete occlusion of the vessel lumen or turbulent flow causing thrombosis [1•, Class II]. Initial loss of vision is often unilateral, but it can quickly progress to bilateral blindness in most patients if treatment is delayed.

Vision loss occurs primarily through occlusion of the short posterior ciliary artery, or less commonly the central retinal or ophthalmic artery. Rarely, occipital lobe CVA can also occur secondary to GCA.

Ophthalmologic findings depend upon the mechanism of vision loss. Occlusion of the short posterior ciliary arteries most often causes ischemia of the optic nerve head, producing visual loss with a swollen optic disc (arteritic anterior ischemic optic neuropathy [AAION]). Loss of vision can range from partial to complete but is typically permanent, without significant improvement. In some cases, patients lose vision from ischemia to the choroid, which is also supplied by the short posterior ciliary arteries. If the choroidal ischemia is isolated, then visual loss can recover completely with prompt initiation of corticosteroids [2, Class IV]. Central retinal artery occlusion (CRAO) results in the characteristic fundus appearance of macular whitening with a central "cherry red spot." Finally, ophthalmic artery occlusion can present with posterior ischemic optic neuropathy (normal-appearing fundus), AAION, retinal artery occlusion, or any combination of the three. Without treatment, loss of vision in the other eye typically occurs in days to weeks.

Vision loss is typically sudden, often with marked deterioration of visual acuity. However, normal visual acuity does not rule out AAION. Patients may note a preceding history of transient vision loss or diplopia. Visual field testing often demonstrates extensive and severe defects. Pupillary examination may reveal a relative afferent pupillary defect with unilateral or asymmetric visual loss from optic neuropathy or CRAO. In a patient with anterior ischemic optic neuropathy, the presence of intact visual acuity strongly suggests GCA. In atypical cases of AAION, choroidal filling delay on fluorescein fundus angiography is nearly pathognomonic for GCA.

Patients can present with a wide array of systemic symptoms which are often nonspecific. A probing review of systems may reveal previous afflictions such as headache, jaw claudication, scalp tenderness, jaw claudication, visual loss, fevers, sweats, malaise, anorexia, weight loss, and symptoms of proximal myalgias and stiffness resembling polymyalgia rheumatica. The most specific symptom is jaw claudication with an odds ratio of 9.0 for GCA. Clinicians should palpate the temporal arteries for tenderness, induration, and pulse. Serologic evaluation should include acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Various formulas for the upper limit of normal values for these have been proposed. The simplest formula for ESR remains age divided by 2 for men and age divided by 2 plus 5 for women. As a confirmatory study, up to 21% of patients with visual loss from GCA can present with a normal ESR or lack of systemic symptoms. Accessible, each laboratory has its own normal range for CRP. It is crucial to note that some laboratories report CRP in mg/dL and others in mg/L. Hayreh et al. [3, Class III] proposed a CRP threshold of 2.45 mg/dL. Based on this value, the sensitivity for detecting GCA was found to be 100% with CRP and 92% with ESR at least 40 mm/h. Using a combination of ESR and CRP, the specificity for GCA was 97%.

In suspected cases, a temporal artery biopsy should be performed for definitive diagnosis within 7 to 10 days of initiating corticosteroids to avoid a false-negative result. The patchy nature of temporal artery involvement mandates a specimen at least 2 cm in length. Temporal artery biopsy is considered the "gold standard" diagnostic test for GCA, with a specificity of >90%. Studies of bilateral temporal arteries in the ophthalmology setting have a remarkable rate of 56% (95% CI 39%–71%) [4, Class III]. The sensitivity of temporal artery biopsy has been estimated at 87.1% [5, Class IV]. Debate exists over the value of performing a unilateral versus bilateral biopsy. We prefer to perform a unilateral biopsy (but obtaining at least 2 cm of artery). If the biopsy is negative but the clinical history is convincing, we may opt to treat for GCA. If the biopsy is negative and the clinical scenario remains controversial, we will perform a biopsy on the contralateral side.

Treatment

Preemptive Treatment

Glucocorticoids

- The mainstay of treatment for GCA is glucocorticoids. Immediate therapy suppresses inflammation and attempts to prevent further visual loss in the affected eye and, more importantly, in the unaffected eye. Despite high-dose glucocorticoid therapy, further unilateral or bilateral vision loss can occur [6, Class IV]. When vision loss occurs during treatment, it usually does so within the first 5 days of initiating high-dose steroid therapy [7, Class IV]. Considerable debate surrounds dosing, administration route, tapering of therapy, and total duration of therapy.
- A short course of intravenous methylprednisolone is often initiated for both GCA patients presenting with visual symptoms and patients with visual loss suspected of harboring GCA. There is little consensus about dosing and duration of therapy, with methylprednisolone regimens ranging from 250 mg for a single day to 1,000 mg per day for 3 days. The typical therapy consists of 15 mg/kg per day for 3 days, prior to oral prednisone therapy.
- Oral prednisone is widely used to treat GCA. The initial dose seems to vary by medical specialty, perhaps owing to inherent differences in training or reflecting the higher doses often used when vision loss occurs. Some trials in the rheumatology literature have included both patients with polymyalgia rheumatica and those with GCA, whereas trials in neuro-ophthalmology have included only patients with GCA and recent or impending vision loss. The rheumatology literature often suggests beginning at lower doses of prednisone, on the order of 20 to 40 mg/day. The neuro-ophthalmology literature suggests beginning prednisone at 1 mg/kg per day, which generally means 60 to 120 mg/day. We treat patients with visual loss suspicious for GCA with 250 mg of methylprednisolone four times daily, but a reasonable alternative is 1 g of methylprednisolone once daily.
- The evidence remains inconclusive regarding whether initiating intravenous or oral corticosteroids is more beneficial with respect to visual acuity. To study the course of visual deterioration during initial treatment of GCA, Hayreh and Zimmerman [7, Class IV] followed GCA patients presenting both with and without vision loss. Patients presenting with vision loss did not experience deterioration of vision during therapy. Of those GCA patients presenting with vision loss, the authors reported further visual deterioration among 6 (12.5%) of 48 patients who received intravenous dexamethasone (150 mg every 6 h for 1–3 days) and 3 (3.1%) of 97 patients who received high-dose oral prednisone (80–120 mg daily). This study did not find that intravenous therapy was more effective than oral therapy in preventing visual deterioration, but this was a retrospective study of nonrandomized patients, and those patients who received intravenous therapy had significantly worse visual acuity, which could have affected the final outcome.
- Once vision loss has occurred, substantial improvement of visual acuity is unusual. Danesh-Meyer et al. [6, Class IV] reported a visual acuity improvement in 8 of 29 eyes, but the visual fields did not change significantly. The apparent improvement in visual acuity without improvement in the central visual field may represent eccentric visual fixation with more effective use of remaining vision [8, Class IV].

- The active phase of GCA becomes quiescent once systemic symptoms have resolved, visual changes have remained stable, and serologic markers of inflammation have maintained their nadir. Tapering of glucocorticoids is a highly individualized process. Relapse of GCA while tapering steroids can threaten vision. Therefore, tapering requires a close follow-up process and often takes 1 or 2 years to achieve a maintenance dose or eventual discontinuation of steroids. Systemic symptom monitoring or laboratory evaluation alone is insufficient to direct tapering [10, Class IV]. Increases in ESR and CRP could indicate a relapse of GCA and may call for increasing the oral steroid dose to the previously effective dose [11, Class IV]. Corticosteroids should be administered daily while tapering, as alternate-day dosing appears increase relapse risk [12, Class II].
- Glucocorticoids carry the risk of significant adverse effects, especially in treating an elderly population. Serious effects include peptic ulcer disease, avascular necrosis of the femoral head, psychosis, and sudden death possibly due to acute myocardial infarction. Long-term systemic glucocorticoid use can affect other health problems, including obesity, osteoporosis, diabetes, and hypertension. During their course of treatment, 58% of patients had at least one steroid-related adverse effect [13, Class IV]. Vigilance in the prevention and treatment of adverse effects is essential during the management of long-term therapy with glucocorticoids in this elderly patient population.

Antiplatelet and anticoagulant therapy

- Aspirin reduces the risk of secondary stroke and myocardial infarction. It has also been shown to reduce the risk of primary stroke in women. Heparin is often given in patients with an acute cerebrovascular accident, and Coumadin reduces the risk of cardioembolic stroke. GCA can cause occlusion or thrombosis of the affected vessel, which can result in visual loss. Though thrombocytosis is common in active GCA, with platelet counts greater than 400,000/mm^3 [14, 15, Class III], the effect of thrombocytosis on vascular occlusion remains unclear. Some authors have reported an association between thrombocytosis and vision loss in GCA, possibly from an increased risk of thrombosis [16, Class IV]. Other authors have found no significant difference in the incidence of severe ischemic events associated with thrombocytosis [15, Class III].
- Three retrospective studies have evaluated the use of aspirin as an adjuvant therapy to steroids in GCA. Nesher et al. [17, Class III] demonstrated that aspirin decreased the rate of cranial ischemic complications in patients with GCA. The decreased incidence of vision loss and CVAs was observed both at presentation with GCA and at follow-up, compared with those not taking aspirin (OR, 0.2). At follow-up, cranial ischemic events developed in 2 (3%) of 71 patients taking aspirin and prednisone, compared with 12 (13%) of 93 taking prednisone alone. The incidence of ischemic events in the aspirin group was decreased despite a higher prevalence of risk factors for cerebrovascular disease.

- A study by Narváez et al. [18, Class III] retrospectively evaluated severe ischemic complication in GCA patients taking aspirin. The authors did not observe a protective effect of antiplatelet therapy in comparing the incidence of severe ischemic complications. Only 5 patients received intravenous glucocorticoids for visual symptoms at presentation. This study differed from the previous study by defining four severe ischemic complications in their outcome:
  - Visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia)
  - Cerebrovascular accidents (stroke and/or transient ischemic attacks)
  - Large-artery stenosis of the extremities that caused signs of occlusive manifestations (limb claudication) of recent onset
  - Acute coronary syndromes (acute myocardial infarction or unstable angina)

  This difference in outcome measure is worthy of mention, as it included extracranial ischemic events and transient ischemic events. Additionally, the antiplatelet group in this study (n=37) was substantially smaller than the control group (n=84) and had significantly higher risk factors for atherosclerosis (65% vs. 20%). The methodology of this study makes it difficult to draw conclusions related specifically to vision loss in GCA.
- A retrospective study by Lee et al. [19, Class III] evaluated both antiplatelet and anticoagulant agents during treatment for GCA. Fewer ischemic events occurred in the groups of patients who received antiplatelet or anticoagulant therapy. This study also observed no increased risk of bleeding complications. The authors concluded that either antiplatelet or anticoagulant therapies may reduce the risk of ischemic events in GCA. The authors recommended consideration of adjunctive low-dose aspirin in the treatment of GCA for patients without contraindications.
- The ideal dosage of aspirin therapy remains unknown. Studies have not shown any differences between 50 and 300 mg of daily aspirin in reducing secondary stroke [20, Class I]. Therefore, we recommend an 81-mg daily aspirin tablet as adjunctive therapy.
- Isolated case reports have demonstrated significant improvement in visual function with the use of heparin [21, 22, Class IV] and low-molecular-weight heparin [23, Class IV] in the treatment of visual loss from GCA, but the benefit of heparin remains unknown.

Occupational and physical therapy

- Low-vision therapy may involve a variety of rehabilitation interventions that can assist in social, occupational, and home activities. Eccentric fixation training teaches patients to improve the use of existing vision. Visual training skills can assist with reading, switching points of interest, and locating and tracking targets both near and at a distance.
- Occupational therapy can assist patients with self care, meal preparation, and writing, and functional mobility training increases safe walking and fall prevention. Assessment of the home or workplace can improve lo-

dependent living. Training may be necessary to assist some patients with driving, or to explore alternative transportation. Therapists also can work with patients to increase their awareness and use of community services.

Assistive devices

- Many devices are available to assist patients with impaired vision. Low-vision aids include spectacles, magnifiers, telescopes, video magnifiers, closed-circuit televisions, and changes in lighting to improve contrast. Nonoptical aids include large-print text or expanding font on computers or tablet devices. Alternatively, sight substitutes including audio books or computer programs capable of reading text aloud may be used to minimize dependence on vision.
- Canes and service dogs represent other aids for mobility.
- Those patients who have lost significant vision in one eye need to take additional precautions to protect the vision of their better-seeing eye. These precautions include wearing unbreakable plastic lenses at all times to prevent unexpected injury.

Emerging therapies

Steroid-sparing agents

- Because of the substantial adverse effects of prolonged use of glucocorticoids, there is strong interest in finding alternative therapies. Studies have compared the effect of immunosuppressive agents as adjunctive therapy versus the use of corticosteroids alone, to determine whether the adjunct treatment hastens the corticosteroid taper.

Methotrexate

Methotrexate, the most studied of steroid-sparing therapies, has conflicting evidence regarding its efficacy. Two studies found that methotrexate had no significant effect upon GCA relapse rate or overall steroid dose during 1 year of follow-up [24, 25, Class II], but another study showed a significant reduction in relapse rate and cumulative steroid dose after 2 years [26, Class I]. A meta-analysis of trials studying adjunct methotrexate found a significant reduction in cumulative steroid dose at 48 weeks of therapy [27, Class I], but the benefit did not become apparent until therapy had continued for 6 to 9 months. The meta-analysis also demonstrated a reduction in relapses of GCA with adjunct methotrexate therapy. Although the methodology differs between trials, it seems that methotrexate does offer a steroid-sparing effect with prolonged therapy. These studies did not find a significant difference in adverse events, and the possible clinical benefits of methotrexate must be weighed against the small risks of therapy.

Azathioprine

Azathioprine may have a slight steroid-sparing effect during the tapering of glucocorticoid therapy in GCA and polymyalgia rheumatica [28, Class II]. Again, this effect of azathioprine did not become apparent until after a year of therapy. Azathioprine can be associated with significant adverse effects, including carcinogenesis and liver toxicity.

Cyclosporine A

In a trial designed to study cyclosporine for the treatment of GCA, cyclosporine did not demonstrate a significant improvement over corticosteroids alone [29, Class II]. Adverse effects were frequent among patients taking cyclosporine and caused many to halt therapy.

Infliximab

Two prospective, randomized trials studied the use of infliximab for GCA [30, 31, Class II]. Both showed no benefit from infliximab therapy. No safety issues were identified, but one of these trials was terminated early after no beneficial effect was found [31, Class II].

Adalimumab

Case reports have suggested a benefit to TNF-α receptor–mediated therapies such as adalimumab [32, Class IV] and etanercept [33, Class IV]. There is currently little evidence for the use of these agents, but a randomized controlled trial is currently ongoing to study the efficacy of adjunct adalimumab in GCA as a potential agent to decrease steroid dosage [34].

Other therapies

- Proposed therapies have include the blockade of cytokines involved in GCA, such as interleukin-1 and interleukin-6; these remain under investigation [35, Class IV].

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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- • Of importance

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This paper revealed that GCA causes occlusion of vessels by stenosis or thrombosis, suggesting a role for adjuvant antiplatelet or anticoagulant therapy.

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The Efficacy and Safety of Teprotumumab in Geriatrics Patients: A Multicenter Study

[illegible]

METHODS

[illegible]

[illegible]

Statistics

[illegible]

RESULTS

Demographics

[illegible]

Short-Term Treatment Outcomes

[illegible]

Long-Term Treatment Outcomes

[illegible]

Adverse Events

[illegible]

Musculoskeletal Disorders

[illegible]

Metabolism and Nutrition Disorders

[illegible]

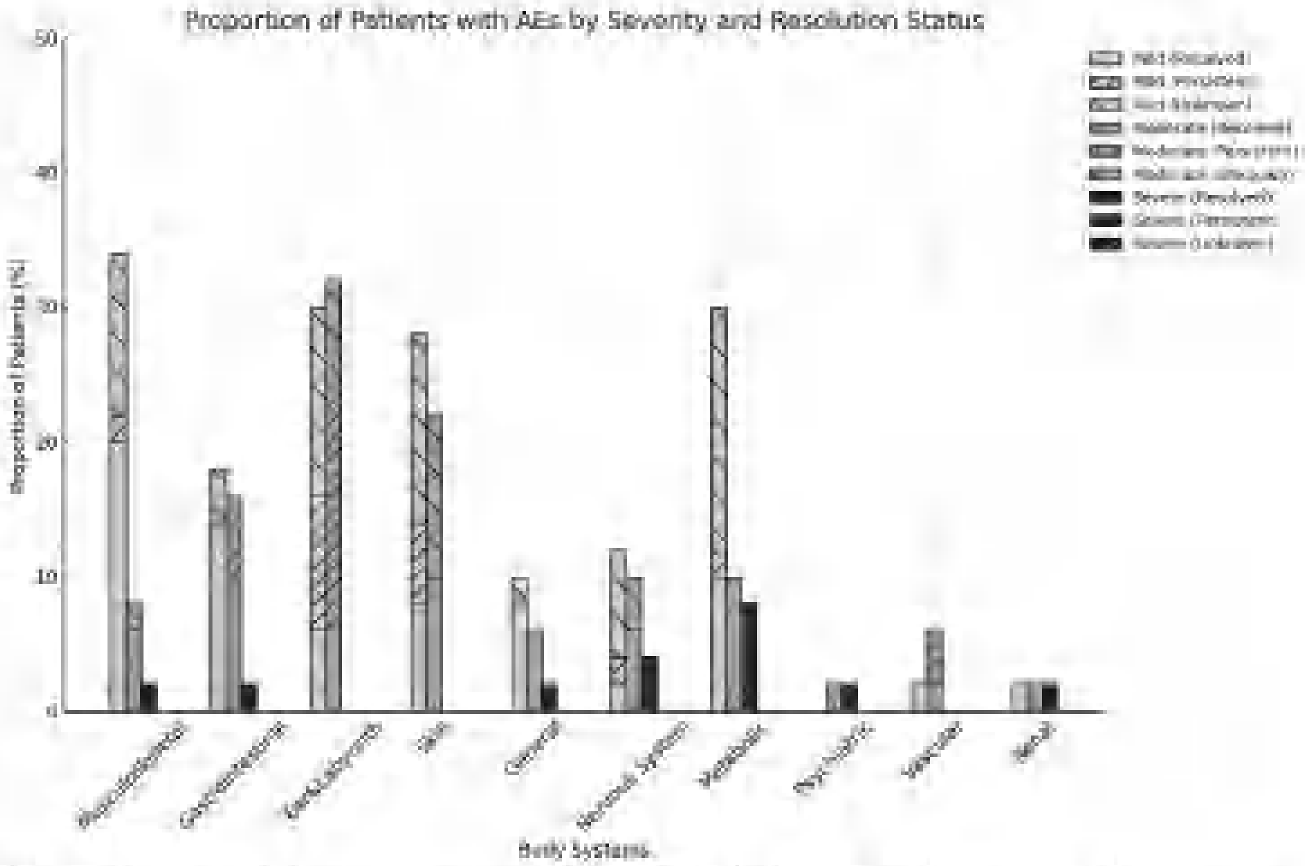

FIG. [illegible]

Hospitalization

[illegible]

Nervous System

[illegible]

General Disorders

[illegible]

Vascular Disorders

[illegible]

Renal Disorders

[illegible]

Psychiatric

[illegible]

Hospitalization

[illegible]

Discontinuation

[illegible]

DISCUSSION

[illegible]

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Brief Reports

Retrobulbar Hemorrhage Nine Days after Cosmetic Blepharoplasty Resulting in Permanent Visual Loss

Christopher A. Tyler, M.D., Shivani Bhatt, M.D., Jeffrey J. Weiss, M.D., and Richard D. Gunton, M.D.

Abstract: A healthy 45-year-old man had a retrobulbar hemorrhage 9 days after cosmetic upper eyelid blepharoplasty that resulted in permanent visual loss. After performing a left lateral canthotomy and cantholysis, intraocular pressure returned to normal and vision improved from no light perception to 20/30; however, the patient did have permanent visual field loss. To our knowledge, this is the longest period of time after blepharoplasty that a retrobulbar hemorrhage occurred. Ophthalmologists should have a heightened level of suspicion 1 to 2 weeks after surgery.

Retrobulbar hemorrhage is one of the most serious complications of blepharoplasty, with an overall incidence of 0.052%.[1] Typically, symptoms of the hemorrhage (pain) or sign (a tense orbit) are noticed within 24 hours after surgery.[2,3] We present the unique case of a patient who had development of a retrobulbar hemorrhage 9 days after cosmetic blepharoplasty, with loss of light perception and permanent visual loss.

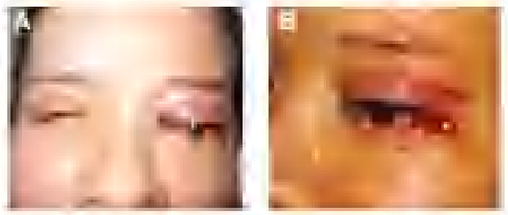

FIG. 1. A, 45-year-old man with severe periorbital ecchymosis, chemosis, and subconjunctival hemorrhage 9 days after cosmetic upper eyelid blepharoplasty. B, The patient after lateral canthotomy and cantholysis.

CASE REPORT

A 45-year-old Hispanic man presented to the emergency room with an eye injury, limited extraocular movements, chemosis, subconjunctival hemorrhage, and eyelid ecchymosis 9 days after bilateral cosmetic upper eyelid blepharoplasty performed by an ophthalmologist (Fig. 1A). He had no medical problems and was taking no medications or supplements and denied an ocular history of trauma. On the afternoon of presentation, he reported that vision suddenly decreased in his operative eye. Before coming to our emergency department, he had called the operating physician and was instructed to go to the nearest hospital. He arrived in our emergency department 7 hours after the onset of symptoms.

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FIG. 2. A, Axial CT of the left orbit (bone window) demonstrating compound proptosis with widening of lamina papyracea. B, Coronal reformatted (bone window) CT of the left orbit.

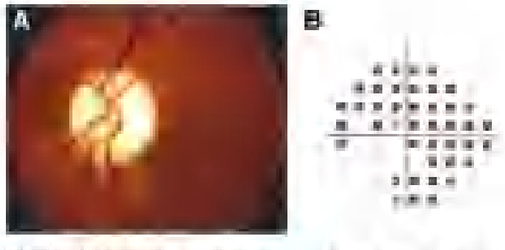

FIG. 3. A, Optic disc pallor (arrow) consistent with optic atrophy in the left eye. B, Humphrey visual field of the left eye demonstrating superior and medial defects.

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Cavernous Sinus/Orbital Apex Syndrome Associated With Indwelling Orbital Catheter Use

Timothy Lee, M.D., and John D. Xu, M.D.

Abstract: A 40-year-old man with a history of right orbital fracture and blindness underwent simultaneous fracture repair and enucleation with orbital implantation. During surgery, an orbital catheter was placed for administering local anesthetic for initial postoperative pain. After administering 40 ml of anesthetic through the catheter on postoperative day 1, the patient had development of a complete ptosis, total ophthalmoplegia, mydriasis, vision loss from 20/20 to NLP, and hypesthesia of the V1 and V2 trigeminal nerve distribution. Intraocular pressure and dilated fundoscopic examination were normal. There was no evidence of central nervous system effects or respiratory depression. After 4 hours of observation, the vision, sensation, motility, ptosis, and pupil response all returned to normal. Although rare, cerebral cavernous sinus/orbital apex syndrome may occur with indwelling orbital catheter administering of local anesthetic in an orbit with fractures.

Recognized symptoms of local anesthetic toxic reactions have been reported as early and transient events in connection with or related to the administering surgeon. The most frequent symptoms of local anesthetic toxicity are complications

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FIG. 1. Patient with cherubic cyst side (left profile) and right profile. There is significant retrognathism and hypoplasia.

FIG. 2. A, Axial and B, coronal CT demonstrating right orbital mass, midface width and depressed orbital structures.

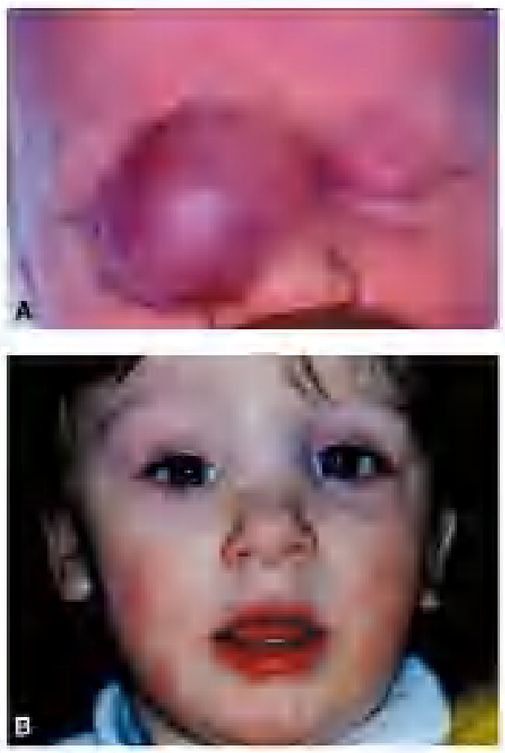


FIG. 3. A, Two-day-old infant presenting with unilateral orbital encephalocele. B, Three years after surgery, with excellent orbital symmetry and normal neurologic development.

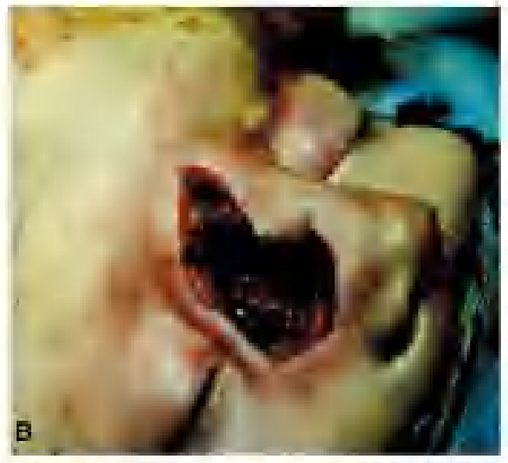


FIG. 5. A, Transcranial view of meningoencephalocele. The infantile neural tissue is connected and the dural and bone defects are repaired. B, Anterior view. Redundant skin and the mass are resected from the nasal cavities and orbital area with repositioning of the medial canthal tendon.

DISCUSSION

REFERENCES

Juvenile Dermatomyositis Presenting With Periorbital Edema

Mehmet Yildiz, M.D., and Jamil B. Reyes, M.D.

Abstract: Juvenile dermatomyositis is a rare disease that affects the skin and muscles. It often presents with a classic heliotrope eyelid rash. We present a case of juvenile dermatomyositis presenting with significant bilateral periorbital edema, with its complete resolution after systemic antiinflammatory therapy.

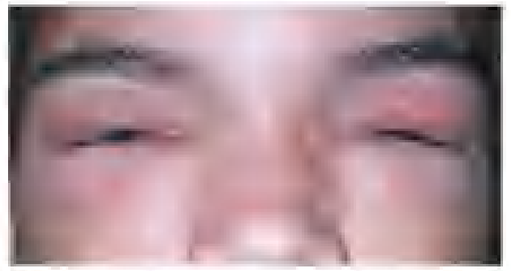
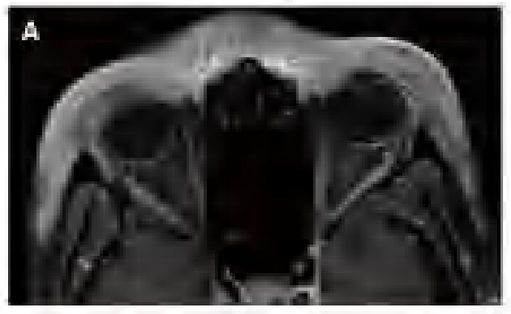


FIG. 1. Significant bilateral periorbital edema with overlying heliotrope rash, characteristic of dermatomyositis.

FIG. 3. Hematoxylin and eosin stain at ×5 magnification. A, Right eyelid biopsy shows lymphocytic inflammation. B, Right deltoid biopsied in close proximity shows perivascular inflammatory infiltrate consisting of lymphocytes and macrophages. Also note the variation in muscle-fiber sizes.



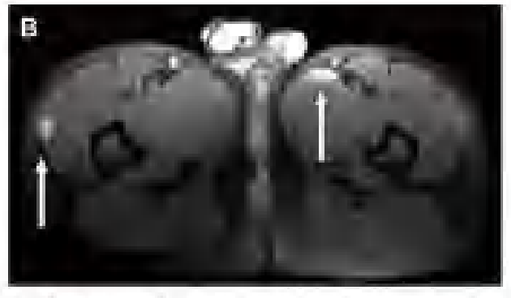


FIG. 2. A, Orbital MRI illustrates prominent bilateral periorbital soft tissue swelling. B, Lower extremity MRI shows scattered foci of inflammation in thigh muscles (arrows).

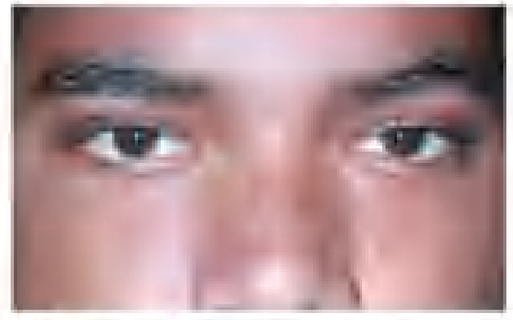


FIG. 4. Resolution of periorbital edema after systemic treatment for juvenile dermatomyositis.

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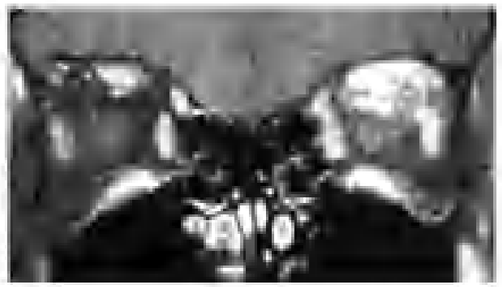

FIG. 1. Coronal computed tomographic [illegible]

CyberKnife Radiosurgery and Rituximab in the Successful Management of Sclerosing Idiopathic Orbital Inflammatory Disease

*Alexander V. [illegible], Max J. Rosenbaum, M.D.**
W. James Williams, M.D.†, and
*Nicola M. Bennett, M.D.**

Abstract: A 26-year-old man presented with symptoms suggesting idiopathic orbital inflammatory disease. After a poor initial response to oral steroids, an orbital biopsy confirmed the diagnosis. A polyclonal lymphocytic infiltrate with areas of fibrosis was seen to replace normal tissue. With the development of exposure keratopathy and diplopia associated with eyelid retraction, lagophthalmos, and decreased motility, increasing doses of steroids and periocular steroid injections were instituted without effect. On the basis of successful treatment of malignant lymphocytic lesions, he was treated with CyberKnife radiosurgery and rituximab. This resulted in symptom resolution with improved eyelid closure and motility. Eighteen months after treatment, he is essentially symptom-free, with almost complete radiographic regression of his disease process.

[illegible]

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CASE REPORT

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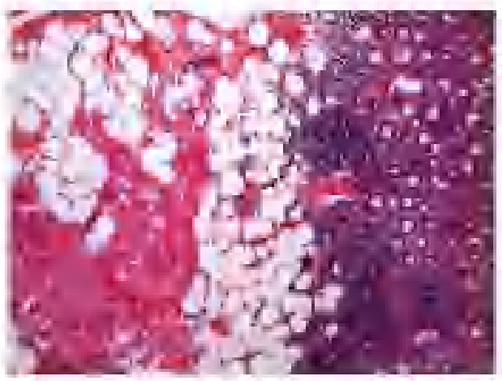

FIG. 2. Biopsy specimen from the left orbit demonstrating a [illegible]

DISCUSSION

[illegible]

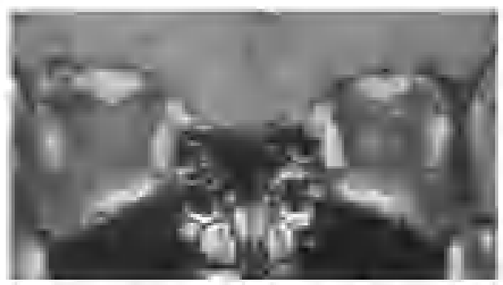

FIG. 3. [illegible]

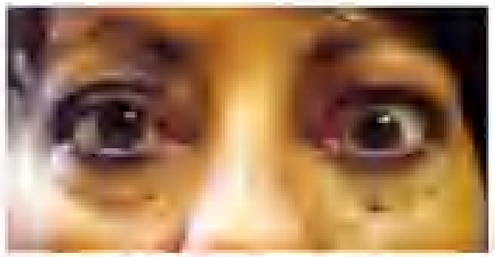

FIG. 1. [illegible]

relative lack of side effects. Optimum permissible injection dose, residual duration, and optimal cosmetic benefit need to be determined in prospective studies with larger numbers of patients.

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Thyroid Eye Disease Presenting After Cosmetic Botulinum Toxin Injections

Andrew K. Harrison, M.D., and Jonathan P. Lyssikatos, M.S.**

Abstract: A 50-year-old woman with left periorbital swelling 4 days after botulinum toxin injection in the lateral canthal area presented after noticing left eye prominence. Physical examination demonstrated proptosis and eyelid retraction. Computed tomography of the orbits confirmed extraocular muscle enlargement consistent with thyroid eye disease. In this case, the patient had development of proptosis after receiving botulinum toxin injections. Although the proptosis may represent progression of the patients' thyroid eye disease, it is worthwhile to consider incidents by botulinum toxin as a possible cause given its widespread use.

Thyroid eye disease (TED) is the most common cause for proptosis in [illegible]. Existing studies have reported the reduction of progress by medications such as corticosteroids and radiotherapy, and the prevention of TED after orbital surgery.[1–3] The cosmetic use of botulinum toxin (BTX) has grown during the past decade as the quality of the

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FIG. 1. Patient with left upper periorbital swelling and mild proptosis.

CASE REPORT

A 50-year-old white female with a history of periorbital swelling after BTX injections was referred to the ophthalmology clinic for evaluation. Two days before presentation, she had undergone cosmetic injections of BTX in the lateral canthal area. Approximately 24 hours after the injections, she noticed left periorbital swelling. She also reported mild headache, but no diplopia or pain. She had no history of ocular disease. Her medications included [illegible]. Her visual acuity was 20/20 in both eyes. Pupils and extraocular motility were normal. Hertel exophthalmometry measured 20 mm OD and 24 mm OS with a base [illegible]. There was no [illegible]. Fundoscopic examination was normal. CT showed enlarged extraocular muscles bilaterally (Fig. 2).

DISCUSSION

Thyroid eye disease has an incidence of 8 in 100,000 in the United States with a 5:1 predilection for females and typically manifests during the fourth or fifth decades of life. Ophthalmic manifestations include eyelid retraction, proptosis, and restrictive myopathy. TED generally lasts over a period of 1 to 3 years but is often present concurrently with the hyperthyroid dysfunction.[4]

FIG. 2. Coronal CT demonstrates extraocular muscle enlargement.

The exact cause of TED remains unknown; however, it is generally considered an autoimmune disorder and the multiplicity of normal orbital tissue antigens are expressed, such as retrobulbar and thyroid receptors.[5]

Reasons given for the recent increase in the number of applications. Common ophthalmic indications include [illegible] use of botulinum toxin therapy in the treatment of facial [illegible]. Side effects common with BTX injection include [illegible] at the site of injection, ptosis, and diplopia.[6] In our patient, the proptosis was evident [illegible] 4 days after cosmetic BTX injection in facial canthal rhytids.

While the pathogenesis of proptosis in TED is ongoing, it is [illegible] with [illegible] after BTX injection. This case report suggests the onset of the diffuse clinical effects after injection. Other studies have shown purported [illegible] the administration of BTX after formation of periorbital wrinkles and surgery.[7,8] The proptosis and eyelid retraction may simply represent the patient's TED in some developing coincidentally at the time of the BTX injection. Another possible explanation is that the proptosis of the lateral canthal area by the BTX injection [illegible] retrobulbar inflammation that worsened previously undiagnosed TED. Whether or not the proptosis was a coincidental finding or the patient was predisposed to the presence of BTX diagnosis remains unclear. After the [illegible] of thyroid disease, it seems a potential pathway to consider BTX in this syndrome.

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Orbital Cysts Lined With Both Stratified Squamous and Columnar Epithelia: A Late Complication of Silicone Implants

Cecily S. H. Tan, M.Med(Ophth), M.R.C.S.(E), Leonard C. K. See, F.R.C.S.,† Ong Lipeng, F.R.C.S.,† Chee-Tuck Chan, F.R.C.S.,† Jimmy Y. T. Chan, D.G.P., L.R.C.P.(Ire), L.R.C.S.(Ed.), L.R.C.P.(Lond.),‡ and Seang-Mealk Chan, F.R.C.S., F.R.C.P.(Edin.)§*

Abstract: Two patients presented with orbital cysts 5 and 7 years after orbital blowout fracture repair with silicone plate implants. The orbital cysts caused significant cosmetic disfigurement and restriction in ocular motility. Surgical excision revealed thick-walled cysts that were displacing the globe and encapsulating the silicone implant. On histopathologic examination, the cysts were lined with both stratified squamous and ciliated columnar (respiratory) epithelia. We propose that squamous and respiratory epithelial cells may have been deposited during surgery from the conjunctival and sinus epithelia, respectively. This case series illustrates that although an uncommon complication, epithelium-lined inclusion cysts may develop several years after orbital fracture repair with a silicone implant. A transconjunctival surgical approach is a possible risk factor.

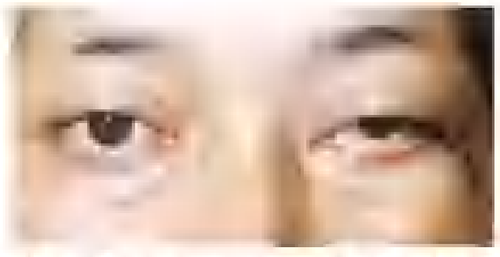

FIG. 1. [illegible]

The [illegible] of silicone sheet implants in orbital fracture repair has been associated with the subsequent formation of epithelium-lined implant cysts.[1–3] We report two patients who underwent repair with silicone sheet implants and developed orbital cysts 5 and 7 years later. Both cysts were lined by both stratified squamous and columnar epithelia. We propose that squamous and respiratory epithelial cells may have been deposited during surgery from the conjunctival and sinus epithelia, respectively. This case series illustrates that although an uncommon complication, epithelium-lined inclusion cysts may develop several years after orbital fracture repair with a silicone implant. A transconjunctival surgical approach is a possible risk factor.

CASE REPORTS

Case 1. A [illegible] underwent [illegible] and [illegible] 5 years after orbital blowout fracture repair and was seen [illegible]. Examination of the left eye revealed [illegible] 4 hypoglobus, 3 mm of enophthalmos, impaired ocular movements, and a large, firm mass along the floor of the left orbit (Fig. 1).

CT [illegible] a unilocular extraconal mass displacing the [illegible] inferiorly. Partial [illegible] of the inferior [illegible] was noted. The mass was compressing the inferior rectus and extraconal fat and was closely related to the [illegible] (Fig. 2).

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DOI: 10.1097/01.iop.0000251531.09952.f7

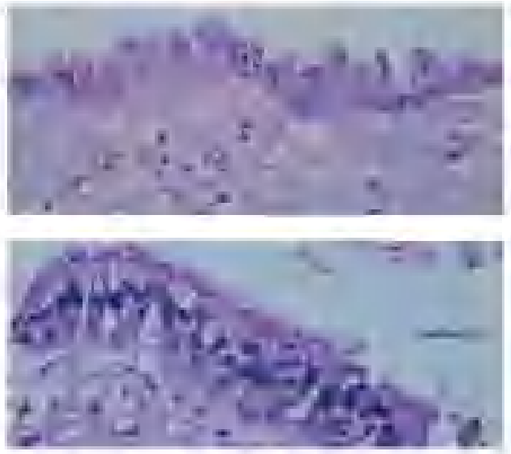

FIG. 2. Histopathology of the cyst wall from patient 1 (hematoxylin-eosin stain) (magnification ×180). The cyst was lined by stratified squamous epithelium (top) and ciliated columnar epithelium (bottom).

Case 2. A 10-year-old woman had sustained multiple 6 years earlier involving the right orbit and anterior implant to the nasal fossa on the floor and medial wall of the left orbit. The left eye demonstrated 4 mm of proptosis, hypoglobus, and minor optic atrophy and moderate exotropia on CT revealed a bony defect in the lateral aspect of the orbit (Fig. 3, left).

Attempts to remove the cyst via a lateral canthotomy with inferior and the entire implant (Fig. 3, right). On histopathologic examination, the cyst wall lined with multi-stratified squamous and columnar epithelia.

DISCUSSION

Most orbital cysts related to orbital implants are iatrogenic. Dermoid inclusion cysts due to implantation after orbital trauma, or epithelial implant (IEC) involving conjunctival epithelium. Mucocele formation is a rare and less common cause of allogenic implants.[1] In our study of conjunctivalized

FIG. 3. Left. The thick-walled cyst and sinus path removed from patient 2 during orbitotomy. Right. Coronal CT of patient 2 demonstrating a soft-tissue mass arising from the inferomedial aspect of the left orbit.

[illegible] allogenic implant over a 10 year period, only 2 presented [illegible] cysts related to partial absorption of the Gelfilm implant. However, any epithelium lined implant cysts developing without obvious orbital implant are rare.

Orbital cysts are usually lined by epithelium[2] or pseudostratified columnar respiratory epithelia.[3] The mechanism of orbital cyst formation is not clearly understood. Implanting epithelial cells from the conjunctival surface may be introduced either at the time of surgery[4] or during surgical procedures at the time of repair.[5] Squamous epithelial cells probably arise from the conjunctiva, particularly in the presence of surgical sphincterotomy.[6,7]

The patients in this study implant the cysts were lined with both squamous and respiratory epithelial cells. This suggests that orbital seeding of epithelium may have occurred during surgery, since both tissue types encountered at this time. Another possibility is that columnar epithelia implanted from the nasal mucosa undergo squamous metaplasia due to the chronic foreign body inflammation resulting in the formation of both types of epithelium in the cyst wall. This explanation would be more likely if goblet cells were present among the squamous epithelial cells. Mucoceles associated with hypothalamic pseudocysts are rare.

Given the ability of conjunctival cells, seeding of epithelial cells in the orbit may not be sufficient to produce cysts. Previous cysts previously described arose during surgery. We did not implant conjunctiva exclusively to explain the cysts in patient 2. Cysts in Gelfilm implant sinuses in shelter for epithelial cells deposited during the surgery. Sinuses implants are known to stimulate a foreign body reaction that results in fibrous tissue encapsulation and possible implant migration.[8,9] If the cysts are lined by epithelial cells [illegible] from the conjunctiva or the nasal mucosa.

This report highlights that implanted tissue migration may develop several years after a silastic implant. The most frequent is a fibrovascularized surgical approach with [illegible] every effort to [illegible] the implant.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Wee-Siek Hwang and Dr. Yeo Kiat Liat Yap from the Department of Pathology, Singapore [illegible] for their kind consideration in this case.

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Lymphoplasmacytic Lymphoma Isolated to an Extraocular Muscle

Kiarash J. Maki, M.D.[1]
Daniel L. Rootman, M.D.[2] *and*
Andrew R. Harrison, M.D.[3]

Abstract: **A 44-year-old woman presented with a 1-month history of right-sided tearing, redness, and chronic headache. Clinical examination was notable for 4-mm proptosis and decreased visual acuity OD. Orbital CT demonstrated isolated enlargement of the right lateral rectus. Surgical biopsy was undertaken after an unsuccessful trial of oral steroids. Histopathology and immunophenotyping demonstrated a lymphoplasmacytic lymphoma. External beam radiation induced regression of the lymphoma with decreased proptosis and improved visual acuity.**

Lymphomatous infiltration of [illegible] has been well documented. Isolated involvement of an extraocular muscle is the most unusual presentation and may [illegible] previously described. We report a rare case of lymphoplasmacytic lymphoma in the right lateral rectus muscle. An [illegible] approach [illegible] the diagnosis [illegible] and [illegible] treatment to an [illegible].

CASE REPORT

A [illegible]-year-old woman presented [illegible] of right-sided proptosis. Over the previous month, the patient had developed redness, tearing, and a dull, [illegible] headache. Examination revealed visual acuity of 20/25 OD and 20/20 OS. No afferent pupillary defect was noted, and extraocular motility was full. Hertel exophthalmometry revealed 4 mm of proptosis OD. Slit-lamp examination revealed [illegible] conjunctival injection and chemosis. Orbital CT demonstrated isolated enlargement of the right lateral rectus (Fig. 1). The [illegible] remainder [illegible] unremarkable. A presumptive diagnosis of idiopathic orbital inflammatory syndrome was made, despite the absence

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[illegible] presented in part at the [illegible] Meeting of the American Society of Ophthalmic Plastic and Reconstructive Surgery, New York, New York, U.S.A., and the Royal and Eastern Ophthalmological Society, Edinburgh, Scotland.

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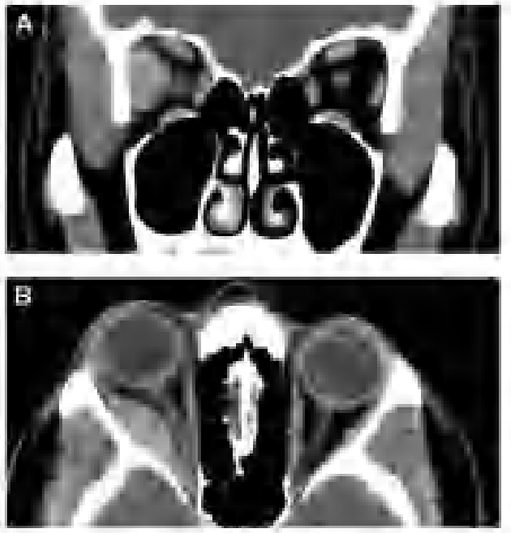

FIG. 1. A and B. Axial orbital CT images demonstrating isolated enlargement of the right lateral rectus muscle. Arrowheads depict axis of distal tendinous insertion muscle.

[illegible] pain, as it is a frequent [illegible] extraocular enlargement and a [illegible] of orbital [illegible].

After initial improvement, the patient's symptoms returned, and she returned for evaluation after 2 weeks. Visual acuity had diminished to 20/70 OD and an afferent pupillary defect was noted. Extraocular motility was full. Hertel exophthalmometry revealed 6 mm of proptosis OD. Slit-lamp examination revealed [illegible] conjunctival injection and chemosis. Dilated fundus examination revealed [illegible] of the optic disc [illegible] of the macula and optic nerve. A [illegible] was performed with [illegible] biopsy.

[illegible] revealed a dense [illegible] with [illegible] lymphocytes, [illegible] cells, and [illegible] cells. The pathologic report [illegible] [illegible] [illegible] [illegible].

FIG. 2. Photomicrograph shows [illegible] and [illegible] cells. [illegible] (hematoxylin-eosin stain, original magnification ×20).

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Large, Rapidly Growing Pilomatrixoma of the Upper Eyelid

Vittorio Rosato, M.D., M.S., M. Carmen Sánchez, M.D., and Aldo Tosoni, M.S.

Abstract. A 41-year-old woman presented with a rapidly growing mass on the upper left eyelid that had first appeared 3 months earlier. The tumor was dark red in color, alternating with reddish pseudocyst formations, and measured 3 cm long with a 1-cm base protruding. The rapid growth had caused a mechanical pinch and bleeding as the result of erosion of the skin covering the tumor. The initial clinical diagnosis suggested a malignant lesion or vascular tumor; excisional biopsy was performed. The eyelid cream was approached for incision and resection as for a bipolar ruglosty. Pathologic examination yielded a diagnosis of giant pilomatrixoma. Pilomatrixomas are rare in adults and rarely attain such a large size. After 1 year of follow-up, no recurrence of the tumor has been observed.

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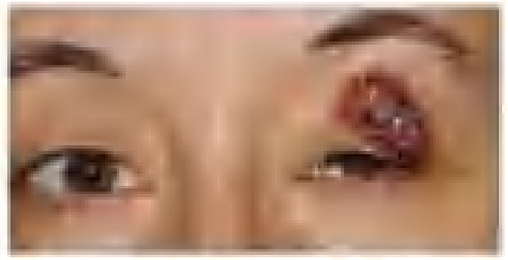

FIG. 1. Large tumor of the eyelid's lateral aspect on the upper eyelid measuring 3 cm long × 1 cm base with dark-red coloring, alternating with whitish pseudocyst formations. Rapid growth caused mechanical pinch and bleeding as the result of erosion of the skin covering the tumor.

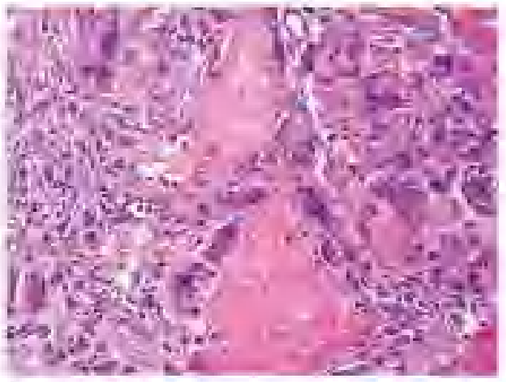

FIG. 2. Histopathology demonstrates characteristic ghost cells of pilomatrixoma and numerous foreign body giant cells in the stroma. There is an absence of atypical cells. (Hematoxylin-eosin-safranin stain.)

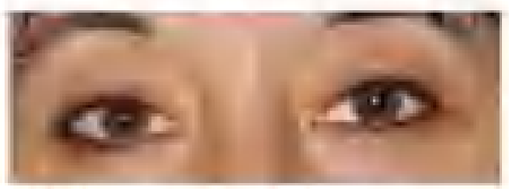

FIG. 3. One month after excision, the patient has a symmetrical eyelid shape with a small scar remaining.

The differential diagnosis of pilomatrixoma in children includes congenital dermoid cyst, occasional epidermal inclusion cyst, chalazion, juvenile xanthogranuloma, vascular tumor, and rhabdomyosarcoma.[1,6,7] In adults, a red-blue discoloration should be differentiated from a large epidermoid cyst, which is freely movable, painless, and covered by intact epidermis with diffuse homogeneous yellow coloration when filled with keratin. Dermoid cysts appear in children and in young adults. The overlying skin, with normal appearance, is easily movable over the lesion. Conversely, vascular tumors are frequent hamartomas in the periorbital region. They have a dark-blue feature, with red-blue coloration and very slow growth. The differential diagnosis in adults also includes rare, benign hair follicle-derived eyelid tumors such as trichoepithelioma, trichilemmoma, trichoblastoma, and inverted follicular keratosis, where in approximately 65% of the cases the diagnosis is histologic, without any clear previous clinicopathologic correlation.[2,3,5]

In conclusion, we present a new case of large rapidly growing pilomatrixoma in an adult, wherein diagnosis was only possible after histologic examination. A large red-blue mass with rapid growth in the upper eyelids and eyebrows in adults may suggest a pilomatrixoma. Its excision, taking advantage of the eyelid space, leads to an excellent cosmetic result.

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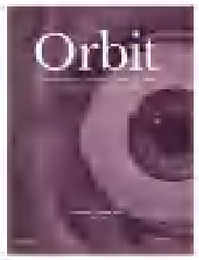

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Thyroid eye disease presenting with superior rectus/levator complex enlargement

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ORIGINAL INVESTIGATION

Thyroid eye disease presenting with superior rectus/levator complex enlargement

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ABSTRACT

Purpose: To describe the demographic and clinical characteristics of patients with thyroid eye disease (TED) who present with predominantly superior rectus/levator complex involvement.

Methods: A multi-institutional retrospective review was performed to identify patients with TED who presented with superior isolated or predominate rectus/levator involvement. Baseline and subsequent visits were reviewed to characterize the clinical course.

Results: Nineteen patients were identified. All patients had imaging demonstrating an enlarged levator/superior rectus complex. At presentation, the mean clinical activity score (CAS) was 2.1 (range: 0–5). Nineteen (100%) patients had proptosis on the affected side. Lid abnormalities, including upper/lower eyelid retraction and ptosis were higher on affected side compared to the unaffected side. Eleven (58%) patients had vertical misalignment. Mean thyroid stimulating immunoglobulin (TSI) was 367 (range: 1–721). Mean follow-up time was 18 months (range: 0–80 months). At last follow-up, the mean CAS was 1.1 (range: 0–5). Ten (53%) patients had proptosis. Eleven (58%) patients had vertical misalignment. Repeat imaging in eight patients showed lateral enlargement of other extraocular muscles.

Conclusions: The presentation of TED with isolated rectus/levator complex enlargement may be underappreciated. Orbital imaging, as well as laboratory evaluation, may help support a diagnosis of TED in the setting of abnormal TSI and/or thyrotropin receptor antibody, presence of upper eyelid retraction, and an otherwise unremarkable laboratory and systemic evaluation. A presumptive diagnosis of TED may be made and the patient can be followed closely, as they are likely to develop involvement of other extraocular muscles, consistent with a more typical presentation of TED.

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Extraocular muscle; Graves' eye disease; superior rectus; thyroid eye disease

Introduction

Thyroid eye disease (TED) is an autoimmune inflammatory condition associated with characteristic clinical ophthalmic findings of exophthalmos, restrictive strabismus, eyelid lag, eyelid retraction, and optic neuropathy.[1,2] TED most frequently accompanies Graves' hyperthyroidism, although it can occur in any dysthyroid state, such as primary hypothyroidism or Hashimoto's thyroiditis, and even in euthyroid patients.

In 1965, Bartley and Gorman outlined the diagnostic criteria of TED in an attempt to summarize and incorporate a wide array of inclusion characteristics published in the preceding 20 years.[3] In the presence of eyelid retraction without an identifiable alternative cause, the diagnosis of TED can be made if at least one of following is also present: thyroid dysfunction, exophthalmos, optic neuropathy, or extraocular muscle involvement. These ophthalmic signs may be unilateral or bilateral. In a related study, 90% of patients with TED had eyelid retraction.[4] In the absence of eyelid retraction, TED can be diagnosed only if exophthalmos, optic nerve dysfunction, or extraocular muscle involvement is associated with thyroid dysfunction.

Orbital imaging can confirm the characteristic pattern of extraocular muscle involvement, including relative sparing of the muscle tendons. Classic clinical teaching dictates that the inferior rectus muscle is most frequently involved, followed by the medial, superior, and lateral recti. When comparing computed tomographic (CT) images of 142 orbits from patients with TED to images of 40 orbits of healthy[5] subjects, Nugent et al. found that the most common extraocular muscle pattern in TED is no involvement (22.5%), followed by involvement of all five extraocular muscles (14.8%).[5] The superior rectus/levator complex was the most commonly involved solitary muscle group but was present in only 4.2% of their study.[5]

In this study, we describe the demographic and clinical characteristics as well as the clinical course of patients with TED presenting with isolated or predominate superior rectus/levator complex enlargement. As a reference group, we compared the population of patients to an incidence cohort of TED cases previously identified in Olmsted County, Minnesota.[6] We believe that a better understanding of this atypical presentation of TED can help guide healthcare providers on initial workup and help counsel patients regarding their clinical course.

Methods

This was a multi-institutional retrospective cohort study. This study was approved by the Institutional Review Board at each institution. At the University of Minnesota, patients' charts with the diagnosis code of thyroid eye disease who visited the Center for Thyroid Eye Disease from 2007–2016 were reviewed. A total of 253 patient charts were identified. Charts were reviewed to identify patients with enlarged superior rectus/levator complex determined on CT or magnetic resonance imaging (MRI) scans. The presence or absence of extraocular muscle enlargement was determined by a neuro-radiologist. Eight patients presented with isolated superior rectus enlargement.

An additional five patients were identified at the Mayo Clinic, five from Washington University and one from Johns Hopkins. Clinical characteristics, radiographic images, laboratory values and biopsy results were extracted for both baseline visit as well as subsequent visits. Descriptive analysis was performed to characterize the clinical course of the cohort.

Results

A total of nineteen patients were identified (Table 1). Seven (36.8%) patients were male, and 12 (63.1%) patients were female. The majority (68.4%) were Caucasian. Mean age at initial ophthalmic presentation was 39.4 years (range: 11–80 years). Upon further review of imaging, four of these 19 patients had subtle enlargement of other extraocular muscles (Table 2). Thyroid function at the time of presentation to the ophthalmology clinic was hyperthyroidism (63.2%), euthyroidism (26.3%), and hypothyroidism (5.3%). The average time between diagnosis of thyroid dysfunction and initial ophthalmic consult was 5.6 years (range 0–48 years).

The majority (89.5%) of patients had unilateral disease (Table 2). Two patients (10.5%) had sight-threatening disease – one from exposure keratopathy and one from optic neuropathy. Mean clinical activity score (CAS) was 2.1 (range: 0–5). Nineteen (100%) patient had relative proptosis on the affected side, with mean exophthalmometry at 21 mm (range: 16–28 mm) on the affected side versus 17.9 mm (range: 15–22 mm) on the unaffected side. Of note, the presence or absence of proptosis was based on qualitative documentation (proptosis was documented if the difference between eyes was > 2 mm) upon chart review. Eyelid abnormalities, including upper/lower eyelid retraction and ptosis were more prevalent on the affected side compared to the unaffected side. Eleven (57.9%) patients had vertical misalignment. Seven (36.8%) patients still will have diplopia. Five (26.3%) had intermittent diplopia, two (10.0%) had gaze-evoked diplopia, and five (26.3%) had diplopia in

Table 1. Demographic and Clinical Data of [illegible] Patients with TED Presenting with Superior Rectus Involvement.

Institution, n (%)	
University of Minnesota	9 (47.4)
Mayo Clinic	5 (26.3)
Washington University	2 (10.5)
Johns Hopkins	3 (15.8)
Male, n (%)	7 (36.8)
Female, n (%)	12 (63.2)
Ethnicity, n (%)	
Caucasian	13 (68.4)
African-American	5 (26.3)
Hispanic	1 (5.3)
Asian	0 (0.0)
Middle Eastern	1 (5.3)
Age at initial presentation to ophthalmology clinic (years), mean (range)	39.4 (11–80)
Smoking, n (%)	
Current	3 (15.8)
Former	6 (31.6)
Never	10 (52.6)
Thyroid function, n (%)	
Hyperthyroid	12 (63.2)
Hypothyroid	1 (5.3)
Euthyroid	5 (26.3)
Unknown	1 (5.3)
Treatment of hyperthyroidism (total n = 12), n (%)	
Not treating	1 (8.3)
Antithyroid medication	5 (41.7)
Radioactive iodine ablation	4 (33.3)
Thyroidectomy	2 (16.7)
Unknown	1 (8.3)
Time between thyroid diagnosis and initial consult to eye clinic, mean (range)	5.6 (0–48)

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Table 2. Clinical Data at Initial Presentation.

	n = 19
TED laterality, n (%)	
Right	12 (63.2)
Left	5 (26.3)
Bilateral	2 (10.5)
Sight threatening disease, n (%)	
No	17 (89.5)
From corneal disease	1 (5.3)
From optic neuropathy	1 (5.3)
Previous steroids for TED, n (%)	
No therapy	12 (63.2)
Oral steroids only	6 (36.8)
CAS (mean, range)	2.1 (0–3)
Proptosis n (%)	
Affected side	15 (100)
Unaffected side	2 (10.5)
Exophthalmometry (mm, mean)	
Affected side	21
Unaffected side	17.9
Upper eyelid retraction, n (%)	
Affected side	12 (63.2)
Unaffected side	3 (15.8)
Lower eyelid retraction, n (%)	
Affected side	7 (36.8)
Unaffected side	2 (10.5)
Blepharoptosis, n (%)	
Affected side	3 (15.8)
Unaffected side	1 (5.3)
Gorman diplopia score, n (%)	
None	7 (36.8)
Intermittent	5 (26.3)
Occasional	2 (10.5)
Constant	5 (26.3)
Ocular alignment, n (%), range	
Orthotropia	5 (26.3)
Esotropia	0
Exotropia	1 (5.3)
Right hypertropia	4 (21.1) 2–45
Left hypertropia	4 (21.1) 5–45
Esotropia with right hypertropia	0
Esotropia with left hypertropia	1 (5.3)
Exotropia with right hypertropia	3 (15.8)
Exotropia with left hypertropia	0
Orthotropia	2 (10.5)
TSI (mean, range) *	3.7 (1–7.1)
TRAb (mean, range) **	2.5 (0.9–5.9)
Imaging, n (%)	
MRI	17 (89.4)
CT	2 (10.6)
Extraocular muscle enlargement, n (%)	
Inferior rectus	1 (5.3)
Medial rectus	1 (5.3)
Superior rectus	19 (100)
Lateral rectus	1 (5.3)
Superior oblique	1 (5.3)
Contralateral eye (any EOM)	2 (10.5)

* Based off of 15 values.
** Based off of 5 values.

Table 3. Clinical Data At Last Follow-up.

	n = 19
Time to most recent follow-up in years (mean, range)	1.5 (0–5)
Interval treatment, n (%)	
None	8 (42.1)
Oral steroid	3 (15.8)
IV steroid	3 (15.8)
Local injection	2 (10.5)
Radiation + oral steroids	1 (5.3)
Unknown	2 (10.5)
Sight threatening disease, n (%)	
No	16 (84.2)
From optic neuropathy	1 (5.3)
From corneal disease	1 (5.3)
Unknown	2 (10.5)
CAS (mean, range)	1.3 (0–3)
Proptosis n (%)	
Affected side	10 (52.6)
Unaffected side	4 (21.1)
Exophthalmometry (mm, mean)	
Affected side	20.5
Unaffected side	19.2
Upper eyelid retraction, n (%)	
Affected side	8 (42.4)
Unaffected side	2 (10.5)
Lower eyelid retraction, n (%)	
Affected side	4 (21.1)
Unaffected side	3 (15.8)
Blepharoptosis, n (%)	
Affected side	1 (5.3)
Unaffected side	1 (5.3)
Gorman diplopia score, n (%)	
No	5 (26.3)
Intermittent	3 (15.8)
Occasional	3 (15.8)
Constant	7 (36.8)
Unknown	1 (5.3)
Ocular alignment, n (%), range	
Orthotropia	6 (31.6)
Esotropia	0
Exotropia	1 (5.3) 4
Right hypertropia	2 (10.5) 2–45
Left hypertropia	2 (10.5) 30
Esotropia with right hypertropia	1 (5.3)
Esotropia with left hypertropia	4 (21.1)
Exotropia with right hypertropia	1 (5.3)
Exotropia with left hypertropia	1 (5.3)
Unknown	2 (10.5)
TSI (mean) *	1.7
TRAb (mean, range) **	2.8 (1.9–4.7)
Repeat imaging, n (%)	
CT	8 (31.6)
MRI	2 (10.5)
None	7 (36.8)
Unknown	4 (21.1)
Extraocular muscle enlargement on repeat imaging, n (%)	
Inferior rectus	6 (75)
Medial rectus	6 (75)
Superior rectus	8 (100)
Lateral rectus	2 (27.3)
Superior oblique	3 (37.5)
Contralateral eye	3 (37.5)

* Based off of 1 value.
** Based off of 3 values.

primary gaze. Mean thyroid stimulating immunoglobulin (TSI) was 3.7 (range: 1–7.1), with normal ≤ 1.3. Mean thyrotropin receptor antibody (TRAb) was 2.5IU/L (range: 0.9–5.9 IU/L), with normal ≤ 1.75. All patients had orbital imaging demonstrating an enlarged levator/superior rectus complex. Additional information regarding extraocular muscle changes identified by orbital imaging is included in Table 2.

Mean follow-up time was 18 months (range: 0–60 months). Interval medical treatment consisted of oral, local, intravenous steroids or radiation (Table 3). Surgical intervention included orbital decompression, strabismus, and eyelid surgery (Tables 4 and 5). During the follow-up period, one patient developed sight threatening disease from optic neuropathy. Mean CAS was 1.3 (range 0–3) at final follow-up. Ten (52.6%) patients had proptosis at final follow-up, with mean exophthalmometry of 20.5mm (range 13–35mm) on the affected

Table 6. Patients Who Underwent Orbital Biopsy (n = 7).

	Patient 1	Patient 2	Patient 3
Institution	U of M/Mayo	Mayo	U of M
Gender	M	M	M
Race	Caucasian	Caucasian	Caucasian
Age at initial presentation	58	73	57
Reason for referral	Proptosis, lid retraction	Orbital mass	Proptosis, corneal ulcer
Thyroid disease status	Unknown	Euthyroid	Hypothyroid
Previous thyroid treatment	None	Unknown	Medical
Smoking status	Former	Former	Current
Time between thyroid and TED onset	30 days	Unknown	60 days
Treatment with steroids prior to consult	None	None	Oral
Laterality	Right	Right	Bilateral
Sight threatening disease	No	No	Corneal disease
CAS	0	1	5
Proptosis *	No	Yes	Yes, bilateral
Lid abnormalities *	Ptosis	Upper eyelid retraction	Ptosis
Gorman diplopia score	1	3	1
TSI	<1.0	Not done	4.7
Imaging modality	MRI	MRI	MRI
EOM enlargement	Yes	Yes	Yes
Biopsy results	Chronic inflammation	Thymic tissue	Chronic inflammation
Follow-up data			
Time since initial consult	55 days	3 years, 4 months	1 year, 4 months
Sight threatening disease	No	No	No
CAS	0	0	0
Proptosis *	No	No	No

	Patient 4	Patient 5	Patient 6	Patient 7
Institution	U of M	U of M/Mayo	Mayo	Wilmer
Gender	M	F	M	M
Race	Caucasian	Caucasian	Caucasian	Middle Eastern
Age at initial presentation	30	76	57	51
Reason for referral	Proptosis, lid retraction	Orbital mass	Eyelid swelling	Soft tissue swelling
Thyroid disease status	Unknown	Euthyroid	Hypothyroid	Euthyroid
Previous thyroid treatment	None	Medical	Medical	None
Smoking status	Former	Former	Former	Former
Time between thyroid and TED onset	30 days	Unknown	15 years	6 days
Treatment with steroids prior to consult	None	None	Oral	Oral
Laterality	Right	Right	Right	Right
Sight threatening disease	No	No	No	Optic neuropathy
CAS	0	1	1	3
Proptosis *	Yes	Yes	Yes	Yes
Lid abnormalities *	Ptosis	Upper eyelid retraction	Upper eyelid retraction	Upper eyelid retraction
Gorman diplopia score	1	3	1	2
TSI	<1.0	Not done	1.3	4.2
Imaging modality	MRI	MRI	CT	CT and MRI
EOM enlargement	Yes	Yes	Yes	Yes
Biopsy results	Chronic inflammation	Thymic tissue	Chronic inflammation	Chronic inflammation
Follow-up data				
Time since initial consult	55 days	3 years, 4 months	1 year, 4 months	588 days
Sight threatening disease	No	No	No	No
CAS	0	0	0	0
Proptosis *	No	No	Yes	No

(Continued)

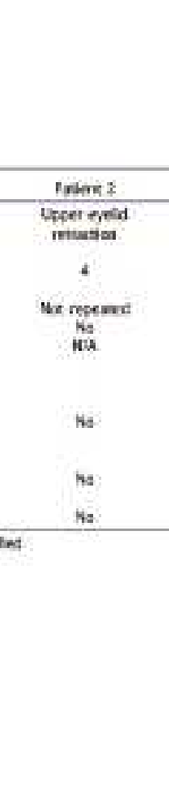

Figure 1. 50-year-old male who presented with diplopia, eyelid and right-sided nasal pain, left optic disc edema, and papilledema. Ophthalmic examination revealed a large right hyperemic, lobulated mass involving the medial canthus and caruncle, with proptosis, lagophthalmos, and restricted abduction. Laboratory testing showed a 3-fold elevation of IgG4 concentration (serum IgG4 concentration 1.46 g/L; normal range: 0.03–0.86 g/L). Contrast-enhanced orbital MRI revealed a right lacrimal gland mass with extension into the orbital soft tissues, consistent with IgG4-related disease. Systemic evaluation revealed no additional organ involvement, and the patient was diagnosed with isolated IgG4-related ophthalmic disease. He received systemic corticosteroid therapy with rituximab, resulting in rapid regression of the orbital mass and normalization of serum IgG4 levels. Follow-up MRI at 6 months showed near-complete resolution of the lesion.

patients with eyelid retraction (75% to 86%, even though the prevalence of patients with vertical misalignment was lower (~50% compared to ~25% at presentation). Internal entrapment of the inferior rectus muscle as confirmed by MRI in eight patients who underwent repeat imaging likely explains this finding. Repeat TSI was only drawn in one patient (Patient 1, Table 3), as mentioned, the repeat test was abnormal, and the patient was progressed to involvement of other extraocular muscles (Figure 2).

Data exist for 17 (50%) patients with unilateral involvement presented with hypertrophy of the involved side. Two patients later developed bilateral disease. Three patients had muscle involvement. These patients developed hypertrophy contralateral to the side of presentation—one did not have repeat imaging, one underwent orbital decompression and one had contralateral extraocular muscle involvement. Three of these 17 patients did not have eyelid abnormalities other at presentation or at follow-up. Therefore, the majority of patients presented with eyelid retraction from an enlarged superior rectus/levator complex.

Patients presenting with superior rectus/levator complex enlargement in TED have historically been considered atypical. Our data show the number of eye muscles involved are relevant for either potential causes of extraocular muscle enlargement. A total of seven patients with varying clinical presentations underwent orbital biopsy at the discretion of the physician or the different institutions (Table 6). In all cases, the biopsy was non-diagnostic of any characteristic for connective tissue enlargement. As mentioned previously, four of the patients had orbital decompression with otherwise normal orbits. Therefore, careful assessment of extraocular muscles can direct the clinician towards TED and avoid unnecessary surgical biopsy.

Limitations of this study included its retrospective and primarily descriptive nature. Additionally, patients in follow-up were variable. Due to a lack of a direct comparison group, we compared our group to a cohort of TED patients diagnosed between 1976 and 1990. This has been described in detail in a landmark publication.[1]

Conclusions

In this study, we identified a group of patients that have previously, and perhaps commonly, been misdiagnosed. The presentation of TED with superior rectus/levator complex enlargement may be underappreciated. Orbital imaging should be obtained in these patients as well as laboratory testing including TSI and TRAb. Based upon our findings, we assert that in a patient presents with eyelid retraction, unilateral involvement, and a normal TSI, the clinician should consider alternative diagnoses, including neoplastic, infectious, and inflammatory processes. Additionally, a normal TSI should not preclude the diagnosis of TED, as it may be normal in patients with TED and superior rectus/levator complex enlargement.

Table 6. (Continued).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Lid abnormalities*	Upper+lower eyelid retraction	Upper eyelid retraction	Ptosis	Upper eyelid retraction	Upper eyelid retraction	Upper eyelid retraction	None
Gorman diplopia score	4	4	4	1	3	4	3
TSI	1.7	Not repeated	Not repeated	Not repeated	Not repeated	Not repeated	Not repeated
Repeat imaging	CT	No	No	Unknown	CT	MRI	MRI
EOM enlargement	IR, MR, SR, LR, SO, contralateral eye	N/A	N/A	N/A	IR, MR, SR, SO, contralateral eye	SR	SR, LR
Orbital decompression	Urgently for optic neuropathy	No	No	Unknown	Urgently for optic neuropathy	No	Yes
Strabismus surgery	Yes (1)	No	No	No	Yes (multiple)	No	No
Eyelid repair	No	No	No	No	No	No	No

*Assume affected side unless otherwise specified.

Figure 2. Orbital imaging of the patient shown in Figure 1. (A) T1 post-contrast magnetic resonance imaging demonstrating enlarged right superior rectus/levator complex (R SR/LP). Other extraocular muscles were not enlarged. (B) Computed tomography of the same patient at follow-up 14 months later demonstrating enlargement of many extraocular muscles bilaterally. The superior rectus/levator complex remains enlarged.

abnormal TSI and/or TRAb, a presumptive diagnosis of TED can be considered, and careful observation for the development of more classic TED (i.e. involvement of other extraocular muscles with sparing of the tendon) is appropriate. If, however, a patient has a normal TSI and TRAb, or fails develop more classic TED over time, an orbital biopsy should be considered.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Article

Development of a Patient-Centered Outcome Tool for Blepharospasm: A Stepwise Modified Delphi Study

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Abstract

Blepharospasm (BSP) is characterized by excessive orbicularis oculi muscle activity leading to abnormal blinking and involuntary eyelid closure. Botulinum neurotoxin (BoNT) injections are the main treatment for BSP, but they only partially and transiently resolve symptoms, leading to a waxing and waning therapeutic response. A patient-centered outcome (PCO) tool that measures BSP symptoms in a simple and efficient way could inform the development of better treatments. Using a stepwise modified Delphi approach, patient PCO items were first identified using the Dystonia Coalition Database with data from over 200 individuals with BSP who had provided responses to existing clinical assessments scales. These items were then analyzed for contribution to overall severity using a Random Forests approach, and redundant items were merged and revised in a series of iterative meetings with a specialist panel along with input from patient advocacy group representatives and focus groups. An online survey was conducted with 330 individuals with BSP to validate and verify the items' relevance. Finally, the specialist panel provided content validity ratio, which was reported until it showed good agreement for relevance and clarity of all items. In the end, an easy to use PCO tool designed for smartphones and tablets containing 17 items covering three symptom domains (motor, disability, and psychosocial/quality of life) was created. This novel PCO tool for BSP may be used to characterize the cyclical response that an individual patient experiences from BoNT treatments and provide a valid tool for future investigations of long-acting BoNT preparations or adjunctive therapies.

Keywords: blepharospasm; patient-reported outcomes; botulinum neurotoxin; self-assessment; symptom monitoring; treatment interval

Key Contribution: Botulinum neurotoxin (BoNT) injections are the main treatment for blepharospasm (BSP), but they only partially relieve symptoms for many patients. Existing assessments do not capture therapeutic response. A novel BSP-specific patient-centered outcome (PCO) tool was created so that patients can easily assess their symptoms and patient experiences from BoNT treatments. This tool can be used in clinical investigations of improving BoNT preparations and adjunctive therapies.

1. Introduction

Blepharospasm (BSP) is a focal dystonia characterized by involuntary bilateral orbicularis oculi muscle activity leading to abnormal blinking, involuntary eyelid closure, and difficulties with eye opening [1,2]. The prevalence of BSP varies by geographical region but has been estimated to affect up to 130 per million people worldwide [3]. Those with BSP frequently experience spread of dystonia to muscles beyond the orbicularis oculi with approximately half of affected individuals experiencing spread to other muscles such as the lower face and jaw [4–6]. BSP is also often associated with sensitivity to bright lights or wind, irritating sensations in the eyes such as dryness or grittiness, impaired activities of daily living, psychosocial difficulties, and diminished quality of life [7]. Furthermore, psychiatric symptoms including depression and anxiety frequently occur with BSP [8,9], which can further impact quality of life [10].

Presently, intramuscular injection of botulinum neurotoxin (BoNT) into the orbicularis oculi and other affected muscles remains the treatment of choice for BSP as no current oral medication provides adequate relief [11]. BoNT treatments generally continue for life because BSP remains incurable and rarely remits. While BoNT injections improve the motor symptoms of BSP and quality of life, they frequently only partially relieve symptoms and they can be painful, wear off quickly, or induce undesirable weakness or other adverse effects. Many BSP individuals are treated at a fixed interval of 12 weeks, despite several studies showing considerable inter-individual differences in duration of effect and repeated calls for more flexible dosing intervals based on individual needs [12–14]. One study showed that nearly half of all individuals with BSP perceived a treatment interval < 12 weeks, while some preferred an interval > 16 weeks [14]. The cyclical pattern of waxing and waning symptoms also occurs with BoNT treatment of cervical dystonia, where the phenomenon has been called the *inhibitor* [15] or *poor-to-good* effect [16]. More clinical trials with newer BoNT formulations or effective adjunctive medications are desperately needed to accelerate the development of new and more effective treatments for BSP.

Treatment satisfaction in BSP could be improved by customizing treatment intervals according to individual needs, developing novel BoNTs with longer duration of action and less prominent fluctuations over the treatment cycle, or developing novel adjunctive oral medications to mitigate symptoms that emerge when BoNT wears off [12,17,18]. Customizing treatment intervals according to individual needs requires methods to assess efficacy during these treatment intervals, which currently rely almost exclusively on patient recollection at the time of a repeat treatment; however, tools for measuring duration of action in a clinically meaningful way have not been available for BSP. To advance therapeutic treatment options for BSP, more precise temporal information is needed regarding the associated disability and psychiatric symptoms that may or may not align with the magnitude of motor benefit from BoNT.

To aid in measuring the temporal effects of BoNT on motor and non-motor symptoms, usability and quality of life in BSP, a brief and efficient patient-centered assessment tool is needed to pharmacologically optimize BoNT treatment intervals. Clinician-rated scales such as the Jankovic Rating Scale [19] or the DeGroot Blepharospasm Severity Rating Scale [20] are not suitable for this purpose, because both require in-person assessment by trained clinicians. The Blepharospasm Disability Index (BSDI) [21] has several items (such as driving, social functioning, disability from motor symptoms) but may not change in response to short-term interventions [22]. The Craniocervical Dystonia Questionnaire (CDQ-24) [23] can be used to assess quality of life in individuals with BSP, but it is cumbersome for repeated uses and has many items not relevant to individuals with BSP alone. A patient-centered outcome (PCO) measure that does not require direct assessment by a clinician and can be implemented on a handheld device could provide a detailed assessment of cycling motor and non-motor symptoms in BSP patients receiving BoNT treatment and identify gaps in therapy for novel therapies.

The goal of this study was to develop a pragmatic PCO that incorporates the unique and specific motor and non-motor features affecting those with BSP and that could similarly be easily administered through a digital platform such as a smartphone or tablet. A major advantage of this approach is that real-time data may be collected in the natural environment of individuals with BSP. This enriched and frequent data sampling (ecological momentary assessment) will enable the generation of a rich source of information for individual subjects that allows for a fuller appreciation of the contributions of different phenotypes to the overall neurological disorder.

2. Materials and Methods

2.1. Study Design

The PCO for BSP was designed following U.S. Food and Drug Administration (FDA) guidelines for development of novel patient-centric measurement tools that incorporate input from all relevant stakeholders (FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, 2009). Participant data included in this study were collected through the Dystonia Coalition Projects-3: Natural History: Objective Measures; Biobank; Patient-Centered Outcomes [redacted], accessed on 12 August 2025. Inclusion criteria included the diagnosis of isolated BSP, age 18 years or older, fluency in English, ability to complete questionnaires on a smartphone, and stable treatment with BoNT. Exclusion criteria included evidence for acquired dystonia or complex patterns of dystonia, known resistance or atypical responses to BoNT, receiving or BoNT injections to body regions beyond the upper face, and treatment with deep brain stimulation. Institutional ethical standards committee on human experimentation approval was obtained prior to study initiation at each participating site ([redacted], accessed on 12 August 2025).

Content development involved a conceptually driven iterative process with three stages followed by a performance-testing stage that paralleled the development of a PCO for cervical dystonia [24] and integrated input from clinicians with expertise in treating BSP (movement disorders trained neurologists and ophthalmologists), patient advocacy groups, and patients with BSP. As BSP often co-occurs with cervical dystonia, one overall objective was to create a PCO that aligns well with a PCO recently created for cervical dystonia [24]. As such, items were grouped into a similarly structured set of three main clinical domains relevant to individuals with adult-onset focal dystonia that can potentially respond to therapeutic intervention (MOTOR, DISABILITY, and PSYCHOSOCIAL). While the number of final items included in the PCO was not strictly defined, another overall

[illegible] was to have experts mainly provide feedback pertaining to [illegible] sufficient depth within the questionnaire. An assessment questionnaire was developed and [illegible] was piloted with [illegible].

2.1.2. Stage 1: Content Development and Item Generation

The preceding was grounded in existing and specific dystonia-related quality of life questionnaires and previously used clinician-assessment tools such as the [illegible] severity questionnaire used in [illegible] BSP [12], the Blepharospasm Disability Index (BSDI) [13], the Craniocervical Dystonia Questionnaire-24 (CDQ-24) [14], the Beck Depression Inventory II (BDI-II) [15], and the Rand 36-Item Short Form Survey Instrument (SF-36) [16]. Items were categorized into three domains: MOTOR, which included BSP-related motor symptomatology; DISABILITY, which focused on the impact of symptoms on activities of daily living; and PSYCHOSOCIAL, which included mental well-being and health-related quality of life issues (physical and mental health domains). Items not felt to be suitable for the PCO, such as questions pertaining to regions outside of interest for BSP patients (like the fingers), and items not responsive to short-term changes, were eliminated or modified, while similar or overlapping items were merged. Each question was considered to be of equal value and the sum of all values was the Total Score.

Random Forest analysis was performed to identify items that significantly impacted the Total Score across the three domains. This is an ensemble learning technique with robust handling of high-dimensional data, along with the construction of multiple decision trees during training [17]. The mean prediction of each tree was identified for multiple linear regression analysis, aiding the recognition of the relative importance of each item. The significance of items in the Random Forest regression models was determined via an impact on out-of-bag mean square error, a widely used measure of model accuracy that estimates prediction error using unseen data [18]. Variables yielding larger values of out-of-bag mean square error values were considered more influential, as their removal led to substantial increases in prediction error, indicating their importance in predicting the total score. This strategy helped in prioritizing variables to include, and it ensured effectiveness in capturing nuances influencing BSP severity and impact.

2.1.3. Stage 2: Item Improvement and Revision of Items

The second step included revision and improvement of each item. This iterative process began with a panel of clinical specialists (movement disorders-trained neurologists and ophthalmologists with extensive expertise with BSP), as well as patient advocacy group representatives from the Benign Essential Blepharospasm Research Foundation (https://[illegible].org, accessed on 12 August 2025) and the Dystonia Medical Research Foundation (https://[illegible], accessed on 12 August 2025). The panel assessed all candidate items to determine if key items were missing and they ranked all according to perceived level of importance. The ranking involved a 9-point Likert scale ranging from not important (1) to critically important (9). The final candidate list was reduced to the most important items.

Candidate items identified by the specialist panel were then refined via three live conferences with stakeholder focus groups held approximately one week apart with ~10 individuals with BSP per focus group. The objectives given to the focus groups were to rank the items across the three domains according to the personal perspective of individuals with BSP, help improve the clarity of any confusing items, and to identify any important missing or overlooked items. Qualitative analyses were carried out following the principles of thematic narrative analysis to identify common themes found through participant feedback [19]. Qualitative data were evaluated by counting thematic categories of coded responses for each of the items.

Candidate items incorporated all feedback from the focus groups, and then the Chair of the BSP specialist panel (BDB) worked with the chair of the cervical dystonia specialist panel (SFK) to make a set of minor modifications to help harmonize the language structure of DISABILITY and PSYCHOSOCIAL items with overlapping items in the recently developed PCO tool for cervical dystonia. Harmonization included matching the language used for comparable symptoms across dystonia types to avoid overlapping and redundant questions should the BSP PCO be combined with the PCO being developed for CD. While the current instrument is not tailored for patients with both BSP and CD, future opportunities could include combined PCO assessments for those with multiple affected areas by dystonia. After this step, the finalized candidate items were evaluated in a content validity stage.

2.1.5. Stage 3: Content Validity

The quantification of content validity ratio (CVR) protocol was used to assess content validity [20]. All members of the BSP specialist panel rated each candidate item for the degree of RELEVANCY and CLARITY using a 4-point scale: 1 for "not relevant/clear", 2 for "item needs some revision", 3 for "relevant/clear but needs minor revision", and 4 for "very relevant/clear." After compiling results from all members of the panel, any items with CVR < 0.62 were revised and reassessed until consensus was reached [21]. At this stage, rating anchors for each item were selected (e.g., "Never" to "Always" or "None" to "Extreme").

Next, an online patient survey was conducted to collect additional feedback from a large population sample of individuals with BSP. The survey was advertised through patient advocacy groups, and any affected individual could participate. The survey began with a screening question asking the participant to self-report if they had a diagnosis of BSP. Individuals who responded affirmatively were then asked to read the instructions and consent for subsequent survey questions. Participants were then presented with each PCO domain item and asked three questions: (1) "Does this item reflect your experience with blepharospasm?", (2) "Would a treatment that can improve this symptom be meaningful to you?", and (3) "What minimal amount of improvement would be meaningful to you (sliding from 0% for no improvement to 100% for full improvement)?".

Responses to the third question were analyzed to determine the Minimal Meaningful Improvement threshold for each symptom. Descriptive statistics, including medians, quartiles, and percentiles, were calculated to assess the distribution of responses. Clinically relevant thresholds were established by defining small, medium, and large effect sizes based on cumulative response distributions. A small effect size was defined as the minimum improvement percentage at which at least 50% of respondents considered the change meaningful, a medium effect size was determined at the 60% threshold, and a large effect size was defined as the improvement level reported by at least 75% of participants. An additional exploratory threshold of 50% was applied to identify substantial perceived benefit. These calculations were conducted using SAS v9.4 software, and results were analyzed separately for each symptom domain (MOTOR, DISABILITY, and PSYCHOSOCIAL) to account for variations in symptom burden and patient-reported impact.

2.1.4. Stage 4: Testing Performance of PCO

The performance of the PCO in capturing changes in the severity of individual items at weekly intervals over a single BoNT treatment cycle was assessed for five individuals with BSP. Final PCO items from Stage 3 were programmed into an application (SymptomSnap, developer: TekSynap Corporation, Reston, VA, USA, all rights reserved) and downloaded on the participant's smartphone or tablet. Responses for all PCO items were collected using

a sliding scale from 0 (null) to 100 (each item between the anchors). An automatic reminder to enter ratings was sent to the participant's mobile device once every week. After 12 weeks, each individual was asked three additional anchor questions regarding usability including (1) "How easy was the tool to use?", (2) "Do you think it is useful to document changes in the severity of your condition?" and (3) "Would you recommend this tool to others?"

3. Results

As shown in Figure 1, the content development and item generation stage yielded 10 items within the MOTOR domain subsequently reduced to 5 items. A similar process was used to reduce 30 items within the DISABILITY domain to 11 items (Figure S1A) and 63 items within the PSYCHOSOCIAL domain to 16 items (Figure S1B). Items were subsequently removed after Random Forest regression and due to duplication or lack of expected response to treatment interventions. All items included wording emphasizing the relevance of the question to BSP, to avoid answering in a way that reflected other comorbidities. Given that about half of those with BSP will develop involvement of the craniomandibular region, an item was added to the MOTOR domain to try and capture the severity of lower-face (tongue, mouth, and jaw) dystonia. In addition, items were added to the DISABILITY and PSYCHOSOCIAL domains to capture the impact of craniomandibular involvement on these domains.

At the content validity rating stage, item wording and anchors were revised. With several iterations of the CVR process within the specialist panel, all final items were above the cutoff for clarity and relevancy (see Table 1). In Table 1, only the medium effect size (90% threshold) is reported to provide a standardized measure of meaningful improvement across symptoms. Relevance was then tested in the broader dystonia community using an online patient survey. The survey was advertised via email by the Benign Essential Blepharospasm Research Foundation and Dystonia Medical Research Foundation. The survey remained open for four weeks, and during this time 330 unique responses were collected. All items had a concurrence rate higher than 70% for relevancy with the exception of the three questions related to craniomandibular muscle involvement (Table 1). The decreased relevancy for the lower face involvement is expected given that only about half of patients with BSP have craniomandibular involvement.

Table 1. Patient-centered outcome items evaluated for content validity by specialist panels and for relevancy by patient panels.

DOMAIN	ITEMS	Content Validity Ratio		Patient Concurrence (Item Relevancy, %)	Desired Improvement Threshold (90th Percentile)
		Relevancy	*Clarity*		
MOTOR	How often do you blink too much?	1.0	0.71	83	40
	How much difficulty do you have keeping your eyes fully open?	1.0	1.0	84	40
	How much discomfort do you have with bright light?	0.86	0.86	93	35
	How much discomfort do you have due to any gritty, sandy or burning sensations in your eyes?	0.86	1.0	74	30
	Do spasms close your eyes against your will?	1.0	1.0	94	57
	How often do you experience uncontrollable movements of your tongue, mouth, or jaw?	1.0	1.0	43	25
DISABILITY	How much limitation do you have in work performance (either household work or outside employment) due to your eye or mouth problem?	1.0	1.0	77	28
	How much limitation do you have in driving due to your eye or mouth problem?	1.0	1.0	83	42
	How much limitation do you have in your leisure activities due to your eye or mouth problem?	0.86	0.86	86	30
	How much limitation do you have in talking and/or eating due to uncontrollable movements of your tongue, mouth, or jaw?	1.0	1.0	34	23
PSYCHOSOCIAL	How often do you feel anxious due to your eye or mouth problem?	1.0	1.0	86	27
	How often do you feel down or depressed due to your eye or mouth problem?	1.0	1.0	73	27

Table 1. Cont

DOMAIN	ITEMS	Content Validity Ratio		Patient Concurrence (Item Relevancy, %)	Desired Improvement Threshold (90th Percentile)
		Relevancy	Clarity		
PSYCHOSOCIAL	How often do you feel frustrated due to your eye or mouth problem?	0.86	1.0	93	30
	How often do you feel embarrassed due to your eye or mouth problem?	1.0	1.0	81	27
	How much limitation do you have in social situations (e.g., visiting friends and family, attending events outside the home, etc.) due to your eye problem?	0.86	0.71	84	26
	How much limitation do you have in social situations (e.g., visiting friends and family, attending events outside the home, etc.) due to uncontrollable movements of your tongue, mouth, or jaw?	0.86	0.71	41	30
	How much is your quality of life affected due to your eye or mouth problem?	1.0	1.0	92	30

As shown in Table 1, the items with best concurrence were questions on difficulty "keeping your eyes fully open" and whether spasms cause eyes to close "against your will", both endorsed by 94% of respondents. In contrast, the item with the lowest concurrence was whether there was limitation in "talking and/or eating", which was endorsed by only 34% of participants. There was substantial variability in the desired level of improvement among individuals with BSP. The largest minimal meaningful improvement threshold was observed for driving limitations (42%), while the smallest meaningful improvement threshold was reported for talking and/or eating limitations (23%) (Table 1). Regarding effect size thresholds, at least 95% of respondents reported that a 20% improvement (SD 6.1%) was the smallest meaningful change (small effect size). At least 90% of respondents required a 31% improvement (SD 5.8%) for the change to be considered clinically significant (medium effect size), while at least 75% of respondents required a 49% improvement (SD 3.1%) to consider the change meaningful (large effect size). Additionally, 50% of

respondents identified a 61% improvement (SD 6.5%) as the threshold for substantial perceived benefit.

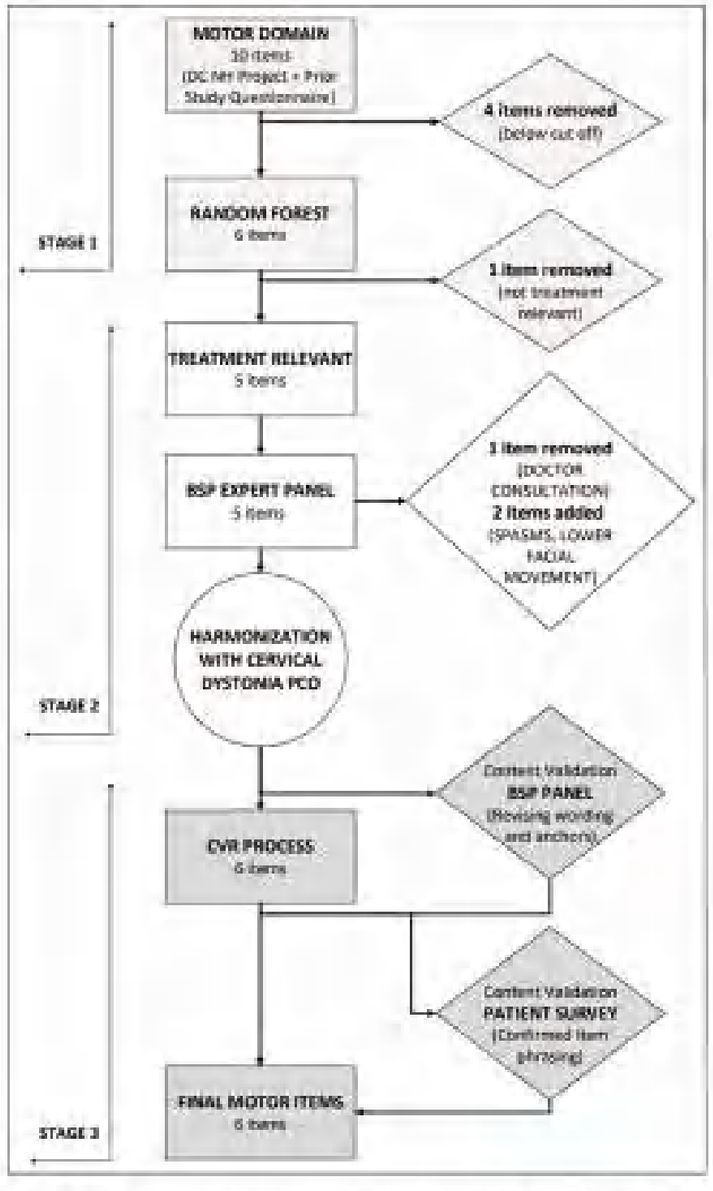

Figure 1. Flow diagram for the development of the blepharospasm (BSP) patient-centered outcome (PCO)—MOTOR domain. Item selection, revision, and finalization went through three stages of the process for the MOTOR domain (see Supplemental Materials for flow diagrams of DISABILITY and PSYCHOSOCIAL domains). Stage 1 involved content development and item generation, Stage 2 was focused on item improvement and reduction of items, and Stage 3 involved a content validity rating (CVR) process to ensure content validity.

To assess real-world performance in a pilot project, the PCO was made available on the SymptomSnap app to five individuals with BSP. Each participant was asked to record

reported weekly over a single BoNT injection cycle and of those five were individuals with BSP were asked to record responses weekly over three complete BoNT cycles (Figure 2). These participants showed good adherence with weekly assessments with less than 5% missing data. They further reported that the app was easy to use and required less than 10 min to enter symptoms, and that they would recommend the app to others. As can be seen in Figure 2, the total PCO MOTOR scores for the two individuals followed for three BoNT cycles followed an expected "yo-yo" pattern with subjective improvement in motor symptoms after each injection and waning of benefit prior to the next BoNT injection. The patterns of the two pilot participants further revealed that their perceived total motor symptom severity tends to vary from week to week.

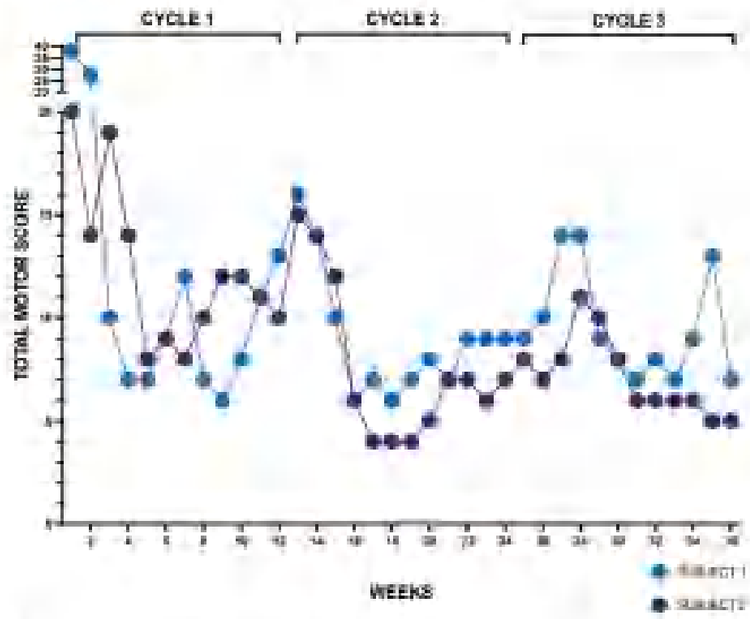

Figure 2. [illegible] MOTOR scores for two individuals followed [illegible] Duchenne type). Scores recorded [illegible] weeks over three 12-week botulinum neurotoxin treatment (BoNT) treatment cycles. The total MOTOR scores for both individuals decrease after the BoNT treatment cycles, with the greatest benefit observed around 6–8 weeks after the injection and worsening of symptoms often observed around 10–12 weeks after the injection.

The percent changes in the Global Impression of change scores rated by clinician (CGI-C) and patient (PGI-C) along with the percent changes in the PCO scores from peak effect to morning baseline BoNT injection at the five BSP participants followed over a single 12-week cycle are plotted in Figure 3A. Interestingly, one participant reported a worsening in motor symptoms in this small pilot sample. Nevertheless, the data reveal general congruence of motor severity as measured by the CGI-C, PGI-C, and PCO MOTOR scores. When looking at the responses of two representative patients (Figure 3B), it is apparent that while subjective motor improvement following BoNT injections tended to align with clinician ratings of dystonia improvement (PGI-C), the PCO-based disability and psychosocial/quality of life changes may not align. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

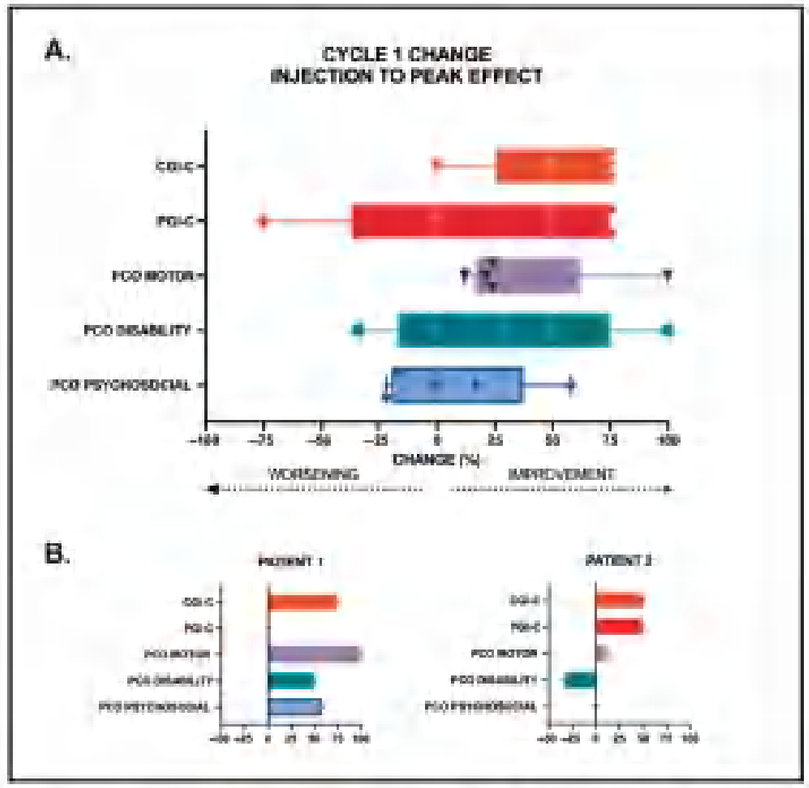

Figure 3. Percent change from assessments at time of botulinum neurotoxin (BoNT) injections to peak effect (typically 6–8 weeks after injection). Results are shown for five individuals in a pilot patient assessment (A) with data from two individuals shown separately (B) to highlight individual differences across the different rating measures. Change in the positive direction indicates improvement in symptoms from injection to peak effect. Congruence largely exist with clinician ratings (CGI-C: Clinical Global Impression of change) and patient ratings (PGI-C: Patient Global Impression of change) as well as with total patient-centered outcome (PCO) MOTOR domain score change. Less congruence was seen with percent changes in the total PCO DISABILITY and PSYCHOSOCIAL domain scores.

4. Discussion

Described here is the development of an easy-to-use digital tool for gathering information at frequent intervals regarding changes in the motor and non-motor symptoms that are most meaningful to individuals with BSP, and preliminary results demonstrating the feasibility of this novel PCO tool are provided. The app-based tool can be used to collect data at any interval, with good adherence observed using weekly intervals in a small pilot. The weekly collection interval was sufficient to document the temporal profile of responses of individual symptoms in response to BoNT over three 12-week treatment cycles, as shown in the pilot data presented here.

A critical aspect of this study was the rigorous statistical methodology employed to refine and validate the PCO tool. The application of Random Forest regression, a widely used machine learning technique for high-dimensional data analysis, allowed for an objective, data-driven selection of the most relevant items while eliminating redundancies [22]. This approach has been increasingly applied in healthcare and clinical

[illegible] and it ensures that the final tool maintained high predictive validity and retained the most meaningful symptom dimensions. Furthermore, the iterative involvement of both clinical experts and patient advocacy groups through multiple rounds of validation aligns well best practices in PCO measure development as recommended by the US Food and Drug Administration and the Patient Centered Outcomes Research Institute [ ]. This approach maximizes the relevance and applicability of the tool, ensuring that it accurately captures the most clinically and patient-relevant symptoms.

The minimum clinically important difference (MCID) in a clinical rating is often defined as the smallest change in a patient-reported outcome measure that a patient would perceive as beneficial, such as a patient global impression of change rating or a quality-of-life measure (e.g., SF-36) [ ]. In the current study, the MCID was obtained by directly asking patients about each of the PCO symptom items deemed most relevant, a method aligned with best practices in PCO-based MCID estimation [ ]. An interesting finding that emerged from this study is that the degree of desired improvement was symptom-specific rather than uniform across all domains. This is expected, as some BSP symptoms are more intrusive than others. In particular, the statistical analysis highlighted variability in the thresholds of desired meaningful improvement across PCO items and symptom domains. Motor symptoms such as difficulty keeping the eyes open and involuntary spasms were associated with higher thresholds for meaningful improvement (40% and 37%, respectively), whereas symptoms of anxiousness and limitation in social situations due to the eye problem had lower thresholds (27% and 26%, respectively). This finding suggests that a standardized interpretation of PCOs may not be appropriate as different symptoms carry different burdens for individual patients. Future studies should therefore consider a symptom-specific approach when assessing treatment efficacy and utilizing clinical benchmarks, rather than relying on a single global MCID threshold [ ].

Presently, prospective BSP PCO data are being collected in a multi-site study through the Dystonia Coalition that will enable a formal analysis of data acquired with the PCO tool and Symptom Follow-up app in a large cohort and over multiple initial new BoNT cycles. This newly developed PCO measure in BSP could have several applications. First, it has immediate practical value for ongoing BoNT treatment, serving as a medical symptom diary similar to the digital PCO recently developed for cervical dystonia that was also found to be sensitive to short-term changes in motor and non-motor symptomatology [ ]. The PCO could help clinicians better understand an individual patient's response to BoNT injections, as real-time data collection is likely more reliable than relying on patient recall at follow-up visits. The development of a valid app-based PCO tool in BSP could further inform the development of PCOs for other adult-onset focal dystonia subtypes such as hemifacial hemispasm and help guide BoNT and rehabilitative strategies aimed at improving motor performance and reducing disability [ ]. Additionally, these data could also be used to inform dose and/or treatment interval adjustments to optimize the treatment outcomes. Third, the PCO tool could be used to chart the temporal dynamics of one to more BoNT treatment cycles, permitting assessment of symptom responses to novel BoNT formulations that may have longer durations of effect or reduced symptom fluctuations compared to existing formulations. Finally, the PCO could serve as a valuable instrument for documenting the potential benefits of adjunct oral therapies across one or more BoNT treatment cycles.

Limitations of the present study include the potential for sampling bias in the selection of the expert panels used for the modified Delphi approach, as well as the potential consequences stemming from reduced anonymity in both the expert panels and patient groups. Limited interview rounds could have also affected the robustness of the modified Delphi method. Another limitation of our study is that the number of overall items to be included in the final PCO tool, while not strictly defined, were limited in overall number to their perceived clinical relevance and to ensure symptoms and quality of the measure did not become overly burdensome. Therefore, some [illegible] have not been included. This was a necessary tradeoff in order to be able to collect many frequent assessments and not create a PCO tool that was felt to be too burdensome to complete by patients.

5. Conclusions and Recommendations

In conclusion, an app-based PCO tool was developed for BSP that enables the capturing of real-time disease and treatment symptom fluctuations that commonly occur during routine BoNT treatment cycles. The PCO was designed to enable the frequent collection of survey information for the most relevant symptoms affecting those with BSP in a user-friendly manner. The use of this PCO tool can easily be integrated into clinical care and has the potential to promote the evaluation of novel combination therapies, ultimately guiding future treatment of patients with BSP. The cost-effectiveness of the app and these applications pose the PCO as a useful and easy-to-use, yet valuable, clinical rating scale in future clinical trials.

Supplementary Materials: The following supporting information can be downloaded at: [illegible]. Figure S1: Flow diagram of our blepharospasm (BSP) patient-centered outcome (PCO) item selection, revision, and finalization through the three stages of the process for the DISABILITY and PSYCHOSOCIAL domains.

Author Contributions: Conceptualization and methodology, R.D.B., S.P.R., H.A.J. and J.S.P.; formal analysis, F.Q.; writing—original draft preparation, R.D.B. and S.P.R.; figure production, A.T.; manuscript review and editing, R.D.B., F.Q., A.D.H., A.R.H., G.D., M.H., G.K.-B., L.W., S.P., P.R., A.T., J.J., J.B., C.P., J.H., J.S.P., H.A.J. and S.P.R.; funding acquisition, H.A.J. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The studies involving humans were approved by the Washington University Institutional Review Board, 202001137-1071, (2 February 2021). These studies were conducted in accordance with the local legislation and institutional requirements.

Informed Consent Statement: All participants provided their written informed consent to participate in this study.

Data Availability Statement: Data that were used in the generation of our patient-centered outcome tool are publicly available from the Dystonia Coalition through a data request. Requests to access the datasets should be directed to [illegible], accessed on 12 August 2025.

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Conflicts of Interest: BDB has received research grant support from the Dystonia Coalition, the Dystonia Medical Research Foundation and the Benign Essential Blepharospasm Research Foundation, serves on the Medical and Scientific Advisory Council of the Dystonia Medical Research Foundation as the director of the Medical Advisory Board of the Benign Essential Blepharospasm Research Foundation and a member of the National Spasmodic Torticollis Association and has also served as a consultant for the Dystonia Medical Research Foundation. AEH has received research support from Ipsen and served as an advisor for Ipsen and Sanofi-Pharmaceuticals. AEH has received research support (principal subject) as a consultant for Allergan, served as a consultant and received speaker fees from Ipsen and has served as a consultant for Allergan. MH serves as a member of medical advisory boards for the Dystonia Medical Research Foundation and the Benign Essential Blepharospasm Research Foundation, as well as for Broadway, QuintessX and VoxNeuro and receives grants/income fees from Broadway (FT-CO-1). JJ and CH serve on the Board of Directors for the Benign Essential Blepharospasm Research Foundation. JJ serves on the Board of Directors for the Dystonia Medical Research Foundation. MJ has received grant support from the NIH as funding help the principle investigator for the Dystonia Coalition, which has received the majority of the support for its research projects through the NIH (NS116025 and NS065701 from the NINDS and TR001456 from the Office of Rare Diseases Research of the National Center for Advancing Translational Sciences), private philanthropic organizations (Cure Dystonia Now and Lesch-Nyhan Syndrome Children's Research Foundation), and industry (Abbvie, Addex, Aeon, Merz, Sage, Ipsen, and Ionis) has served on advisory boards or as a consultant for the NIH (CREATE Bio-ESMB) and industry (Addex, Ipsen, Merz, and Ionis), and has received stipends for administrative work from the International Parkinson's Disease and Movement Disorders Society and served on scientific advisory boards for the Benign Essential Blepharospasm Research Foundation and the Dystonia Medical Research Foundation. SPB has received grant support from the National Institutes of Health, the Department of Defense and the Michael J Fox Foundation. He received honoraria from the International Parkinson and Movement Disorder Society and the American Academy of Neurology, and serves on the Medical Advisory Board of the Benign Essential Blepharospasm Research Foundation. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors had access to the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

BSP	Blepharospasm
BoNT	Botulinum neurotoxin
BSDI	Blepharospasm Disability Index
CDQ-24	Cervical Dystonia Questionnaire
PBCO	Pattern-centered outcome
CVR	Content-valid by rating
SAS	Statistical Analysis Software
CGI-C	Clinical Global Impression Change
CGI-I	Clinical Global Impression-Patient
MCID	Minimum clinically important difference

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ORIGINAL ARTICLE

Eyelid Position and Patient-Reported Aesthetic Outcomes Following Administration of Topical Oxymetazoline: A Prospective Cohort Investigation

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ABSTRACT

Background:

Objective:

Methods and Materials:

Results:

Conclusions:

INTRODUCTION

Eyelid rejuvenation surgery is currently the most common aesthetic procedure performed worldwide and in the United States. According to the American Society of Plastic Surgeons, blepharoplasty has ranked among the top 5 most common cosmetic surgeries for over a decade.[1]

In recent years, topical oxymetazoline, an alpha-adrenergic agonist that stimulates alpha-1 and alpha-2 receptors, has been studied as a pharmacologic agent for eyelid elevation. By leveraging a subset of adrenoceptors found in the Müller's muscle of the upper eyelid, this agent has shown promise in the pharmacologic management of patients with blepharoptosis. Two randomized controlled trials have reported improvements in objective measures including change in palpebral fissure height and margin to reflex distance 1 (MRD1) assessment following oxymetazoline administration.[2,3] By targeting alpha-2 receptors, this agent may play a role in reducing ocular surface exposure and improving eye redness.[4] A recent randomized trial reported improvements in patient perception of appearance following oxymetazoline administration.[5]

MATERIALS AND METHODS

Study Design

A prospective cohort investigation was conducted at a single institution. The study protocol was reviewed and approved by an independent institutional Review Board for conducting clinical research on human subjects. All study participants provided written informed consent prior to participation in the research study. The study adhered to the tenets of the Declaration of Helsinki and was HIPAA-compliant.

Individuals at least 18 years old with no history of eyelid surgery were prospectively enrolled. Exclusion criteria included individuals with any younger than 18 years history of eyelid surgery, absence of blepharoptosis (defined as MRD1 of greater than or equal to 5 mm), substantial dermatochalasis (limited or reduction) eyelid skin covering within 3 mm of the upper eyelid margin), ocular comorbidities, and concomitant ptosis. Individuals were excluded if they had a history of comorbidities that may be associated with cerebrovascular accident (stroke), transient ischemic attack, or cerebral aneurysm. Home treatment medications group, lack of ability to move the eyes in more eye position uncomfortable or corneal lipidosis. Individuals were also excluded if they had a history of untreated narrow-angle glaucoma as well as medications use, including alpha-adrenergic agonists (eye drops, nasal sprays, and oral medications), systemic

FIGURE 1 Photographs of participants pre-study and 15 minutes after administration of oxymetazoline ophthalmic solution 0.1%.

Outcome Measures

Primary outcome measures included change in margin reflex distance 1 (defined as the distance between the pupillary light reflex and the upper eyelid margin) and palpebral fissure height (defined as the distance between the upper eyelid margin and the corneal light reflex) measured from pre-to-post intervention.

Secondary outcome measures included change in patient-reported outcome measures following topical oxymetazoline administration. On the numeric FACE-Q questionnaire – satisfaction with eyes, psychosocial functioning, social functioning, and quality of life – participants rated their responses with options ranging from 1 to 10, corresponding to the number of years younger or older than chronological age, respectively.

Participants were trained regarding trial efficacy from drop administration at the conclusion of the study.

Statistical Analysis

Categorical variables were analyzed using chi-squared testing and continuous variables were assessed using two-tailed t-tests. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of [illegible] participants were enrolled in the study. Enrollment [illegible] 100 participants met inclusion criteria, and 4 were excluded based on the presence of marked dermatochalasis (2 individuals), cornea [illegible] (1), and history of stroke (1). No participants withdrew from the study. Participants were between 24 and 75 years old, with a mean age of 52.8 years. Overall, 92% of study participants self-identified as female and 84% self-identified as white, while 8% identified as [illegible] as Native American, Pacific Islander, Asian, or Hispanic.

FIGURE 2 Margin to reflex distance 1 (MRD 1) and palpebral fissure height pre- and post-administration of oxymetazoline hydrochloride ophthalmic solution 0.1%

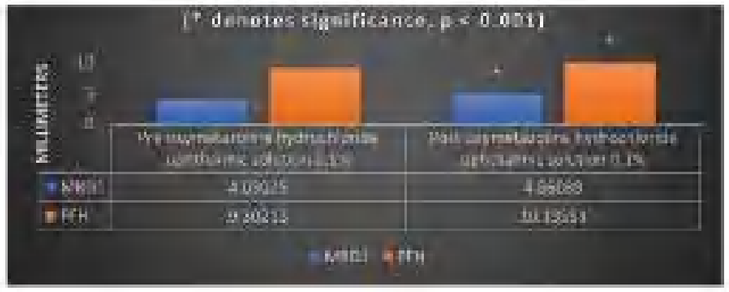


FIGURE 3 Appraisal of upper eyelids and perceived age pre- and post-administration of oxymetazoline hydrochloride ophthalmic solution 0.1%

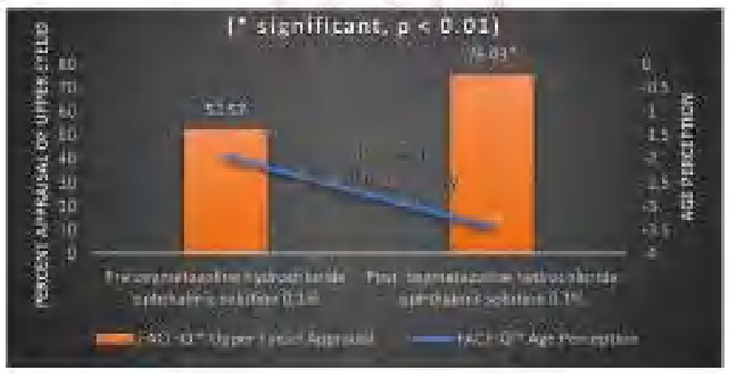
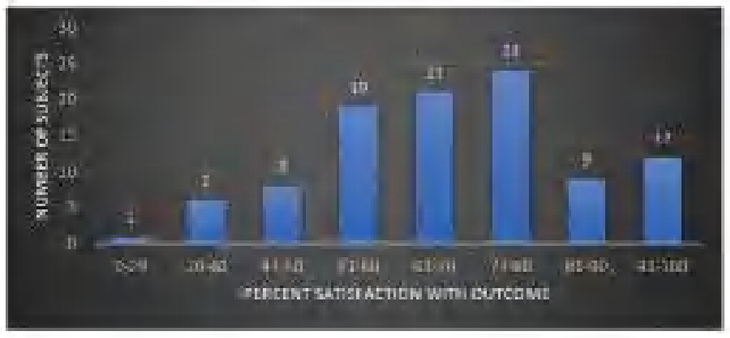


FIGURE 4 Satisfaction with outcome post-administration of oxymetazoline hydrochloride ophthalmic solution 0.1%



An average post-intervention MRD1 and PFH measurements were 4.0 mm and 9.3 mm respectively in comparison to baseline measurements, there were statistically significant increases in margin reflex distance 1 (mean 0.8 mm, range 0.2 – 1.7 mm, $P<0.01$) and in palpebral fissure height (mean 1.1 mm, range 0.1 – 1.9 mm, $P<0.01$) following topical oxymetazoline administration. Compared to baseline, patient-reported appraisal of upper eyelids improved by 73.5% ($P<0.01$), and patient-reported perceived age compared to chronological age decreased by 1.4 years ($P<0.01$) after topical oxymetazoline application. Overall, 91% of participants reported 91% or higher satisfaction with the outcome of the intervention, 88% of participants reported 70% or higher satisfaction, and 71% reported 91% or higher satisfaction.

Some of the participants in this study reported treatment-emergent adverse events, including corneal verticillata, conjunctival hyperemia, dry eyes, eyelid edema, or headache, upon prompting by investigators.

DISCUSSION

Overall, 100 individuals met the inclusion criteria for the prospective cohort investigation. Study participants had a mean age of 52 years and predominantly self-identified as female (78% of the study) and white (94%).

Administration of topical oxymetazoline 0.1% was associated with statistically significant increases in both margin reflex distance 1 and palpebral fissure height by an average of 0.8 mm ($P<0.01$) as compared to baseline. Prior studies have reported similar reductions in the degree of upper eyelid ptosis, ranging from 0.5 mm to 1.2 mm[2,3]. At the upper limit of improvement in MRD1 (1.7 mm) observed in this study following topical oxymetazoline instillation, the pharmacologic effect surpassed the mean upper eyelid elevation previously reported after Müller's muscle-conjunctival resection (1.0 mm)[4]. Given 78% of participants experienced a PFH ≥ 1 mm of improvement in MRD1 following drug administration.

In addition to the observed changes in upper eyelid position and palpebral fissure height, participants demonstrated a statistically significant improvement by 73.5% in appraisal of their upper eyelids following administration. Individuals older than 60 years reported a more favorable appraisal. Further, participants described themselves to look younger following topical oxymetazoline administration. In patient-reported perceived age compared to chronological age demonstrated a statistically significant decrease by 1.4 years ($P<0.01$). Finally, the majority of patients (85%) reported satisfaction with the outcome of the intervention.

In this study, an individual's perceived improvement in eyelid position after administration of oxymetazoline ophthalmic solution 0.1% was shown to be more significant than objective measurements. Importantly, blepharoptosis has not been classified in correlation with upper eyelid elevation[1].

Limitations

Limitations of this study include the absence of a control group. While changes observed in subjective measures, including MRD1 and PFH, were similar to this study compared to prior randomized controlled trials examining patients receiving oxymetazoline, the patient-reported outcome measures were due to oxymetazoline administration alone. The objective measurements may also vary with time following drop instillation, for instance, it is possible that the reported MRD1 and PFH values may have been higher had the investigators waited longer than 15 minutes to obtain measurements. Further, patient perception regarding the outcome of the proposed intervention may constitute an important bias in the questionnaire employed in this study. Finally, while no severe events were reported following application of topical oxymetazoline, more detailed investigation with consistent slit lamp examination may be useful to better categorize the ocular side effects noted in prior trials.

CONCLUSION

This prospective cohort investigation suggests that among patients with microcoria, blepharoptosis, or without blepharoptosis, use of topical oxymetazoline may provide a safe and effective substitute for, or bridge to, surgical intervention while offering potential for similar benefit in improved eyelid position and patient-reported cosmetic outcomes.

DISCLOSURES

AK and MMS report no financial disclosures. DDZ reports grants and medical writing support (MMS) paid with Accuray and Gore® research grants from Gore, Bio Dermaceuticals, Mori, and Zenga. PFH reports consultant and speaker work for Novartis Pharmaceuticals and BVI Pharmaceuticals; consultant work for Lumen Therapeutics and Viridian; and unrelated research with Viridian. Financial Support: This study was investigator initiated. The study was partially supported by a research grant from BVI Pharmaceuticals.

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Surgical Treatment

Ultrasonic Aspiration for Debulking Infiltrative Masses of the Orbit

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Purpose: To demonstrate the utility of an ultrasonic aspirator (Sonopet, Stryker Corporation, Kalamazoo, MI) for debulking fibrous, soft tissue masses of the orbit.

Methods: Case series. The ultrasonic aspirator was used to debulk fibrous soft tissue masses in 5 cases. The initial presentation was a large orbital mass encroaching on the orbital and lateral orbital rim, associated with globe displacement. The surgical approach was a lateral orbitotomy in 4 cases and a transconjunctival approach in 1 case. The mass was debulked using the ultrasonic aspirator to the desired volume, followed by resection of the remaining tumor capsule and surrounding orbital soft tissue. Histopathologic examination revealed 2 cases of solitary fibrous tumor, 1 case of orbital myofibroma, 1 case of orbital myositis, and 1 case of orbital inflammatory pseudotumor.

Results: The ultrasonic aspirator facilitated debulking of infiltrative lesions with tissue texture of the orbit. The device's ability to emulsify, irrigate, and aspirate allows one to work through tissue planes, debulking orbital tumors which would have been difficult otherwise due to location.

Conclusions: The ultrasonic aspirator allows precise sculpting of infiltrative fibrous soft tissue tumors in the orbit and is particularly useful in cases with challenging anatomical access.

(Ophthalmic Plast Reconstr Surg 2020;36:406–409)

Orbital surgeons are frequently challenged with the task of obtaining adequate surgical exposure and access while protecting vital structures in delicate anatomy of the orbit. In recent years, advances in radiology and technology have improved surgical access and accuracy, such as application of the transnasal endoscopic approach for medial and apical orbital pathology[1] and utilization of intraoperative navigation.[2,3] Despite these advancements, many challenges remain in approaching, surveying, debulking or excising certain orbital pathology tumors.

The Sonopet Ultrasonic Aspirator (Stryker Corporation, Kalamazoo, MI) is a modified device with emulsification, irrigation, and aspiration capabilities. Utilization of the instrument in orbital surgery has been previously described for bony decompression and diagnostic biopsy,[4–6] and there are case reports of debulking fibrous, glandular, and meningioma-like orbital tumors.[7–9] We report utilization of this instrument in 5 cases of infiltrative, soft tissue masses of the orbit in order to provide the surgical settings to allow safe tissue debulking. The traditional approaches yet safe debulking of tumors that would have otherwise been difficult or unsafe with alternative approaches due to location of the tumor or proximity to critical structures.

MATERIALS AND METHODS

The ultrasonic aspirator was used to debulk fibrous, soft tissue masses of the orbit in 5 cases. The patients' medical records were retrospectively reviewed. The study was performed in accordance with the Declaration of Helsinki.

The first case involved a 61-year-old man with a previously documented orbital soft tissue mass that displaced the globe inferiorly and caused mild proptosis and diplopia. Computed tomography revealed a large, homogenous, enhancing soft tissue mass extending from the retrobulbar space to the anterior orbit. The mass was in close proximity to the medial rectus muscle and optic nerve, but did not appear to invade these structures. The patient underwent a lateral orbitotomy for debulking of the mass. The mass was encountered in the lateral orbit and was found to be fibrous in texture. Debulking was performed using the ultrasonic aspirator to remove the bulk of the tumor, followed by resection of the remaining tumor capsule and surrounding orbital soft tissue. Histopathologic examination revealed a solitary fibrous tumor. The patient was lost to follow-up after the surgery.

The third case was a 62-year-old woman with a 2-year history of worsening proptosis and diplopia in the left eye. She had previously undergone bilateral cataract surgery with uncomplicated postoperative courses. Computed tomography revealed a large, homogenous, enhancing soft tissue mass extending from the retrobulbar space to the anterior orbit. The mass was in close proximity to the medial rectus muscle and optic nerve, but did not appear to invade these structures. The patient underwent a lateral orbitotomy for debulking of the mass. The mass was encountered in the lateral orbit and was found to be fibrous in texture. Debulking was performed using the ultrasonic aspirator to remove the bulk of the tumor, followed by resection of the remaining tumor capsule and surrounding orbital soft tissue. Histopathologic examination revealed a solitary fibrous tumor. The patient was lost to follow-up after the surgery.

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FIG. 1. CT scan of a large invasive lateral orbital mass extending to the apex and into the cavernous sinus (top left). Intraoperative muscle dissection following debulking of the mass (top right). Lateral orbital gross specimen showing the mass with the multiple adjacent structures, including rectus muscles, optic nerve, and lacrimal gland (bottom left). Histopathologic examination revealed a solitary fibrous tumor (bottom right). Hematoxylin and eosin stain, original magnification ×200.

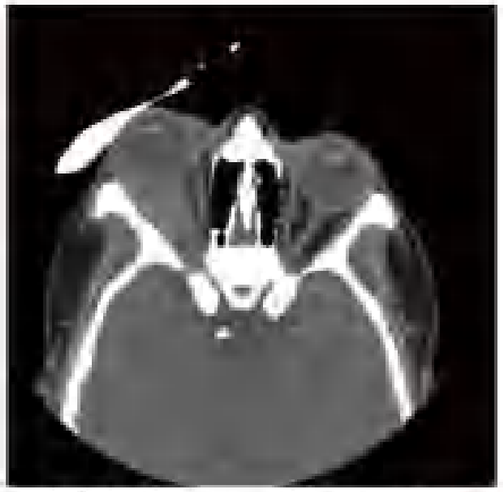

FIG. 3. Axial CT scan of a previous and intraoperative (3 months later) orbital CT, consistent with CRAO, extending into the optic canal (lateral view). While the patient obtained symptomatic improvement in her ocular compressive optic disc cup neuropathy, she did not regain vision (unchanged light perception) and refused systemic therapy.

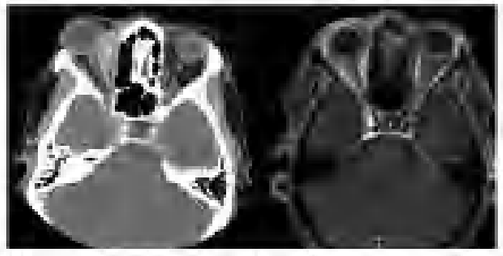

FIG. 2. CT scan of an extraconal medial orbital mass, radiographically consistent with cavernous hemangioma (asterisk), extending posteriorly along the medial orbital wall (double-headed arrow), displacing the medial rectus muscle (left). The mass was debulked with the aid of an ultrasonic aspirator. Postoperative (1 day) gadolinium-enhanced MRI prior to initiation of adjuvant therapy revealed near complete debulking of the mass.

FIG. 4. The hand piece and soft tissue tip of the Sonopet ultrasonic aspirator. The small footprint facilitated precise sculpting of firm, soft tissue masses, particularly in areas where surgical access is challenging.

Surgical Technique: In the case of the 62-year-old male with right exophthalmos, a superior lateral eyelid crease incision was made and dissection was carried down to the orbital rim. The periosteum was incised and the lateral orbital wall was exposed. A key hole craniotomy was performed using a 3 mm high speed drill (Anspach, Palm Beach Gardens, FL) and the bone flap was removed. The dura was incised and the lateral orbital wall was exposed. Orbitotomy was performed using the ultrasonic aspirator (Sonopet, Stryker Corporation, Kalamazoo, MI) fitted with a 15 mm, 45° angled tip. The tip was inserted into the tumor and the ultrasonic aspirator was activated. The tumor was debulked using the ultrasonic aspirator to the desired volume, followed by resection of the remaining tumor capsule and surrounding orbital soft tissue. Histopathologic examination revealed a solitary fibrous tumor. The patient was lost to follow-up after the surgery.

RESULTS

DISCUSSION

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Quantitative efficacy of external and internal browpexy performed in conjunction with blepharoplasty

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CLINICAL RESEARCH

Quantitative efficacy of external and internal browpexy performed in conjunction with blepharoplasty

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ABSTRACT

Browpexy surgery is a minimally invasive surgical adjunct to upper blepharoplasty. The traditional internal (IB) approach is well documented. While the newer external (EB) variant has only recently been described, to date, there is little quantitative data to evaluate the efficacy of either procedure and no data to compare results between the two. We describe the efficacy of and compare surgical results between internal and external browpexy surgery in lifting the central and lateral brow. A 3.5-year retrospective review of patients undergoing internal and external browpexy surgery to assess the amount of central and lateral lift to the brow was performed. Patients undergoing blepharoplasty without brow lift were used as a control group. The Massachusetts Eye and Ear Infirmary FACE-gram program was used to quantify surgical outcomes. Ninety-eight patients are included for review, with an average follow-up of 4.5 months. The average elevation in lateral/central brow position was 2.09 mm and 1.42 mm in the IB group, and 2.97 mm and 1.98 mm in the EB group. These were not statistically significant ($p = 0.164$, and $p = 0.107$, respectively). There was a statistically significant elevation in central and lateral brow heights for both browpexy techniques and the control group ($p < 0.001$). External and internal browpexy surgery offered a similar, and non-statistically different, elevation of the central and lateral brow at 4.5 months. When compared to standalone blepharoplasty (control), the amount of lift for both procedures is statistically significant.

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KEYWORDS
Blepharoplasty; brow ptosis; brow lift

Introduction

Traditional brow lifting techniques involve the implementation of supralateral incisions, or mobilization of the entire forehead and brow through open or endoscopic approaches. These techniques produce a powerful lift, and are excellent options for the appropriate patient. However, they can be associated with unsightly scarring, alopecia, neurosensory deficit, and can be cost prohibitive.[1–3] Additionally, many patients are fearful of the "operated look" which can be associated with a significant elevation of the medial brow. Consequently less invasive brow lifting alternatives can be of value to meet the surgeon and patient.

Ptosis of the tail of the brow is the most frequently encountered brow deficit,[4] and minimally invasive "browpexy procedures" procedures have been described to address this issue.[1,5–11] The traditional browpexy was described by McCord and Daniels.[5] In 1990, it involves an internal brow suspension accessed through an eyelid crease incision during blepharoplasty. For this reason it has been called the "internal browpexy (IB)." In 2011, one of the authors (GGM) elaborated on a variant of this procedure which suspends the brow through a small incision just within or above the upper brow ridge.[1] As this technique requires a cutaneous incision it has been called the "external browpexy (EB)." One of the major concerns of all detractors of browpexy surgery is that the adjunct does not work.[1] To date, there is little evidence based data to address this question.

ARH (one of the study authors) routinely uses both browpexy approaches for lateral brow stabilization or lifting during both functional and aesthetic upper eyelid surgery. He has long felt that both browpexy options provide a reliable and consistent minimal lift or stabilization of the brow when combined with blepharoplasty. This is important because the literature is

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Color versions for one or more of the figures in the article can be found online at www.tandfonline.com/iorb.

This research was presented at the 2016 ASOPRS Spring Meeting, in Palm Springs, CA.

unclear on the effect of standalone blepharoplasty on brow position. Many studies suggest that tissue excision, with an inherent shortened browfat distance, and a diminished drive to recruit the frontalis will worsen brow ptosis after blepharoplasty. [1–5] Others have found no change in brow position following surgery. [6–11] In either case it is clear that "at least" maintaining brow position after blepharoplasty is critical to enhance outcome.

The authors know of only two studies which have quantitatively assessed brow position after browpexy with blepharoplasty. Georgescu, et al.[7] showed that with the EB there was a 2.34-mm elevation of the lateral brow at 8.5 months follow-up. More recently, Baker et. al. showed less elevation of 0.9mm (left side) -1.3 mm (right side) at 4.4 months' follow-up, again after EB.[8] Similar quantitative data on the EB is lacking. In this study the authors quantify and compare the results in both the IB and EB performed in conjunction with upper blepharoplasty and ptosis repair when added. Isolated blepharoplasty, with or without ptosis repair, is used as a control. The results suggest that both browpexy variants provide a mild yet statistically significant, elevation of the central and lateral brow postoperatively at 4–5 months follow-up. This is the first report quantifying results to the ED, and comparing quantified outcomes of IB versus EB.

Materials and methods

The charts of patients who underwent EB or IB and blepharoplasty, with or without ptosis repair, by one of the authors (ARH), over a 3.5-year period (2010–2013) were retrospectively reviewed. Patients undergoing blepharoplasty (plus/minus ptosis repair) without brow lift were used as a control group. The study was approved by the Institutional Review Board of the University of Minnesota and the review was in adherence with the Declaration of Helsinki, and Health Insurance Portability and Accountability Act (HIPPA). Patients with a history of trauma, prior brow or eyelid surgery, thyroid eye disease, blepharospasm, and those with inadequate photographs were excluded.

Preoperative and last postoperative photographs were analyzed utilizing the Massachusetts Eye and Ear Infirmary FACE-gram Program (https://sun.hanlonlab.org/facial_nerve_program/).html).[12] The software draws a line through the center of each cornea (roughly the mid pupillary line), and measurements are made from that line to the central brow, defined as in line with the pupil, and we defined the lateral brow, as in line with the lateral canthus (Figure 1). The software standardizes measurements by setting the corneal diameter as 10mm. Statistical analysis comparing change in central and lateral brow height was performed using one-way analysis of variance (ANOVA) with the Tukey posttest.

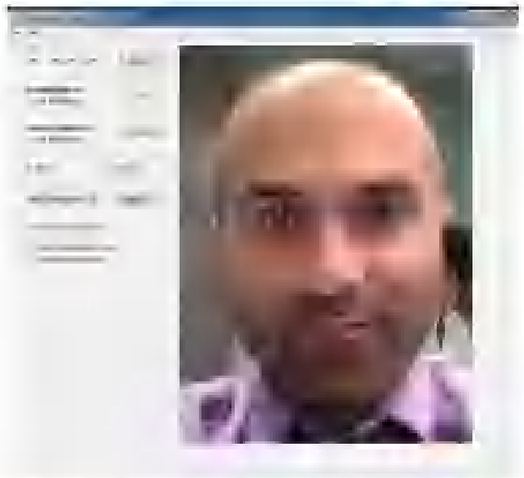

Figure 1. Screen grab from Massachusetts Eye and Ear Infirmary FACE-gram Program with line connecting center of both corneas. Marks have been added showing central brow height, at mid pupillary line, as well as lateral brow height at lateral canthus.

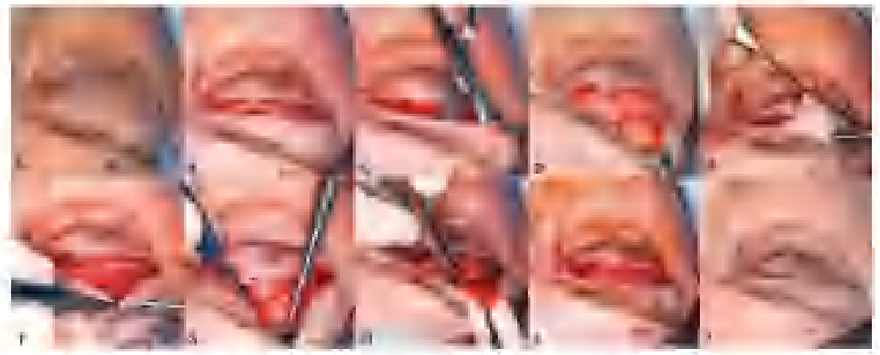

Figure 2. Surgical series of the IBP. (A) Surgical markings for standard blepharoplasty. (B) Skin and muscle have been excised. (C) Preseptal dissection to orbital rim. (D) Brow fat pad exposed. (E) Marking suture passed transcutaneously, and (F) retrieved internally. (G) Brow fat pad engaged. (H) Periosteum secured. (I) Browpexy completed. (J) Wound closed.

Surgical technique

The surgical techniques for IB[7] and EB[1] have been previously described. For the IB, the desired location of lateral brow is typically set by elevating the inferior brow to a level 1 cm above the superior orbital rim. A mark is made at the inferior brow cilia, or brow-eyelid skin junction, if there are no brow hairs. After a standard blepharoplasty, dissection proceeds in a preseptal plane to the orbital rim, and then preperiosteally (beneath the brow fat pad) approximately 1.5 cm above the superolateral orbital rim. A 4-0 Prolene suture is brought transcutaneously from the premarked area, into the dissected pocket. The same suture is then used to grasp the underlying periosteum, parallel to, and 1 cm above the superolateral orbital rim. The suture is then passed through the brow fat underlying the inferior brow where the transcutaneous pass was marked. The opposite end of the Prolene suture is then pulled into the dissection pocket and tied so that the brow fat is secured to the periosteum (Figure 2).

For the external browpexy, the amount of elevation is determined in the preoperative area in the sitting position (Figure 3). Please refer to the initial description of the procedure for details on this step.[1] However, as a general rule, the brow is in an ideal position after infiltration of anesthetic (volumetric effect) and with the patient in a supine position during surgery. An 8-mm demarcation is made preoperatively superior to the upper brow cilia at the junction of the middle and outer third of the brow. An incision is made in this predetermined area through dermis following the curvature of the brow.

Westcott scissors are used to incise through orbicularis muscle and the brow fat pad, in a perpendicular fashion, to the level of the periosteum of the frontal bone. A medial and lateral dissection to periosteum proceeds to create a dissection pocket whose horizontal dimension is approximately 25 mm. This allows for a

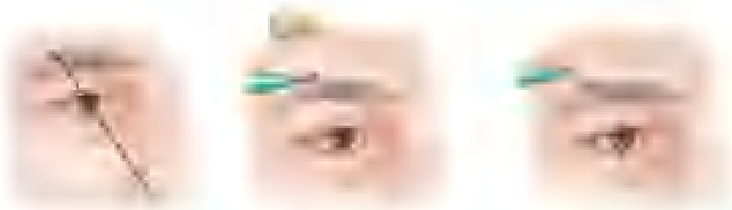

Figure 3. Left: Brow fixation point marked at a point connecting nasal ala and mid-pupillary line. Center: Brow elevated to desired height with marking pen hovering over demarcated fixation point. Right: Brow released and new mark will be made where marking pen is hovering. The distance between two pins is the amount of lift to be made.

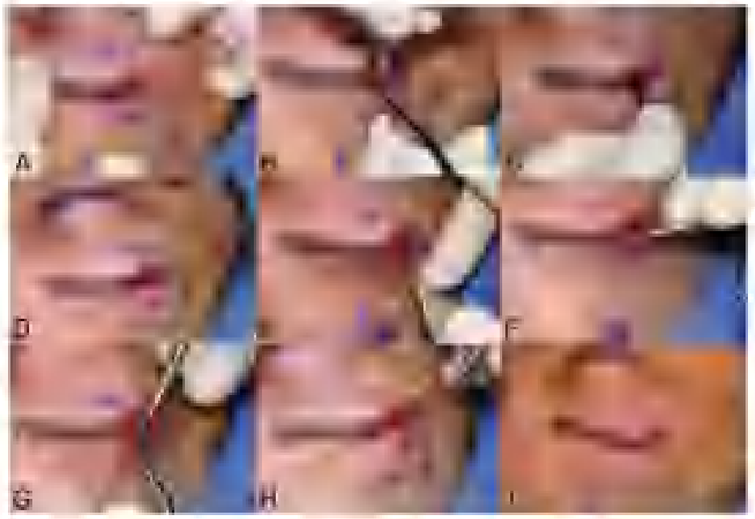

Figure 4. Surgical series of EB. (A) Skin incision. (B) Orbicularis dissection to periosteum. (C) Periosteum engaged with forceps and (D) prolene suture. (E) Brow fat and orbicularis grasped with forceps, and (F) prolene suture passed through both tissues from (C) below, and then (F) above. (I) Suture tied – note brow elevation and anterior projection as ptotic brow fat pad is elevated giving true or relative volumetric enhancement. (J) Wound closed. © The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc. Reproduced by permission of The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc. Permission to reuse must be obtained from the rightsholder.

small skin entry point (reduce visible incision) and a larger internal dissection and resultant scar to help maintain brow position after surgery. The periosteum at this level is engaged with a 4-0 Prolene suture and is secured to the orbicularis muscle and brow fat pad at the inferior lip of the incision in a pseudo-mattress fashion. The subcutaneous tissue and skin are closed with interrupted sutures (Figure 4 and 5).

Results

Ninety-eight patients are included in the study. Seventy-seven brows of 45 patients (46%) underwent EB and blepharoplasty with or without ptosis repair. Fifty-three brows of 29 patients (30%) underwent IB and blepharoplasty with or without ptosis repair. Finally, 48 eyelids of 24 patients (24%) underwent blepharoplasty with or without ptosis repair (control group). A ptosis repair was added to 35 patients (45%) undergoing the external browpexy, 14 patients (26%) undergoing the internal browpexy, and 17 patients (40%) in the control group. The EB cohort included 25 females and 20 males with an average age of 64 years (range 37–77 years). The IB cohort included 18 females and 11 males with an average age of 64 years (range 53–75 years). The control group included 18 females and 6 males, with an average age of 67 years (range 41–83 years).

The surgical results are summarized in Tables 1 and 2. The average follow-up was 143 days, 175 days, and 91 days for each group, respectively. The average change in lateral brow position was an elevation of 2.97 mm in the EB group, 2.29 mm in the IB group, and a descent of 1.10 mm in the control group. The average change in central brow position was a 1.90-mm elevation in the EB group, 1.47-mm elevation in the IB group, and a descent of 0.38 mm in the control group.

Although the difference between lateral and central brow height change between the two browpexy techniques was not statistically significant ($p = 0.164$, and $p = 0.507$, respectively), there was a statistically significant change in central and lateral brow height between the control group and both browpexy approaches ($p < 0.001$). No patients experienced unacceptable scars, facial nerve injury, and no patients complained of loss of brow hairs. Of the 53 brows undergoing internal browpexy, 4 (8%) required revision due to inadequate lift. Of the 77 brows undergoing external browpexy, 3 (4%) required revision due to inadequate lift. This difference in revision rate was not statistically significant ($p = 0.442$). Figures 6 and 7 demonstrate representative examples of surgical outcomes.

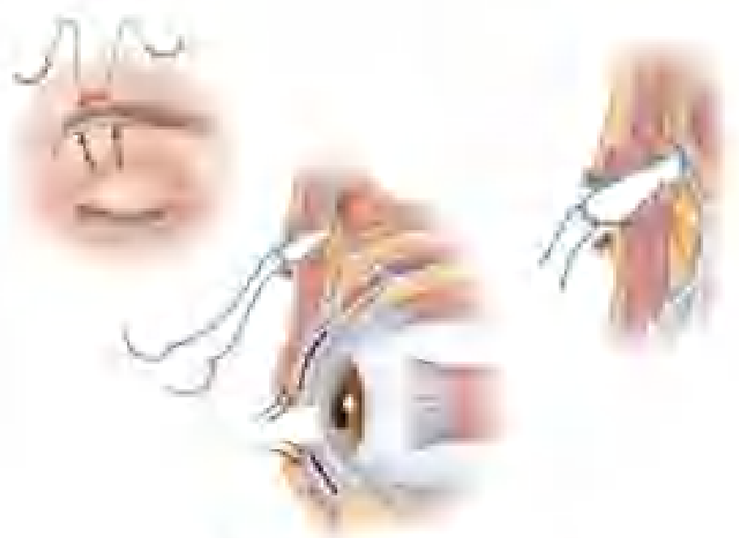

Figure 5. Artists drawing of EB. Left: Incision and suture placement with arrows showing beginning (dotted lines) and elevated position of brow. Center: Sagittal view showing suture secured to periosteum, brow fat pad and inter-digitation of orbicularis and frontalis muscles. Right: Higher magnification view of center drawing. © The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc. Reproduced by permission of The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc. Permission to reuse must be obtained from the rightsholder.

Table 1. Changes in brow height in all groups after surgery.

	Preop Lateral Brow Height	Preop Central Brow Height	Postop Lateral Brow Height	Postop Central Brow Height	Average Lateral Brow Height	Average Central Brow Height	Average Follow-up
External Browpexy	8.27 mm	9.81 mm	11.24 mm	11.71 mm	2.97 mm	1.90 mm	142.65 days (19-361)
Internal Browpexy	9.82 mm	11.75 mm	12.21 mm	13.22 mm	2.29 mm	1.47 mm	174.67 (25-1178)
Control (Blepharoplasty)	12.31 mm	13.57 mm	11.11 mm	13.19 mm	−1.10	−0.38 mm	91.33 (12-429)

Table 2. Statistical analysis of surgical results.

Group Comparison	Difference-in-Change of Central Brow Height (mm)	P value	Difference-in-Change of Lateral Brow Height (mm)	P value
EBP-IBP	0.43	0.507	0.68	0.164
EBP-control	2.38	0.001	4.08	0.001
IBP-control	1.85	0.001	3.39	0.001

Discussion

Patients presenting for upper eyelid evaluation commonly have a component of brow ptosis. Selecting an appropriate brow lifting or stabilizing procedure, when appropriate, should consider preoperative brow position, contour and height, forehead rhytids, hairline position, and the patient's desires. Although endoscopic, pretrichial, and coronal brow lifting techniques can provide a powerful lift, they may be financially prohibitive, and often patients are not looking to drastically change their overall appearance. A direct brow lift can provide excellent results in patients who have deep supratarsal rhytids or bushy eyebrows, but the scar can be difficult to hide, and the procedure can noticeably change the brow contour.[11]

Another surgical option is the less invasive browpexy procedures.[1,2,7–9] These include both a transeyelid IB,[1,2,7–9] or the small incision EB option described by one of the authors (GGM).[1] Unfortunately most of the browpexy publications in the literature are descriptive in nature with only anecdotal suggestions of surgical outcome. In this report the authors quantify surgical results with both procedures (first time for the EB) and compare these results between procedures.

The authors found that there was a modest yet noted elevation of both the lateral and central brow height with both browpexy procedures (EB – 2.97 mm and 1.90 mm, IB – 2.29 mm and 1.47 mm) at 4–5 months

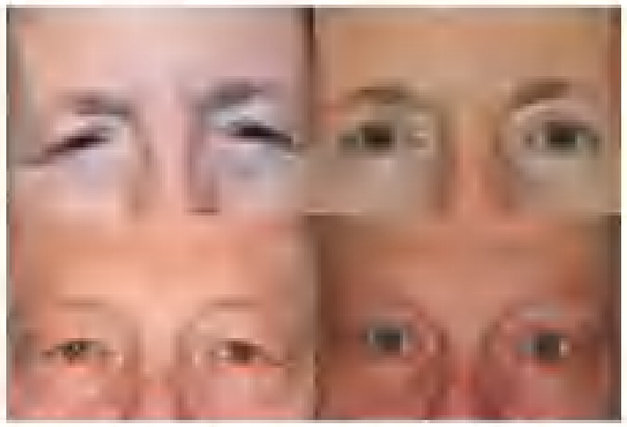

Figure 6. Before and after examples of IB. Top: Before (left) and after (right) example of a 62-year-old female 6.5 months after bilateral IB with upper blepharoplasty and levator advancement ptosis repair. Below: Similar 7-month post-op example of 67-year-old male, but the ptosis repair was a conjunctivo-mueller ectomy approach.

Figure 7. Before and after examples of EB. Top: Before (left) and after (right) example of a 60-year-old female 9 months after bilateral EB with upper blepharoplasty and levator advancement ptosis repair. Below: A similar example of a 68-year-old, 6-month post-op example of a female, but the ptosis repair was a conjunctivo-mueller ectomy approach.

follow-up. This is similar to results previously documented with the internal browpexy in one study (8-month follow-up),[7] and significantly higher than the results from a second reported series at similar follow-up time (4.4 months).[7] Additionally, the authors found no statistically significant difference in the amount (millimeters) of brow lift attained between the external and internal approaches.

This is an important finding, as generally patient are told these are "brow stabilizing" surgical adjuncts to blepharoplasty, but the results suggest that both procedures do provide a moderate true brow lift. Also of note, is that the results show that blepharoplasty without browpexy (control group) resulted in a drop of both the central and lateral brow. Although the literature on this subject is conflicted,[2–4,7–11] the author's results suggest that there is value to adding either form of browpexy to blepharoplasty, when appropriate, to avoid worsening brow ptosis. In addition to the brow lift noted, the authors subjectively found a more pleasing three-dimensional contour in patients undergoing the external browpexy, which was

attributed to the superior rotation and anterior projection of the brow fat pad as has been described (Figure 4). This study was designed to validate [illegible] and these assessments changes in brow [illegible].

Pronounced differences in these issues would be of great value in referring to procedure. Unlike the authors, initially have selected the internal browpexy a patient with very low or non-existent brow ptosis in order to avoid a noticeable scar. With this in mind, the author had no patient complain of an obvious or bothersome brow scar at their final postoperative visit with the external procedure. This substantiates the assessment of the original description. For patients with taller brow ptosis the external procedure is always selected. For patients with severe medial brow ptosis, a browpexy can result in a peaked tail of the brow after surgery. This must be kept in mind when selecting how much to elevate the lateral brow in this patient subset. Interestingly, the authors find this is less common with the external approach although the data from the study does not show why.

Overall the author's general preference has shifted to the external browpexy as they anecdotally believe it is more predictable. This is most likely because with the technique the brow is suspended from above with a full-thickness scar/adhesion, as compared to the internal procedure which secures the brow from below with a partial thickness one. This can allow the heavy brow tissue to evade over the fixation point with loss of effect. The heightened predictability of the external procedure is supported, in part, in this series, as it had a lower revision rate (4% vs. 8%) compared to its internal counterpart. However this was not found to be statistically significant.

The limitations of the study include lack of long-term data and medial brow height assessment. The problem the authors faced with longer term outcome assessment was the lack of patient return for follow up visits. The authors found that with follow up calls, many patients stated they were pleased with their outcome, but no need to return (many from distances) and preferred follow up with their referring physicians. Clearly 4–5 month follow-up does not define what true long-term outcome is, nor does it address the ability to attain a stable elevation with both browpexy variants and is in line with the previously referenced similar study quantifying the EB.[7] A prospective analysis with preoperatively laid out 'marks' and/or longer follow-up is needed as a follow up study. In regards to assessing medial brow heights, the authors did not expect medial brow position changes with lateral browpexy procedures, and thus omitted these measurements.

A lack of patient satisfaction can also be considered a study limitation. The operating surgeon in this cross (ABH) started performing the external browpexy in mid-2012. Before that time he exclusively performed the internal procedure. After this time he performed primarily the external variant. Unless lots of home videos are present, although the patients were not randomized, the authors feel this consistency reduces selection bias.

Also, the study population is weighted to the external browpexy cohort (77 brows of 43 patients underwent this procedure, compared to 53 brows of 29 patients in the internal browpexy group, and 48 brows of 24 patients in the control group). This difference can potentially bias results, but the authors feel strongly that the 53 brows in the IB group and the 48 brows in the control group constitute a valid trend.

Finally, ptosis repair was added in 45% of the external browpexy group, 28% of the internal browpexy group and 40% of the control group. In general, ptosis repair—such as blepharoptosis—by elevating the pretarsal skin can influence medial brow and relatively drop the brow. As there was no ptosis repair performed with the IB group as compared to the EB group, this potentially can confound the comparison to a degree (i.e., relatively overcorrect the corrections attained with the IB group).

However a recent report showed that there was not a statistically significant change in brow position amongst patients undergoing ptosis repair (Müeller's muscle conjunctival resection) alone or ptosis repair with blepharoplasty.[12] Because patient rights to this report were compiled from the practice of one author (ABH), an oculoplastic surgeon whose patient population typically presents with multiple eyelid deformities, ptosis is a common eyelid malposition to address.

Conclusion

In summary, the external browpexy procedure provides 2.47 mm of lateral and 1.9 mm of central brow lift when performed in conjunction with upper blepharoplasty with or without ptosis repair. Similarly, the internal browpexy provides 2.29 mm of lateral and 2.47 mm of central brow lift. There is no statistically significant difference in amount of lift between the two procedures. Finally, both procedures result in a statistically significant improved lateral and central brow lift as compared to isolated blepharoplasty, which in this series, caused a descent of both the lateral and central brow. To the author's knowledge this is the first series that quantifies the results of the IB and that compares quantitative outcomes between the IB and EB procedures.

Declaration of Interest

The author report no conflicts of interest. The author alone are responsible for the content and writing of the [illegible]

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ORIGINAL ARTICLE

Excision of Periorbital Hemangiomas to Correct Visual Abnormalities

Daniel Schneider, MD; Michael S. Tse, MD; Andrew R. Harrison, MD; James Sidman, MD

Objectives: To determine whether early surgical excision of complicated periorbital hemangiomas (CPHs) to remedy refractive errors and prevent/alleviate visual complications, CPHs can cause visual complications including astigmatism, strabismus, and occlusion of the visual axis with resultant amblyopia.

Design: Retrospective review of patients seen from a tertiary care pediatric referral center. Nine patients with CPHs were managed by otolaryngology and ophthalmology services with complete surgical excision. Preoperative eye examination findings were compared with postoperative findings.

Results: Comparison of preoperative and postoperative ophthalmologic measurements such as eye alignment and range indicated reduction of astigmatism and substantial improvement in vision as measured by refractive changes and reduction of pupillary occlusion.

Conclusions: Total excision of CPHs is a safe and effective approach. When completed early, excision provides definitive therapy, reduces or eliminates astigmatism, and can prevent amblyopia in pediatric patients when pupillary occlusion is present.

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Hemangioma of infancy (HOI) is the most common vascular tumor in children, with an estimated incidence of 1% to 10% in the first year of life. Approximately 60% of hemangiomas occur in the head or neck.[1] The specific cause of hemangioma formation is unclear. There is a higher incidence of HOI in premature infants.

The natural history of HOI is biphasic, with an early period of rapid growth (proliferating phase) occurring in the first 3 months of life and lasting up to 1 year followed by a slow regression period (involuting phase) over 5 to 9 years. Fifty percent of HOIs involute completely by age 5 years, and 70% by age 7 years.[2] Hemangiomas can proliferate on the superficial and/or deep portions. Eighty percent of lesions are isolated, the remaining 20% occur at multiple sites.

The benign history of most hemangiomas allows for careful observation. However, periorbital hemangiomas can induce astigmatism and may threaten normal visual development owing to obstruction of the visual axis that culminates in ptosis, gaze abnormalities, or visual field defects. The most common cause of subsequent amblyopia is a result of anisometropic amblyopia.[3] Anisometropia, amblyopia is defined as a measurable difference in refractive or focusing errors between the 2 eyes and is associated with periorbital hemangiomas because of the pressure placed on the anterior segment of the eye.

Current accepted treatment for periorbital hemangiomas to prevent permanent visual loss includes careful observation, administration of systemic and intralesional steroids, propranolol, interferon therapy, superficial radiotherapy, laser therapy, and surgery. Each has its own associated complications and response rate.[1] Surgery for these lesions has been criticized in the past owing to concern over postoperative scarring, infection, and risk to the eye and adnexal structures.[4]

In the present case series of patients, we examine the multidisciplinary treatment by the otolaryngology and ophthalmology services of complicated periorbital hemangiomas treated with surgery to resolve pupillary occlusion, refractive changes, and/or abnormal ophthalmologic eye examination findings to prevent permanent amblyopia.

Methods

Nine children treated with surgery at Children's Hospitals and Clinics of Minnesota and the University of Minnesota Medical Center between 2003 and 2007 were identified. All children treated were younger than 11 months and underwent ophthalmologic examination by otolaryngology/ophthalmology prior to surgery. Patient characteristics are summarized in the **Table**.

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Table. Characteristics Before and After Excision of Periorbital Hemangioma

Patient No./ Age/Age at Presentation, mo	Imaging	Preoperative Therapy	Tumor Location	Pediatric Eye Exam	Preoperative Refraction	Postoperative Refraction
1/M/2	CT	Steroids[a] (systemic)	Left preseptal and orbital	20/40 (+2.5 sphere)	−2.00 sphere −0.50 cylinder × 170	−2.50 sphere −1.00 cylinder × 180
2/M/4	MRI	Steroids[a] (systemic); IL laser therapy	Left eyelid, subcutaneous tissue, orbit	20/30 (+1.5 sphere)	+1.50 sphere +0.50 cylinder × 180	+1.50 sphere +1.00 cylinder × 170
3/F/8	None	Intralesional steroid	Left upper eyelid, subcutaneous tissue	20/30 (+2.5 sphere)	+2.00 sphere +1.00 cylinder × 90	+1.50 sphere +1.00 cylinder × 45
4/F/2	CT	None	Right lacrimal fossa, orbit	Fix and follow	N/A	N/A
5/F/3	None	Amblyopia treatment only (+)	Left orbit	20/40 (+4.5 sphere)	+4.50 sphere −0.50 cylinder × 150	+4.50 sphere −0.50 cylinder × 150
6/M/2	None	Propranolol (systemic)	Right upper eyelid, orbit	20/40 (+4.5 sphere)	+4.25 sphere −0.50 cylinder × 180	+4.75 sphere −0.50 cylinder × 170
7/M/1	None	None	Left orbit	20/30 (+3.5 sphere)	N/A	N/A
8/M/1	MRI	None	Left orbit	20/30 (+3.5 sphere)	N/A	N/A
9/M/8	None	None	Right orbit	Fix and follow	N/A	N/A

Abbreviations: CT, computed tomography; L, left; MRI, magnetic resonance imaging; N/A, not applicable; R, right.
[a] Prednisolone sodium for intravenous and oral administration by Pediatric Hospital Specialty, Apothecary, Bronx, New York.
[b] Fix and follow refers to eye examination.

Prospectively, 4 patients underwent conventional therapy with incomplete response. Prior to referral to our institution, 2 patients received laser therapy (pulsed dye and argon), 1 with carbon dioxide laser, and the other with potassium titanyl phosphate laser, so that the superficial components had been treated. Both lesions were unresponsive. One patient required intravenous steroids therapy for lack of response to outpatient medications. All patients underwent a period of nonsurgical eye patching prospectively to ensure equal visual development.

Surgery was performed with glycopyrrolate, intramuscular succinylcholine, and intravenous propofol. Local anesthetic with epinephrine was injected into the lesion. Incisions were placed in the eyelid crease when the lesion involved the eyelid. Lesions of the surgical site were completely excised to preserve anatomy. Meticulous hemostasis was achieved at the time of surgery in the orbit. No implants were needed, and all operations were done on an outpatient basis.

All of the hemangiomas were well circumscribed deep processes apparent at surgery, not unlike what is seen in young infants with giant cavernous hemangiomas who receive medical therapy as well as a lack of normally expected vascular dilation of observation in patients with periorbital hemangiomas whose presentation of amblyopia and permanent visual loss is prominent.

RESULTS

A total of 9 infants (4 boys and 5 girls) underwent surgical excision of complicated periorbital hemangiomas to treat refractive error and/or abnormal eye examination findings during the study period. All patients had abnormal eye examination findings prior to surgery. Four of the patients underwent computed tomography or magnetic resonance imaging prior to surgical excision to rule out an orbital component.

Refractive measurements were made in 5 of 9 patients preoperatively and postoperatively, including in the contralateral eye. Postoperatively, all 9 patients showed improvement in their original eye examination findings, as determined by a neuroophthalmologist, pediatric ophthalmologist, and all of those who had refractive errors measured preoperatively also showed improvement postoperatively. At the last follow-up, none of the patients showed evidence of amblyopia, hyphema, eyelid ptosis, or signs of recurrence. All patients demonstrated substantial improvement in cosmetic and functional results with no appreciable visual sequelae. There patients developed superficial infections that were managed with oral antibiotics and topical wound care. Excellent surgical results were obtained with normal appearance by 2 to 3 weeks postoperatively, as shown in the **Figure**. Given the retrospective nature of this case series, data on average scar length and width were not obtained.

COMMENT

Periorbital hemangiomas may threaten visual development for several reasons. They can cause refractive errors. Strabismus may occur if the ocular muscles or their associated cranial nerves are involved, and ptosis develops when prolonged visual obstruction occurs, and optic atrophy and even loss of the eye have been reported. Frequent ophthalmologic examination is warranted to follow the progression of the malformation and monitor for these effects on the visual axis. Most hemangiomas in the periorbital region will not require treatment because they are small and do not affect vision. However, if close observation of patients with these lesions demonstrates worsening of refractive measurements or pupillary obstruction, surgical therapy should be considered.

A recent survey by Waszkiewicz et al[1] revealed that obstruction of the visual axis, profound astigmatism, and poor cosmesis were the most common indications for aggressive intervention therapy. Intralesional steroid therapy remains the most common treatment, but excision is gaining acceptance. Schwartz et al[2] sought to identify the risk factors of subsequent development of amblyopia due to anisometropia from capillary hemangiomas of the eyelids and orbit. They concluded that lesions larger than 1 cm are more likely to cause blepharoptosis and have enough mass effect to exert pressure on the anterior segment of the eye with resultant refractive changes. Their work also suggests that nasal location of the hemangioma, rather than temporal location, is more likely to cause amblyopia. Proptosis and globe displacement were also identified as substantial risk factors for visual changes. Brandhall and Qvarfo[3] reported that any degree of pupillary obstruction will result in visual complications and that refractive errors occur at a high rate prior to the development of amblyopia.

Corticosteroids remain the mainstay of treatment for periorbital PHH. Reinhold et al[4] systematically evaluated the literature and found few objective studies documenting the efficacy of topical, intralesional, and systemic steroids in terms of pretreatment and posttreatment refractive measures. Of those treated with corticosteroids, we have found success using intralesional injection consisting of a 50:50 mixture of betamethasone, 4%, and triamcinolone for initial therapy. Other equally potent steroid mixtures have been shown to be equally effective.[5] Intralesional steroid injection treatment has been shown to improve ptosis;[6] however, considerable variation in posttreatment refraction measurements was present within this published series.[7] Risk of embolization of steroid particles has been reported and includes ophthalmic artery occlusion, retinal embolization, and central retinal artery occlusion.[8] Local adverse effects include eyelid hypopigmentation, subcutaneous fat atrophy, scleroderma-like tissue atrophy, periocular calcification, and eyelid necrosis.[9]

Systemic corticosteroids administered at doses between 1 and 4 mg/kg of prednisone are typically used for 6 to 8 weeks. If signs of involution are present after 7 to 10 days of therapy,[10] systemic steroids will accelerate involution in 80% of lesions and cause stabilization in 40%, while the remaining 30% of lesions display no response.[11] Early signs of involution usually occur within several days to 1 week of treatment initiation and manifest as lightening of hemangioma color, tissue softening, and diminished growth. Steroid therapy in patients who are unresponsive after several days to 1 week is substantially tapered off. Systemic corticosteroids have been shown to accelerate the involution of both superficial and deep portions of the hemangioma, but substantial adverse effects have been reported, including development of cushingoid features, growth deceleration, irritability, personality changes, gastrointestinal upset, weight gain, adrenal suppression, increased susceptibility to infections, and hypertension.[12] Newer treatments with propranolol[13] and low-dose cyclophosphamide with interferon have been described in small series.[14,15]

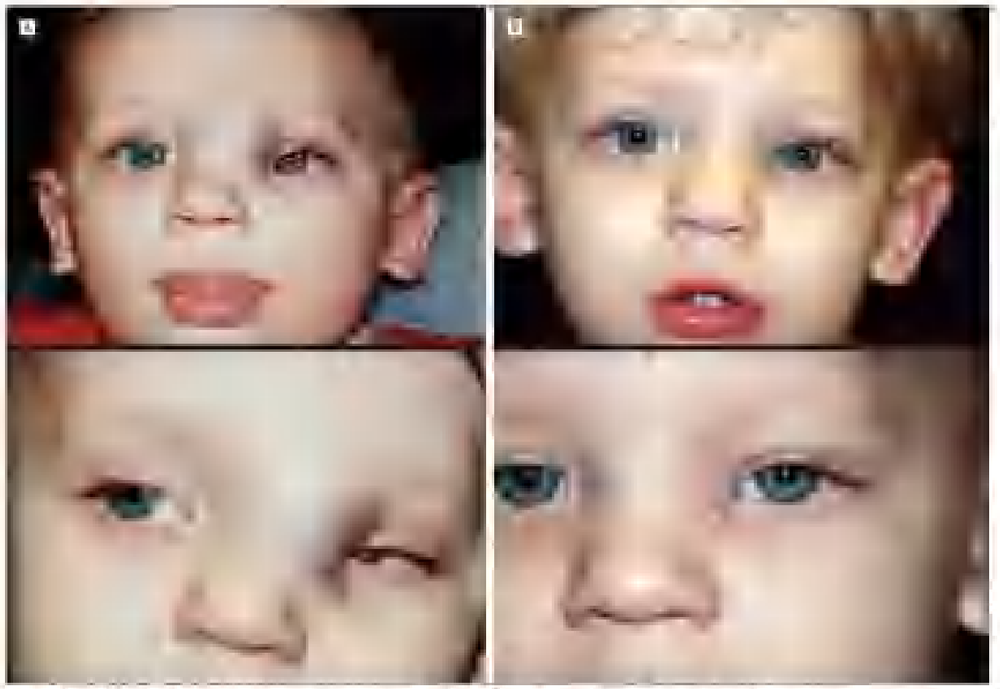

Figure. Patient 1 has left periorbital capillary hemangioma. A, Preoperative image. B, Postoperatively, with resolution of the lesion and resolution of residual hemangioma at 2-week follow-up.

surgical excision of hemangiomas that are well circumscribed and noninfiltrating. Curettage is a procedure the tumor behaves similar to a tissue expander with a small number of feeding vessels that can be carefully cauterized with meticulous surgical technique. Blood transfusions have been avoided with this technique. Subtenon closure is uncomplicated, and postoperative eyelid malposition is unlikely owing to skin excess at the time of closure as a result of the underlying subcutaneous expanding nature of the hemangioma. This type of hemangioma does not require preoperative embolization and sclerotherapy has not been used owing to the additional risks of skin necrosis and the potential for systemic dissemination of the sclerosant.[10]

Controversy remains regarding the optimal timing of surgical treatment. Levy et al[9] discussed surgical excision of periorbital hemangiomas resistant to steroid treatment and found success when the technique was used on patients younger than 21 months to relieve pupillary occlusion and diminish deprivation. Our criteria for surgical intervention relied on ophthalmologic determination of worsening eye examination findings and/or refractive changes with or without failure of corticosteroid therapy. This is in contradiction to the approach outlined by Waner et al[4] who recommend surgery for advanced periorbital hemangiomas that are rapidly growing and unresponsive to steroid therapy or when vision is impaired or completely occluded. We have developed our approach based on our experience of complex resection without visual or eyelid complications.

CONCLUSIONS

Patients with periorbital hemangiomas that present prior to consultation with the ophthalmology service but long after refractive changes have occurred. The traditional "wait and see" management of these lesions may lead to unnecessary visual sequelae when appropriate referral and treatment is not delivered in a timely manner. If medical therapy fails or the patient presents with refractive changes or pupillary occlusion, surgery alone can be used to successfully treat and correct early-onset astigmatism and vision changes and reduce the number of office visits and the potential need for other therapies. Surgical complications are low-risk when lesions are smaller, circumscribed, noninfiltrating, and lack an orbital component. Periorbital hemangiomas unresponsive to less invasive therapies should be strongly considered for early surgical excision, especially when refractive changes and/or pupillary occlusion are present.

Surgical excision of periorbital hemangiomas can reduce astigmatism, improve visual field deficits, and prevent sequelae in amblyopic vision mediated in a timely manner. Surgery should be considered early to decrease the duration of these patients because it can be done safely and with minimal morbidity.

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ORIGINAL ARTICLE

Persistent Blurred Vision After Blepharoplasty and Ptosis Repair

Mitra Shai, MD; Patrick Blum, MD; Andrea Hamrick, MD; Teri Wheat, MD; Peter Aliger, MD

Background: Visual disturbance after upper (eyelid) blepharoplasty is a relatively common postoperative complaint. Recent ophthalmology literature has demonstrated alterations of corneal curvature after procedures that reposition the upper eyelid using corneal topography. Astigmatic changes induced by eyelid repositioning may be a source of persistent blurred vision after upper eyelid procedures. This observation has not been reported in the facial plastic literature.

Objectives: To determine the incidence of persistent visual disturbances after upper blepharoplasty.

Methods: A retrospective review of upper blepharoplasties by 2 facial plastic surgeons and 2 oculoplastic surgeons during the year 2000. Patient interviews were conducted via telephone.

Results: A total of 146 patients were identified, and 126 of them responded to the study request. Six patients (5.7%) had subjective visual acuity changes 1 year after upper blepharoplasty, and 4 of the 6 patients had combined blepharoplasty and ptosis repair. Three patients had worse vision, 2 had improved vision, and 1 was unable to wear rigid contact lenses because of tearing.

Conclusions: Prior studies have shown that most patients have measurable astigmatic changes 3 months after blepharoplasty and ptosis repair. We found that only a small percentage of these have persistent subjective symptoms 1 year postoperatively. It is important for facial plastic surgeons to properly advise patients, especially those with combined procedures, that upper eyelid repositioning procedures may induce long-term vision changes. Patients may need to obtain new prescription spectacles and contact lenses postoperatively.

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Upper blepharoplasty is one of the most frequent eyelid procedures performed by facial plastic surgeons. Blurred vision has long been recognized as a potential complication of the procedure. Its cause has often been attributed to dry eye.

Recent literature indicates that procedures that reposition the upper eyelid may alter pressure exerted on the opposing cornea and change preexisting corneal curvature. Such changes potentially alter corneal refraction and may be responsible for persistent blurred vision after upper blepharoplasty, ptosis repair, and gold-weight implantation.

Using corneal topography, some investigators found that most patients who undergo blepharoplasty and ptosis repair had measurable refractive changes.[1-7] Nevertheless, our clinical experience indicates that few patients require new prescriptions for lenses after blepharoplasty. This study was designed to determine the incidence of persistent symptoms of visual disturbance after upper blepharoplasty.

METHODS

The study design was retrospective and uncontrolled. The patient population was selected from 2 university-affiliated academic practices in Edina, Minn. All patients who underwent upper blepharoplasty by 2 facial plastic surgeons (P.B. and T.W.) and 2 oculoplastic surgeons (E.L.N. and A.R.) during the year 2000 were included. Patient information was collected from clinic medical records and telephone interviews were conducted by the first author (M.S.) at the end of year 2001. Patients who could not be contacted were excluded from the study.

Four questions were asked during the telephone interview: (1) Have you had any change since your surgery? (2) Have you had your vision change last 4 mo? (3) Do you wear eyeglasses or contact lenses before your sur-

Patients With Visual Acuity Change 1 Year After Upper Blepharoplasty

Patient No./ Age, y	Procedure	Visual Symptoms
1/67	Bilateral upper blepharoplasty and ptosis repair	Improved, corrected acuity 20/20 for glasses; no change for contact lenses
2/59	Bilateral upper blepharoplasty and ptosis repair	Improved, corrected acuity 20/20 for glasses; right contact lenses decentering frequently; left contact lens fitting difficult
3/56	Bilateral upper blepharoplasty and ptosis repair	Decreased, corrected acuity 20/30 for glasses; worse with contact lenses
4/59	Bilateral upper blepharoplasty and ptosis repair	Minor change, corrected acuity 20/20 for glasses; poor contact lens performance
5/63	Bilateral upper blepharoplasty and ptosis repair	Improved, corrected acuity 20/20 for glasses; poor contact lens performance
6/58	Bilateral upper blepharoplasty and ptosis repair	Improved, corrected acuity 20/20 for glasses; poor contact lens performance

ages 18–70. Did you have to get a new prescription for contact lenses after your surgery?

RESULTS

A total of 146 patients were identified, with 128 from the oculoplastic surgery service and 18 from the facial plastic surgery service. Forty patients could not be contacted and were excluded. For the remaining 106 patients, 94 (88.7%) were from the oculoplastic surgery service and 12 were from the facial plastic surgery service. Of the 94 oculoplastic surgery patients, 38 had upper blepharoplasty and 33 had combined upper blepharoplasty and ptosis repair. Of the 12 patients from facial plastic surgery service, all had upper blepharoplasty. Other concurrent procedures included endoscopic brow lift, septorhinoplasty, submental lipoplasty, face-lift, chemical peel, lower eyelid retropalpebral fat resection, transconjunctival blepharoplasty, and canthoplasty.

A total of 16 patients (15.1%) reported persistent visual acuity change at least 1 year after surgery (**Table**). Three patients had persistent blurred vision. Two patients had unequivocal visual acuity after their surgery. One patient became intolerant of right contact lenses following combined upper blepharoplasty and ptosis repair. After her surgery, she complained of frequent fogging of her right contact lenses. The symptom was debilitating and disruptive, especially during driving. She returned to wear soft lenses and now uses prescription eyeglasses.

One of the 6 patients with visual acuity changes had a combined blepharoplasty and ptosis repair.

COMMENT

Patients who have upper blepharoplasty often complain of blurred vision postoperatively. The symptom is frequently attributed to dry eyes and usually is temporary. The common causes of postoperative dry eye include eyelid edema interfering with normal production and secretion of tear film, increased exposure of ocular surface topographic irregularities, lower eyelid malposition, a diminished Bell reflex from surgical anesthesia or edema, and preexisting dry eyes, either recognized or occult.[1] Careful preoperative and postoperative evaluation usually yields the correct diagnosis. If edema in the entire bilateral upper eyelid subsides as the edema reabsorbs (Patients 3 weeks after the operation, do not wish to discuss long-term visual consequences after upper blepharoplasty can be explained by examination of the shape of the cornea itself in addition to changes in the tear film overlying the cornea.

In recent years, ophthalmologists have noticed refractive changes in the operated eye after eyelid reconstructive surgery.[2] Others of the same patients developed a hyperopic refractive shift (better distance vision and worse near vision without spectacles) after ptosis repair. Knapp[3] suspected that long-standing ptosis caused refractive changes by flattening the upper cornea with subsequent increase in the curvature of the central cornea. Similar effect has also been noted after implanting gold weight in the upper eyelid for improving eyelid closure.[4] The recent development of computer topography of both central and peripheral cornea has made sequential corneal mapping after eyelid surgery possible. In a prospective study, Brown et al[5] reported that a majority of patients with blepharoptosis and ptosis repair have measurable corneal astigmatic changes 3 months postoperatively. Hirokawa et al[6] reported that 72.4% of patients with ptosis repair had astigmatic changes 9 weeks postoperatively and 20% maintained a significant change at 12 months postoperatively.

It has been hypothesized that eyelid tension interaction is an important factor in postoperative corneal astigmatism. Gullstrand[7] suggested that the upper eyelid exerts pressure as it naturally drapes over the cornea. It is possible that the aging process lessens the eyelid elasticity. Upper blepharoplasty or ptosis surgery repositions and tightens the upper eyelid vertically, leading to increased curvature of the anterior cornea in the vertical axis. Such altered corneal curvature alters astigmatic changes in focal length and brings about visual disturbances.

On the other hand, our visual system is capable of tolerating mild degree of astigmatism before it becomes symptomatic. In this study, 94% of patients were free of symptoms after 1 year. However 4 (67%) of the 6 symptomatic patients had combined blepharoplasty and ptosis repair. It may suspect that combined blepharoplasty and ptosis repair potentially have additive effect on the upper eyelid and may more likely exceed patients tolerance capability.

In addition to the astigmatic changes and dry eyes, other possible causes of the postoperative blurred vision include uncorrected refractive errors, preexisting cataract, ill-fitting contact lenses, new medications such as diuretics and steroids,[8] new or worsening diabetes, and uremia. Uremia and other conditions cause large shifts in the body's water pool and may produce large refractive changes.[9]

Preoperative corneal keratometry may help identify the upper eyelid procedures owing to the subtle

induced astigmatism. Ill-fitting rigid lenses in particular can further modify the shape of cornea underneath, leading to greater refractive error.[10] Patients who obtain a new pair of properly fit rigid lenses can become accustomed to the corneal reshaping to its subtle postoperative shape over time. The new accommodating intraocular spectacle prescription, Soft contact lenses conform to the anterior cornea and fit more properly. The main time patients use rigid contact lenses is that they are more gas permeable than soft lenses. Nevertheless, recent technology has made soft contact lenses much more gas permeable than before.

Although most astigmatic changes induced by upper eyelid procedures are probably of low magnitude, persons whose daily living requires a high visual acuity are more likely to notice small visual changes. For patients of certain professions, such as those requiring prolonged binocular vision, we should advise them that any oculoplastic procedures can potentially alter vision as a result of induced or altered astigmatism and that they may have to change their spectacle or contact lens prescriptions postoperatively.

In the study by Brown et al,[5] no statistical significance was found among any of the corneal topographic measurements. One major obstacle in analysis of preoperative corneal topography is that a variety of diurnal corneal changes affect its normal topography.[11,12] Besides the effect from rubbing and sleeping changes in vertical shape across the cornea and the peripheral cornea tend to vary throughout the diurnal cycle. It also has been shown that at the beginning of the cycle, the cornea is more curved and gradually flattens after awakening.[13] It has also been shown that the central thickness varies throughout the day. After awakening in the morning, the central is 3% to 9% thicker and returns to baseline within 1 to 2 hours.[14] These uncontrollable variations widen the standard error for topographic measurements and pose significant challenges for future prospective and controlled studies.

Because of the lack of preoperative and postoperative corneal topographic measurements, this study cannot directly demonstrate eyelid-cornea interaction to corneal astigmatism after upper blepharoplasty. Nevertheless, the small percentage of symptomatic patients suggests that a large, usually population is required for future studies to clearly link postoperative corneal astigmatism to persistent blurred vision.

CONCLUSIONS

The anterior corneal film and eyelid-cornea interaction are potentially important concepts in understanding some of the postoperative visual acuity changes after oculoplastic procedures. Our study shows that fewer than 6% of patients have symptomatic visual disturb-

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The Bleph and the Brain: The Effect of Upper Eyelid Surgery on Chronic Headaches

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Purpose: [illegible]

Methods: [illegible]

Results: [illegible]

Conclusions: [illegible]

[illegible]

The World Health Organization lists headache as a major cause of disability [illegible]

[illegible]

[illegible]

METHODS

[illegible]

RESULTS

[illegible]

TABLE 1. Comparison of headache location before surgery

Laterality	Study	Control	p
	[illegible]	[illegible]	[illegible]
Frontal	[illegible]	[illegible]	[illegible]
Temporal	[illegible]	[illegible]	[illegible]
Periorbital	20	9	[illegible]
Occipital/neck?	[illegible]	6	[illegible]
Midline	[illegible]	2	1.00
Lower face?	[illegible]	[illegible]	
Total	28	19	

[illegible]

[illegible]

TABLE 2. Comparison of preoperative answers between the study arm and control group, and postoperative answers between the cohorts

HIT-6 question	p value preoperative answers	p value postoperative answers
1	0.64?	[illegible]
2	0.72?	[illegible]
3	[illegible]	[illegible]
4	0.35?	[illegible]
5	0.73?	[illegible]
6	0.37?	[illegible]

[illegible]

TABLE 3. Patient response postoperatively to "How do you feel your headaches have changed, if at all, since surgery?"

Response	Study arm	Control group
Markedly worse	[illegible]	[illegible]
Moderately worse	[illegible]	[illegible]
Somewhat worse	[illegible]	[illegible]
Unchanged	[illegible]	[illegible]
Somewhat better	[illegible]	[illegible]
Moderately better	[illegible]	[illegible]
Significantly better	[illegible]	[illegible]
Resolved	[illegible]	[illegible]
Total	[illegible]	[illegible]

[illegible]

DISCUSSION

The authors present a prospective study showing significant improvement in headache symptoms following functional upper eyelid surgery as compared with a control group undergoing other oculoplastic procedures. [illegible]

[illegible]

[illegible]

[illegible]

Despite these limitations, the authors believe that the results are valid. [illegible]

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Medial Rectus Muscle Injuries Associated With Functional Endoscopic Sinus Surgery

Characterization and Management

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Objective: To characterize and evaluate treatment options for medial rectus muscle (MR) injury associated with functional endoscopic sinus surgery (FESS).

Design: Retrospective interventional case series.

Participants: A total of 39 cases were gathered from 10 centers.

Methods: Cases of orbital MR injury associated with FESS surgery were obtained from members of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) through an e-mail discussion group.

Main Outcome Measures: Variables assessed included patient demographics, date, presumed iatrogenicity and operative findings; extent of MR injury and entrapment; secondary orbital/ocular injuries; initial and final ocular alignment and ductions; and neuroimaging.

Results: A spectrum of MR injury ranging from simple contusion to complete MR transection, with and without entrapment, was observed. Four general patterns of presentation and corresponding injury were categorized.

Conclusions: Medial rectus muscle injury is a complex result of FESS in many instances. Proper characterization and treatment are important, particularly with reference to the degree of direct MR injury (muscle tears, scars and entrapment). Patients with severe MR disruption can benefit from intervention to continue to show persistent limitations of ocular motility and binocular impairment. Prevention and early recognition and treatment of these injuries are emphasized.

Functional endoscopic sinus surgery (FESS) has become the primary surgical approach for treatment of obstructive sinus disorders. In contrast to many external approaches, the orientation during certain portions of FESS is typically toward the orbit, and inadvertent penetration of the orbit (typically through the medial orbital wall) may occur. Complications of FESS have been widely documented, including nasolacrimal duct injury, orbital hemorrhage, optic nerve damage, and extraocular muscle injury.[1–3] Medial rectus muscle (MR) muscle injury in particular, presents special considerations regarding initial and long-term treatment. We noted 17

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reported cases of damage to the MR after FESS.[4–7] Including unilateral intranasal (nonendoscopic) sinus surgery, an additional 7 cases of MR injury have been published since 1977.[8–13] However, many of these reports are case reports or small series with relatively limited long-term follow-up and treatment recommendations. The purpose of this study was to better characterize and evaluate treatment options for MR injury associated with FESS.

METHODS

Cases of orbital MR injury associated with FESS were solicited retrospectively from members of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) through an e-mail discussion group. Approximately 150 members participate in this e-mail group, which includes specialists frequently called on to treat these types of orbital injuries. Variables assessed included patient demographics, presumed iatrogenicity and operative findings; extent of MR injury and entrapment; secondary orbital and ocular injuries; initial and final ocular alignment and ductions; and neuroimaging. Injury to the MR was identified as muscle contusion when there was an abduction deficit and/or esotropia associated with a greasy sign. Medial rectus entrapment was defined as tethering of the MR to the orbital wall or to orbital fat. Interpretation of entrapment was based on radiographic impression confirmed clinically by forced duction testing. The requested data were provided by the contributing physicians and interpretations were confirmed by them.

RESULTS

A total of 39 cases from 1994 to 2000 were gathered from 10 centers. Sixteen of the patients were men and 11 were women, with a mean age of 45 years (range, 9 to 76 years). Follow-up from time of initial injury averaged 12 months (range, 1 to 48 months). A spectrum of MR injury ranging simple contusion to complete MR transection, with and without entrapment, was observed.

Four general patterns of presentation and associated injury were categorized as follows (Tables 1 through 5). Patient I cases showed a large right esotropia (>25 PD) and marked abduction deficit with relatively intact adduction and little or no entrapment. These cases were typically associated with complete transection of the amputation of the MR muscle (Table 2). Patient II cases revealed a residual to large-angle esotropia with combined adduction and abduction deficits in most cases, suggesting partial MR transection or severe contusion, usually with moderate MR and orbital soft tissue entrapment (Table 3). Patient III cases generally demonstrated no or only mild ocular deviation (typically small esotropia in primary gaze) but a marked abduction deficit, suggestive of a grossly intact or moderately contused muscle with marked entrapment within the bony orbital wall defect (Table 4). Patient IV cases were characterized by only mild degrees of ocular misalignment caused by muscle contusion without entrapment, except for one unusual case also involving third cranial nerve palsy (Table 5).

In several of these cases, proximal orbital tissue damage and edema acutely overshadowed other injuries, producing an orbital compartment syndrome and generalized ocular motility limitation in several fields of gaze. Other injuries included central damage to the eyeball (lens, choroid, and retinal) arteries, nasolacrimal duct injury, and optic nerve injury. Direct optic nerve injury, in particular, was a concern, especially with patients I and II. CT was helpful in diagnosis, particularly if complete MR transection could be visualized.

Treatment of these injuries, particularly patient I and patient II injuries with MR tissue loss, was challenging. Of the 4 patient I cases, 4 (cases 1 through 4) underwent early initial surgical intervention for MR injury (within 2 to 3 weeks after injury); 1 (case 8) had surgery 4 months after injury. These cases had no surgical intervention in one of the early surgical intervention cases (case 4), additional secondary surgery in the superior and inferior rectus muscles was performed four (3 observation alone (cases 5 and 7) or treatment with intravenous steroids alone (case 6) did not result in improved ocular alignment or motility. Early exploration with suturing to groove of the remaining muscle stump, along with botulinum toxin injection of the ipsilateral (antagonist)

TABLE 1. [illegible] OF MR injury (1 to 4)

Patient	MR injury	Entrapment	Diplopia	Abduction	Adduction
I	MR transection	Variable	Large XT	Markedly limited	Intact
II	Partial MR transection or severe contusion	Common	Moderate esotropia XT	Limited	Variable
III	MR contusion only (minimal)		Small to moderate XT	Normal to mildly limited	Markedly limited
IV	MR contusion only (minimal)		None to small XT	Intact	Variable

MR = medial rectus; XT = esotropia; ET = exotropia.

TABLE 2. Patient Accounts

Case	Age/sex	Procedure	EOM injury type (+/− enlargement)	CT findings	Initial ocular alignment and duction limitation*	Intervention	Follow-up time**	Final ocular alignment and duction limitation	Secondary Final findings
1	76/M	Right FESS	MR transection (+)	Medial wall defect, 1.2 cm defect in the MR (enlargement was small because of retract in the apex and brain remnant remaining at the insertion	>25 PD XT AD: −4, AB: 0, SD: 0, ID: 0	4 d after FESS: MR was explored through nasal conjunctival incision, and ruptured with considerable "rubber-band" retract between muscle segments, yet both ends easily (5 mm) was identified and LR, which was exposed through a small lateral peritomy.	15 mo	15 PD XT, 8 PH hypotropia, AD: −4, AB: 0, SD: 0, ID: 0	* Diplopia persisted on all fields of gaze, until central related to SBV * Pt was fitted with opaque occlusion lens in R eye for persistent diplopia
2	44/M	Left FESS	MR transection (+)	Medial wall defect, asymmetry of MR	40 PD XT AD: −7, AB: 0, SD: 0, ID: 0	2 wk after FESS: MR was explored, conjunctival peritomy and dissection of the MR was performed, repaired using a "rubber-band" suture between the muscle segments. Insertional segment was 1.0 cm in length, adhering to thick band of scar tissue which extended toward medial orbital wall. ON was identified, apical segment was located, gap in MR of ~ 10 mm. Rectangular tenon (5 mm) was injected into LR, which was exposed through a small inferotemporal conjunctival incision.	12 m	2 PD X AD: −4, AB: −5, SD: 0, ID: 0	* SBV, fusion 20–40° * Pt wears patch intermittently over L eye but usually functions binocularly using field of single vision measuring 30 to 15° on each side of midline
3	37/F	Right FESS	MR transection (+)	Medial wall defect and possible MR transection	40 PD RXT AD: −4, AB: 0, SD: 0, ID: 0	4 d after FESS: IOR botulinum toxin injection 1 wk after FESS: R medial orbitotomy, R eyelid incision for repair of R medial wall defect w/Multiple and repair of transected RMR posterior stump recessed through Lynch incision (for the fracture repair) and periorbital incision. Anterior stump identified through medial conjunctival peritomy. Posterior stump was secured w/double-armed 5-0 Vicryl and then approximated to anterior stump through conjunctival incision.	12 mo	Trace (0.5 PD) 6 L gaze: 10–20 XT, 2 HT R gaze: 20–25 ET, 4 HT AD: −1, AB: −5, SD: 0, ID: 0	* Diplopia in most of R gaze and extreme L gaze * SBV = 60° (corresponding from 20° R to 40° L * 20/20 OU
4	23/M	Left FESS	MR transection (+)	Medial wall defect (posteriorly); post-rehabilitation of MR and superior oblique muscles (absence) on CT for a distance of ~ 1 cm	40 PD XT AD: −4, AB: −1 SD: 0, ID: 0	4 wk after FESS: Underwent orbital exploration through anterior orbitotomy accompanied w/an endoscopic view, although was unable to engage/retrieve the muscle belly but due to significant damage to the muscle (both the anterior and posterior can edges were retracted). This task was considered "fruitless" botulinum toxin injection of LR. 6 wk after FESS: Still severe RDH restriction and diplopia. Transposition surgery of lateralizing recti (Left IR and SR transposition to area of MR, w/botulinum toxin to LR)	7 mo	40 PD LXT AD: −4, AB: 0, SD: 0, ID: 0	* Diplopia everywhere * 20/30

FESS = functional endoscopic sinus surgery; R, OD = right; L, OS = left; B, OU = bilateral; MR = medial rectus; LR = lateral rectus; ON = optic nerve; NLP = no light perception; PD = prism diopters; Ortho = orthophoria; XT = exotropia; X = esophoria; ET = esotropia; E = esophoria; HT = hypertropia; (T) = intermittent tropia; AD = adduction; AB = abduction; SD = supraduction; ID = infraduction; SBV = single binocular vision; APD = afferent pupillary defect; Pt = patient; deg = degrees; IOP = intraocular pressure; EOM = extraocular movements; NIDD = non-insulin dependent diabetes

*Duction limitations on scale of 0 to −4.

**Time from initial injury.

TABLE 2. Continued

Case	Age/sex	Procedure	EOM injury type (+/− enlargement)	CT findings	Initial ocular alignment and duction limitation*	Intervention	Follow-up time**	Final ocular alignment and duction limitation	Secondary Final findings
5	39/F	Bilateral FESS	MR transection (+)	R medial wall scarring. Transection of RMR, R hematoma of conjt and possibly ON sheath	30 PD XT AD: −4, AB: 0, SD: −2, ID: −3.2	None	2 mo	Unchanged	* Small area of SBV limitation, head turn * 30/20 OU * Pt is scheduled for muscle transposition surgery
6	34/M	Bilateral FESS	MR transection (+)	Loss of R medial wall, (question ON/OS, and MR D/C	>45 PD XT OD: AD: −4, AB: 0 SD: 0, ID: 0 OS: AD: −4, AB: 0 SD: −2, ID: −4	Admitted for high dose intravenous steroids for 48 hours	6 mo	Unchanged	* 20/25 OD, NLP OS * Lipomatosis, Head OS, decreased motility OD * ON injury
7	29/F	FESS	MR transection (+)	Orbit filled with blood and air, medial wall and floor defect	>40 PD XT AD: −4, AB: 0, SD: 0, ID: 0	None	12 mo	Unchanged	
8	23/M	Left FESS	MR transection (+)	Medial wall defect (posteriorly); post-rehabilitation of MR and superior oblique muscles (absence) on CT for a distance of ~ 1 cm	40 PD XT AD: −4, AB: −1 SD: 0, ID: 0	4 wk after FESS: Underwent orbital exploration through anterior orbitotomy accompanied w/an endoscopic view, although was unable to engage/retrieve the muscle belly but due to significant damage to the muscle (both the anterior and posterior can edges were retracted). This task was considered "fruitless" botulinum toxin injection of LR. 6 wk after FESS: Still severe RDH restriction and diplopia. Transposition surgery of lateralizing recti (Left IR and SR transposition to area of MR, w/botulinum toxin to LR)	7 mo	40 PD LXT AD: −4, AB: 0, SD: 0, ID: 0	* Diplopia everywhere * 30/30

FESS = functional endoscopic sinus surgery; R, OD = right; L, OS = left; B, OU = bilateral; MR = medial rectus; LR = lateral rectus; ON = optic nerve; NLP = no light perception; PD = prism diopters; Ortho = orthophoria; XT = exotropia; X = esophoria; ET = esotropia; E = esophoria; HT = hypertropia; (T) = intermittent tropia; AD = adduction; AB = abduction; SD = supraduction; ID = infraduction; SBV = single binocular vision; APD = afferent pupillary defect; Pt = patient; deg = degrees; IOP = intraocular pressure; EOM = extraocular movements; NIDD = non-insulin dependent diabetes

*Duction limitations on scale of 0 to −4.

**Time from initial injury.

TABLE 3. *Patients B (cases 9–15)*

Case	Age/sex	Procedure	EOM injury type (+/− enophthalmos)	CT findings	Initial ocular alignment and duction limitation[a]	Interventions	Follow-up time[b,c]	Final ocular alignment and motility limitations	Secondary final findings
9	30/M	Left PESS	MR partial transection (−)	Violation of medial wall of orbit on L side, elongation of MR muscle ~20 mm posterior to insertion	25–30 PD L XT ADD: −4, AB: 0 SD: 0, IO: 0	Immediate: Lateral canthotomy 8 wk after PESS: LMR resection of 8 mm and 19 mm LR recession on adjustable suture	4 mo	Ortho in primary gaze, L gaze; 5 PD LET ADD: −2, AB: −1, SD: 0, IO: 0	* No longer complained of diplopia * 20/20 OU
10	7/F	Right PESS	MR partial transection (+)	MRI shows interruption of RMR muscle	40 PD RXT with a 2 PD RHT ADD: −4, AB: 0, SD: 0, IO: 0 Forced AB: −2.5	16 wk after PESS: R eye orbitotomy via transconjunctival approach to release of entrapped RMR muscle and repair of medial wall defect w/Gortex	6 mo	25 PD RXT w/ diplopia ADD: −4, AB: 0, SD: 0, IO: 0	* Patient wears opaque contact lens to avoid diplopia
11	6/M	Bilateral PESS	MR contusion and possible partial transection (+)	R medial wall bony defect w/R MR bulging into ethmoid sinus. CT results appear intact but is camouflaged by soft tissue, suggesting possible scar formation	−30 PD RXT ADD: −4, AB: 0, SD: −4, IO: −4	Postop: Pt was noted to have significant periorbital edema and NLP vision OD. Suspected intraorbital hemorrhage and ON injury. High dose intravenous methyl prednisolone began, followed by combustomy and cardiolyte as well as medial wall decompression and optic canal decompression. Intraoperatively, ON appeared undamaged (no canal sever), and there was no intraorbital hemorrhage. Postop, the pt. still demonstrated NLP vision and subsequently developed uncontrollable IOP increase with pain 1 yr after PESS: Evisceration was performed for pain control	4 yr	Eye evisceration	* Blind painful eye, throbbing pain despite ultrapulse and prophylactic drops. Complete loss of vision * OU rotoscanned 1 yr after PESS. Fusion at time of evisceration showed some softening of MR.
12	45/F	Left PESS	Right MR contusion and possible partial transection (+)	R medial wall defect "irregular MR," "fuzzy ON" (surgeon claimed evidence during PESS on L)	30 PD RXT ADD: −4, AB: −1–2, SD: 0, IO: 0	24 h after PESS: intravenous steroids	12 mo	Discharged	* 20/20 OS, NLP OD * ON injury
13	33/M	Bilateral PESS	Probable MR transection (+)	Bilateral orbital floor and medial wall defects, absent ONs. Post MR detection	40 PD XT OU ADD: −4, AB: −2, SD: 0, IO: 0	None	6 mo	40 PD XT OU ADD: −4, AB: 0, SD: 0, IO: 0	* NLP OU * ON injury
14	51/M	Left PESS	Right MR partial transection (+)	R post medial wall and floor defect, orbital apex hemorrhage	20 PD HET ADD: −4, AB: −2, SD: −2, IO: 0	1 h after PESS: intravenous steroids	8 mo	Discharged	* SD removed NLP * ON injury
15	44/F	Right PESS	MR partial transection (+)	R Medial wall defect, orbital edema	20 PD XT ADD: −4, AB: −2, SD: −2, IO: −2	2.5 wk after PESS: Medial wall repair 1 y after PESS: Ptosis repair	14 mo	Ortho in primary ADD: 0, AB: −1, SD: 0, IO: 0	* SBV (lat. up, down) * Diplopia w/>45° R * 20/20 * Subjectively, transient vision and chronic pain

MR = medial rectus; XT = esotropia; ET = esotropia.

TABLE 4. *Pattern III cases*

Case	Age/sex	Procedure	EOM injury type (+/− entrapment)	CT findings	Initial ocular alignment and duction limitation*	Intervention	Follow-up time**	Final ocular alignment and duction limitation	Secondary final findings
20	55/F	Right FESS	MR contusion (+)	Defect in R medial wall w/RMR herniating into defect	Primary: 8 PD RET R gaze: 30 PD RET ADD: 0, ABD: −3, SD: 0, ID: 0	Immediate: Treated with intravenous dexamethasone (tapered) and diamox with return of vision to 20/20 4 wk after FESS: Release of RMR (consisted of fused fibrous) under general anesthesia and repositioning of MR and Sx free transnasal approach)	9 mo	Ortho in primary gaze ADD: 0, ABD: −1, SD: 0, ID: 0	* Diplopia only on extreme gaze R * 20/15 OU * Esophalmos (2 mm), RUL ptosis (0.5 mm), inferior scleroma OD, poor APD OD (ON injury)
21	40/F	Right FESS	MR contusion (+)	R-Medial orbital wall defect with herniated orbital fat	8 PD ET on R-gaze, ADD: 0, ABD: 0, SD: 0, ID: 0, but globe retraction w/ abduction of affected R eye	5 mo after FESS: Revision sinus surgery incl bilateral maxillary antrostomies, left sphenoidotomy, ethmoidectomy, and frontal sinus exploration	5 mo	Ortho ADD: 0, ABD: 0, SD: 0, ID: 0	* 20/20
22	55/F	Right FESS	MR contusion (+)	MR stuck in medial wall defect	Mild RHT (5 PD) S.O. injury ADD: −1, ABD: −3, SD: −2, ID: −1	None	4 mo	Unchanged	* 20/20 OU
23	45/M	Right FESS	MR contusion (+)	Medpore medial wall defect w/RMR entrapment	10 PD RET ADD: −2, ABD: −4, SD: 0, ID: 0	6 mo after FESS: R medial orbital wall repaired with Gelfilm	12 mo	Ortho ADD: 0, ABD: 0, SD: 0, ID: 0	* SBV normal * 20/20
24	44/M	Bilateral FESS	MR contusion (+)	L Post ethmoid/medial wall defect, L MR entrapment	Ortho ADD: −1, ABD: −3, SD: 0, ID: 0	6 mo after FESS: L medial orbital wall repaired with Medpore bone implant	6 mo	Unknown	* Pt did not return after L orbital wall surgery, unable to contact
25	48/M	Right FESS	MR contusion (+)	Small focal defect in R medial wall with RMR possibly adherent to defect site	Ortho ADD: −2, ABD: −3, SD: 0, ID: 0 Positive forced duction	3 mo after FESS: Orbit was explored via postcaruncular approach, focal adhesion of MR to scar tissue in defect (3 × 4 mm) site was released, then Medpore sheet was placed, gel film was placed between MR and implant	6 mo	Unchanged	* 20/20 * Neg. forced duction and decreased symptoms 1 mo postop. Readhesion occurred and symptoms returned. Repeat CT, looked same except for wall defect repaired. No change in chart 6 mo later

MR = medial rectus, XT = exotropia, ET = esotropia.

TABLE 5. *Pattern IV cases*

Case	Age/sex	Procedure	EOM injury type (+/− entrapment)	CT findings	Initial ocular alignment and duction limitation*	Intervention	Follow-up time**	Final ocular alignment and duction limitation	Secondary final findings
26	26/M	Left FESS	MR contusion (+)	Medial wall fracture (no definitive CT findings of entrapment LMR)	Abducts to full order but easily breaks down to 30 PD EX w/ prism cover ADD: −4, ABD: 0, SD: 0, ID: 0	2 wk after FESS: L medial orbitotomy (transcaruncular) w/repair of L orbital fracture w/Medpor	4 mo	12–14 PD EXT ADD: −1, ABD: 0, SD: 0, ID: 0	* SBV L gaze = 20° to 45° R head turn * 20/20 OU
27	56/F	Left FESS	MR direct contusion and orbital hemorrhage (+)	Lateral sphenoid wall defect, blood in orbit apex	−15 PD EXT ADD: −4, ABD: −4, SD: −4, ID: −4	1 h after FESS: Lateral canthotomy (intravenous steroids 1 wk after FESS: Neuroangiographic repair (repair of injured L cavernal sinus fistula/carotid aneurysm/biopsy)	8 mo	Ortho ADD: 0, ABD: 0, SD: 0, ID: 0	* SBV (normal) * 20/20 * Orbit reformed
28	49/F	FESS	MR direct contusion (+)	Anterior medial wall defect, blood and air in orbit	20 PD XT ADD: −3, ABD: −2, SD: −1–2, ID: −1–2	2 hr after FESS: Sun Ganthotomy → (aerosol propofol) orbit explored, large hematoma removed	12 mo	Ortho ADD: 0, ABD: 0, SD: 0, ID: 0	* SBV (normal) * 20/25
29	58/M	Right FESS	MR contusion (+)	Medial wall defect, medial orbital edema	Ortho ADD: −1, ABD: 0, SD: 0, ID: 0	Immediate: Intranasal medial wall decompression by ENT surgeon or contralateral orbitotomy same time	2 mo	Ortho ADD: 0, ABD: 0, SD: 0, ID: 0	* SBV full * 20/20 * Diplopalmos (1 mm) * No patient complaints
30	20/F	Right FESS	MR contusion, 3rd CN palsy (+)	Orbital floor defect w/ small defect of orbital apex	30 PD RXT 1 PD R Hypo ADD: −4, ABD: −85°, SD: −4, ID: −4	12 wk after FESS: Anterior orbitotomy (transconjunctival) repair of orbital wall defect w/Medpor 21 wk after FESS: Strabismus surgery: RSO lengthening (7 mm), RLR recess (8.5 mm) w/Transposition to IR w/RMR recess (7 mm)	7 mo	5 PD RAC T1, 4 PD RHT2 ADD: −1, ABD: −1, SD: −1, ID: +3	* SBV full * 20/20 * Esophalmos (1 mm) * No patient complaints ** Pupil fixed* at primary with effort, no useful fusion * 20/20 OU * R lower lid retraction * Anisocoria (larger OD pupil/pupil) (1.5 mm)

MR = medial rectus, XT = exotropia, ET = esotropia.

lateral rectus (LR) improved primary ocular alignment; however, severely restricted range of rotational duction usually persisted. Late orbital exploration was reported to be difficult because of extensive orbital soft tissue scar tissue formation and the results were limited to case 6. Medial rectus muscle transposition (cases 4 and 8) was performed in two cases as a secondary late procedure, and moderate improvement in ocular alignment and motility in one case (case 8) and only improvement in the other (case 4).

Of the 12 cases classified as pattern II injuries, three underwent early surgical intervention for MR injury (cases 15, 9 [in cases 9–10, 16, 17, and 19]) and 4 with some (cases 12 through 14 and 18). Cases 12 included early treatment for orbital hemorrhage and, in two cases, acute fracture of orbital wall decompression, ophthalmic and decompression; however, the patient subsequently required enucleation because a blind, painful eye developed. With cases 13 through 18, as with pattern I cases, delay (case 16) in treatment with conservative medical care (cases 12, 14, and 18) did not result in improved ocular alignment or motility. Treatment of most of these injuries entailed repair of the medial orbital wall and release of the entrapped MR. In case 15, the only pattern II case with early surgical intervention, medial wall repair resulted in improvement in retinoscopy and a primary gaze with mild residual horizontal diplopia limitation. Late surgical intervention (4 to 16 weeks after injury) resulted in only minimal improvement in ocular alignment and horizontal diplopia in cases 13 and 14 and in no improvement in cases 16 and 17. Extensive tissue scarring was noted as the problematic in late orbital surgery. In case 6, with a fixed, persistent MR abducted s combined MR recession, lateral rectus muscle recession, performed as a late procedure (at 5 weeks), to correct the ocular deviation in primary gaze and improve abduction. A secondary late orbital apex exploration in case 17 was ineffective.

Pattern III injuries entailed 6 cases consisting of 4 with (at 10 weeks to 6 months after injury) and 2 with no intervention for MR injury. Treatment by orbital exploration, release of entrapped orbital tissues, and repair of the orbital wall defect produced ocular alignment and improved diplopia in 2 of the cases (cases 20 and 21). There was no postoperative improvement in one case (case 23) and the results of the 3 with (five cases 24) were unknown. Of the two cases with no treatment, one (case 22) showed persistent residual deficit of 4 months; case 23 was unusual in that initially the patient had only mild exotropia and no diplopia limitation on gaze; retraction with abduction, which improved to normal at 9 months without treatment, was noted.

Pattern IV injuries lapsed 5 cases. Early (1 day and 1 week) surgical intervention (pattern IV) injuries typically required early treatment of hemorrhage and edema. MR injury was mild (consistent with an entrapment reported in most of these cases. Surgery included orbital exploration/decompression (cases 26 and 29) and repair of orbital wall defects (cases 26 and 30). With the exception of case 30, intervention was immediate or early. A case of final cranial nerve palsy (case 30) improved with late repair by a combination of inferior oblique disinsertion, lateral rectus recession with transposition to the inferior rectus muscle, and MR resection. Most of these pattern IV cases demonstrated improved final ocular motility.

DISCUSSION

MR injury as a complication of FESS can very unfortunately. Reportedly the most commonly injured extraocular muscle, the MR may have severe symptoms, traumatic ocular interruption, or development of adhesions with adjacent structures.[1] We made models to obtain information for all of the 10 cases described in this study. However, the incidence of MR injury during FESS appears to be low. Using our center as an example, 1 case of MR injury occurred out of 738 FESS procedures completed over the last 5 years. There are relatively few reports in the literature detailing the evaluation and treatment of these types of injuries, most of which report on small series. The current series is the largest to our knowledge, to present the largest collection of cases in one study. Proper communication on treatment and prognosis, particularly with reference to the degree of direct MR injury (mainly the degree of muscle tissue loss), muscle entrapment, and associated orbital soft tissue hemorrhage/edema. The size and location of the medial orbital wall bony defect is also an important consideration. After surgery, direct muscle injury should be suspected if the patient has double vision and is unable to adduct the involved eye. When treatment or intervention to prevent entrapment or other causes of restrictive motility are suggested, [illegible] should be considered.[1] When free motions of the eye is possible, then weakness in the muscle is likely. If postoperative evaluations take place, muscle or muscles after the acute injury. The possibility of secondary orbital fibrosis must also be considered in the development of muscle entrapment. Postoperative CT examination is important in assessing the medial wall bony defect and the gross physical status of the MR and surrounding orbital soft tissues. In some cases, definitive

determination of the integrity of the MR may be difficult because hemorrhage or fibrosis (depending on the timing of CT evaluation) may obscure details. The role of magnetic resonance imaging in this setting is unclear.

Although a spectrum of injury may be noted, we found that 4 general patterns of injury and presentation could be characterized. These patterns had implications for the type of treatment in many cases. Pattern I cases showed a large angle exotropia (>25 PD) and marked adduction deficit with relatively intact abduction and little or no entrapment. These cases were typically associated with complete transection of the MR insertion at the MR muscle (Figs. 1 through 3). Pattern II cases showed moderate to large-angle exotropia with confirmed adduction and abduction deficits in most cases suggesting partial MR transection or severe avulsion, usually in conjunction with some degree of MR and orbital soft-tissue entrapment. Pattern III cases generally showed a small-angle exotropia and marked abduction deficit suggestive of a grossly intact or modestly contused muscle but marked MR and soft tissue entrapment within the bony orbital wall defect. The mechanism of injury in these cases differs somewhat from "blowout fractures" in that tissue is "pulled" in the bony defect. Pattern IV cases showed only mild degrees of ocular misalignment caused by muscle entrapment, typically without any entrapment in several of these cases, prominent orbital hemorrhage and edema greatly overshadowed other injuries, producing an orbital compartment syndrome and generalized ocular motility limitation in several fields of gaze early on. Other injuries, particularly optic nerve injury, were common. As previously stated, CT was a helpful adjunct for diagnosis, particularly if complete MR transection could be visualized.

FIG. 2. Same patient as in Figure 1, showing marked limitation of adduction of the left eye.

The treatment of these injuries is complex. The issues involved include treatment of acute orbital hemorrhage and associated orbital compartment syndrome, delayed treatment of the bony orbital wall defect, and treatment of the MR injury. Treatment of the sequelae of more severe acute orbital hemorrhage involves immediate medical and surgical maneuvers (such as lateral canthotomy) to lower orbital pressure if ocular compromise is noted. Approximately a quarter of all injuries described in this series included intervention of this nature. Treatment of the orbital wall defect, similar to that for orbital wall fractures, depends on the size of the defect and whether clinically significant muscle or soft-tissue entrapment is noted. Intervention includes exploration of the medial wall of the orbit, freeing of entrapped tissues, and covering of the bony defect with an implant if necessary. In this series, this type of treatment was

FIG. 4. Representative case of pattern I, case 2. Patient after left FESS demonstrating large exotropia in primary gaze associated with subconjunctival hemorrhage and eyelid ecchymosis.

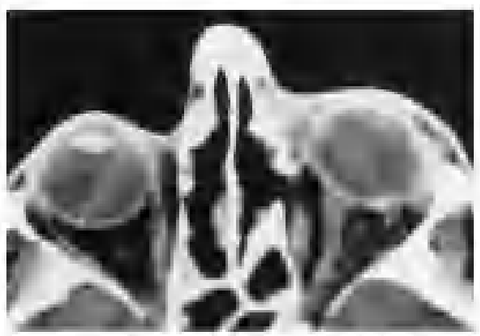

FIG. 3. CT scan showing patient in medial orbital wall defect and midportion of MR.

performed for many of the cases considered to be pattern II or pattern III, in which MR entrapment was suspected. The results suggest that earlier intervention within 2 to 3 weeks, tends to be technically easier and beneficial before fibrosis becomes more advanced.

The treatment of direct MR injury can be the most difficult aspect of these cases, corresponding to the degree of loss of muscle tissue and function. When most muscle continuity is lost, the potential for recovery is obviously lesser the majority of pattern III and pattern IV cases in this series. With complete muscle transection (pattern I injuries) or with muscle tissue deficiency or loss (part of pattern II injuries), treatment choices vary. In reviewing the results of our series, a trend toward earlier intervention (within 2 to 3 weeks of initial injury) was noted for pattern I injuries and later intervention for pattern II injuries. Whether this reflects a propensity to observe for spontaneous improvement or to delay surgical in cases in which the muscle is not clinically completely transected cannot be determined from our study. Other authors, based on a limited number of cases, have advocated prompt evaluation and treatment for the best chance of minimizing residual ocular motility problems. A delayed report of extraocular muscle dysfunction is frequently unsatisfactory because of loss in tissue and fibrosis.[1,2,5,6] In our series, the cases of early intervention were more likely to show improvement in head-scale alignment. Therefore, within the limitations of our study, we cautiously agree that early exploration and freeing or repair of the MR either the first 2 or 3 weeks of the injury can be beneficial.

When the muscle is completely transected, reconstruction of the fascial ends by a "hang-back" suture to bridge the interposing defect in the muscle can achieve improved primary globe position alignment.[1] Adjunctive weakening of the antagonist LR with botulinum toxin injection (typically 5 units under direct visualization) may be helpful. Effectively, the clinical result is agonist-antagonist balance for the globe, improving ocular alignment in primary position (Figs. 4 and 5). However, little improvement in adduction is expected and treated esotropic patients may also have subsequent abduction deficits after intervention. Thus, while even patients with severe MR disruption can benefit from intervention to improve ocular alignment, persistent limitation of horizontal motility is likely and significant functional improvement can still be expected.

Finding the posterior stump of residual MR deep in the globe can be challenging. Several clinical maneuvers have been described to help with the diagnosis and recovery of "lost muscles." These include the oculocephalic reflex, saccadic velocity measurements, active forced duction tests, differential intravitreal pressure, CT scanning,[7] and high-resolution dynamic magnetic resonance imaging.[8,9] Like many of these maneuvers, we have limited the scope of complete muscle transection as an exposed or slipped muscle encountered intraoperatively during surgery. Arnold et al.[1] describe retrieval by means of a subperiosteal medial orbitotomy and Lessner et al.,[10] by a transcutaneous medial orbitotomy through a medial fold (Lynn) incision. A transconjunctival endoscopic approach may offer an alternative for patients at whom a lost medial rectus muscle is recovered by the conventional orbitotomy approach.[11,12] In this series, CT was helpful to determine the approximate location and remaining amount of posterior MR muscle. Various approaches were used to explore the orbit in this series, including

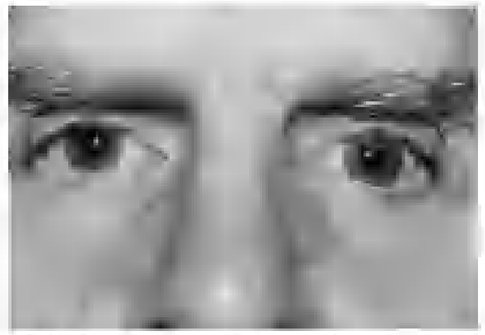

FIG. 4. Ocular alignment much improved after exploration with hang-back suture of remaining MR segments and botulinum toxin injection of LR.

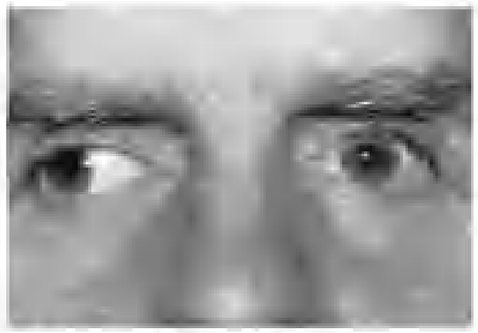

FIG. 5. Adduction deficit after surgery (left) and after recession.

transconjunctival, transcutaneous and endoscopic techniques. Moreover, visualization was believed to be possible by some surgeons.

When surgical intervention is more than 3 weeks from the initial injury, scar, fibrosis, adhesions and scleral thinning of the MR and surrounding orbital soft tissues is often found extending in the area of the medial rectus tendon sheath. This scarring and loss of muscle elasticity may have contributed to entrapment and decreased forced duction. The MR, sometimes, becomes more difficult to identify, and it is hard to free, trace or separate the stiff and scarred muscle is challenging. Under these conditions, whether it is best to alternate surgeries of the lesser degree or to follow the original line previously have not been clear.[1] In our study, patients I and patients II cases without additional intervention showed essentially no improvement or worsening over the extended period of time. Of the cases that underwent late exploration (but in which a direct orbital exploration only started in an improvement was small in primary duction alignment and motility. Surgery usually involved exploration and attempt to identify and free the MR. If visible muscle cannot be found or identified, or when secondary contracture prevents realignment by simple recession of the ipsilateral LR combined with posterior fixation of the involved MR, then manipulation of the adjacent vertical rectus muscles may be indicated, along with a weakening procedure on the antagonist LR.[1,2,5,6,13] Several of these latter cases subsequently underwent additional secondary surgery for additional augmentation of the vertical rectus muscles to treat the MR.

Retraction, recession and augmentation generally result in full width dissection, disrupting the muscle pulley system of the involved muscle. In cases in which the MR is already weakened or markedly disrupted, as seen in many cases, the risk of inducing anterior segment ischemia with additional muscle surgery must be considered. Thus, anterior segment ischemia is a potentially serious complication of strabismus surgery, usually occurring with involving 3 or 4 four rectus muscles although it has occasionally been reported with surgery on as few as 2 rectus muscles, especially in high-risk patients. Muscle-sparing procedures, such as the Hummelsheim and Knapp procedures and the numerous modifications, have been devised to preserve a portion of the anterior ciliary arterial circulation that may not be as effective as full-width procedures. Other alternatives described include plication techniques and the Wright modified myopexy by McKeown and others have suggested dissection and preservation of the anterior ciliary vessels during either conventional 180 rectus recession muscle surgery by using operating microscope or standard loupe magnification.[14,15] A more recent modification of the Hummelsheim procedure incorporates a muscular and symmetric amount of muscle resection from the rectus muscle's future insertion site.[16,17] In our series of cases, transposition procedures were performed as late secondary interventions in 3 cases, with moderate improvement in one and no improvement in two. Recently, the use of partially tuned, autogenous peritoneal flaps to globe before the passive globe fixation in the primary position has been described for cases of acquired paralytic or restrictive strabismus such as complete third nerve palsy and Graves' ophthalmopathy.[18] This approach was not evaluated in this series but may prove useful.

The results of our series should be considered within the limitations of the study. The study represents a retrospective compilation of cases from multiple pediatric and academic centers across the country, and we acknowledge the possible inconsistencies in examination and treatment philosophies. The classification of the injury was based on data provided by the individual physicians – interpretation of the clinical and radiologic findings – which could be affected by the timing of referral. The degree of gross muscle injury was sometimes difficult to ascertain. Ideally, surgical exploration should be performed in partial transection from a gross anatomic standpoint may effectively "act" like complete transection from a functional standpoint. The type of surgical intervention described in general terms may vary in some specific details. Follow-up was complicated in all cases by some cases 20% in which the patient did not return for post-surgery examination and could not be studied thereafter. We believe, however, that the results of this study will provide a basis perspective on the options and limitations of treatment for these difficult cases. Although patients with more severe MR disruption from FESS can benefit from surgical intervention, most will continue to show persistent limitation of ocular motility and functional impairment. Prevention of MR injury in patients undergoing FESS is emphasized. Detection of traumatic avulsions by a preoperative CT scan is important. Additionally, however, most normal anatomic landmarks may be altered in chronic inflammatory disease processes, surgical procedures, and other factors that make sinus surgery more difficult.[19,20]

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2. [illegible]

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REVIEW

Minimally invasive brow lifting techniques

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Purpose of review
Aesthetic concerns about upper eyelid and brow position are very common in ophthalmic practice. Management of brow ptosis and dermatochalasis (eyelid redundancy) is commonly complicated by such patient-driven considerations preoperative examination and patient counseling. This article will review several minimally invasive techniques that can be used to address the needs of patients with mild to moderate brow ptosis.

Recent findings
Recent publications describe and analyse efficacy of several variations of browplasty techniques.

Summary
Browplasty techniques provide a minimally invasive way to provide stabilization and modest elevation of the forehead brow. They can enhance outcomes of upper eyelid surgery in patients who both have mild brow ptosis and who desire to avoid the recovery and morbidity of more formal brow lifting techniques.

Keywords
browplasty, brow ptosis, brow pexy

Patients with periorbital concerns, whether they are purely aesthetic or functional, should have an evaluation that includes both eyelids and eyebrows. These structures function together and changes in one can affect changes in the appearance and function of the other. Consequently, patients who present for evaluation of droopy eyelids may have dermatochalasis, ptosis, brow ptosis, and often some combination of all of these. A growing body of research is aimed at understanding the interplay between the eyelid and brow position and how intervention be it surgical, with neurotoxin, or combination, affects brow position and contour. Customizing management of brow position needs to take into consideration numerous factors, including brow position, contour, forehead rhytids, asymmetry, and most importantly patient desires.

Three articles have specifically addressed the question of whether brow position changes after ptosis surgery. Taken together these articles suggest that ptosis surgery, whether done by Müller's muscle-conjunctival resection or by external levator advancement, leads to a decrease in brow height [1,2,5*]. Though the amount of brow descent and new effort it is clinically relevant is still debated.

The spectrum of rhytids in and between patients alone results in a change in brow height as a question that has been examined several times with mixed results [1,4,5*,6*,7**,8–11]. These studies vary significantly in their methodology and conclusions making it difficult to form a definitive opinion or appealing to the existing literature.

It is clear that the regulation of the position of the eyelids and brows is a complex one with interplay between muscles and connective tissue structures with neuronal pathways and interactions that are not fully understood. Taken together, the body of literature indicates that there is a subset of patients who will manifest latent brow ptosis after eyelid surgery. Each patient should be assessed as an individual with a customized treatment plan. In such complex situations it can be difficult to generalize results from population-based studies to an individual.

It is our experience that unrecognized lateral brow ptosis prior to surgery or unrecognized lateral brow ptosis following surgery both lead to patient dissatisfaction. Attempting to remedy this with additional skin excision can shorten the distance between the eyelid and the brow causing both aesthetic and functional concerns [2,13]. The most appropriate course is often to address the lateral

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KEY POINTS

- Patient selection is important in order to avoid brow ptosis in patients with considerable brow laxity, redundant forehead skin, and poor muscularity.
- Selecting an appropriate technique to address brow ptosis needs a balance between the desired brow position, stability, and patient satisfaction.
- Direct excision techniques may be associated with a more noticeable scar.

brow position during eyelid surgery which allows for appropriate debulking of redundant upper eyelid tissues. Browpexy techniques are very effective in this role.

We do not agree that browpexy procedures should be considered to be 'last resort' as forced brow lifting procedures such as endoscopic, pretrichial, and coronal brow lift are invasive procedures that predispose patients with mild to moderate brow ptosis with stabilization and resection/repositioning of the lateral brow, as well as creating a subjectively more pleasing three dimensional contour secondary to remodelling of the brow fat pad. Browpexy techniques are most often performed at the time of upper eyelid blepharoplasty and provide both an additional aesthetic and functional benefit to these cases, though they can be used successfully as isolated procedures for some patients. These procedures do not provide a significant amount of brow elevation and patients with severe brow ptosis or dermatochalasis will be better served with traditional brow lifting techniques. Traditional brow lifting procedures can provide powerful lift, they may be financially prohibitive, more invasive, and have significant potential complications than the procedures that will be discussed in this review. In addition, some patients desire more subtle changes which may not be associated with the more traditional brow lifting techniques. This article will review three browpexy techniques including direct excision, suture, and external browpexy.

TECHNIQUES

Internal browpexy

Mitchell and Bosniak [14] first described what has become known as an internal browpexy. This procedure takes advantage of the blepharoplasty incision and can be performed in conjunction with debulking of the dermatochalasis with removal of some of the brow fat pad. After making a standard blepharoplasty incision the dissection is carried superiorly above the superior orbital rim. A 4-0 polypropylene suture is placed from the skin through the full thickness of the dissection flap at the level of the lateral border of the brow ridge. The polypropylene is then passed through the periosteum and adjacent tissue at a level about 1 cm above the orbital rim. The suture is then passed through the orbicularis/dermal eyebrow tissue at the level of the previously placed transcutaneous suture. The suture is pulled through the skin, leaving the suture to approximate the orbicularis tissue to the periosteum above the orbital rim. They recommend the placement of two to three sutures for good fixation. This technique did not report any quantitative results of brow lifting with this procedure.

Several authors have presented modifications of the original technique. Other groups have suggested a better lift can be achieved if the lateral orbicularis is removed and the dissection extended laterally to include the release of lateral retaining ligaments [15,16]. Additional modifications include the placement of sutures in preplacement and with more aggressive lateral brow lift pull. In contrast, this report suggested that the most cephalad suture should be placed at 5 mm above the orbital rim, the most lateral suture at 8 mm above the rim and the most lateral suture at 12 mm above the orbital rim. This procedure was also performed with a 3-0 braided permanent suture as opposed to the 4-0 polypropylene reported elsewhere. Still others have recommended using a bioabsorbable fixation device for fixation in place of a more traditional suture [14].

Baker *et al.* [7**] attempted to quantify the brow lift in patients undergoing blepharoplasty and internal browpexy. Their technique differed slightly from previous publications following blepharoplasty dissection, was carried superiorly above the superior orbital rim in a preperiosteal plane. Using a caliper to measure 12–15 mm above the superior orbital rim in line with the peak of the brow a 4-0 polypropylene suture is passed through the native tissue. They then measure the same distance from the edge of the blepharoplasty incision, and the suture was then passed through the orbicularis muscle and secured at this level. It was done with the intent that the superior border of the blepharoplasty incision ends up at the level of the superior orbital rim. They reported that an blepharoplasty only patients the lateral brow fell 1.4 mm (right eye) and 1.6 mm (left eye) following the procedure. With the addition of the internal browpexy, they report a lateral brow elevation of 1.3 mm (right eye) and 0.8 mm (left eye).

The [illegible] personally to our own data. We found that in a cohort of 57 eyelids from 29 patients who underwent blepharoplasty (with and without ptosis repair) and internal browpexy provided an average lift of 3.29 mm at the lateral brow [18**].

Brassiere suture

The current procedure was first reported by Zarem and lateral orbicularis muscle fixation but since then it has come to be called the brassiere suture [19,20]. After performing a standard blepharoplasty incision, then proceeded with excision of orbicularis but not the entire amount as the resection varied case to case. The septum was then opened to allow for retraction of fat to the central and lateral fat pads. At this point, an absorbable suture is placed through the superior edge of the remaining remnants and securing this to the arcus marginalis with 5-0 sutures. They advise avoidance of permanent suture because of concern that it can show through the thin skin of the eyelid.

One variation of this technique was published by Saleem *et al.* [21]. In this version of the procedure, the blepharoplasty incision and skin removal is completed as usual. But the remnants is then divided into equal superior and inferior portions and divided along the lateral to medial length of the incision. Two 3-0 absorbic sutures are then used to secure both the lower and upper edges of the divided orbicularis to the periosteum of the lateral orbital rim. They report initial concerns about tethering of the eyelid resulting in lagophthalmos, but this was not more in any of their postoperative patients. We prefer to perform the brassiere suture as described above with the small variation of not fixating the lower edge of the resected orbicularis (Fig. 1).

The current technique has been described as a bipolar suture in that it fixates the brow fat pad [21]. We agree that this technique provides an independent to the descent of the brow fat pad and is very effective in achieving a strong brow position in the lateral superior sulcus and allows for elevation of the lateral aspect of the lateral upper eyelid (Fig. 2). This can be very helpful to achieve a pleasing cosmetic result for patients whose complaints include fullness of their lateral tarsal plate by overhanging skin and brow fat.

As described the brassiere suture does not usually convey significant elevation of the eyebrow. Armstrong *et al.* [22**] recently published a variation of the brassiere suture which combines some elements of internal browpexy with the brassiere suture. They advocate excision of the orbicularis external to arcus only. Blepharoplasty lateral to the lateral fixation. Then the soft of the remaining orbicularis is secured to the frontal periosteum with a horizontal mattress polyglactin suture an average of 10 mm above the orbital rim. They recommend tightening the suture to correct for any brow asymmetries noted preoperatively. They report an average elevation of the lateral brow by 2.42 mm with this procedure [22**].

External browpexy

The most [illegible] described in an article by Mersy [12] published in 2012. In the original

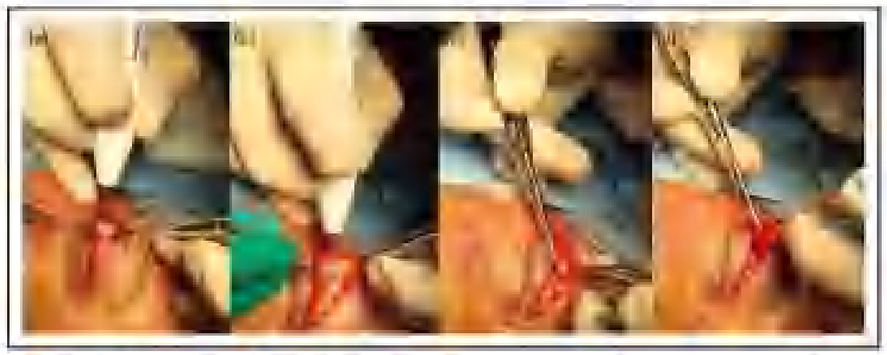

Figure 1. Photos of brassiere suture procedure. (a) After skin resection, the orbicularis muscle is opened using high-dissection scissors. (b) Dissection is carried to the preorbicularis lateral plane to the lateral aspect of the superior orbital rim. (c) The needle of a 3-0 chromic suture is then passed through the orbicularis muscle just medial to the lateral canthus. (d) The needle is then passed through the inferior edge of the superior portion of the orbicularis muscle and the suture is tied. Additional sutures can then placed laterally and medially.

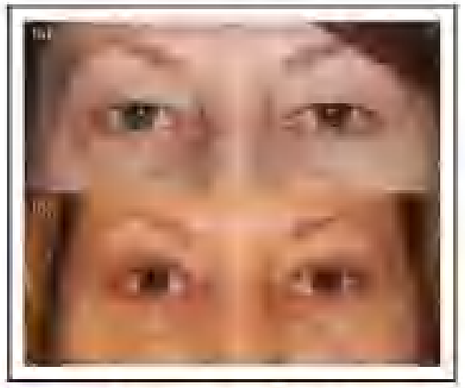

Figure 1 Before and after photos following bladeless suture suture. (a) Preoperative photo. (b) Postoperative photo, 24 days after bilateral upper eyelid blepharoplasty with skin removed and bladeless suture. Note the well defined pulse and refurbished brow.

Incisional, he reported the qualitative results of this procedure in 78 patients. 18 of these were brow. The procedure as described is minimally invasive, the patient while sitting up in the perioperative area. A mark is made over the desired point of elevation usually near the point where the body and the tail of the brow curve. The brow is then elevated to the desired height and the skin is pressed while the marking pen is kept steady in place. Once the brow has taken a forward resting position the skin is marked at the level of the pen, identifying a point for fixation during surgery. It is recommended that the distance from the orbital rim to the intended fixation point be measured so not to lessen the fixation point once the patient is supine and the level of the brow has changed. A proposed 5-mm incision, in line with the proposed fixation point at the upper border of the brow, is marked. The proposed incision is completed and dissection is carried down vertically to the level of the periosteum. Subcutaneous dissection laterally and temporalis to extend the internal extent of the incision is similar to as recommended. The superior edge of the wound is elevated and the periosteum or adjacent tissue is grasped with a forceps. The tissue grasped by the forceps should be the same distance from the orbital rim as the preoperative fixation mark. It is noted by the author that this is usually at the plane of the incision as the brow elevates to an approved position when the patient takes a supine position for surgery. A 4-0 polypropylene is then passed through the previously grasp tissue. Then the forceps is used to capture a small amount of tissue and pass through the internal edge of the wound and pulls it superficially. The 4-0 polypropylene is passed through this tissue and tied securely. Following the periosteum, there should not be any significant bone dissection. The wound is then closed with a layered closure.

The most common complications from the procedure were pain and swelling at the site of the incision. These complaints resolved between 1 and 4 weeks after surgery. In the experience, patients often describe tightness over the suture site, but this has always subsided over the following month. As this temporary procedure requires an additional external incision, there is some concern with the cosmetic appearance of the scar. The original report indicates that 20 of the patients underwent five fluorescein/steroid injections following surgery [12]. None of the reported patients expressed dissatisfaction with the cosmetic appearance of the scar. Our experience is that, as patients with full brow ptosis that this incision heals to a cosmetically pleasing finding. Our data show that patients who underwent external browplexy with or without ptosis surgery had an average lift of 2.97 mm of the lateral brow [13••].

Conclusion

Browplexy procedures are minimally invasive and can be very effective tool to address midface–periorbital brow ptosis. There are several variations on the basic technique that can be used to tailor the surgical approach to an individual patient's anatomy and surgeon preference. Quantitative analysis of these procedures shows that each of these techniques provides rehabilitation and treatment lift of the lateral brow when combined with upper eyelid surgery.

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Conflicts of interest

There are no conflicts of interest.

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A retrospective review of 22 patients who underwent brow resection of the internal browplexy. Quantitative results showed an average of 9% of the lateral brow (~3.42 mm).

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ORIGINAL RESEARCH

Combined Endoscopic Medial and External Lateral Orbital Decompression for Progressive Thyroid Eye Disease

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OBJECTIVE: To compare the efficacy of endoscopic medial and lateral orbital wall surgery to 3-wall decompression in patients with thyroid eye disease.

STUDY DESIGN AND SETTING: A retrospective study of patients with thyroid eye disease with severe proptosis, exposure keratitis, or compressive optic neuropathy was conducted.

RESULTS: Mean reduction in proptosis was 4.?? mm in the 2-wall approach and 4.?? mm in the 3-wall group. Seventy-five percent of patients in the 2-wall group demonstrated improved visual acuity; 30% improved after 3-wall decompression. Vertical palpebral fissure height decreased by an average of ?.?? mm in the 2-wall group and by 2.?? mm in the 3-wall group. [illegible]

CONCLUSIONS: Improvement in the degree of proptosis, visual acuity, and palpebral fissure height was seen in the majority of our patients and compared favorably to our results with 3-wall orbital decompression.

EBM rating: C-4

Ocular involvement is present in [illegible] of patients with Graves' disease and contributes significantly to ophthalmologic morbidity in 2% to 5% of patients with this disorder.[1] The sequelae are both functional and cosmetic and relate to the volumetric constraints placed on the ocular contents by the bony framework of the orbits. The progressive nature of this disease ultimately manifests itself in several ophthalmologic consequences including lid lag and proptosis, diplopia, exposure keratitis, strabismus, diplopia, compressive optic neuropathy, alterations in visual acuity, and potentially blindness.

Thyroid-stimulating hormone (TSH) appears to be the receptor affected through a common autoimmune antigen.[2] Other shared molecular antigens have also been described in association with ophthalmopathy in patients with Graves' disease.[3] Thyroid eye disease arises as T lymphocytes migrate into the orbital fat and extra-ocular musculature as a response to immune-complex formation. Retroocular fibroblasts deposit glycosaminoglycans, provoking interstitial edema of the extraocular musculature. Eventually, the chronicity of this process leads to fibrosis and may result in decreased effectiveness to decompressive surgery.

In early stages of thyroid eye disease, high-dose steroid therapy can limit the progression of ocular sequelae, likely as a result of reduction of infiltrating lymphocytes in the extra-ocular musculature and retro-orbital fat. With disease progression, treatment with external limiting radiation ranging from 2.4 to 20 gray has been described. Improvement in visual acuity is noted in the majority of patients,[?] though little benefit with respect to exophthalmos, restrictive ophthalmopathy, strabismus, or optic neuropathy is appreciated.[?] Robertson et al[?] describes early complications that involve radiation effect on the microvasculature of the retina and has significantly limited its use in this patient population.

The surgical practice of orbital decompression has been the principle treatment modality for thyroid eye disease for greater than 100 years. The methods of decompression have varied, and attempts at combining each of the 4 walls of the orbit have demonstrated varied results with respect to symptomatic improvement and morbidities.

To evaluate endoscopic medial and lateral (external) orbital wall decompression surgery in the treatment of patients with severe thyroid eye disease, we reviewed our experience of 2-wall and 3-wall decompression. Particular attention is focused on improvements in proptosis, visual acuity, and associated complications and morbidity.

METHODS

Consecutive patients undergoing orbital decompression for thyroid eye disease were retrospectively studied from [illegible] 2001 through January 2004. All patients were evaluated preoperatively and postoperatively in the otolaryngology and ophthalmology clinics at the University of Minnesota. Clinical and demographic information was collected before and 6 months after decompression including age at diagnosis, age at surgery, and patient gender. Formal ophthalmologic evaluation was also undertaken including Hertel exophthalmometry to evaluate degree of proptosis, visual acuity testing, including Snellen eye chart, visual field testing, biomicroscopy, funduscopy, and vertical palpebral fissure height measured with standard calipers or [illegible]. Preoperative computed tomography (CT) imaging was obtained to evaluate for potential sinus disease as well as anatomic variables, particularly with respect to the relationship of the lamina papyracea to the orbital contents. Nasal examination, including endoscopy, was routinely performed to evaluate for intranasal pathology and accessibility to the ethmoid air cells. All patients exhibited signs of severe proptosis, exposure keratitis, or compressive neuropathy.

Patients underwent either endoscopic medial and external lateral orbital wall decompression or 3-wall decompression (including the orbital floor) for thyroid eye disease. Patients were grouped according to the millimeters of exophthalmos. Those with less than 25 mm of proptosis underwent 2-wall decompression, whereas patients with 25 mm or greater of proptosis underwent 3-wall decompression. Patient's symptoms and findings in the ophthalmologic examination were used to determine the timing of surgical intervention. All operative procedures were performed under general anesthesia. Postoperatively, all patients were observed overnight to monitor their eye examination. Pre- and postoperative comparisons were made for both surgical techniques. Reduction in proptosis was determined by comparing pre- and postoperative Hertel exophthalmometry readings. Changes in visual acuity were analyzed by comparing the lowest readable line on a Snellen eye chart. The number of line changes (ie, changing from 20/40 to 20/30 would be a positive 1 line change) between pre- and postoperative examinations were determined. Changes in resting eyelid position were determined by comparing the vertical palpebral fissure height at its maximum level. Differences between the pre- and postoperative findings, as well as between the 2 surgical groups, were made using a Student's t test with a P < 0.05 considered significant.

OPERATIVE TECHNIQUES

Medial Orbital Wall Decompression

Cotton pledgets soaked in 4% cocaine are placed intranasally. After allowing time for initial hemostasis, 1% lidocaine with 1:100,000 units epinephrine is used locally injected into the nasal septal mucosa and lateral nasal wall mucosa. Using endoscopic visualization, an uncinectomy is performed followed by complete anterior and posterior ethmoidectomies. The maxillary sinus ostium is identified and enlarged posteriorly. The sphenoid ostium is then identified and enlarged [illegible]. Mucosa is then removed from the medial aspect of the lamina papyracea. Decompression is performed from the anterior wall of the sphenoid to where the medial orbital wall thickens anteriorly. An oval-shaped defect with an average maximum height of 1.5 cm and an average maximum length of 3.5 cm is created in the lamina papyracea. The periorbita is then incised with a sickle knife. Gentle retropulsion of the globe is performed for assessment of ocular fat extrusion. Gelfilm is then placed into the middle meatus.

Lateral Orbital Wall Decompression

The lateral canthal region is infiltrated with a 50/50 mixture of 2% lidocaine with 1:100,000 units epinephrine and 0.5% [illegible]. After allowing time for hemostasis, a lateral canthal incision is made straight laterally for 2 cm. Dissection is then carried through the subcutaneous down to the lateral orbital rim. The superior and inferior crura of the lateral canthal tendon are then released. The lateral orbital periosteum is elevated posteriorly, followed by dissection of the temporalis muscle from the lateral orbital wall. The periorbita is elevated from the medial aspect of the lateral orbital wall. Next, the zygomaticotemporal and zygomaticofacial neurovascular bundles are divided with electrocautery. An oscillating sagittal saw is then used to make bone cuts superiorly at the frontozygomatic suture and at the junction of the body of the zygoma and the zygomatic arch inferiorly. The lateral orbital wall is then outfractured. The lateral orbital wall resection is carried posteriorly to the inferior orbital fissure with either a drill or rongeur. The bone is removed posteriorly to the thick diploic space of the sphenoid bone. The periorbita is then incised in the inferior and superior temporal quadrants. A Stephens scissors is used to gently open the septae within the intraconal fat, and the eye gently retropulsed. The incisions are then closed after replacing the crura of the lateral canthal tendon.

Inferior Orbital Wall Decompression

A transconjunctival incision is made in the conjunctival fornix with monopolar cautery to the inferior orbital rim.

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[illegible] presented at the 2004 Annual Meeting of the American Academy of Otolaryngology–Head and Neck Surgery Foundation, New York, [illegible].

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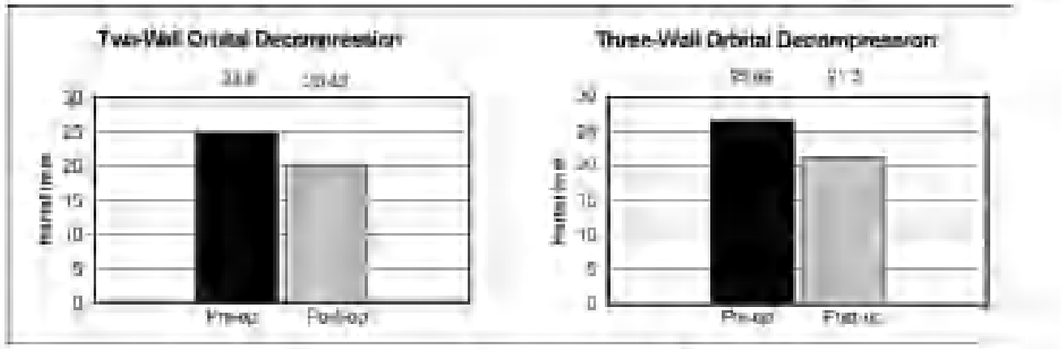

Figure 1 Mean reduction in proptosis as measured by Hertel exophthalmometry. (A) Two-wall orbital decompression achieved a mean reduction of 4.17 mm. (B) Three-wall orbital decompression achieved a mean reduction of 4.59 mm. Reduction in proptosis from the measured preoperatively was significant in both groups ($P < 0.001$ and $P < 0.001$, respectively), but no significant difference was demonstrated between patient populations.

The periorbita is then elevated and the orbital floor is exposed. The orbital floor is exposed back to the posterior maxillary sinus and anteriorly to the infraorbital rim. The floor is excised laterally to the infraorbital nerve. The periorbita is then incised anteromedially and posterolaterally (if performed in conjunction with lateral wall decompression, the periorbita is incised after completion of the inferior decompression). Incisions are then closed.

RESULTS

A medial- and lateral-wall decompression was performed in 22 orbits of 17 patients and a 2-wall decompression was performed in 15 orbits of 8 patients. Patients in which orbital floor decompression was performed demonstrated more severe and advanced signs of compressive optic neuropathy necessitating attention to visual acuity and extraocular impairment. One patient underwent a revision procedure to unroof limited orbital floor exposure and previous endoscopic surgery had previously been performed. Patients chosen for 3-wall decompression had progressive thyroid eye disease for approximately 4 times as long as those in the 2-wall decompression group.

Reduction in proptosis was achieved in both groups. Mean reduction in proptosis was 4.17 mm (range, 0.5 to 8 mm; $P < 0.001$) using the 2-wall approach and 4.59 (range, 1.0 to 9 mm; $P < 0.001$) with the 3-wall group (Fig. 1) demonstrates the mean reduction in proptosis as measured by Hertel exophthalmometry. The outcomes of decompression achieved in each group from pre- to postoperation is significant; however, no difference is demonstrated between postoperative results from the 2-wall group to the 3-wall group. The time interval from diagnosis with thyroid eye disease to surgical intervention was evaluated. Patients undergoing a 2-wall decompression demonstrated a shorter interval from diagnosis to surgical intervention (Fig. 2). Forty-seven percent of patients in the 2-wall group were operated within 2 years from diagnosis. In the 3-wall decompression group, however, 62% of patients were operated beyond 9 years from the time of initial diagnosis. The median time from diagnosis to intervention was 5.0 years in the 2-wall group and 10 years in the 3-wall group.

Postoperative change in Hertel exophthalmometry was evaluated as a factor of time from diagnosis (Fig. 3 demonstrates no correlation in change of reduction in proptosis after orbital decompression by either technique ($R^2 = 0.00074$).

Seventy-five percent of patients in the 2-wall group demonstrated improved visual acuity, while 50% improved after surgical decompression in the 3-wall group. Fig. 4 demonstrates the occurrence of either improvement or decline in visual acuity postoperatively in the 2- and 3-wall decompression groups. Four and 6 patients, respectively, demonstrated a 1 to 2 line decline in visual acuity by the Snellen eye chart at 6 months postoperatively (denoted as −1 or −2 in Fig. 4).

Vertical palpebral fissure height (Fig. 5) decreased by an average of 2.50 mm (range, 0 to 7 mm) in the 2-wall group and by 2.05 mm (range, 0 to 5 mm) in the 3-wall group. New onset diplopia was seen in 2 of 17 patients (11.8%) in the 2-wall group and 1 of 8 (12.5%) was noted in patients who underwent 3-wall decompression.

No intra-operative complications were encountered in our series. One patient required nasal packing as a result of postoperative epistaxis; this was removed in less than 24 hours. Two patients in the 2-wall decompression group noted an increase in diplopia, and 1 patient noted intermittent esotropia that resolved by 6 weeks postoperatively. One patient in the 3-wall decompression group noted increased diplopia postoperatively.

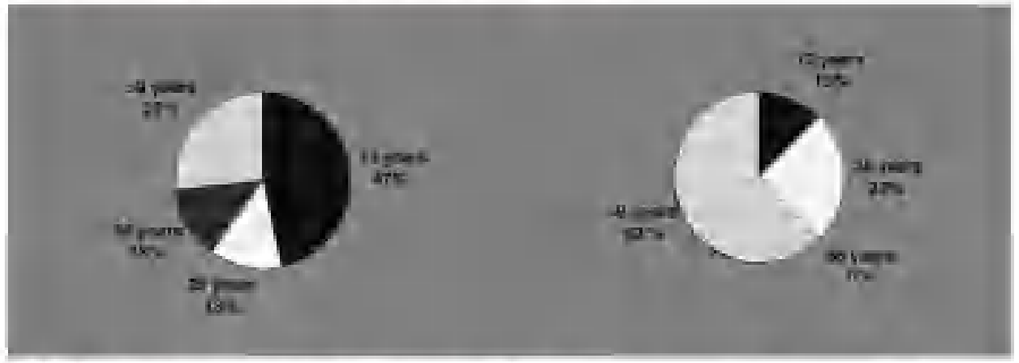

Figure 2 Interval from diagnosis to surgical intervention. (A) Two-wall decompression group demonstrates 47% of patients were operated within 2 years from diagnosis with ocular involvement by Graves' disease. (B) Three-wall decompression demonstrates 62% of patients were operated beyond 9 years from the time of diagnosis.

DISCUSSION

Surgical decompression of the orbits for patients with Graves' orbitopathy dates to the 1890s. In 1911, Dollinger adapted a technique described by Krönlein for lateral decompression of the orbit in a patient with an orbital dermoid cyst. Moure subsequently described removal of orbital fat to facilitate tarsorrhaphy. In 1931, Naffziger described the transcranial approach for the treatment of progressive exophthalmos after thyroidectomy in which decompression was achieved via the orbital roof into the anterior cranial fossa. Sewell then proceeded to decompress the orbits into the ethmoid air cells in 1936, followed by Hirsch, who in 1950 described removal of the orbital floor for decompression from the maxillary sinuses. In 1957, Walsh and Ogura[10] described transantral access as a combined procedure for decompression of the medial wall and inferior orbital floor. Other adaptations for access to the orbital floor have been described including subciliary and transconjunctival approaches. It was not until 1990 that Kennedy[11] described endoscopic transnasal orbital decompression.

The transnasal approach to the medial orbital wall and orbital floor was a preferred technique since described by Walsh and Ogura.[10] More recently, however, advances in endoscopic sinus surgery have allowed for improvement in the transnasal medial wall approach, providing for better

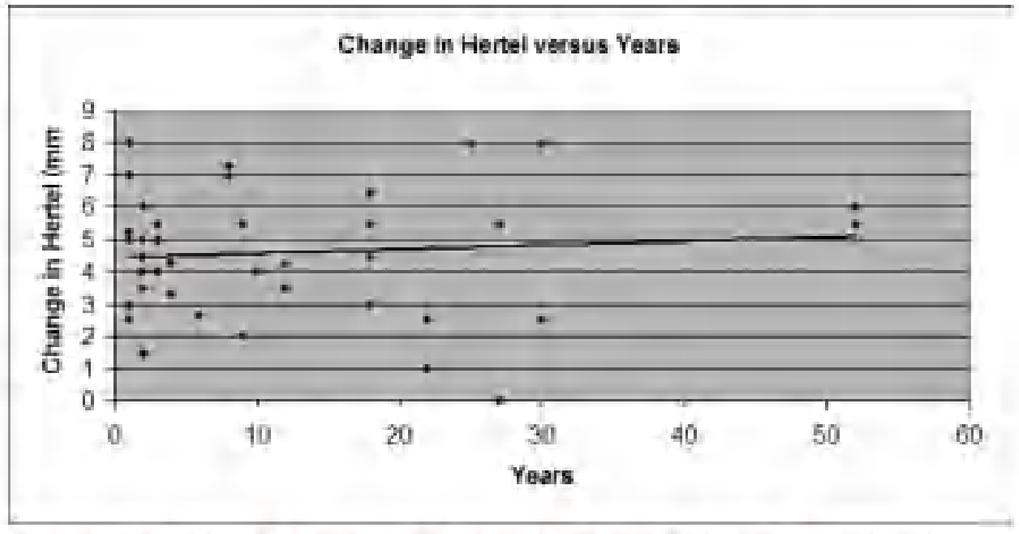

Figure 3 Change in Hertel exophthalmometry as a factor of time from diagnosis ($R^2 = 0.00074$). The trend line demonstrates no correlation in change as measured by Hertel exophthalmometry in the 2- and 3-wall decompression groups.

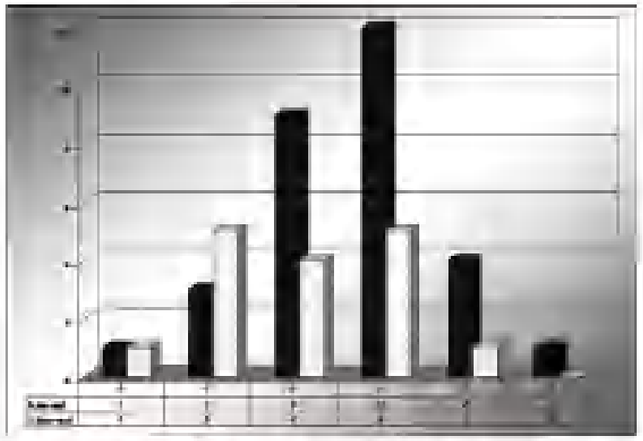

Figure 4 Visual acuity was analyzed by comparing the lowest readable line on a Snellen eye chart. The number of line changes (ie, a change from 20/40 to 20/20 would be a positive 1 line change) between pre- and postoperative examinations were determined.

functional outcomes and cosmesis. Kennedy achieved an average of 5.7 mm reduction in Hertel measurements in orbits decompressed transnasally and 4.5 mm in orbits decompressed with a Walsh-Ogura approach. Removal of orbital fat was noted to benefit these patients with elevated intra-ocular pressures and Hertel measurements greater than 21 mm by reducing proptosis on average by 4.7 mm.[12,13] Various combinations of these approaches are undertaken. For the patients reviewed in this series, the endoscopic medial orbital decompression used in conjunction with an open lateral approach provides for effective decompression with respect to improvement in Hertel exophthalmometry, visual acuity, and reduction in vertical palpebral fissure height.

Endoscopic medial with open lateral 2-wall dissection allows for effective decompression of orbital contents with reduced morbidity. The endoscopic transnasal approach to the medial orbital wall provides easier access for decompression of the orbital apex than is possible through either a traditional maxillary sinus dissection or by exposing the orbital floor via a transconjunctival or subciliary approach. Postoperative diplopia is an additional concern. It is reported to occur in the range of 2.6% to 63% and varies by the surgical approach.[1,12,13] Gerdemann et al[10] recently reported on reduction of postoperative diplopia after endoscopic medial and open lateral orbital wall surgery for balanced decompression in thyroid eye disease. They note an incidence of postoperative diplopia to be 10%, with only 5% of patients with new postoperative diplopia that required subsequent strabismus surgery. In our series, we demonstrated an 11.8% rate of new onset diplopia in the 2-wall decompression group

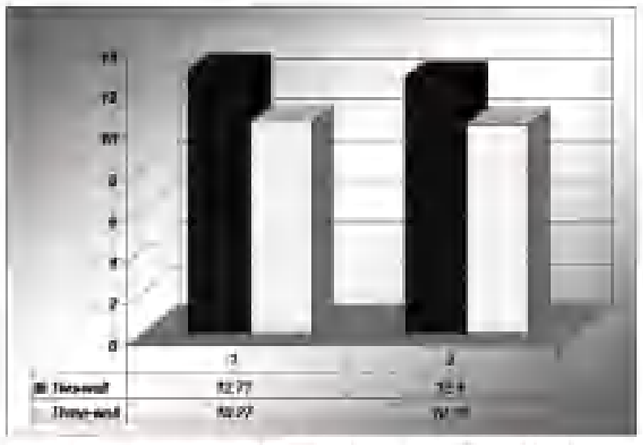

Figure 5 Mean postoperative reduction in vertical palpebral fissure height. Vertical height is measured in millimeters.

and 12.5% in patients after 3-wall decompression. Strabismus surgery is offered to all patients with postoperative diplopia. The assessment of thyroid eye disease is not linear and uniform, but over time patients can have variable ocular sequelae arising in the eyelid, anterior extraocular musculature, corneal tear, and optic nerve. Selection criteria for either approach in our patient population was directed toward late sequelae including severe proptosis, exposure keratitis, and progressive optic neuropathy. Patients in the 3-wall decompression group may have demonstrated slower progression from the onset of ocular involvement to the later stage sequelae that have the potential for significant ocular morbidity. Staged decompression was performed within 1 to 2 years after the onset of orbital symptoms in the majority of patients. Those patients in which a longer interval from the onset of orbital symptoms to the time of surgical decompression existed are likely to have a greater degree of proptosis and were offered a 3-wall decompression. The decision to perform 3-wall decompression in our patients was based on the degree of exophthalmos and was not influenced by symptoms. By proptosis criterion, patients in the 3-wall group demonstrated worse disease. However, this is debatable and inconclusive in individuals with asymmetric exophthalmos. Some patients with less proptosis demonstrated more advanced signs of optic neuropathy at an earlier stage in their disease process. It is notable that 8.2% of our patients in the 2-wall group had an average of greater than 2 years from the time of diagnosis to surgical treatment. This supports the unpredictable nature of thyroid eye disease. A randomized trial of 2-wall versus 3-wall decompression in patients with similar degrees of thyroid eye disease could help answer the debate. Despite the difference in extent of preoperative proptosis, the improvement in Hertel reduction is also similar between the groups. We were unable to demonstrate a statistically significant difference between groups when matched either 2- or 3-wall decompression with respect to the measured postoperative proptosis. Patients in the 3-wall group had evidence of thyroid eye disease for 3 times longer than those patients in the 2-wall group on average. The progressive nature of thyroid eye disease tends toward increasing fibrosis over time and may be a factor to why the 3-wall approach did not produce a significant reduction in proptosis over a 2-wall decompression. On the other hand, only the orbital floor portion of the infraorbital nerve is removed and the periorbita in this region excised. A limited annular periorbitotomy is also performed. This approach provides less decompression than a more extensive 3-wall excavation. Effective decompression is achieved, however, with limited optic nerve manipulation. Extension of greater numbers of patients may demonstrate that the 2-wall approach is less effective in more severe cases.

The time interval from diagnosis of surgical decompression [illegible] Patients with a longer duration of disease also demonstrated higher degrees of exophthalmos and, due to our selection criteria, typically received 3-wall decompression. It is possible that 3-wall decompression is necessary in this patient population given their longer disease progression likely leads to subtle changes in the extraocular musculature and progressive fibrosis of the conjunctival contents. This is commensurate to our understanding of the pathophysiology of thyroid eye disease.[1,10]

Operative decompression for thyroid eye disease has been evolving over the past 115 years since advances of the lateral orbital wall was first described. The endoscopic medial and lateral orbital wall decompression offers patients good results with limited morbidity. This approach allows for effective orbital decompression without permanently altering the course of thyroid eye disease.

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Predictive Modeling of New-Onset Postoperative Diplopia Following Orbital Decompression for Thyroid Eye Disease

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Purpose: To identify risk factors for the development of new-onset postoperative diplopia following orbital decompression surgery based on patient demographics, clinical exam characteristics, orbital CT measurements, and surgical technique.

Methods: We conducted a multicenter retrospective chart review of patients who underwent orbital decompression for thyroid eye disease (TED). Patient demographics, including age, gender, smoking history, preoperative ophthalmometry, duration of TED, use of prednisone and/or systemic steroids, detailed clinical activity score, and presence of preoperative compressive optic neuropathy. Imaging findings of enlarged muscle/total area of each bony muscle in the orbital cross-section also underwent analysis. Risk of postoperative diplopia. Regarding surgical factors, postoperative diplopia was more common among those undergoing medial wall decompression, deeper inferomedial orbital wall decompression was found to be relatively protective.

Conclusions: The main contributors to the increased risk of diplopia following orbital decompression surgery are predictable. This study demonstrates that small changes in orbital anatomy can affect ocular motility. Surgeons should consider the orbital cross-sectional muscle to orbital ratio. In addition to the type of orbital decompression surgery, the predictive factors for the development of new-onset postoperative diplopia.

(Otolaryngol Head Neck Surg 2006;134:454–459)

The clinical manifestations of thyroid eye disease (TED) can range from mild to devastating, due to a cascade of orbital and soft tissue changes that occur within the periorbital region. Proptosis, eyelid retraction, periorbital soft tissue changes, extraocular incomitance, and optic neuropathy can result in visual disability, cosmetic scarring, and irreversible vision loss. The clinical course of the disease typically exhibits an active process [1–3 years], followed by a quiescent phase. The clinical activity score (CAS) is one system used to grade disease activity. Biologically, TED is characterized by lymphocytic infiltration of the orbital tissues. These processes lead to adipogenesis, and the production and deposition of glycosaminoglycans in the extraocular muscles, the intramuscular connective tissue, and the orbital fat compartment, leading to expansion of these tissues [4–6]. A different subset of individuals, however, can exhibit a form of "burned-out" disease characterized mostly

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METHODS

RESULTS

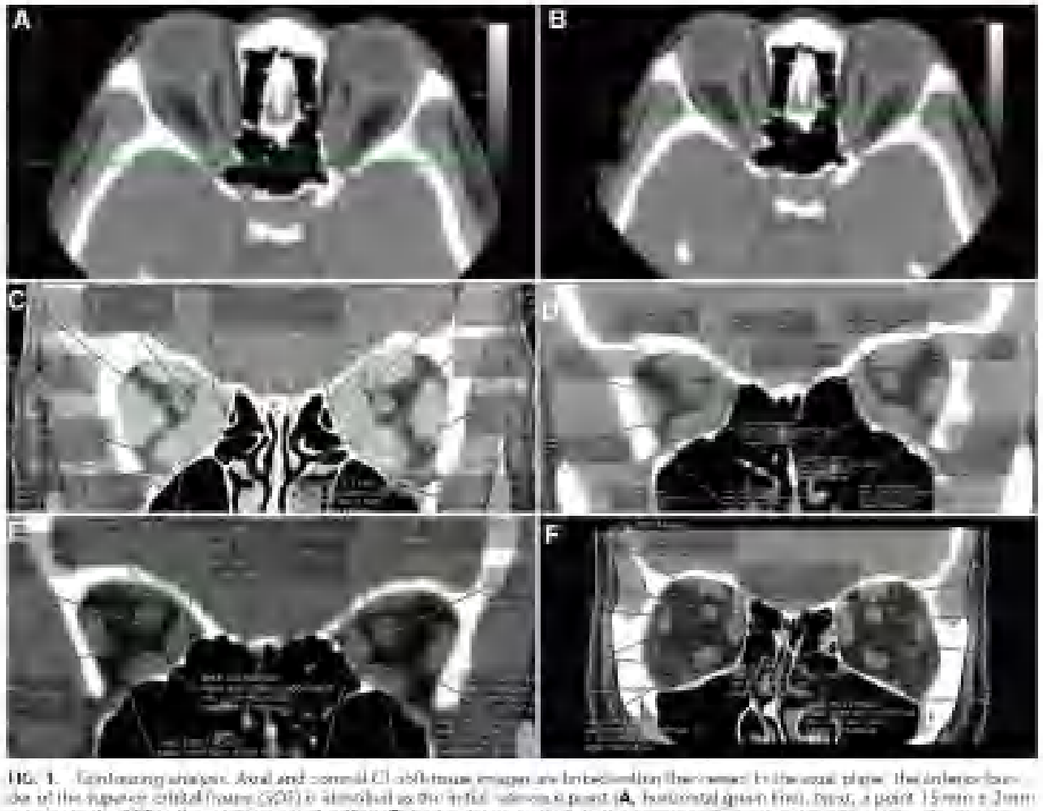

FIG. 1. Landmarking analysis. Axial and coronal CT orbit tissue images are in isocenter (the viewer is in the axial plane, the inferior border of the superior orbital fissure (SOF) is identified as the orbital reference point (**A**, horizontal green line), next, a point 15 mm ± 2 mm anterior to the SOF to the optic canal is identified (**B**, horizontal green line). In the corresponding coronal image, calipers (for 15 Mile Eyelight, Iowa, IA) are manually placed by centering between orbital walls (**C**) at 75% (as, **D**) 50%–75%, (**E**) 25%–50%, and (**F**) <25%. All measurements were done using OsiriX Imaging Software (Bellaire, TX).

TABLE 3. Perioperative factors*

Variable	Surgical-up diplopia	Post-op diplopia	p
Deep lateral wall decompression (%)	60.2	69.5	0.253
Optic decompression (%)	48.1	57.9	0.198
Medial wall (%)	53.8	93.1	<0.001
Endoscopic decompression (%)	30.2	3.9	0.015
Medial wall endoscopic (%)	28.3%	10.3%	0.029
Anterior medial wall endoscopic	28.3	89.6	<0.001
Balanced (%)	37.0	41.2	0.800
Graft reconstruction	85.8	93.9	0.061
Revision surgery (%)*	44.1	85.7	0.044
Graft reconstruction (%)	91.2	86.2	0.613
Endocrine steroids (%)	64.7	74.4	0.481
Systemic steroids (%)	51.6	47.6	0.867
Tobacco exposure (%)	23.2	9.5	0.259

*Revision surgery defined as any surgery after initial decompression.

Logit output of diplopia (logit) = 1.86*a -1.38*b -0.06*c -0.39*d -0.17*e + 0.27*f + 0.78 *g + 1.85*h -1.07*i -1.86*j +0.38 *k + 0.55*l + 0.36*m + 0.05*n -2.65

Probability estimation of postoperative diplopia (p*) = $p = e^{logit}/(1 + e^{logit})$

TABLE 4. Multivariable logistic regression analysis

Variable	Odds ratio	Coefficient	p
Intercept	2.01	1.46	<0.001
Age 20–40 years	6.28	1.84	0.290
Age 40–60 years	0.25	−0.61	0.010
Age 60–80 years	0.78	−0.35	0.767
Female	0.98	−0.27	0.852
Radiometric orbital biopsy	1.31	0.31	0.702
Bilateral surgery	2.19	0.78	0.443
Periorbital steroids	0.38	−0.97	0.081
Medial endoscopic	0.54	−1.07	0.093
Graft preservation	6.46	1.86	0.014
Balanced decompression	1.47	0.38	0.427
Flow decompression	1.72	0.55	0.254
Systemic steroid use	1.43	0.36	0.545
Smoking history	1.05	0.05	0.937

Logit output of diplopia (logit) = 1.86*a −1.38*b −0.06*c −0.39*d −0.17*e + 0.27*f + 0.78 *g + 1.85*h −1.07*i −1.86*j +0.38 *k + 0.55*l + 0.36*m + 0.05*n −2.65

Probability estimation of postoperative diplopia (p*) = $p = e^{logit}/(1 + e^{logit})$

*Use conversion table to convert logit output to probability (see online use Table 1 and 2, Supplemental Digital Content 1, http://links.lww.com/IOPRS/B301).

DISCUSSION

Preoperative counseling is essential to prepare patients for the potential of new-onset postoperative diplopia following orbital decompression surgery. The focus of this study is strictly on NOPD and excludes patients with preexisting or intermittent diplopia. Our bivariate analysis showed that older age, previous, higher clinical activity score, and compressive optic neuropathy were each correlated with increased risk of NOPD. Horizontal rectus/medial rectus and inferior rectus/inferior oblique hypertrophy have been associated with more severe disease.[12] We postulate that certain patient demographics and clinical characteristics also increase the risk of diplopia. Particular and systemic steroid use are also correlated with increased risk of NOPD. This may be because patients with more clinically active disease are often treated with steroids, confounding the result. Preoperative ophthalmologists should therefore be given when clinically indicated. For example, the use of perioperative steroids have been shown to lead to improvement in CAS, and the reduction in the degree of apical retraction, rates of strabismus, and amount of proptosis.[13]

While imaging may be useful in differentiating between active and quiescent TED,[14] in this study's knowledge-consistent, real-world, retrospective analysis in which preoperative imaging was not routinely performed, we did not find any correlation between preoperative imaging findings and postoperative diplopia. Although CT imaging is helpful for surgical planning, it is not routinely performed for patients with TED who have only mild disease. Additionally, it is difficult to grade the orbital fat on CT, with studies not even showing consistent correlation between the degree of fat prolapse and postoperative diplopia.[15] Some studies have suggested that the volume of orbital fat prolapse may be a predictor of postoperative diplopia.[16] We have found that the degree of preoperative proptosis is not correlated with postoperative diplopia. Our study is limited by its retrospective nature and potential confounders in analysis, such as the clinical activity score. The authors identified a 29.1% overall rate of new-onset postoperative diplopia, varying from 11.8% when the patient was hypertonic, which increased to 46% when the procedure was bilateral.

Different surgical techniques are associated with varying risks of developing NOPD. For medial wall decompression, an endoscopic approach was found to be correlated with lower risk compared to the transorbital approach. In 2011, a review group reviewed 189 articles in the literature and identified 17 case series that reported the unwanted sequelae of NOPD.[17] In contrast, these reviews highlighted rates of new postoperative diplopia between 0% and 9.5% with the endoscopic medial wall, transcaruncular medial wall, and combined endoscopic and transconjunctival approach to inferior medial wall with orbital preservation, respectively.[18–20] It may be the case that differences in endoscopic approaches and the varying incidences of diplopia are highly technique-dependent. We did not specifically review the techniques and protocol all cases of endoscopic medial wall decompression together. In our study, endoscopic procedures were performed at 3 institutions. A preorbital approach was used in 50% of cases. All performed as a single institution, which may also influence the protective effect.

The drug tocilizumab and drug prophylaxis treatments have been described to prevent medial rectus shift after medial wall decompression, whereby a temporary drop of percutaneous sutures is used to prevent the prolapse of the medial rectus into the ipsilateral sinus anatomically (rather decreasing NOPD).[21] The impact of implementing the protocol was studied by Malmfeldt and Ahlgren, who evaluated 270 orbits in 170 patients with orbital wall fracture, 1, 2, or 3 wall decompression. The procedure was carried in some cases during the medial decompression to allow the ipsilateral rectus and periorbital contents to prolapse into the ipsilateral sinuses. The authors identified a 29.1% overall rate post-operative diplopia varying from 11.8% when the periorbital was hypertonic, which increased to 46% when the procedure was bilateral.

Probability estimation of post-operative diplopia (p*)

$$p = e^{logit}/(1 + e^{logit})$$

Where Logit output of developing diplopia (logit) = 1.86*a -1.38*b -0.06*c -0.39*d -0.17*e + 0.27*f + 0.78 *g + 1.85*h -1.07*i -1.86*j +0.38 *k + 0.55*l + 0.36*m + 0.05*n -2.65

Independent Variable	Description	Type
a	Discrete dx severity ratio	0: <25% fat 1: 50-75% fat 2: 25-50% fat 3: >25%
b	Age 20-40 years	0: no 1: yes
c	Age 40-60 years	0: no 1: yes
d	Age 60-80 years	0: no 1: yes
e	Female	0: no 1: yes
f	Radiometric orbital biopsy	0: no 1: yes
g	Bilateral surgery	0: no 1: yes
h	Periorbital steroids	0: no 1: yes
i	Medial endoscopic approach	0: no 1: yes
j	Strut preservation	0: no 1: yes
k	Balanced decompression	0: no 1: yes
l	Flow decompression	0: no 1: yes
m	Systemic steroid use	0: no 1: yes
n	Smoking history	0: no 1: yes

FIG. 2. Modeling the data: multivariable logistic regression analysis. full color

It has been postulated that low-orbit diplopia could be reduced by preserving the intermuscular orbital septum and thereby minimizing orbital shift, and preserving the anterior 10–15 mm of the orbital floor.[9] On multivariable logistic regression analysis, our study identified strut preservation to be an effective intervention to reduce the incidence of NOPD.

It has also been suggested that patients who undergo balanced medial and lateral wall decompression are more likely to have symmetric medial and lateral rectus shifting, thereby theoretically reducing the risk of postoperative diplopia.[9] Our study found balanced decompression to harbor an increased risk of developing NOPD. In reviewing the literature, 1 group looked at balanced endoscopic medial and lateral decompression via upper eyelid crease and found a 40% rate of NOPD,[22] whereas a different study combined both transcaruncular or endoscopic medial wall decompression with lateral decompression and found a 10% rate of NOPD.[23] From our study and literature review, it appears that the wide range of medial wall decompression techniques leads to the greatest variance in diplopia onset post decompression. This study does confirm that surgical indications and clinical case features also play an important role in the risk of NOPD.

Analysis of our cohort revealed that lateral decompression similarly did not increase the risk of NOPD, whereas bilateral surgery did. One study sought to compare balanced orbital decompression (medial and lateral walls) to deep lateral wall decompression. The authors identified rates of NOPD in 33% (5/9 patients) who underwent balanced decompression, compared to only 7% (1/14) of patients who had isolated lateral wall decompression.[24] Several similar studies looked at solo lateral

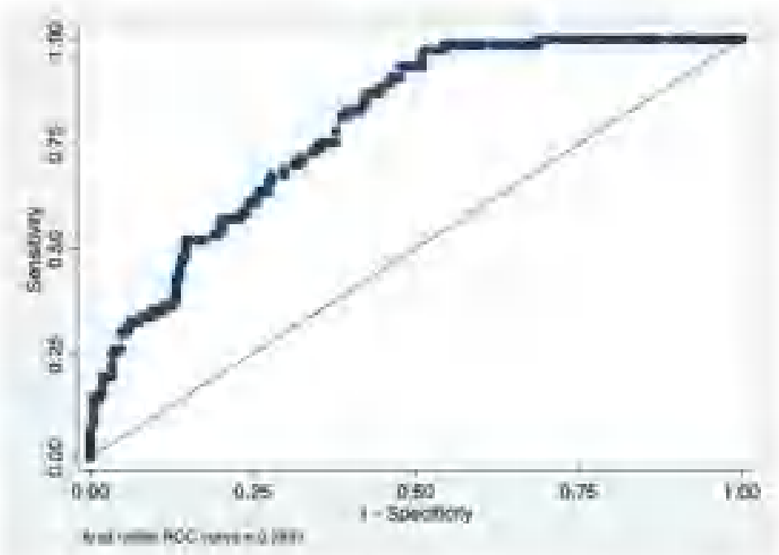

FIG. 3. Multivariable regression analysis with receiver operating characteristic (ROC) curve. ROC curve for a multivariable logistic regression model predicting probability of developing postoperative diplopia following orbital decompression for thyroid eye disease. full color

wall decompression via transconjunctival or emergency eyelid

Approach and found rates of NOPD to be 0%–7.7%.[6,9,10] Published rates of NOPD following 3-wall decompression are reported to be 6.1%–12.5%.[5,7,8] Interestingly, our results also show that 3-wall decompression with preservation of the inferior orbital strut did not significantly increase the risk of NOPD.

This is the first study that reports a multivariable logistic regression model to predict NOPD. Our logistic regression model does allow the clinician to estimate the theoretical possibility of diplopia based on this cohort of patients. Application of this formula to broader populations will require validation. Also, as this is a retrospective multicenter study, it does have several shortcomings. The lack of standardized protocols for perioperative steroid treatment, and potential biases such as the tendency for medical therapy over surgical therapy in each individual center may have played a role in management. Although an effort was made to include surgeons that collectively performed similar procedures, there are likely some technical differences that are not standardized. Patients with worsening preexisting diplopia following surgery are similar to existing cohort that were excluded in this article. As a retrospective study, the degree of intermittent diplopia and gaze-induced diplopia was not reliably assessed across the centers and therefore this cohort was not included in this study. We focused solely on primary gaze diplopia. Prism additional therapy information was also not collected in this cohort of patients. All surgeons documented the patient's resting surgery, consequently, orientation was not included as a variable which is present in other studies, may play a role, particularly in medial wall decompression. The type of postorbital preoperative was only studied for the endoscopic medial approach. Finally, it is possible that the ROC curve is more or less accurate in other cohorts. Given the size of our patient population, we were unable to divide the current dataset into a training and validation cohort. Future investigations including the model with a new cohort of patients and corroborating the overall results via prospective, randomized clinical outcomes studies.

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External vs. endonasal dacryocystorhinostomy: six of one, a half dozen of the other?

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Current Opinion in Ophthalmology

Purpose of review
The purpose of this review is to describe the results from published clinical studies evaluating the efficacy of two types of dacryocystorhinostomy, namely external and endonasal.
Recent findings
Many studies report high success rates with either procedure in ultrastructural correspondence of nasolacrimal duct obstruction. However, only a few studies have compared the two approaches in a prospective, randomized fashion.
Summary
Both types of procedure achieve excellent outcomes and there are sufficient evidence from published, large-scale studies that one approach is superior to the other.

Keywords
dacryocystitis, dacryocystorhinostomy, endonasal endoscopic nasolacrimal duct obstruction

Introduction

Nasolacrimal duct obstruction is a condition that frequently encountered by the ophthalmologist and oculoplastic surgeons. As Dr Hugo Monod remarked in an article on lacrimal surgery in 1921, 'Nature intended the tears to run into the nose.' [1], page 429. With an anatomical connection between the ocular surface and the nasal cavity, tears will run to the eye and patients experience epiphora. Rather than see 'Nature a mistress, Dr Mosher forcefully commented that 'this natural teaching a hardship and if the patient's work calls for the constant use of the eyes, it is seriously interfered with to make impossible' [2], page 429). Although the conservative approach to the nasolacrimal duct obstruction in infancy is successful in a majority of cases [3], it is rarely indicated in adulthood. Therefore, apart from the lacrimal sac and the nasal cavity are involved in the pathology of the nasolacrimal duct obstruction, and the earliest reports of procedures to address these conditions go back to 1250 BC [4]. For a long time, surgery dealt with dacryocystitis in the following manner: '... and taking the calf for the head is a wise [ophthalmic surgeon] ... course therein' [1], page 429). After excision of the sac ('sacheocystectomy') 'suppuration usually stops and the eye is rid of the constant danger of infection' [1], page 429). However, the unfortunate elimination of the nasolacrimal duct remains unresolved, and patients continue to experience epiphora.

Advances in surgical technique near the end of the 19th century allowed surgeons to reestablish a patent pathway between the lacrimal sac and the nose by creating an opening from the floor of the infundibulum (lateral nasal wall) into the nasal cavity (rhinostomy). The earliest report described an endonasal approach in 1893 [5], which was replicated later by others [1,6]. At around the same time, Toti described an 'external' technique using a cutaneous incision [6]. This technique was subsequently modified by others to include the opening of the periosteum, the lacrimal sac and the nasal mucosa, thereby forming an epithelium-lined fistula [6]. Because of the difficulties in visualizing the intranasal structures during the procedure, the endonasal approach quickly fell out of favor, and for most of the 20th century, dacryocystorhinostomies (DCRs) were performed using the external approach.

Several important advances in technology were made near the end of the 20th century, especially when the nasal endoscope was developed [7]. Since surgery in the late 1980s [7,8], allowing for much improved visualization of the intranasal structures, an increased interest in performing DCRs through an endonasal approach [9]. Endonasal DCR has received considerable popularity and several organizations such as the American Academy of Ophthalmology and the National Institute of Clinical Excellence in the United Kingdom have released position papers endorsing endonasal DCR as a procedure that is both effective and well tolerated [10,11]. Nevertheless, external DCR continues to be performed by many ophthalmic surgeons as the procedure of choice for nasolacrimal duct obstruction.

For the past 20 years, surgeons performing these two different techniques have aimed to answer the question as to which one – external or endonasal DCR – is the better procedure, provides superior outcomes and has fewer complications. Advocates of the external technique insist that there continues to be the 'gold standard' and achieves better results. Proponents of the endonasal approach, on the contrary, state that the method is not only faster and economically more appealing, given the use of a camera system, but that their outcomes are now comparable to those of external DCRs and even that external DCRs are outdated procedures and no longer indicated. Believing that medicine is a scientific discipline that allows such disputes to be settled by well designed clinical trials, we set out to search the published literature for studies comparing external DCR with endonasal DCR. We present our findings in this review.

Clarification of terminology

Before describing our methods and results, it is necessary to clarify some of the terminology used in current publications when describing DCR (Fig. 1). To summarize, DCR can be described as either external (when the bone of the lacrimal sac fossa is accessed through a cutaneous incision over the medial canthus or internal (where no such cutaneous incision is made and all instruments used to access the fossa between the lacrimal sac and the nasal cavity are introduced through naturally occurring openings of the body, such as the aperture of the lacrimal system). Internal DCR is now commonly performed through an endonasal approach. However, some authors describe an endocanalicular approach (the term 'canaloplasty' is also used by some). With the endocanalicular approach, the fistula creation and dilatation is performed through the lacrimal system and advanced through the canaliculi into the lacrimal sac (for a review, see [12]). These procedures usually involve the use of a laser to open the lining of the lacrimal sac. The bone of the lacrimal sac fossa and the anatomy of the nasal cavity with the endonasal approach are identical to those with endonasal DCR. The only difference between the two procedures is the method of creating the fistula between the lacrimal sac and the nasal cavity. With the endonasal approach, as the name implies, this is performed through the nasal cavity, and the same instruments are inserted in a reverse sequence to that described above. Then a small incision is made in the lacrimal sac, and the edges of the incision are sutured to the edges of the fistula between the lacrimal sac and the nasal cavity. With the endonasal approach, on the other hand, these instruments are inserted through the nostril into the nasal cavity, and the same instruments are inserted in a reverse sequence to that described above. Then a small incision is made in the lacrimal sac, and the edges of the incision are sutured to the edges of the fistula between the lacrimal sac and the nasal cavity. With the endonasal approach, the fistula is created externally with a nasal speculum and a headlight and/or operating microscope, using a surgical endoscope. Various instruments are employed to remove tissue and create the bony opening (osteotomy). This approach can be done either with laser-assisted endonasal DCR or with some type of instrument such as Freer elevator. Endonasal lasers require a trained surgeon to perform endonasal DCR.

Figure 2 shows external and endonasal images of the same cadaveric anatomy, indicating that the anatomic landmarks for DCR surgery are found between the inferomedial aspect of the lacrimal sac fossa and the lateral nasal wall just anterior and superior to the tip of the middle turbinate.

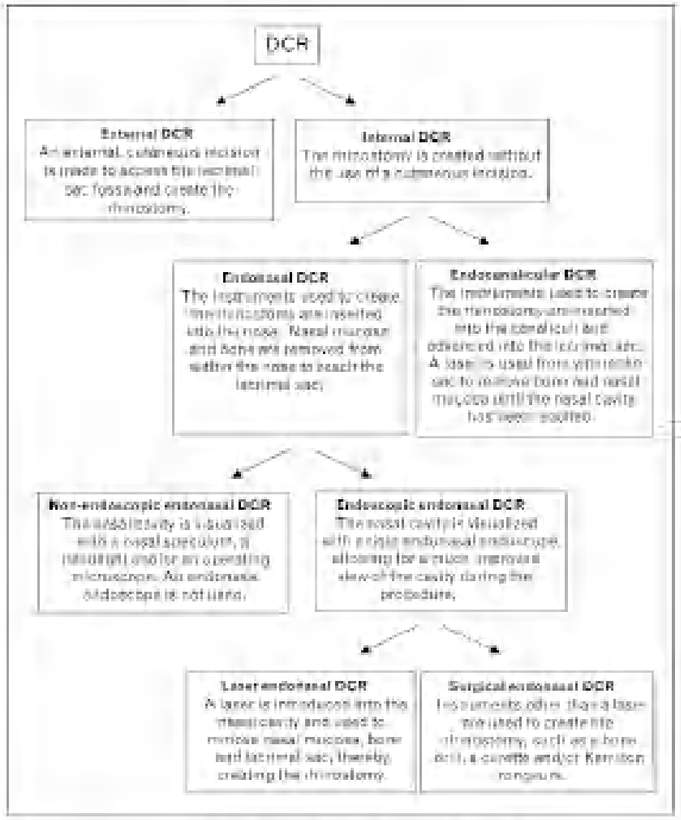
Figure 3 shows endoscopic views obtained during an endonasal DCR outlining the relevant anatomy and the individual steps of the procedure.

To optimize the correct position of the lacrimal bone will also require the surgeon to introduce a small light probe into the lacrimal sac through the punctum. This will allow the surgeon to see the light shining through the lacrimal sac wall and into the nasal cavity. The osteotomy can then be enlarged in all directions until the light is seen shining through the entire lacrimal sac fossa and can be seen from within the nasal cavity, allowing the surgeon to excise the lacrimal sac and bone in one piece if desired.

Methods

To identify relevant clinical trials, we performed a PubMed search using the search term 'dacryocystorhinostomy' in various combinations with other keywords. A large number of publications was retrieved. Those articles that described conventional medical reports of the outcomes of various types of DCR were reviewed. Additional publications were identified from the bibliographies of the reviewed articles. Publications were grouped according to the design of the reported clinical studies. The first group consisted of prospective randomized comparative studies; the second group of prospective, nonrandomized comparative studies; the third group of retrospective comparative studies; and the fourth group of uncomparative case-series studies. We aimed to consider the strength of evidence we derived in studies from the first and second groups.

Figure 1 Different types of dacryocystorhinostomy



This figure outlines the different types and variations of DCR surgery that are discussed in the text.

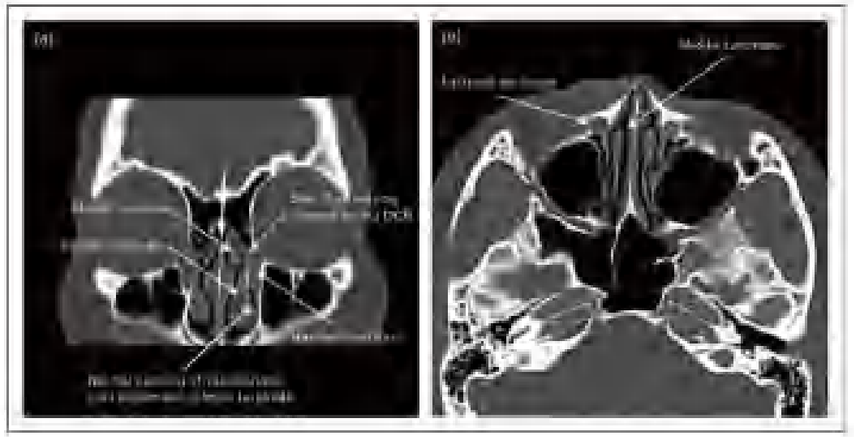
Results from prospective, randomized comparative studies

Despite the large number of publications reporting the outcomes of various types of DCR surgery, only very few of the studies have been designed in a prospective randomized comparative manner. In fact, there are only two such studies that compare external DCR with endonasal DCR [14••,15••]. Both were performed in 1994/1995 (published in 1998) and contained only 52 cases in each cohort.

The first of these studies compared external DCR with endonasal laser-assisted DCR without the use of an endoscope [14••]. The success rate after 1 year was 91% and 64% in the external and endonasal groups respectively, and the difference was statistically significant. There was also a difference in the duration of each procedure (53 min for endonasal and 76 min for external DCR). Although this study shows that external DCR achieves superior outcomes compared with endonasal DCR, it may not be as relevant today as it was in the early 1990s, as most surgeons today would visualize the nasal cavity with a rigid endoscope during endonasal DCR, rather than with an operating microscope.

The lead author for the second study was the same as for the study described above. He used the same external DCR cohort described above, comparing it with a cohort that was randomly and prospectively assigned to undergo

Figure 2 Computed tomography images of nasolacrimal anatomy



A coronal view (a) and axial bone window (b) section (at the level of the nasolacrimal system) that is reconstructed during DCR surgery, including the medial and inferior turbinates and the location of the maxillary and ethmoid sinuses. (b) Sagittal view of the nasal cavity that shows the relationship between the nasal cavity and the nasal septum. (c) Oblique coronal view that shows the relationship between the nasal cavity and the nasal septum. (d) Oblique coronal view that shows the relationship between the nasal cavity and the nasal septum.

endoscopic endonasal surgical DCR using 1 diamond burr and suture [15••]. The success rates at 1 year were 90% for external and 59% for the endonasal DCR. However, given the small sample sizes, the difference was not statistically significant. Hence, the results could only be interpreted as showing a trend towards equivalency of external DCR. The average duration was 58 min for endonasal DCR and 78 min for the external DCR.

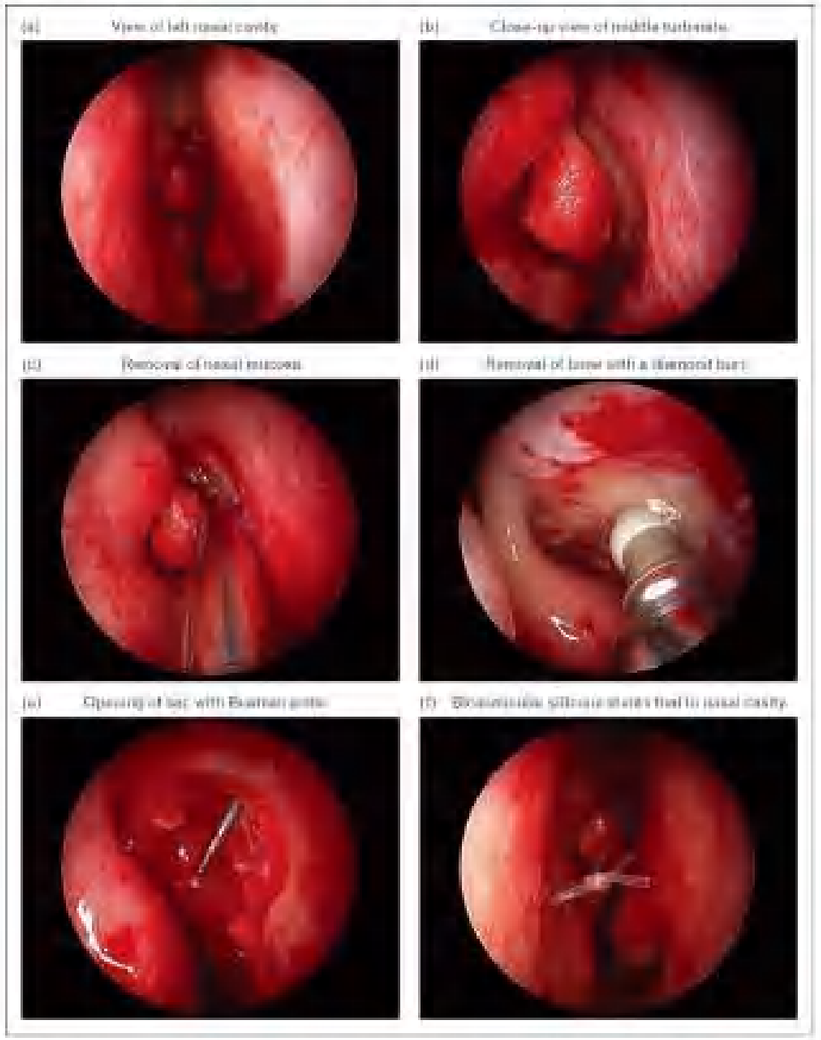
It is surprising that no additional prospective randomized studies comparing these two procedures have been published since 1998. As outlined above, the two studies by Tarbuchman *et al.* [14••,15••] suggest that external DCR may achieve superior outcomes. Considering this, the results were performed when endonasal DCR was still 'the new kid on the block' compared to endoscopic cortical microdrill and drill dacryocystorhinostomy. As many surgeons point out, there is a steep learning curve involved in endonasal DCR surgery.

We found two other prospective randomized studies comparing one type of DCR surgery with another [16,17]. However, neither of these compared external DCR with endonasal DCR.

The first of these was published in April 2005 comparing external DCR with endocanalicular laser DCR [16]. The authors of this study refer to the external DCR approach as 'endonasal laser-assisted DCR'. However, it is clear from the description of the surgical technique that the incision was introduced into the lacrimal sac through one of the canaliculi, rather than the nose. No endoscope, but only a headlight was used to visualize the nasal cavity. A total of 241 procedures were performed. The success rates were similar in the two groups (92.4% for external DCR, 94.2% for endocanalicular DCR). However, complications (DCR is performed in some surgeons' hands a serious operation [1,2]). It seems from my review of the literature that most experienced external DCR surgeons prefer the endonasal approach. Nevertheless, good outcomes of the endonasal approach have been reported in various case series with success rates from 85% to 98% [18–21] and procedure times as short as 12 min.

Another prospective, randomized study was published in June 2005, comparing two types of endonasal external DCR techniques with each other, namely laser-assisted with surgical DCR [17]. A total of 150 patients were evaluated. At 3 months, the laser-assisted group had superior outcomes (82% success and complete) with 2 (n = 3) failures. At 12 months, the surgical group had superior outcomes (74% complete success (68%), indicating that results from the surgical approach were inferior to the laser-assisted approach) and the latter group had a more rapid healing process. A separate retrospective case series of endonasal laser-assisted DCR also reported that the success of this technique diminished over time, from 96% after 3 years [22] to 81% after 5 years

Figure 3 Steps of endonasal surgical DCR: views through rigid endoscope



Views of the endoscopy are depicted that were obtained with an endoscope during endonasal DCR surgery. The relationship of the middle and inferior turbinates to each other, to the lateral nasal wall and to the nasal septum are shown in (a and b). The nasal mucosa is removed from the lateral nasal wall overlying the bone of the lacrimal sac fossa (c), followed by removal of the bone with a drill (d). After the lacrimal sac has been opened, a Bowman probed is advanced from above through the canaliculi and pushed through the lining of the sac into the nasal cavity (e). A silicone stent is then passed through the upper and lower canaliculus, and the two ends are tied to each other to prevent the newly created ostia from scarring down (f). The tubes are left in place for 3 months.

new data emerges to refute these patients longitudinal and prolonged periods of time.

Results from prospective, nonrandomized comparative studies

We identified two additional studies that were performed in a prospective manner, comparing external DCR with endonasal DCR, but the lacked randomization [23–24]. One study compared 55 patients undergoing external DCR with 48 patients undergoing endoscopic endonasal surgical DCR [23]. The success rate was significantly higher in the endonasal group (89.5% compared with 69.1%). A second group compared 54 patients undergoing external DCR with 50 patients undergoing endoscopic endonasal surgical DCR [24]. The success rates were high in both groups (95.8 to 93.8% respectively). A third group compared 78 patients undergoing external DCR with 63 eyes undergoing endoscopic endonasal surgical DCR [25]. The success rates were essentially both in both groups (89.8and 88.2% respectively). A fourth group compared 50 patients undergoing external DCR with 50 patients undergoing either endoscopic endonasal DCR [26]. The success rates were high in both groups (94 vs 90% respectively).

In fact, it has to be concluded from these studies that external DCR and endoscopic endonasal modern DCR are equivalent and yield success rates of over 85%, with the exception of the first study, which showed significantly lower success rates with external DCR at only 69%. A pooled analysis of a recent systematic review on the subject [27], a meta-analysis of these various studies is extremely difficult because of wide variations in patient selection, definition of outcomes (primary vs secondary), evaluation of symptoms and associated complications.

One other prospective, nonrandomized comparison between external DCR (mostly 20 cases of external DCR with 32 cases of endonasal DCR [28]. The success rates were 93 vs 71% respectively, showing a much need to the preparative, randomized study comparing the two techniques that we mentioned in mind. However, due to the small sample size the difference in results was not statistically significant.

Other studies

One series of the literature identified many more studies that were retrospective in nature, often comparing different types of DCR surgery with each other but not external vs endonasal. In reporting outcomes of endonasal surgical DCR technique. One of the largest prospective studies, including the evaluation of 347 patients, showed anatomic success rates in both groups (96.2% success for external DCR vs. 90.1% for endonasal DCR) [29]. However, many other retrospective studies demonstrated outcomes with endonasal DCR [30], which often report better results than endonasal DCR [31]. Because of the inherent limitations of retrospective studies in showing cause-effect relationships and the superiority of one technique over another, we will not include these studies in our review. A more comprehensive table, listing many of these studies can be found in a review by Woog and Metson [27].

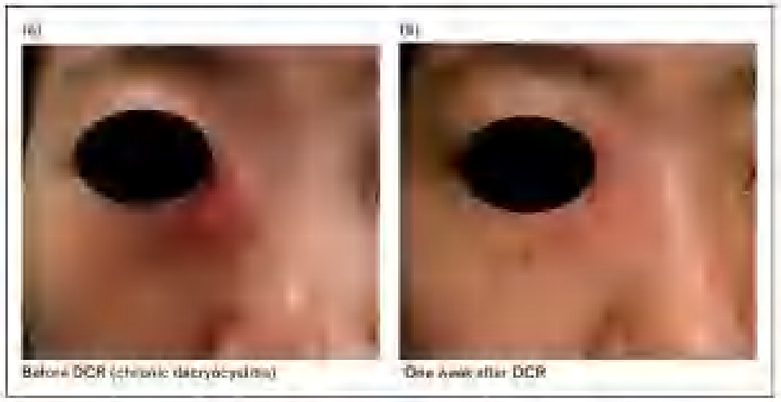
Discussion

After a careful review of the literature the answer to the question "Which is better, external or endonasal DCR?" remains elusive. There is no definitive evidence from well-designed, large-scale, prospective, randomized comparative studies that clearly shows superior outcomes with one technique compared with the other. The comparative studies that have been published between the two techniques are mostly equivalent. Because the reported outcomes in many studies are the same, a true power difference between the two techniques would have to be very large and would require several hundred patients in each group. The real question may be whether one technique is better than the other, not whether both are equivalent. Does it really matter that we have the choice and is it worth the effort and expense of a large, specially designed trial? Even if such a trial showed that one approach had better outcomes compared with the other and many statistical significance, is it not likely that the difference would be clinically significant. Given that most of the reported success rates from various studies are within a few percentage points of each other,

It seems to be a different question. Even if we could demonstrate that one approach had a slightly better success than the other, would we want to apply this to an individual patient who may possibly prefer to the approach in favor of the other? Would the result somehow link to facial cyst to worthwhile or change their overall impression of surgery? Given the many variations in technique (endoscopic vs nonendoscopic, laser-assisted vs surgical diamond burr vs bone punch) we may well wish through the "very best" techniques severely specialized one study with our recommendations therefore may be applicable to the vast majority of patients with the same pathology.

Furthermore, it appears that many of these studies, during academic meetings ophthalmologists and otolaryngologists, external DCRs whereas ophthalmologists, due to their exposure to endoscopic equipment for removing nasal or sinus endonasal DCRs. However, there is some consensus, and a multidisciplinary approach to endonasal DCR surgery [31,32]. As with any endonasal surgical technique, there is a steep learning curve for both

Figure 4 Patient with flat nasal bridge before and after endoscopic endonasal DCR for chronic dacryocystitis



(a) A patient with Asian forehead with a relatively flat nasal bridge is depicted. She had a swelling with a long history of recurring redness, swelling and pus oozing (dacryocystitis). (b) A picture of the same individual 1 week after endonasal DCR surgery, which was performed under general anesthesia. Note the change of the nasal profile, with a more elevated nasal bridge. Although this patient is a male, the same result can be expected in female patients undergoing endonasal endoscopic DCR with similar characteristics of dacryocystitis.

possibilities. To ensure patients in both ophthalmic surgeries would need to be exposed to endoscopic endonasal surgery in some parts of their training, and currently this option is not part of most residency curricula. Interestingly, a study in Japan found that in the first set of 38 consecutive endonasal DCRs performed by a surgeon not familiar with the technique, the success rate was only 39%, although it improved to 79% in the second set of 38 procedures [33], demonstrating that there is a steep learning curve for the procedure.

Other than surgeon's unfamiliarity, another reason for opting for external DCR over endonasal DCR is that certain cases, such as procedure length, cost and surgical complications may be additional factors that could favor one technique over the other. One clear advantage of the endonasal approach is that it avoids the cutaneous incision and thereby the postoperative cutaneous scar. In our experience with external DCR, the scar tends to fade well over time, and most patients are not bothered by it. A more formal review of the cosmetic significance of external DCR scars was conducted by our group, who questioned 363 patients about the visibility and significance of the scar on a scale of 1 (least significance) to 5 (greatest significance) [34]. About 90% of patients responded that their scar was not visible at all. Of those that could notice it, 80% rated the degree of its significance equal 1 or 2. Overall only 7% of participants reported a score of moderate to great significance. Younger age and female sex were reported as risk factors for postoperative cosmetic dissatisfaction. In our experience, there are some patients who are particularly concerned about scarring, others with a history of keloid formation and those in whom the external incision makes the hiding of the scar on the side of the nose very difficult. These patients may be better candidates for the endonasal approach. We recently performed a DCR on a patient of Asian origin who was particularly fine nasal bridge, in whom a postoperative scar from an external DCR would likely have stood out noticeably (Fig. 4). We offered this patient an endoscopic endonasal DCR and performed the procedure in conjunction with an otolaryngologist, with an excellent outcome.

The differences in surgical times noted in the early article by Hartikainen *et al.* [19**,35**] on the external DCR-lasting two minutes longer, as long as endonasal procedures may be unwarranted. A subsequent study with a relatively small number of patients compared the surgical times for external DCR, endonasal surgical DCR and endonasal laser DCR with each other [34]. The authors showed that external and endonasal surgical DCR had similar procedure times (44.1 vs. 50 min), whereas endonasal laser DCR was significantly faster (30.0 min). Surgical times will vary according to the experience of the surgeon. In our experience, the uncomplicated external DCR can be completed in 30–45 min from skin to mouth.

Conclusion

In summary, there is no hard evidence from the published literature that external DCR has better or worse outcomes than endonasal DCR. Both procedures are probably equivalent in their outcomes and yield a high success rate in experienced hands. A large-scale study that could determine whether one procedure is superior to the other is unlikely to be undertaken. As with any condition that is termed 'surgical', traditional fine observations prevail with unique circumstances in each patient, and it is up to the surgeon to realize when the procedure he or she is able to offer is appropriate to meet the patient's needs and when it would be advised to refer the patient to someone else.

Acknowledgement

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Additional references related to the topic can also be found in the Current Opinion in Ophthalmology 2010 publication.

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ORIGINAL ARTICLE

Infection Rates in Outpatient Eyelid Surgery

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Purpose: [illegible] eyelid surgeries performed at the Phillips Eye Institute in Minneapolis, MN, [illegible] infection rate in outpatient eyelid surgery.

Methods: [illegible] between January 1, 1999 and December 31, 2004 at the Phillips Eye Institute in Minneapolis, MN.

Results: [illegible] 2,227 patients [illegible] oculoplastic procedures. [illegible]

Conclusions: The infection rate in outpatient eyelid surgery is extremely low.

(Ophthal Plast Reconstr Surg 2009;25:109–110)

Since the 1940s, [illegible] infection. [illegible] in the United States [illegible] prophylaxis.[2] Unfortunately, in the field of oculoplastic surgery, there is a relative paucity of data with regard to infection rates specifically involving oculoplastic procedures. [illegible] surgical specialties. For example, in general surgery literature, the rate of infection in wounds that are surgically clean and [illegible] Other data show that infection rates in [illegible] procedures may approach [illegible] This may support the use of prophylactic antibiotics in these procedures. Because of various factors involving blood supply and [illegible], we hypothesized that the rate of infection in routine eyelid procedures is lower than the above-mentioned procedures and does not necessitate the use of perioperative antibiotic treatment.

An attempt to describe the routine usage of perioperative antibiotics by oculoplastic surgeons in the United States was published by Hurley et al.[3] In this study, a survey was sent to 213 members of the American Society of Ophthalmic Plastic and Reconstructive Surgery with a high response rate [illegible]. It was found that there was a wide disparity in the use of antibiotics in various oculoplastic procedures. We assume that this disparity exists partly because of a lack of data regarding infection rates in oculoplastic procedures and partly because surgeons often do not change their ways due of habit or prior training. It is hoped that this study will help guide decisions in the use or absence of perioperative antibiotics.

METHODS

We retrospectively reviewed the medical records of all eyelid surgeries performed between January 1, 1999 and December 31, 2004, at the Phillips Eye Institute (PEI) in Minneapolis, MN. [illegible]

RESULTS

A total of 2,227 [illegible] oculoplastic procedures at PEI from January 1, 1999 through December 31, 2004. [illegible]

DISCUSSION

According to our study, the infection rate for outpatient eyelid surgery is extremely low. Carter et al.[5] recently reported a postoperative infection rate of [illegible] after upper and lower eyelid blepharoplasty procedures. Our findings confirm that infection is rare after eyelid surgery. This low rate of infection is likely attributable to the rich vascular anatomy of the eyelid.

Most oculoplastic surgeons at PEI use topical antibiotics after eyelid surgery as a routine prophylactic regimen. [illegible] postoperative infection. It is possible that our data may [illegible] due to underreporting of complications by surgeons. However, this is unlikely [illegible] quality control purposes. [illegible] sterilization protocols to avoid endophthalmitis.

[illegible] and Meyer[6] reported a postoperative infection rate of [illegible] after external dacryocystorhinostomy. [illegible] cellulitis requiring oral antibiotics were encountered. In light of this finding, routine prophylactic antibiotic use for dacryocystorhinostomy seems unnecessary. With regard to orbital surgery, however, prophylactic antibiotic usage may or may not be unnecessary, given the lack of evidence to substantiate either stance.

Although it might be assumed that prophylactic antibiotics are necessary for patients with immunocompromise or with a history of infection after prior eyelid surgery, our study cannot confirm these assumptions.

Hildebrand et al.[7] suggested that prophylactic perioperative antibiotics may be used inappropriately up to 93% of the time. Resistant strains of bacteria, in particular methicillin-resistant *Staphylococcus aureus*, have been reported to be on the rise in surgical site infections.[8] Our study suggests that perioperative systemic antibiotic administration is unnecessary in routine eyelid procedures. Topical antibiotics in the postoperative period seem to be sufficient for preventing infection. Perioperative systemic antibiotics in eyelid surgery should be used judiciously to prevent antibiotic overuse.

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Intersurgeon Variability in Proptosis Reduction After Orbital Decompression for Thyroid Eye Disease: A Multicenter Analysis

[illegible]

[illegible]

[illegible]

METHODS

[illegible]

RESULTS

[illegible]

TABLE 1. Baseline demographics of patients who underwent orbital decompression among surgeons

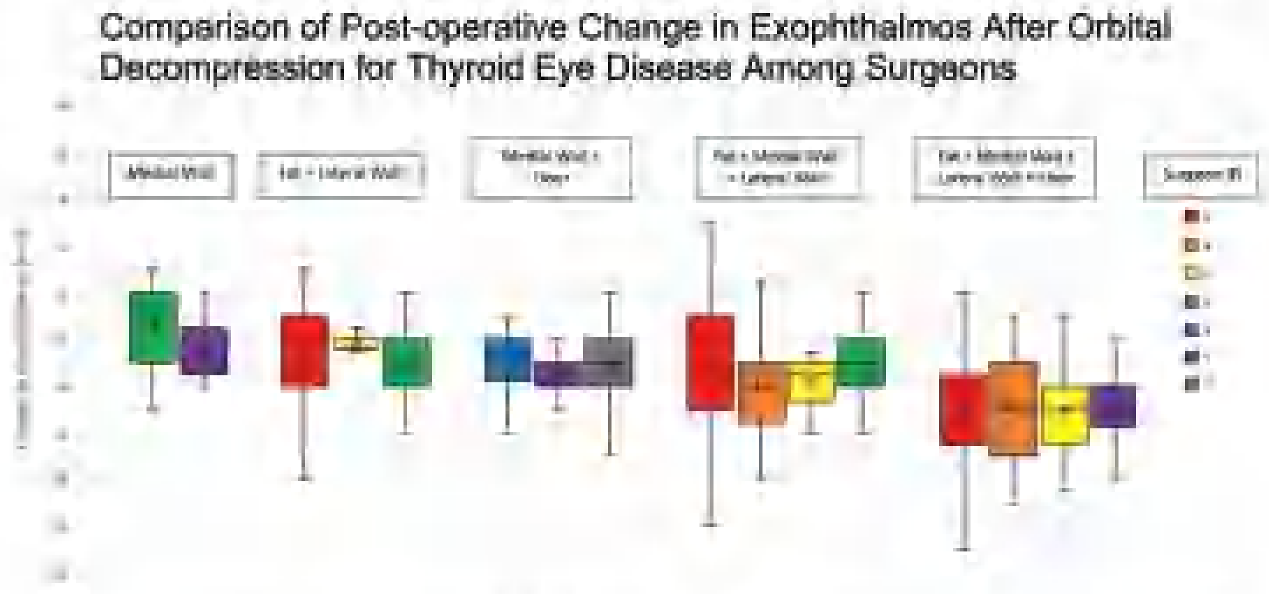
	Surgeon A	Surgeon B	Surgeon C	Surgeon D	Surgeon E	Surgeon F	Surgeon G	p value
Orbits (n)	167	81	89	116	91	37	54	NA
Age (years)	47 ± 15.8	47 ± 11.3	50 ± 14.8	52 ± 14.9	52 ± 15.5	57 ± 11.9	58 ± 14.2	<0.0001
Gender (% M)	n = 41 (25%)	n = 18 (20.7%)	n = 26 (29.2%)	n = 19 (16.4%)	n = 34 (37.4%)	n = 14 (37.8%)	n = 12 (20.7%)	0.01
Smoker (% smoker)	n = 50 (30.5%)	n = 59 (71.1%)	n = 21 (23.6%)	n = 52 (44.8%)	n = 42 (46.2%)	n = 6 (16.2%)	n = 24 (41.4%)	<0.0001
Average CAS	2.0 ± 1.5	2.5 ± 1.7	0.8 ± 1.2	1.1 ± 1.2	3.4 ± 2.6	1.7 ± 2.2	3.7 ± 1.6	<0.0001
Average preoperative exophthalmos (mm)	24.2 ± 3.2	23.5 ± 2.5	24.3 ± 2.5	23.5 ± 2.8	24.2 ± 3.8	22.5 ± 5.6	24.3 ± 3.0	0.006

All data are expressed as mean ± standard deviation.
CAS, clinical activity score; M, male.

TABLE 2. Comparison of postoperative change in exophthalmos after decompression among surgeons

Decompression technique	n	Surgeon A	Surgeon B	Surgeon C	Surgeon D	Surgeon E	Surgeon F	Surgeon G	p value
Medial wall	29				−1.40 ± 2.06 (n = 15; SE = 0.53)		−2.29 ± 1.73 (n = 14; SE = 0.46)		0.22
Fat + lateral wall	113	−2.94 ± 2.43 (n = 19; SE = 0.56)		−3.57 ± 1.73 (n = 14; SE = 0.46)	−3.14 ± 1.45 (n = 80; SE = 0.16)				0.55
Medial wall + floor	123					−2.61 ± 1.50 (n = 46; SE = 0.22)	−3.67 ± 0.69 (n = 51; SE = 0.14)	−3.20 ± 1.79 (n = 54; SE = 0.24)	0.06
Fat + lateral + medial wall	140	−3.31 ± 2.43 (n = 90; SE = 0.74)	−3.76 ± 2.13 (n = 51; SE = 0.30)	−3.88 ± 1.37 (n = 18; SE = 0.32)	−3.16 ± 1.69 (n = 21; SE = 0.37)				0.45
Fat + lateral wall + medial wall + floor	228	−4.55 ± 4.43 (n = 94; SE = 0.46)	−4.89 ± 2.41 (n = 32; SE = 0.43)	−4.74 ± 2.06 (n = 57; SE = 0.27)		−4.98 ± 2.03 (n = 45; SE = 0.30)			0.90

All data represent postoperative change in exophthalmos (mm) as mean ± standard deviation.
SE, standard error.



[illegible]

[illegible]

DISCUSSION

[illegible]

TABLE 3. Temporal trends in change in postoperative exophthalmos among surgeons

	Surgeon A	Surgeon C	Surgeon D	Surgeon E	Surgeon F	p value*
Medial wall decompression						
2002–2007	NA	NA	NA	NA	NA	NA
2008–2013	NA	NA	NA	NA	−1.65 ± 1.40	NA
2014–2018	NA	NA	1.40 ± 2.06	NA	NA	NA
p value†	NA	NA	NA	NA	NA	NA
Lateral wall decompression						
2002–2007	NA	NA	NA	NA	NA	NA
2008–2013	−2.75 ± 1.44	−2.21 ± 0.90	−1.96 ± 2.51	NA	NA	0.06
2014–2018	−3.04 ± 2.03	−2.30 ± 0.57	−2.99 ± 1.50	NA	NA	0.01
p value†	[illegible]	0.70	[illegible]	NA	NA	NA
Medial wall + floor decompression						
2002–2007	NA	NA	NA	−3.41 ± 1.43	NA	NA
2008–2013	NA	NA	NA	−2.52 ± 1.18	NA	NA
2014–2018	NA	NA	NA	[illegible]	−1.65 ± 1.86	0.40
p value†	NA	NA	NA	[illegible]	NA	NA
Lateral wall + medial wall decompression						
2002–2007	−2.75 ± 1.96	NA	NA	NA	NA	NA
2008–2013	[illegible]	[illegible]	NA	NA	NA	0.47
2014–2018	[illegible]	[illegible]	[illegible]	NA	NA	0.77
p value†	0.55	0.12	NA	NA	NA	NA
Lateral wall + medial wall + floor decompression						
2002–2007	−4.20 ± 4.55	NA	NA	−4.27 ± 1.34	NA	0.70
2008–2013	[illegible]	[illegible]	NA	[illegible]	NA	0.31
2014–2018	[illegible]	[illegible]	NA	[illegible]	NA	0.37
p value†	[illegible]	[illegible]	NA	[illegible]	NA	NA

[illegible]
*[illegible]
†[illegible]

TABLE 4. Multivariate model for factors associated with change in exophthalmos

	Effect (95% CI)	p value
Preoperative exophthalmos	1.49 (1.42–1.56)	<0.001
Clinical activity score	[illegible]	[illegible]
Age (years)	[illegible]	[illegible]
Orbital size	[illegible]	[illegible]
Disease duration	[illegible]	[illegible]
Gender	[illegible]	[illegible]
Smoking history (Project)	[illegible]	[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

surgeon using the same technique, details regarding intraoperative decision-making (dominant eye, monocular, general anesthesia) were not documented, given the retrospective nature of the study and the limited surgeon pool. Study patient characteristics, including clinical manifestations, ethnic predilection, or visual acuity, were not uniformly available across all participating centers in this dataset. As such, the potential influence of orbital phenotype, preoperative proptosis severity, decompression and enlargement of the orbital width to be assessed in the current study, but may surround an area of future research. Lastly, this study is retrospective in nature with postoperative changes in proptosis assessed at an average follow-up duration of 21.9 months with a wide range in follow-up duration (1–159 months). It is possible that stability in long-term outcomes beyond 22 months may exist; thus, future studies with longer follow-up may be indicated.

In conclusion, this study demonstrates that there is no significant difference in outcomes for proptosis reduction between orbital decompression in TED using selective wall removal, the most surgical technique (three-wall versus medial wall) or extending fat(s) protective multicenter trials studying outcomes of orbital decompression. Prospective protocols and the number of walls included in the surgical decompression may vary based with changes in proptosis severity and the timing of surgery within a surgeon's career as appropriate control for surgeon confounders do not appear to significantly affect outcomes. While limitations exist, the results of this study may strengthen the statistical validity of minimally invasive orbital decompression techniques in orbital decompression and compression of surgeons among multiple centers in the literature. Wider performed by trained ocularists, plastic and orbital surgeons employing standardized techniques, which may facilitate better understanding of optimal surgical management strategies for TED.

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Levator Aponeurosis Disinsertion in Congenital Entropion of the Upper Eyelid

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Purpose: To present a patient with congenital entropion of the upper eyelid caused by levator aponeurosis disinsertion.

Methods: Case report.

Results: Surgical correction of the levator aponeurosis disinsertion corrected the upper eyelid entropion.

Conclusions: Congenital upper eyelid entropion may be caused by levator aponeurosis disinsertion and treated effectively by repairing the anatomic defect.

Congenital upper eyelid entropion is a rare disorder that may cause serious ocular surface damage. A severe form appears as horizontal kinking of the tarsal plate (tarsal kink syndrome). Proposed causes for upper eyelid entropion and tarsal kink syndrome include direct mechanical pressure in utero, orbicularis spasm from corneal abrasion, and intrauterine inflammation in the developing fetal tarsus.

Disinsertion of the lower eyelid retractor muscles is common in involutional entropion (1) and has been noted in congenital entropion of the lower eyelid (2). In this article we describe a newborn who presented with bilateral congenital entropion of the upper eyelids with surgical findings of levator aponeurosis attenuation and dehiscence. The malposition was corrected with aponeurosis reinsertion and pretarsal crease fixation.

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CASE REPORT

A 2-week-old boy presented with infrequent opening of both eyes since birth. The child was the product of an uncomplicated pregnancy and full-term spontaneous vaginal delivery and weighed 3,280 g at birth. There was no history of maternal drug use or illness during pregnancy. Systemic findings included an atrioventricular canal defect with a 6-mm atrial septal defect and a 3-mm ventricular septal defect without hemodynamic compromise. On the third postpartum day, the parents noted a mucoid discharge from both eyes, worse on the right. Erythromycin ophthalmic ointment in both eyes was started five days later, and the child was referred for ophthalmic evaluation at two weeks of life.

The ocular examination revealed bilateral entropion of the upper eyelids (Fig. 1). A tarsal kink of both upper eyelids was suspected. There was whitish mucoid discharge from the right eye with central corneal haze. Slit lamp biomicroscopy of the right cornea revealed a central epithelial defect with no infiltrate. The patient was referred to the oculoplastics service for evaluation and repair of the upper eyelid entropion.

FIG. 1. Two-week-old infant with asymmetrical ptosis, upper eyelid crease and a normal lower OD.

Examination under anesthesia revealed a 5 ⨯ 4 mm 2.5-mm central corneal epithelial defect OD with mild stromal haze and no infiltrate. The horizontal corneal diameter was 10.5 mm in each eye. Horizontal palpebral fissures were 22 mm on the right and 20 mm on the left. The upper eyelid tarsus measured 18 ⨯ 6 mm on the right and 17 ⨯ 5 mm on the left. No horizontal kinking of the tarsus was noted when the eyelids were everted. The upper eyelid creases were present 5 mm above the lid margin bilaterally and all four puncta were normal. The position of each lower eyelid was normal.

Bilateral upper eyelid crease incisions were made. The orbicularis and orbital septum were opened and the underlying levator aponeurosis was identified. The aponeurosis on both sides was attenuated with iris visible through the thinned tissue (Fig. 2). A small amount of preaponeurotic fat was resected. Given the findings on the first side, an attempt was made to open the orbital septum high on the second side to avoid iatrogenic damage to the aponeurosis. There was similar attenuation of the levator aponeurosis in both eyelids. The anterior portion of the tarsus was freed of soft tissue and the attenuated levator fibers were resected. The aponeurosis was secured to the superior edge of the tarsus with three horizontal mattress 6-0 polyglactin 910 sutures. Two additional sutures were placed on the anterior surface of the tarsus. Pretarsal fixation was accomplished using interrupted 6-0 polyglactin 910 sutures and the skin was closed with interrupted 6-0 fast absorbing gut sutures. Postoperatively the corneal epithelial defect healed within six days and a faint stromal scar remained OD. Lid positions were normal four months postoperatively (Fig. 3).

DISCUSSION

Congenital entropion of the upper eyelid is a rare condition that must be differentiated from epiblepharon or distichiasis. The lid margin is inverted, frequently along its entire length. Complications result from the corneal irritation produced by the inverted lashes and may include keratitis, corneal abrasion, ulceration, and stromal opacification. Because the visual axis is commonly involved, compromise of corneal clarity in the newborn may lead to amblyopia with permanent visual loss. Early recognition and treatment significantly improves the visual prognosis in these children.

This patient presented with an upper eyelid malposition and corneal complications consistent with congenital entropion caused by tarsal kinking. Findings at surgery demonstrated only a slight ridge along the superior tarsi with no definite kink. The levator aponeurosis of both eyelids was symmetrically thinned suggesting a congenital malformation of the levator aponeurosis as the cause for the entropion. Interestingly, the patient showed no evidence of ptosis despite the levator malformation. We believe the anterior lamellar tissue overriding the flipped tarsus accounted for the lack of a ptotic appearance.

Previously proposed causes for congenital upper eyelid entropion include direct mechanical pressure on the tarsal plate in utero resulting in tarsal deformity, primary corneal ulceration with secondary orbicularis spasm and hypertrophy, and tertiary tarsal deformity (1). Bosniak and colleagues (3) argue that congenital tarsal kink is not likely to be caused by lid dysfunction defects if unaccompanied by other eyelid deformities. Although the clinical ap-

FIG. 2. Attenuation of the levator aponeurosis. The iris color was visible through the thin tissues.

FIG. 3. Postoperative appearance following bilateral repair of the levator aponeurosis and asymmetrical fixation.

pearance in our patient warranted consideration of tarsal kink syndrome, this was not evident at the time of surgery.

The tarsal plate of the upper eyelid is derived from ingrowth of mesodermal tissue into a folded layer of ectoderm that forms the eyelid skin and conjunctiva. Late in the development of the extraocular muscles from the paraxial mesoderm, the levator palpebrae superioris separates from the medial aspect of the superior rectus muscle (4). The levator then migrates laterally and inserts into the upper tarsus, eyelid skin, and upper fornix where it fans out to become the medial and temporal horns. The clinical course of this patient suggests that developmental abnormalities of the insertion of the levator aponeurosis into the upper tarsal plate and eyelid may play a role in the development of congenital upper eyelid entropion.

This patient's congenital heart defect is consistent with previous reports in which congenital upper eyelid entropion was associated with cardiac abnormalities as well as mental retardation, skull defects, brachysyndactyly, supinovarus, and micrognathia (5). We could not elucidate any infectious, drug, or nutritional insult at the corresponding gestational period that may have been a contributing factor to this patient's findings.

Previously described treatments for congenital upper eyelid entropion include lateral canthotomy (6), the Celsus procedure (7), oblique blepharotomy and Snellen suture, transverse blepharotomy at the tarsal kink with marginal rotation (8–10), suture tarsal stabilization (11) tarsal kink excision and a modified Panas' procedure (12), lamellar tarsoplasty (13) and tarsal resection with scleral graft (14). In our patient, resection of the attenuated aponeurosis with reinsertion into the upper tarsus combined with pretarsal crease fixation corrected the entropion. This case demonstrates that levator aponeurosis dysinsertion may be an etiologic factor in the development of congenital upper eyelid entropion.

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Bilateral Congenital Lacrimal Anlage Ducts (Lacrimal Fistula) in a Patient With the VACTERL Association

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Purpose: To present a case of bilateral congenital lacrimal anlage ducts in a patient with the VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies) association.

Methods: Case report.

Results: A 19-year-old man presented with intermittent facial swelling. Examination revealed bilateral lacrimal anlage ducts. The patient underwent excision of the ducts with silicone intubation.

Conclusions: We add the VACTERL association to the list of systemic conditions associated with lacrimal anlage ducts.

Congenital lacrimal anlage duct (lacrimal sac fistula) is a rare developmental anomaly of the nasolacrimal excretory system. We noticed a patient with bilateral lacrimal anlage ducts with the VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies) association.

A 19-year-old man was referred to the Ophthalmic Plastic and Reconstructive Surgery Unit at Casey Eye Institute for evaluation of intermittent facial swelling of 6 months' duration requiring oral antibiotics. Two weeks before our examination, facial swelling developed and was treated with oral cephalexin. His past medical history was significant for the VACTERL association. He had multiple anomalies including annulorectal esophagus, anal atresia, sacral agenesis, hypospadias, undescended testes, and a dysplastic kidney. He had previously undergone 15 operations to correct the various anomalies.

Ophthalmic examination revealed uncorrected visual acuity of 20/20 for each eye. The pupils were equal, round, and reactive to light, with no evidence of a relative afferent pupillary defect. Versions and duction were normal. Slit-lamp biomicroscopy revealed normal anterior segments in both eyes. Intraocular pressures were normal. External examination revealed bilateral lacrimal anlage ducts inferomedial to the medial canthus (Fig. 1). Jones I and II dye tests were positive bilaterally. There was reflux of the dye through both anlage ducts. A previously obtained computed tomography scan showed the anlage ducts communicating with the lacrimal sac (Fig. 2). The patient subsequently underwent excision of both anlage ducts as previously described by Jones and Wobig[1] with bicanalicular silicone intubation of the nasolacrimal ducts.

Lacrimal anlage ducts are rare developmental anomalies occurring in 1 in 2000 births and occasionally are familial with autosomal dominant inheritance.[2] There does not appear to be any race or sex predilection. These anlage ducts occur when the lacrimal anlage cells proliferate and canalize rather than involute. The anomaly is usually not associated with any systemic abnormalities,

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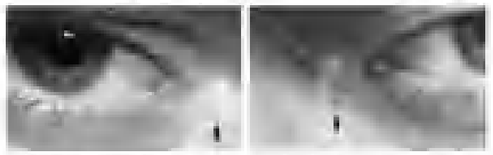

FIG. 1. Bilateral congenital lacrimal anlage ducts (arrows).

but previous reports have described anlage ducts in patients with thalassemia,[3] preauricular fistulas,[4] balanced 6p and 13q translocation,[5] and Down syndrome.[6] There have been no reports to our knowledge of a patient with lacrimal anlage ducts and the VACTERL association.

The VATER (vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, and radial dysplasia) association was first described in 1968 as the polydactyly/imperforate anus/vertebral anomalies syndrome.

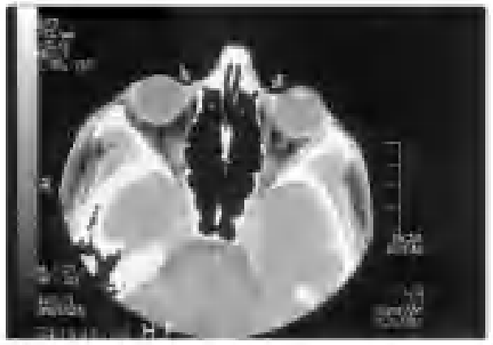

FIG. 2. Computed tomography scan showing anlage ducts coalescing into the respective lacrimal sacs (arrows).

The VATER acronym was described in 1972. Subsequently, this was expanded to VACTERL (vertebral anomalies and anorectal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies) to include cardiac and renal anomalies.[7] Nearly all cases are sporadic, with no recognized teratogen or chromosomal abnormality. One recent paper showed a mitochondrial cytopathy in one patient.[8]

Despite the severity of their physical deformities, these patients may have normal mental development. A previous paper described the ophthalmic abnormalities in four of these patients.[9] Ophthalmic findings included ptosis, internal strabismus, cloudy cornea, severe myopia, anisocoria, and heterochromia iridis. There was no mention of any lacrimal system abnormalities.

Our case illustrates bilateral lacrimal anlage ducts in a patient with VACTERL association. Interestingly, these patients commonly have multiple other congenital fistulous tracts throughout their bodies. We recommend careful evaluation of the lacrimal system in these patients and excision of the ducts when epiphoric infection or chronic sinus irritation occur.

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Comparison of phaco-chop, divide-and-conquer, and stop-and-chop phaco techniques in microincision coaxial cataract surgery

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PURPOSE: To compare the outcomes of coaxial microincision cataract surgery (MICS) performed with 3 phacoemulsification techniques (phaco-chop, divide-and-conquer, and stop-and-chop) according to cataract density.

SETTING: Bundang St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul, South Korea.

DESIGN: Prospective randomized clinical trial.

METHODS: Eyes with nuclear density from grade 2 to 4 were randomly subdivided into 3 groups (phaco-chop, divide-and-conquer, and stop-and-chop). Intraoperative measurements included ultrasound time (UST), mean cumulative dissipated energy (CDE), and balanced salt solution use. Clinical measurements included preoperative and 1 day, 1 month, and 2 month postoperative corrected distance visual acuity, central corneal thickness, and endothelial cell count.

RESULTS: Intraoperative measurements showed significantly less UST, CDE, and balanced salt solution use with the phaco-chop technique than with the divide-and-conquer and stop-and-chop techniques in the grade 4 cataract density group ($P<.05$). The percentage of endothelial cell loss was significantly lower in the phaco-chop group than in the divide-and-conquer and stop-and-chop groups in the grade 4 cataract density group 2 months after cataract surgery ($P<.05$).

CONCLUSIONS: All 3 techniques may be effective for coaxial MICS in mild and moderate cataracts. However, in eyes with hard cataract having coaxial MICS, the phaco-chop technique can be more effective for lens removal, with less corneal endothelial damage, than the divide-and-conquer and stop-and-chop techniques.

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With advancements in cataract surgery technology, incision size, phacoemulsification energy, and endothelial cell loss have been reduced and phacoemulsification efficiency has been increased.[1] Coaxial microincision cataract surgery (MICS) has become a safe and effective technique for performing the procedure.[2]

Endothelial cell loss was initially increased in MICS, especially in eyes with increased nuclear density, because of increased cumulative dissipated energy (CDE), aspiration time, and volume of balanced salt solution used.[3] The intraoperative energy used and ocular damage can be decreased in MICS with the pulse and burst modes compared with the continuous mode for hard cataract.[4]

Advanced phacoemulsification techniques may also decrease energy use.[5] The phaco-chop technique requires lower ultrasound (US) energy for nuclear management than the stop-and-chop technique in dense cataracts; however, it has been reported that the resulting endothelial loss was similar with both techniques in small-incision cataract surgery.[6] Several new techniques were introduced to increase the efficiency of phacoemulsification of hard cataract.[7,8]

To our knowledge, there are no studies comparing MICS phacoemulsification techniques according to cataract density. We compared the outcomes of coaxial MICS performed with 3 phacoemulsification techniques (phaco-chop, divide-and-conquer, and stop-and-chop) according to the cataract density.

Table 1. Preoperative clinical data (Stevens-Johnson syndrome).

Parameter	Phaco-Chop Technique		
	[illegible]	[illegible]	[illegible]
Mean age (yr)	[illegible]	[illegible]	[illegible]
Mean CDVA (log MAR)	[illegible]	[illegible]	[illegible]
Mean corneal thickness (µm)	[illegible]	[illegible]	[illegible]
Mean ECC (cells/mm²)	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Mean ± SD
CDVA = corrected distance visual acuity; ECC = endothelial cell count; SD = standard deviation
*Comparisons of 3 groups by Kruskal-Wallis equality-of-populations rank test (Stevens-Johnson syndrome and Fuchs dystrophy)

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Patients and Methods

This prospective randomized study comprised eyes with cataract that were randomly assigned to have phacoemulsification and posterior chamber intraocular lens (IOL) implantation at the Bucheon St. Mary's Hospital between May 2010 and December 2010. The study protocol followed the guidelines of the Declaration of Helsinki and an institutional review board. Patients provided written informed consent before undergoing an explanation of the surgical options used in the study.

Eyes were equally randomized according to 3 cataract density (nuclear opalescence [NO]) groups (NO2, NO3, NO4). Each density group was randomly assigned to have phacoemulsification with the divide-and-conquer technique, phaco-chop technique, or stop-and-chop technique.

Exclusion criteria included corneal pathology, pseudoexfoliation, history of ocular trauma, and intraoperative complications such as posterior lens capsule rupture, lens dislocation, and ocular inflammation.

Preoperative assessment included corrected distance visual acuity (CDVA), nuclear opacity grading by slitlamp examination, central corneal thickness (CCT) by US pachymetry, and endothelial cell count (ECC) by specular microscopy. The types of cataract and grades of density were classified preoperatively using the Lens Opacities Classification System III.

Intraoperative and Postoperative Measurements

Intraoperative measurements included total balanced salt solution used, ultrasound time (UST), and mean CDE. The postoperative parameters measured at 1 day, 1 month, and 2 months were CDVA, CCT, and ECC.

Phaco Machine Settings

Phaco machine settings were identical in all study groups. Microcoaxial phacoemulsification was performed with the Infiniti Vision System (Alcon Laboratories, Inc.), which uses fixed-mode US. The height of the infusion bottle was set at 100 cm. The aspiration flow rate was 30 mL/min, and the vacuum level was set at 300 mm Hg.

Surgical Technique

Phacoemulsification was performed by the same surgeon (ECK). In all cases, surgery began with a clear incision at a temporal corneal site created with a double-bevel 2.2 mm keratome knife (Alcon). Then, the anterior chamber was filled with sodium hyaluronate 1.0% (Hyal Plus). A 0.9 mm keratome curvilinear capsulorhexis was made using an Inamura capsulorhexis forceps (Duckworth & Kent Ltd). Hydrodissection and hydrodelineation were achieved using a balanced salt solution. In all cases, a 0.9 mm bevel 45-degree MPS Ashman microtip (Alcon) was used.

For the phaco-chop technique, phacoemulsification began with quadrantectomy of peripheral nucleus. After the corneal and epinuclear were removed, the phaco tip was buried in the center of the epinucleus with high vacuum. Then, the phaco chopper was inserted through the sideport and placed opposite the main incision at the edge of the nucleus. The chopper was positioned under the inner edge of the capsulorhexis and pulled toward the phaco tip. The 2 instruments were then moved in opposite directions to divide the nucleus into halves. This process was continued for both nuclear halves by rotating them 90 degrees. The phacoemulsification tip was inserted in

Table 1. (Cont.)

Divide-and-Conquer Technique			Step-and-Chop Technique		
NO2	NO3	NO4	NO2	NO3	NO4
51.1 ± 9.3	47.8 ± 9.7	47.9 ± 9.3	49.7 ± 9.3	49.8 ± 9.7	48.7 ± 7.61
0.28 ± 0.13	0.28 ± 0.14	0.28 ± 0.11	0.26 ± 0.10	0.30 ± 0.16	0.29 ± 0.09
622.7 ± 12.4	5.86 ± 7.34	9.07 ± 12.5	9.98 ± 9.16	5.87 ± 9.86	9.03 ± 15.5
2644.1 ± 49.8	2582.3 ± 140.3	2629.2 ± 166.6	2519.3 ± 75.5	2567.9 ± 144.2	2486.1 ± 202.0
<.05	<.05	<.05	<.05	<.05	<.05

half the nucleus and the chopper was used to break the half into 2 smaller segments, which were then emulsified and aspirated. The procedure was repeated on the other half of the nucleus.

For the divide-and-conquer technique, 4 trenches were sculpted to the maximum set at 65 mm Hg so the nucleus could be cracked horizontally into 4 segments. The 4 quadrants were emulsified in the capsular bag using increased vacuum (up to 90 mm Hg). The rest of the procedure was similar to that used in the phaco-chop technique.

In the step-and-chop technique, the phacoemulsification probe was used to sculpt a central crater down to 65% of nuclear thickness. After the groove was created, the chopper was inserted into the depth of the crater and the posterior plate of the nucleus was cracked in half by laterally moving the chopper and phacoemulsification probe in opposite directions. After the nucleus was split, phacoemulsification was performed and the nuclear halves were cut into fragments and then emulsified and aspirated, as in the phaco-chop groups. Irrigation and cortex removal were performed with manual/aspiration cannulas in all groups.

After the procedure, sterile sodium hyaluronate 1% (Healon) was injected into the anterior chamber and a Y-AG-BBK IOL (Hoya Corp.) was implanted in the capsular bag using a dedicated injector system. In all groups, IOL implantation was performed under the protection of an ophthalmic viscosurgical device (OVD), which was subsequently removed through aspiration. The wound was not sutured.

Central Corneal Thickness

The CCT was measured using US pachymetry (SW-3000; Sonomed) preoperatively and 1 and 2 months postoperatively. The pachymeter was precalibrated for all measurements. The CCT was measured with the patient seated upright. A handheld probe was aligned on the central cornea as perpendicularly as possible. Ten readings were obtained and averaged. The same observer took all measurements.

Endothelial Cell Counts

The ECC was measured using a noncontact specular microscope (Nidek Konan CA SP-8000) preoperatively and 1 and 2 months postoperatively. The center method was used for cell counting. Approximately 30 to 60 cells were counted manually from each photograph in the semiautomatic cell-density algorithm of the microscope. Three central fields were counted, and the average of these counts was used to represent endothelial cell density (ECD) at each point. Endothelial cell loss was evaluated as follows: Endothelial cell loss = (preoperative cell count − postoperative cell count)/(preoperative cell count) × 100%. The examiner was masked as to which group the images belonged. At each FSD, 3 photographs were taken of each eye.

Statistical Analysis

All data are expressed as the mean ± SD. The Tukey highly significant difference (HSD), Duncan, and independent-samples *t* tests were used to compare the groups for statistical significance. The analysis was performed using SPSS for Windows software (version 13.0; SPSS, Inc.). A *P* value less than .05 was considered statistically significant.

RESULTS

The study comprised 135 eyes of 135 patients. Each cataract density group (NO2, NO3, NO4) had 45 eyes. In each cataract density group, the first 15 patients had phacoemulsification with the divide-and-conquer technique, the next 15 patients with the phaco-chop technique, and the final 15 patients with the step-and-chop technique. Table 1 shows the characteristics of the patients in each group. There were no statistically significant differences in age, preoperative CDVA, ECD, or CCT between the groups ($P < .05$).

Intraoperative Parameters

The UST was significantly less in the NO4 group with the phaco-chop technique than with the divide-and-conquer and step-and-chop techniques ($P < .05$). The CDE energy and balanced salt solution used in the NO4 group were also significantly less with the phaco-chop technique than with the divide-and-conquer and step-and-chop techniques ($P < .05$). There was no significant difference in effective phacoemulsification time, CDE, or balanced salt solution used in the NO2 and NO3 groups between the phaco techniques (Table 2).

Table 2. Comparison of UST, CDE, and balanced salt solution use after phacoemulsification between techniques according to cataract density (Tukey HSD and Duncan tests)

	Mean ± SD								
	Phaco-Chop Technique			Divide-and-Conquer Technique			Step-and-Chop Technique		
Parameter	NO2	NO3	NO4	NO2	NO3	NO4	NO2	NO3	NO4
UST (%)	17.9 ± 10.1	26.8 ± 7.4	9.6 ± 12.4*	30.2 ± 10.8	48.8 ± 11.6	55.4 ± 15.6	32.9 ± 14.1	50.9 ± 15.2	49.3 ± 14.9†
CDE	10.2 ± 7.5	12.9 ± 4.2	17.1 ± 3.8*	13.2 ± 4.7	11.7 ± 3.7	19.2 ± 4.3	14.1 ± 5.6	17.5 ± 6.4	18.1 ± 5.6
Balanced salt solution use (mL)	12.3 ± 17.6	78.4 ± 19.8	82.3 ± 23.9*	81.5 ± 30.7	84.5 ± 21.5	127.4 ± 72.1	79.0 ± 11.2	80.5 ± 16.8	112.1 ± 39.7

CDE, cumulative dissipated energy; NO1, nuclear opacity; UST, ultrasound time
*P<.05

Central Corneal Thickness

Although there was less change in the CCT in all cataract density groups with the divide-and-conquer technique than with the divide-and-conquer and step-and-chop techniques 2 months postoperatively, the difference was not statistically significant (Figure 1).

Central Endothelial Cell Loss

Two months postoperatively, the mean percentage of endothelial cell loss was significantly lower with the phaco-chop technique (5.2% ± 0.6%, mean ECC, 2560.8 ± 236.4 cells/mm^2 preoperatively and 2427.6 ± 212.7 cells/mm^2 postoperatively) than with the divide-and-conquer technique (9.1% ± 1.3%; mean ECC, 2633.7 ± 303.6 cells/mm^2 preoperatively and 2394.0 ± 245.7 cells/mm^2 postoperatively) and the step-and-chop technique (7.25 ± 1.0%, mean ECC, 2680.3 ± 267.5 cells/mm^2 preoperatively and 2455.5 ± 258.5 cells/mm^2 postoperatively) in the NO4 group ($P < .05$). Although the percentage of endothelial cell loss was lower with the phaco-chop technique than with the divide-and-conquer and step-and-chop techniques in the NO2 and NO3 groups, the difference was not significant (Figure 2).

Corrected Distance Visual Acuity

There was an equal and significant increase in log-MAR CDVA with the 3 phaco techniques from preoperatively to 2 months postoperatively in the NO2, NO3, and NO4 groups (Table 3).

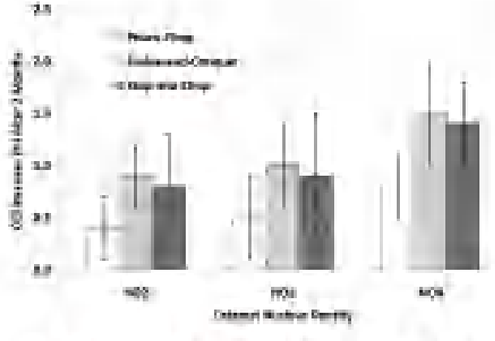

Figure 1. Intraoperative changes in CCT by technique and cataract density (* = Tukey HSD and Duncan tests).

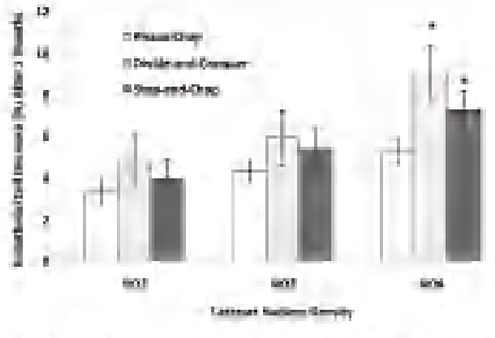

Figure 2. Postoperative endothelial cell loss by technique and cataract density (* = Tukey HSD and Duncan tests).

Table 4. Preoperative and postoperative ECD/VA (Group A and Group B).

	Mean ECD/VA ± SD								
	Phaco-Chop Technique			Divide-and-Conquer Technique			Stop-and-Chop Technique		
Item	Pre-op	1 wk	1 mo	Pre-op	1 wk	1 mo	Pre-op	1 wk	1 mo
Group A	0.04 ± .01	0.07 ± 0.05	0.07 ± 0.04	0.04 ± 0.01	0.09 ± 0.04	0.08 ± 0.04	0.04 ± 0.01	0.08 ± 0.04	0.08 ± 0.04
Group B	0.05 ± .01	0.08 ± 0.04	0.08 ± 0.04	0.05 ± 0.01	0.11 ± 0.05	0.11 ± 0.05	0.05 ± 0.01	0.09 ± 0.05	0.09 ± 0.05
Total group	0.05 ± .01	0.08 ± 0.05	0.08 ± 0.04	0.05 ± 0.01	0.10 ± 0.04	0.10 ± 0.04	0.05 ± 0.01	0.09 ± 0.04	0.08 ± 0.04
Low group	0.04 ± .01	0.06 ± 0.03	0.06 ± 0.03	0.04 ± 0.01	0.08 ± 0.03	0.08 ± 0.03	0.04 ± 0.01	0.07 ± 0.03	0.07 ± 0.03
High group	0.06 ± .01	0.09 ± 0.05	0.09 ± 0.05	0.06 ± 0.01	0.12 ± 0.05	0.12 ± 0.05	0.06 ± 0.01	0.10 ± 0.05	0.10 ± 0.05
P value*	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05

ECD = corneal endothelial cell density; VA = visual acuity.
*Comparison between cataract severity groups (High vs Low) in each technique.

DISCUSSION

Corneal endothelial damage during phacoemulsification can be caused by irregular flow, turbulence and movement of fluids, presence of air bubbles and free-radical release, and direct trauma caused by the instruments or lens fragments.[1] Moreover, the use of longer phacoemulsification time and greater power is believed to cause direct endothelial cell damage.[1] More sophisticated instruments, better OVDs, and improvements in IOLs and surgical techniques have decreased iatrogenic trauma.[1]

The divide-and-conquer technique was introduced to crack the nucleus and facilitate phacoemulsification.[2] This technique requires additional phaco energy for sculpting to divide the nucleus before the fragments are emulsified.[10] Therefore, different nucleus chopping techniques were introduced to further decrease postoperative complications.

Nagahara introduced the phaco-chop concept in 1993.[10] The phaco-chop technique can reduce phaco time and power because manual chopping is used to divide the nucleus into manageable fragments and the only significant use of phaco energy is during trapping emulsification.[7]

The stop-and-chop technique introduced by Koch and Kezirian[11] begins by creating a central groove that provides space and facilitates separation of the posterior plate. After this, the cracking procedure is stopped and chopping in the nonaligned parts begins.[12] The creation of a central groove using US energy at the beginning of the procedure is the important difference between the phaco-chop technique and the stop-and-chop technique.[12]

Several studies have compared various chopping techniques with standard-incision phacoemulsification. Wang et al.[13] used a Legacy system (Alcon) and found a mean phacoemulsification time of 1.2 minutes for the phaco-chop technique and 2.4 minutes for the divide-and-conquer technique. Unlike the divide-and-conquer technique, the phaco-chop technique does not require nuclear sculpting. In addition, the phaco-chop technique tends to direct the US away from the cornea, yet the phaco tip is farther from the posterior capsule than in divide-and-conquer technique.[10] This, combined with less zonular stress, may be particularly important when patients have a potential for weak zonular fibers and low endothelial cell counts.[10] This, combined with less rotational manipulation of the nucleus, creates less zonular stress and reduces cephalocaudal movement of the phaco tip through a tight section, which may decrease the risk for Descemet membrane detachment. Therefore, it would be expected that the phaco-chop technique would produce fewer ocular complications than the divide-and-conquer and stop-and-chop techniques.[11]

Park et al.[5] found that in cataracts with moderate nuclear density, the phaco-chop technique and stop-and-chop technique are equally efficacious in cracking the nucleus. However, the US energy consumption was lower (shorter phacoemulsification time and lower phacoemulsification power) with the phaco-chop technique than with the stop-and-chop technique in denser cataracts and the resulting endothelial loss was similar with both techniques. Can et al.[7] found that the mean phacoemulsification time was shorter and the phacoemulsification power was lower with the phaco-chop technique than with the stop-and-chop technique. The mean times to achieve maximum vision and to return to preoperatively corneal thickness were also shorter with the phaco-chop technique.

In this study, we compared the phaco-chop technique and divide-and-conquer technique in MICS according to cataract density. We found that the stop-and-chop and divide-and-conquer techniques required a longer phacoemulsification time, higher phacoemulsification power, and more balanced salt solution than the phaco-chop technique in hard cataracts ($P < .05$). We found no significant difference in perioperative parameters such as CDVA and ECL between the 3 phacoemulsification techniques with all nuclear opacities; however, the percentage of corneal endothelial cell loss was lower with the phaco-chop technique than with the stop-and-chop and divide-and-conquer techniques in eyes with hard cataract ($P < .05$). However, other studies found no statistically significant difference in endothelial cell loss between the phaco-chop and stop-and-chop techniques[11] and or between the phaco-chop and divide-and-conquer technique in standard-incision cataract surgery.[14]

Endothelial cell damage after MICS and standard-incision cataract surgery has been evaluated, and incision size was not found to be a direct factor influencing endothelial cell loss.[15] Phaco time, US energy, mechanical trauma by instruments, corneal manipulation, fluid turbulence, and aberrant phacoemulsification have been reported as being the main factors in endothelial cell damage.[15]

In contrast, Park et al.[5] found that the ECC loss at 6 months was significantly higher in the stop-and-chop incision group than in the standard-incision group ($P = .049$). Mahdy et al.[7] also found statistically significant endothelial cell loss with microcoaxial phacoemulsification, especially with increased nuclear hardness. With increasing cataract density, there was a need for more time and increased amounts of balanced salt solution to remove the lens. This was associated with fluid turbulence in the anterior chamber and consequently more endothelial cell loss.[7]

It is thought that corneal endothelial cells are more susceptible to damage with MICS than with standard-incision phacoemulsification, especially in eyes with hard cataract. We hypothesize that the phaco-chop technique may decrease the damage to corneal endothelial cells more than the stop-and-chop and divide-and-conquer techniques, especially in microcoaxial phacoemulsification for hard cataract.

To our knowledge, this is the first study comparing 3 phacoemulsification techniques using MICS. We found that the stop-and-chop and divide-and-conquer techniques were as safe as the phaco-chop technique in MICS in eyes with mild to moderate cataract. However, for hard cataract, the phaco-chop technique can decrease intraoperative parameters and postoperative ECC loss more than the stop-and-chop and divide-and-conquer techniques.

The limitation of this study is that the results are short term. A long-term study is needed.

WHAT WAS KNOWN

- In standard-incision cataract surgery, there is no statistically significant change in endothelial cell loss between the phaco-chop and stop-and-chop techniques or between the phaco-chop and divide-and-conquer techniques.

WHAT THIS PAPER ADDS

- In coaxial MICS, the phaco-chop technique can decrease intraoperative parameters compared with the stop-and-chop and divide-and-conquer techniques in hard cataracts using coaxial MICS.
- In coaxial MICS, the phaco-chop technique can decrease postoperative corneal endothelial cell loss compared with the stop-and-chop and divide-and-conquer techniques in hard cataracts.

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CLINICAL SCIENCES

Lash Ptosis in Congenital and Acquired Blepharoptosis

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Objective: To determine the prevalence of lash ptosis (LP) in eyes with congenital and acquired blepharoptosis.

Methods: We retrospectively graded photographs of 326 eyes from 174 patients with congenital or acquired blepharoptosis for LP. We used a 4-point rating scale for LP, in which 0 indicates no LP, 1, minimal; 2, moderate; and 3, severe. A prospective evaluation of LP in 30 eyes from 15 patients without blepharoptosis (control eyes) was also performed.

Results: A total of 107 eyes (80.87 patients) demonstrated congenital blepharoptosis and 131 eyes (80.87 patients) had acquired blepharoptosis. A moderate to severe rating of LP (rating ≥ 2) occurred in 40.7% of eyes with congenital blepharoptosis, 28.9% of eyes with acquired blepharoptosis, and 6.7% of control eyes. Lash ptosis (rating ≥ 1) was present in 93.6% of eyes with congenital blepharoptosis, 85.5% of eyes with acquired blepharoptosis, and 33.3% of control eyes. The mean LP rating was 2.1 for eyes with congenital blepharoptosis, 1.5 for eyes with acquired blepharoptosis, and 0.6 for control eyes.

Conclusions: Lash ptosis was common in the patients with blepharoptosis. Moderate to severe LP occurred more commonly in all forms of blepharoptosis compared with normal eyes, with more frequent and more severe LP demonstrated in eyes with congenital blepharoptosis.

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Lash ptosis (LP) has received minimal attention in the ophthalmic literature and is often an overlooked sign that may coexist with congenital and acquired blepharoptosis. Also known as eyelash ptosis, this term refers to a global displacement of lash follicles of the upper eyelid (**Figure 1** and **Figure 2**).[1,2] Although LP is a well-recognized feature of floppy eyelid syndrome (FES), its significance in congenital and acquired blepharoptosis is underappreciated.[3] To our knowledge, the prevalence of LP in patients with blepharoptosis has not been reported.

Lash ptosis has been associated with FES, congenital lamellar ichthyosis, long-standing ocular leprosy, bilateral acoustic neuromas, and latanoprost-induced LP.[3–5] Colburn and Ostler[6] noted that LP is almost universally present in FES. Guimaraes and Cruz[7] found LP in 48 of 74 patients with long-standing ocular leprosy (65%). Others[3,4] have noted single cases of LP in congenital lamellar ichthyosis[4] and ocular latanoprost use. Mastropasqua et al[5] studied 62 patients with facial palsy and found that 26 had LP as a long-term consequence (42%).

Hypotheses on the etiology of LP are largely based on anatomical changes within the upper eyelid. The eyelid margin is separated by the gray line into the anterior lamella (muscle lamella) and a posterior tarsoconjunctival layer. The eyelash follicles of the upper eyelid lie in a space between the Riolan muscle and the pretarsal orbicularis muscle.[8] The eyelash follicles may extend posteriorly to embed in the tarsus.[9,10] The eyelashes emerge through the septum and exit through the eyelid margin. The normal position of the eyelashes projects downward initially with a curvilinear superior and anterior projection away from the globe (Figure 2A and B).[11]

To our knowledge, the presence of LP in congenital or acquired blepharoptosis has not been studied systematically. A simple, semiquantitative grading scale to categorize LP by severity would aid in identification of eyes with LP and those that may benefit from surgical correction at the time of blepharoptosis repair and those that may be observed. In addition, a more thorough understanding of the factors involved in the etiology of LP is a prerequisite to proper correction at the time of surgery. We conducted a comparative observational study in which the prevalence and severity of LP in individuals with congenital and acquired blepharoptosis were compared with the prevalence and severity of LP in normal control subjects.

METHODS

After obtaining institutional review board approval, patients diagnosed as having congenital or acquired blepharoptosis between [illegible]

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Figure 1. Lid position rating (LPR) scale (reproduced with permission from the Department of Ophthalmology, University of Minnesota). An LPR of 0 indicates no lid ptosis; 1, minimal; 2, moderate; and 3, significant.

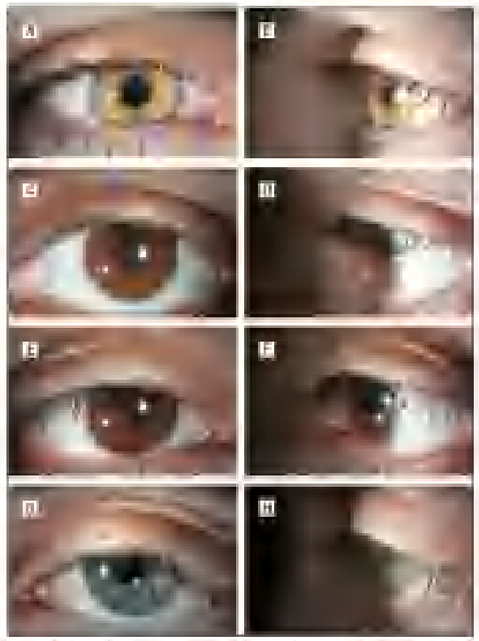

Figure 2. Clinical photographs illustrating variations in the congenital blepharoptosis phenotype. A and B, Right photographs of a 5-year-old girl showing bilateral severe congenital blepharoptosis (LPR, 3) and bilateral epicanthal folds. C and D, Moderate blepharoptosis (LPR, 2). E and F, Mild blepharoptosis (LPR, 1). G and H, Significant blepharoptosis (LPR, 3) with ptosis of the left eyebrow.

as having an LPR of 1. An LPR of 2 characterized eyelashes at the visual pupillary margin (1.5–3.0 mm) below the horizontal meridian. Eyelashes covered at more than 3 mm below the horizontal meridian characterized an LPR of 3. These standard evaluations (A.E.H., K.J.M., and M.M.E.) progressively determined the degree of LPR of each eye in primary gaze. The LPRs were averaged. Any discrepancy in the rating by greater than 1 was adjudicated. Grading consistency and quality assurance (90%–95% agreement) were confirmed by intragrader and intergrader testing based on a random sample of photographs.

RESULTS

The congenital blepharoptosis group consisted of 50 males and 57 females with a mean (SD) age of 19.4 (15.1) years. The acquired blepharoptosis group consisted of 50 males and 37 females with a mean (SD) age of 50.7 (19.8) years. There were 107 eyes with congenital blepharoptosis, 131 eyes with acquired blepharoptosis, and 30 normal eyes (control group). The congenital blepharoptosis group included patients with levator dehiscence (64 patients), dermatochalasis (30), unspecified ptosis (5), thyroid eye disease (3), myasthenia (3), third nerve palsy (1), chronic progressive external ophthalmoplegia (1), globe/orbit (1), and traumatic blepharoptosis (1); and 3 patients with acquired blepharoptosis due to extraocular myopathy.

The mean (SD) LPRs were 2.1 (0.8) (95% confidence interval [CI], 1.9–2.2) in eyes with congenital blepharoptosis, 1.3 (0.8) (95% CI, 1.2–1.6) in eyes with acquired blepharoptosis, and 0.6 (0.2) (95% CI, 0.4–0.7) in control eyes. For comparison, the LPRs of 67 fellow eyes with unilateral congenital blepharoptosis and 33 with unilateral acquired blepharoptosis were evaluated, and the results did not differ significantly from those of control eyes (mean LPR, 0.6 for both).

Each ptosis with a declination below the horizontal plane (LPR, ≥1) was noted in 98 of the 107 eyes with congenital blepharoptosis (91.6%), 101 of the 131 eyes with acquired blepharoptosis (83.3%), and 18 of the 30 control eyes (33.3%). A moderate to severe degree of LP (LPR, ≥2) was observed in 65 of the eyes with congenital blepharoptosis (60.7%), 32 of the eyes with acquired blepharoptosis (26.9%), and 3 (unilateral eyes) (9.7%). No LP (LPR, <1) was observed in 9 eyes with congenital blepharoptosis (8.4%), 30 eyes with acquired blepharoptosis (16.9%), and 20 control eyes (66.7%).

COMMENT

Although LP has been described in association with several conditions, no objective method of grading LP does not exist, to our knowledge. In their analysis of eyelid changes in long-standing ocular ptosis, Guinandeau and Cruz[2] proposed variations of LP. A dichotomous classification was described first (ie, that distinguished LP according to normal much from variations of LP were present), but the authors did not use a scale or rating system. In our study, a simple 4-point grading scale was used to rate the severity of LP. The measurement of angular displacement of the anterior projection of primary gaze determines the LPR (Figure 1).

Three methods of evaluation were provided on equal number of photographs of the eyes of patients with acquired blepharoptosis and congenital blepharoptosis. The investigator (A.E.H.) initially graded the photographs as having mild LP, moderate LP, or severe LP. Comparison of this grading with the LPR revealed that the investigator's grading was consistent with the LPR in 95% of the cases. Second, the photographs were randomly presented to 3 oculoplastic surgeons (K.J.M., M.M.E., and M.M.E.) who were asked to grade the degree of LP. Comparison of this grading with the LPR revealed that the surgeons' grading was consistent with the LPR in 90% of the cases. Third, the photographs were randomly presented to 3 oculoplastic surgeons (K.J.M., M.M.E., and M.M.E.) who were asked to grade the degree of LP. Comparison of this grading with the LPR revealed that the surgeons' grading was consistent with the LPR in 90% of the cases.

blepharoptosis and congenital blepharoptosis. The mean LPR in each group demonstrated a higher prevalence (81%) in all forms of blepharoptosis relative to controls. Eyes with congenital blepharoptosis demonstrated a higher LPR and a greater percentage of moderate to severe LP than did eyes with acquired blepharoptosis. Moderate to severe LP (LPR, ≥2) was more likely to occur in eyes with congenital blepharoptosis (61.7%) than in eyes with acquired blepharoptosis (26.9%). The LPR varied by unilateral versus bilateral congenital blepharoptosis, with a relatively equal frequency across all LPRs. The number of eyes per patient with blepharoptosis were not small to correlate with LPR.

Clinical observations included assessment of LP in the superior bulbar eyes of patients with unilateral congenital or acquired blepharoptosis. Within this subset of eyes, the LPR was similar to that in the control group. The average LPR for both patient groups was 0.6, and we found no significant difference between the groups. Among fellow eyes, severe LP occurred in 0.2% of eyes (1 of 1269), moderate LP in 37.4% (53 of 130); and minimal to no LP in 62.3% (76 of 130). This suggests that LP innocently occurs in eyes with unilateral blepharoptosis.

Lash ptosis has been found in association with several conditions. Review of these cases offers clues to the etiologies of LP. Langford and Lindsey[3] suggest that LP may result from anatomical changes in the orbicularis oculi, Müller muscle, and tarsal plate. Nelson and Hoyt[4] demonstrated a deficiency of elastin in the tarsus and conjunctival collagen in FPS. Deficiency of elastin plays a role in eyelid laxity and similarly may contribute to a deficiency of eyelash support.[5] Mullaney et al[6] studied patients with facial palsy and found that 42% of them had LP as a long-term consequence. One of the proposed antagonists and the lateral muscle may compromise support to these muscle insertions and eyelash follicles. Eyelash skin laxity, as in dermatochalasis, could also alter the underlying eyelid muscle tension. Furthermore, LP has been reported in association with inflammatory conditions in which progressively large eyelashes may contribute the ability of the upper eyelashes to maintain proper projection of the lid lashes. Similar changes in eyelid tension may explain LP in congenital blepharoptosis. Changes in the levator may alter the direction of eyelashes through the fact lid lashes curled posteriorly within the sulcus. Terminal lashes of the levator aponeurosis—that were thought the eyelashes arise as a result from the subcutaneous tissue and skin. Disruption of these fibers in congenital ptosis leads to a lack of an eyelid crease and prolapse of a lack of eyelash support.[7] The close proximity of the aponeurosis and orbicularis suggests that loss of these aponeurotic fibers near the eyelid margin may mechanically cause laxity of the overlying eyelashes and muscle. Newer perspectives LP lash ptosis in congenital and acquired blepharoptosis may stem from a basis of anatomic lamellar abnormalities and an underlying connective tissue dysmorphism.

Surgery for LP requires attention to the primary underlying anatomic process as well as to the degree of LP. Surgical tightening procedures in the form of tarsal strip procedures would not be effective in correcting LP. Conservative management of LP has been effectively corrected with anterior lamellar reposition surgery.[8] Current standard care recommends that anterior lamellar surgery (ie, the correct dissection of the posterior orbicularis and creation of the muscle–skin layer to the levator aponeurosis. The authors have had success with double-armed 6-0 Prolene sutures placed in a horizontal mattress fashion through the orbicularis near the anterior eyelash line and secured to the superior edge of the tarsus or near the eyelashes. Multiple such sutures should be placed because the effect of each suture is limited to an immediately surrounding area.

A preoperative observation for the presence of LP in the patient in primary gaze. Evaluation with the chin parallel to the ground allows for the most accurate assessment of the eyelids and eyelashes in relation to normal anatomy. For the evaluation of LP, it is helpful to examine the patient in primary gaze from frontal and lateral perspectives.

In summary, the prevalence of LP has been underreported and is frequently seen in congenital and acquired blepharoptosis. Eyes with congenital blepharoptosis often demonstrate moderate to severe LP. The presence of severe LP in eyes treated with blepharoptosis surgical correction may be underrated in current literature.

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Overview of CHARGE syndrome and reported lacrimal drainage anomalies

No	Author	Case	CHD findings	Management/Observations
1	[redacted]	1 case/adult	CHD/Del 8q24 Asymptomatic ASD/mild pulm HTN VSD/AP septum AVSD/pulmonary overflow	CHD/TOF - palliative ventricular Normal or typical LDS
2	[redacted]	1 case/adult	CHD/Mitral regurg VSD/Atrial septal defect	Cyanosis in infancy Patent LDS B/L (Crocker sign/probing)
3	[redacted]	12 cases/female	Parental agenesis of ears	Not available
4	[redacted]	4 cases	Conotruncal abnormalities	Not available
5	[redacted]	3 cases/adult	CHD/Pulmonary HTN/cyanosis CHARGE	CHD resolved/DCR x10 B/L patent

CHD, [redacted]

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A Report of Intracranial Meningioma Recurring as Eclopic Orbital Meningioma Associated With Basal Encephalocele

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Abstract: The authors describe a rare case of recurrent ectopic meningioma associated with sphenoid encephalocele in the medial anterior orbit of a 52-year-old man with a history of 4 resected intracranial meningiomas. Typical features of ectopic meningiomas are reviewed as well as potential etiologies of this very rare occurrence of intracranial meningioma in the orbit. Treatment is typically surgical excision.

[redacted] includes the tonic from dichromatic cells [redacted] are the most common intracranial [redacted] by the orbit. Orbital meningio- [redacted] encapsulated cells of the optic nerve [redacted] extension of intracranial meningiomas [redacted]. Rarely, they arise de novo in the orbit [redacted] The authors describe a rare [redacted] initial intracranial surgery presented [redacted] This report addresses the clinical [redacted] Discussion of clinical as intracranial [redacted] Health Awareness Modality and [redacted] and patient outcome assessment.

PRESENTATION

A 52-year-old man was referred for evaluation of mass in the right medial canthus. He had a history of a fully resected large right frontal falx meningioma (World Health Organization grade I) 10 years prior with associated vision loss in the OD. He was asymptomatic in current presentation, without headaches, focal neurologic deficits, or seizure activity.

His examination revealed visual acuity of 20/30 in the right and 20/20 in the left. The pupils were round and reactive to light without afferent pupillary defect. Extraocular motility was full in all gazes. Confrontation visual fields were full to finger counting in all quadrants. Intraocular pressures were 14 mm Hg OU. Slit-lamp examination revealed mild bilateral nuclear sclerosis. Dilated fundus examination revealed a cup-to-disc ratio of 0.3 OU. There was a pink, fleshy, lobulated mass in the right medial canthus with a smooth overlying conjunctiva (Fig. 1). There was no proptosis, globe displacement, or restriction of motility. Hertel exophthalmometry measurements were 16 mm OD and 15 mm OS. The remainder of the ocular examination was unremarkable.

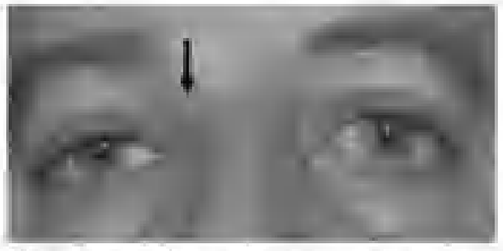

FIG. 1. External photo showing right medial canthal mass below the right eyebrow (arrow).

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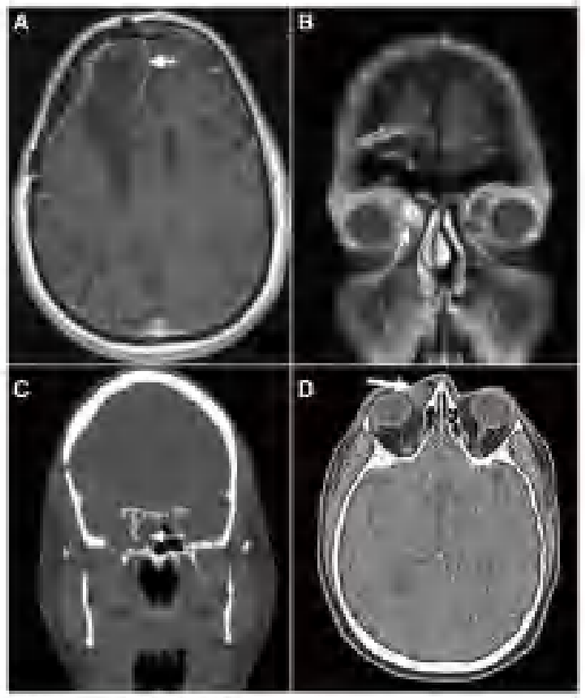

FIG. 2. MRI and CT of the brain and orbit. **A**, Axial T1 TSE MRI image showing the post-resection cavity in the right frontal lobe with associated ex vacuo dilatation of the anterior horn of the right lateral ventricle (arrow). **B**, Axial T1 TSI, MR image the lenticular aspect of the right medial canthus just below the right frontal sinus (arrow). **C**, Coronal CT image showing the defect in the lateral wall of the right sphenoid sinus (arrow). **D**, Axial CT image of soft tissue within soft along the medial canthus of OD (arrow). TSE, turbo spin echo.

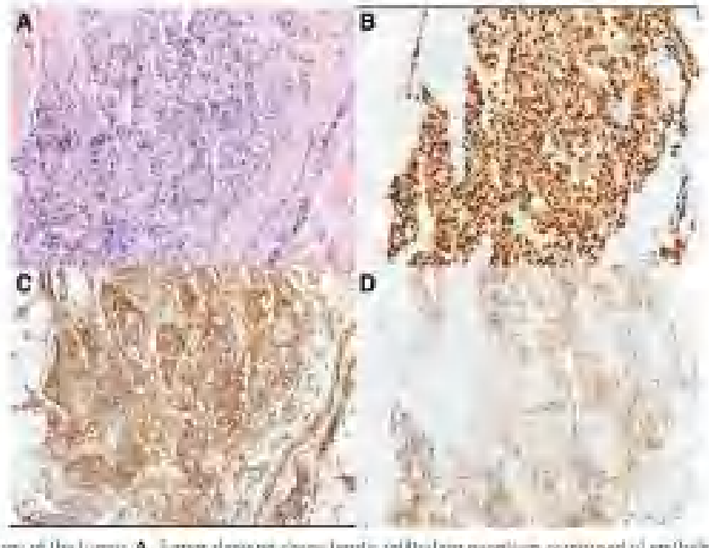

FIG. 3. Histopathology of the tumor. **A**, Tumor showing characteristic infiltrating neoplasm composed of epithelioid cells in nests with whorling and fibrous bands consistent with meningioma (hematoxylin-eosin, original magnification ×100). **B–D**, Immunostains show that the tumor cells are diffusely and strongly positive for (**B**) progesterone (original magnification ×100), (**C**) vimentin (original magnification ×100), and (**D**) epithelial membrane antigen (EMA) (original magnification ×100).

right ethmoid papillary lesion. The first MR scan was also consistent with an ethmoid mucocele. His external examination was notable for a 2-mm mass below the medial brow without associated ptosis (Fig. 1A). His left and right dilated fundus examinations were notable for 2+ optic atrophy in the right and 1+ optic atrophy in the left, which was unchanged from prior examinations.

On MRI, there was thickening of the upper aspect of the right medial rectus just below the optic nerve that was also enhanced with gadolinium (Fig. 2). He also had a small polypoid lesion in the following coronal and sagittal images just to the right of midline measuring approximately 5 × 4 × 7 mm with heterogeneous enhancement extending into the ethmoid sinus. There was also mucosal thickening and enhancement of the right inferior medial rectus (Fig. 2). The lesion was T2 hyperintense and T1 isointense to gray matter. There was also a thin rim of enhancement surrounding the lesion, which was consistent with inflammation. There was no evidence of bony destruction. The right optic nerve was normal in appearance. There was no evidence of orbital cellulitis or abscess. There was no evidence of intracranial extension. There was no evidence of cavernous sinus involvement. There was no evidence of optic neuritis. There was no evidence of demyelinating disease. There was no evidence of vascular malformation. There was no evidence of neoplasm. There was no evidence of infection. There was no evidence of trauma. There was no evidence of foreign body. There was no evidence of inflammatory disease. There was no evidence of autoimmune disease. There was no evidence of systemic disease. There was no evidence of metastatic disease. There was no evidence of primary tumor. There was no evidence of secondary tumor. There was no evidence of lymphoma. There was no evidence of leukemia. There was no evidence of sarcoidosis. There was no evidence of tuberculosis. There was no evidence of syphilis. There was no evidence of fungal infection. There was no evidence of parasitic infection. There was no evidence of viral infection. There was no evidence of bacterial infection. There was no evidence of mycobacterial infection. There was no evidence of actinomycosis. There was no evidence of nocardiosis. There was no evidence of cryptococcosis. There was no evidence of histoplasmosis. There was no evidence of coccidioidomycosis. There was no evidence of blastomycosis. There was no evidence of aspergillosis. There was no evidence of mucormycosis. There was no evidence of candidiasis. There was no evidence of cryptococcosis. There was no evidence of histoplasmosis. There was no evidence of coccidioidomycosis. There was no evidence of blastomycosis. There was no evidence of aspergillosis. There was no evidence of mucormycosis. There was no evidence of candidiasis.

DISCUSSION

Meningiomas are common intracranial tumors, accounting for 13.4% of all primary intracranial and central nervous system tumors. They most commonly arise from the meningothelial cells of the arachnoid villi. The etiology of these tumors is unknown. Risk factors include exposure to ionizing radiation, female hormones, and head trauma. Meningiomas can also arise from ectopic meningothelial cells in the orbit, nasal cavity, paranasal sinuses, and skin. Ectopic meningiomas should be considered in the differential diagnosis of a mass in these locations, especially in the absence of a dural tail or bony hyperostosis.

The prognosis of these tumors depends on the location and histologic subtype. Recurrence rates range from 7% to 20% for benign tumors. Recurrence rates are higher for atypical and anaplastic tumors. Surgical resection is the mainstay of treatment. Complete resection is often difficult because of the tumor's location and its relationship to surrounding structures. Incomplete resection is associated with a higher recurrence rate. Radiation therapy is used as an adjunct to surgery in cases of incomplete resection, recurrence, or malignant histology. Stereotactic radiosurgery is also an option for small, well-circumscribed tumors.

In summary, this case describes an atypical presentation of a rare but commonly encountered tumor. Although meningiomas are typically found in the cranial cavity, they can also arise from ectopic meningothelial cells in the orbit, nasal cavity, paranasal sinuses, and skin. Ectopic meningiomas should be considered in the differential diagnosis of a mass in these locations, especially in the absence of a dural tail or bony hyperostosis. Complete surgical resection is the mainstay of treatment. Radiation therapy is used as an adjunct to surgery in cases of incomplete resection, recurrence, or malignant histology. Stereotactic radiosurgery is also an option for small, well-circumscribed tumors.

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Corneal Laceration Associated With Upper Eyelid Blepharoplasty

Fawaad A. Qazi, MD, Eric Q. Pan, MD, Vishi Bhavsar, MD, and Randy H. Lee, MD

Abstract: A 64-year-old woman underwent bilateral upper eyelid blepharoplasty and subsequently presented with decreased vision at her first postoperative visit 1 week later.

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A Unique Ocular Presentation of Extragenital Lichen Sclerosus

Phyllis W. Rubin, MD, Amanda C. Myers, MD, Jo Montemarano, MD, and Andrew P. Harmon, MD

Abstract: **Lichen sclerosus is a chronic, debilitating, and recurring disease that is most commonly seen affecting the anogenital region. Extragenital locations of lichen sclerosus has been well documented, however, cases in the shoulders, neck, trunk, breasts, and arms, however, infrequently in the face. Specifically, extragenital lichen sclerosus has been reported in several cases to be involving the infraorbital region, but to our knowledge it has never been found affecting the eyelid of the eye. To our understanding, this is the first documented report of a patient with extragenital lichen sclerosus of an eyelid.**

Lichen sclerosus, also known as lichen sclerosus et atrophicus, is an inflammatory disease of unknown etiology. It can affect people of multiple ages in origin. Described first in 1887, lichen sclerosus is a chronic, relapsing disease that most frequently affects the anogenital region. It is a debilitating disease that can cause significant discomfort, functional impairment, and psychological distress. While it is most commonly seen in women of the postmenopausal age group, it can also be found in prepubertal females. Specifically, it is known as lichen sclerosus et atrophicus, when it has been localized to the extragenital regions, but never to the eyelid skin. To the best of our knowledge, the patient described in the case of extragenital lichen sclerosus located on the upper eyelid. The collection and evaluation of protected patient health information was HIPAA compliant.

CASE REPORT

A 76-year-old man presented for evaluation of a recurrent, erythematous lesion on his right upper eyelid. He also had a history of cutaneous basal cell carcinoma, which had been debulked and reconstructed through a right upper eyelid crease incision 5 years before. She developed the lesion shortly following this procedure. The lesion had been present multiple times by the same surgeon, but continued to recur.

The examination there was a 10-mm by 10-mm well-circumscribed plaque that had formed upper eyelid cutaneous incision with suture. The differential diagnosis included recurrent basal cell carcinoma, squamous cell carcinoma, dermal lipid, and cutaneous T-cell lymphoma. Given the previous by dermatology physician specialist in melanoma, the patient opened his lower lids entirely with wide margins. All skin margins were negative for lesion tumor involvement, and deep margins were consistent with scar. The lesion was reconstructed with a full thickness skin graft from the contralateral eyelid.

At the postoperative visit, when the sutures were removed, pathology results with scar, she continued with the full lichen sclerosus affecting her periocular for years.

HISTOPATHOLOGY

Histopathology of the right upper eyelid lesion (Fig. 1) revealed prominent hyperkeratosis, follicular plugging, and dermal fibrosis consistent with lichen sclerosus. There was also evidence of a mild to moderate chronic inflammatory infiltrate in the dermis. The epidermis was unremarkable. There was no evidence of malignancy.

DISCUSSION

Lichen sclerosus is a chronic, inflammatory disease that can occur in all age groups. It is most commonly seen in women in the postmenopausal age group, with a peak incidence between the ages of 50 and 60 years. The exact cause of lichen sclerosus is unknown, but it is thought to be an autoimmune disease. Genetic predisposition, hormonal factors, and environmental factors may also play a role in its development. Lichen sclerosus can affect any part of the body, but it most commonly affects the anogenital region. It can also affect the extragenital regions, such as the face, neck, trunk, breasts, and arms. It can also affect the eyelids, as in this case.

FIG. 1 Nonhealing right upper eyelid lesion.

[illegible]

FIG. 2 Histopathology of right upper eyelid lesion. H&E stain.

[illegible]

REFERENCES

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Immunosuppressant-Related Lower Eyelid Edema in Transplant Patients

[illegible]

Abstract: Solid organ transplantation is the preferred method of treatment for a number of advanced medical conditions, but it requires systemic immunosuppression to prevent transplant rejection. The authors report 2 unique cases of persistent eyelid edema following solid organ transplantation believed to be related to their systemic immunosuppression. The eyelid findings developed after initiation of the immunosuppressant sirolimus. In 1 patient, the eyelid edema has persisted despite discontinuation of the medication. In the second patient, the immunosuppression could not be altered; therefore, he underwent surgical excision of the edematous lower eyelid. Sirolimus-associated eyelid edema is an important medication side effect for ophthalmic and eyelid specialists to consider when a patient with a history of organ transplantation presents with localized noninflamed eyelid edema. This edema can persist despite discontinuation of the medication. Surgical excision of the edematous eyelid can achieve good results.

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CASE 1

[illegible]

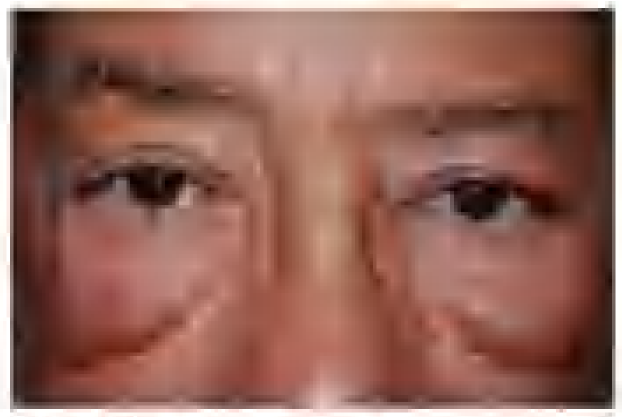

FIG. 1. [illegible]

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Novel Stent for Dacryocystorhinostomy (DCR) and Other Surgical Applications

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Introduction

Dacryocystorhinostomy (DCR) is an operation for the creation of a functional tear obstruction. Applicable to any procedure used to approximate a tear duct to the nasal cavity, the location of the bone of the nasal septum, the common anatomical site of tear duct obstruction, is an ideal location for the creation of a new passage for tears. The first successful external DCR technique was described by Dupuy-Dutemps and Bourguet [1,2]. In 1904, Mullerought and Mosher [3] described the endoscopic or intranasal DCR, and this procedure was described using contemporary [ENT] equipment, certain threads, and KTP/532 [4,5]. An endonasal approach using the neodymium:YAG laser has also been described [6].

Many techniques advocate the use of a silicone stent to keep the newly created tissues open during the healing phase. This is placed in a way to be either in the canaliculi, through the common canaliculus and lacrimal sac, the wall of which is then sutured together in the middle, or into the nose [2,3,7]. The stent is left in situ from 2 months to several years. Despite the use of conventional techniques and have evidence for DCR employing laser as opposed to [5–8]. [9] and [7–9] respectively. These techniques, however, have varying success rates. Failure of DCR has been associated with scarring between the sites of creation of ostomy and internal incision. Furthermore, failure to find or find the duct or to place stent may be responsible for some of the failures [10]. Failure to create a sufficiently large opening between the lacrimal sac and the nasal cavity has also been implicated in the failure of DCR. Additionally, there is a high incidence of granuloma formation around the stent [11]. Because of the inherent difficulties in DCR, this relatively common procedure is associated with a relatively high failure rate [12].

Irrespective of the approach, three issues are typical for these DCR techniques. The first is that the newly created passage is often blocked until the inflammation and edema of the surgery have subsided, typically a period of 3–6 months. The second is that the stent is left in place for a relatively long period of time. Third, the stent is usually placed in the nasal cavity with the assistance of an endoscope. Although the endoscope is a useful tool, it is not always available in the operating room. Also, the endoscope can be difficult to maneuver in the confines of the nasal cavity, especially in the presence of bleeding.

The purpose of this paper is to describe a new stent and delivery system that is designed to address the issues mentioned above. The stent is designed to be placed in the osteotomy at the time of surgery and to remain in place for 3–6 months. The stent is designed to be easily placed and removed, and to have a low profile in the nasal cavity. The following is a description of the stent design and method for its use. The following is a description of the stent design and method for its use.

Device Description. A cylindrical semicompliant balloon is mounted on a [illegible] catheter surrounded by an expandable sleeve (Fig. 2). The stent is placed surgically when an osteotomy is created between the nasal cavity and the lacrimal sac. The stent is placed in the osteotomy so that its medial portion serves as a bridge between the nasal cavity and the lacrimal sac. Upon proper placement, the stent is inflated, lodging itself within the new surgical incision. The softness of the balloon conforms within the irregularities of the new passage. Like current stents, the new stent is designed to remain implanted for 3–6 months after surgery. The stent is removed by deflating the balloon via a nasal approach.

Stent Fabrication. The described stent is a two piece, single use/extreme product part. The typical mold design for the part is shown in Fig. 4. The mold is composed of two main components: (1) a constant cylindrical cavity insert that is open at both ends and (2) a multifeature insert mandrel. Together the two parts form the part cavity. After proper mixing and degassing, silicone is injected into the mold cavity with a syringe that is driven the plunger. The plunger is then left stationary into the cavity, preventing the liquid silicone from escaping the mold cavity. The plunger is then pulled with the cavity in the vertical position. After the injection curing period, the plunger and part are removed from the mold. Then the part is pulled away from the plunger.

The stent assembly process is summarized in Fig. 5. As shown, the molded part consists of two distinct segments, [illegible] and [illegible] which serves as a balloon. At the end of the balloon [illegible] was used to provide the fluid [illegible] ring). The body, balloon, and sleeve are [illegible] are all composed of silicone and are bonded together at regions of the sleeve ends. As shown, the balloon section is covered over the body section with the sleeve [illegible] and [illegible]

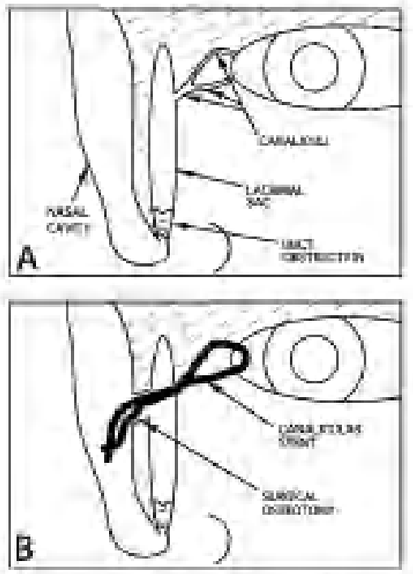

Fig. 1 Obstructed tear duct and illustration of surgical repair. In tear duct obstruction results in interruption of tear flow through the lacrimal system. (b) A new passage (osteotomy) is surgically formed approximately across from the common canaliculus. Tube like stents are threaded through the canaliculi, new osteotomy, and out of the nasal passage. Stent remains 3–6 months after surgery.

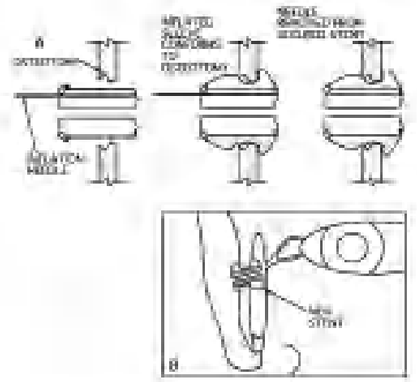

Fig. 3 Stent placement in the osteotomy. Stent is placed in the surgically formed osteotomy such that its medial portion serves as a bridge between the nasal cavity and tear sac. Upon proper placement, the stent is inflated, lodging itself within the new surgical incision. The softness of the balloon conforms within the irregularities of the new passage. Like current stents, the new stent is designed to remain implanted for 3 - 6 months after surgery. The stent is removed by deflating the balloon via a nasal approach.

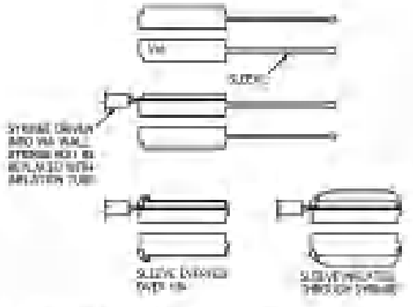

Fig. 2 Stent design and function (general). Image of the general design of new stent. The sleeve balloon is everted over the thicker via wall. A needle driven through the thick wall acts as an inflation tube for the balloon.

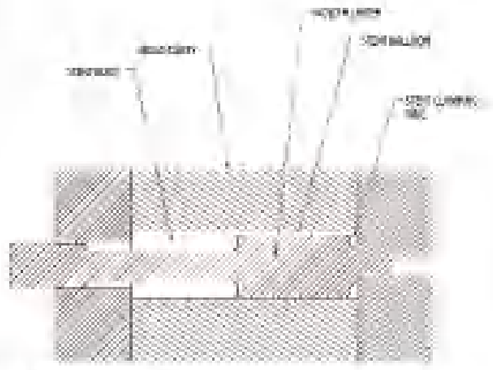

Fig. 4 Typical mold assembly for stent. Silicone is injected into mold body, then the plunger is driven in place as shown, forming the geometry of the stent. Body wall, plunger proportions, and geometry can be varied to change geometry and inflation profile of the final stent.

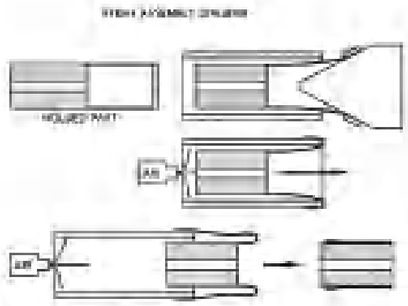

Fig. 5 Illustration of stent assembly process. As shown, the stent is inserted within an assembly tube after the clamping ring is stretched over a conical shoe. The ring is then inverted over the catheter wall at the assembly tube forming cavity. When compressed air is applied through the assembly tube, the balloon is partially inflated and the stent body is driven into the balloon.

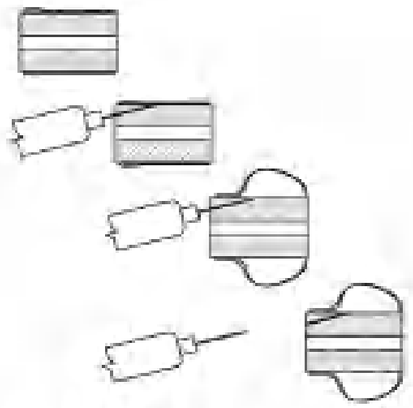

Fig. 6 Detail of stent inflation. A needle is driven into the stent body wall forming an inflation line to the surrounding balloon. Through use of a syringe (as shown) or other pumping device, saline is driven through the inflation line, expanding the balloon. After the balloon is inflated, the needle is removed. The inflation line seals in the needle's wake due to compressive hoop stresses resultant from the inflation pressure of the balloon.

Fig. 7 Assembled and inflated stents shown with a dime

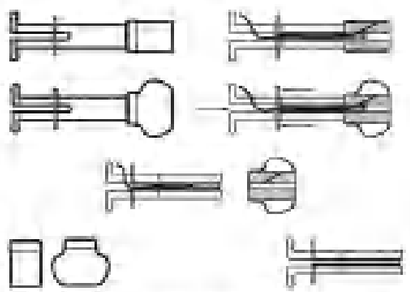

Fig. 8 Illustration of ductal stent with introducer. The inner segment of the introducer is driven into the inside diameter of the stent body while the outer segment rests against the stent's proximal end. As shown, the introducer accommodates an inflation line. The outer segment is scaled such that its outside diameter is the same as that of the stent. The introducer permits placement and inflation of the stent through the nose. The stent is released from the introducer by applying antagonistic finger force between the inner and outer segments, pulling the inner segment out of the stent body.

Upon placement of the stent by means of manual guidance at the introducer proximal end, the stent is inflated. After inflation, the inflation needle is removed by pulling it through the inner tube of the assembled introducer. Finally through the axially aligned motion between the inner and outer tubes the stent is dislodged from the introducer and deployed.

When the cognitive healing period is completed after surgery, the stent is removed easily. The proximal portion of the stent balloon is cut or pierced, causing the entire balloon structure to deflate. The deflated structure, being smaller than the constriction, is then easily removed. Other successful studies have been reported using silicone cylindrical Foley catheters for the same purpose [9]. This work, however, does not address combining luminal occlusion during the recovery/healing period.

Summary and Conclusions. In summary, this project proposes to explore the feasibility of a new temporary implant and surgical technique to improve the DCR procedure. This is a significant improvement over current DCR practice for the following primary reasons: (1) it eliminates the risk of injury to both the eye and upper lacrimal system; (2) it permits tear flow into the nose immediately following surgery, potentially 6 months earlier than current practice and procedure, which frequently does not re-establish normal tear flow until stents are removed. Plans have been made to implant stents of different sizes and proportions into cadavers in order to test implantation and removal of the stent via external and intranasal approaches.

Acknowledgments

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CASE REPORT

Giant Cell Tumor of the Frontal Bone Presenting as an Orbital Mass

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ABSTRACT

A 10-year-old male was referred for evaluation of a right orbital mass present for 3 weeks with associated tenderness to palpation. Magnetic resonance imaging (MRI) and computed tomography imaging (CT) revealed a solid mass centered in the frontal bone with extension into the orbit. Surgical excision and histologic analysis of the lesion was consistent with a diagnosis of a Giant Cell Tumor (GCT) of the frontal bone. The patient tolerated the procedure without complication and is doing well upon follow-up.

Keywords: Frontal bone; Giant cell tumor; Orbital tumor; Osteoclastoma

INTRODUCTION

Primary orbital bone tumors compose less than 2% of all orbital tumors [1]. Of these, GCT is an extremely rare osseous neoplasm that can cause significant bone destruction and has a high propensity for recurrence if not treated appropriately. While GCTs are commonly believed to be benign, there are rare case reports of possible malignant transformation [2–4]. Due to its rarity, much uncertainty and debate exist as to the proper management of these and other primary orbital bone tumors. We describe our experience treating a 10-year-old male who presented with a rare GCT of the frontal bone that was treated with surgical excision. This report is in full compliance with the Declaration of Helsinki and the current Health Insurance Portability and Accountability Act regulations. Informed consent was obtained from the patient for being included in the study.

CASE REPORT

A 10-year-old male was referred for evaluation of a 3-week history of an enlarging right orbital mass (Fig. 1). Past ocular history was notable for a long-standing exotropia (XT). The patient endorsed mild pain to palpation of the lesion but denied vision changes. There was no recent or remote history of periorbital trauma, and he was otherwise healthy. His visual acuity was measured to be 20/25 without correction in each eye. Intraocular pressures were 19 and 20 mmHg in the right (OD) and left (OS) eyes, respectively. Extraocular movements were full, and alternate cover testing revealed a 15-prism diopter XT. Hertel exophthalmometry was symmetric without relative proptosis. He exhibited 2–3 mm of hypoglobus. Cranial nerves V1, V2, V3, and VII were found to be normal. The mass was firm and fixed to the superolateral orbital rim, and was tender to palpation. The remainder of the anterior and posterior segment examinations of both eyes was unremarkable.

The patient underwent magnetic resonance imaging (MRI) with and without contrast as well as computed tomography (CT) without contrast for further evaluation and surgical planning. On MRI, there was a 2.7 cm mass centered in the bone of the superolateral right orbit with associated bone destruction and extension into the superolateral right extraconal orbit and abnormal signal in the right frontal bone and sphenotemporal buttress (Fig. 2). CT revealed bone destruction with only thin bone remaining between the tumor bed and the intracranial space. The patient underwent an uncomplicated right orbitotomy with excision of the mass. Given his lack of an eyelid crease, a sub-brow incision was used to access the mass, which was found to be firmly adherent to the bone. The surrounding periosteum was incised around the mass

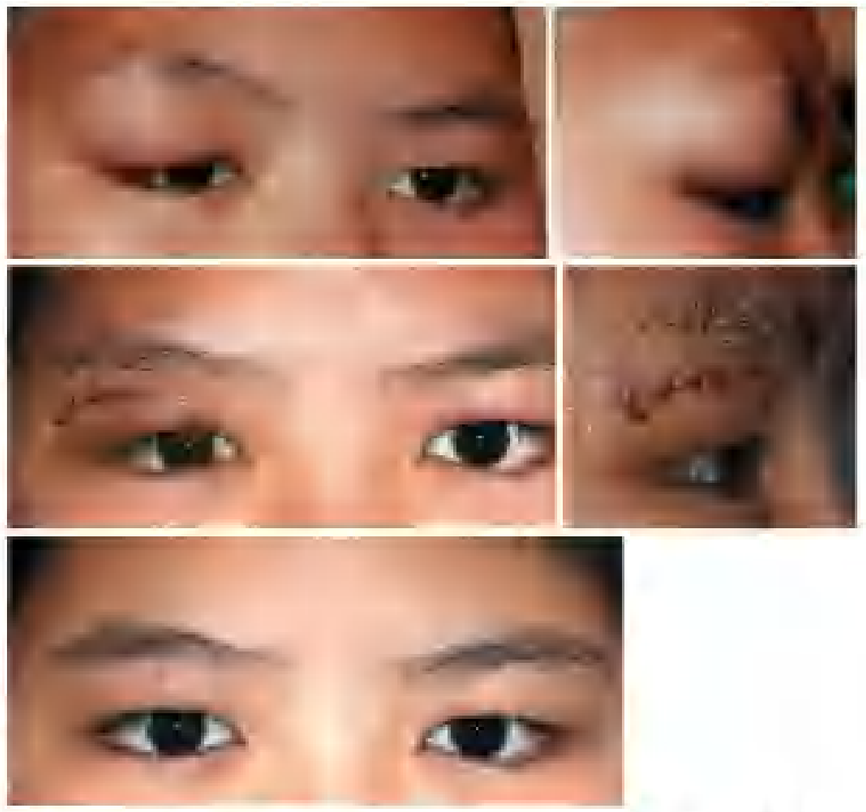

Fig. 1 External photographs show right brow lesion from before (*top*), 1-month (*middle*) and 4-months (*bottom*) after surgical excision

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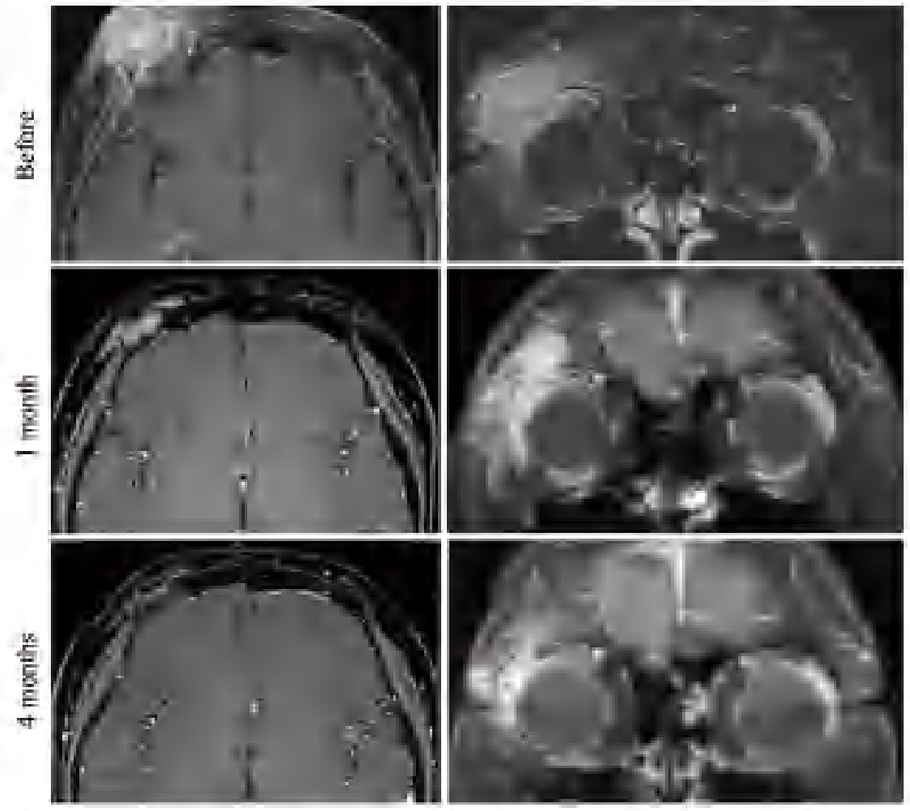

Fig. 2 Post-contrast T1 sequence with fat suppression MR images before (*top*), 1 month (*middle*) and 4 months (*bottom*) after surgical resection

circumferentially with cutting cautery, and the mass was then dissected free using a Freer periosteal elevator. There was a residual defect in the superolateral orbital rim. The incision was closed in layers. Histopathology revealed the lesion to be composed of osteoclast-type giant cells evenly distributed among mononuclear cells with ill-defined cell borders and associated fragments of reactive woven bone rimmed by osteoblasts (Fig. 3). Both the mononuclear and giant cells stained positively for CD68 on immunohistochemistry. Only rare scattered cells stained with CD1a. Ki-67 demonstrated a high proliferation index with 70% of the mononuclear cells being positive. Further analysis of the lesion revealed a loss of one normal copy of chromosomes 5 and 12 with additional material of unknown origin added to the long arm of chromosome 16, and gain of a chromosome 21 and of a marker chromosome of unknown origin. The chromosomal findings indicate a neoplastic process which, in the setting of the imaging and histopathology features, was consistent with giant cell tumor of the bone. Given that the mass was grossly resected, and further curettage would necessitate a craniotomy with reconstruction, observation was elected.

At the 1-month follow-up, MRI with and without contrast revealed residual enhancement that reduced dramatically by his 4-month follow-up scan. Examination at 4 months revealed a palpable defect in the superolateral bony rim; otherwise, he is asymptomatic and continues to have his longstanding well-controlled XT (Figs. 1, 2). He is healing appropriately and denies pain or other symptoms of concern.

DISCUSSION

As the incidence of GCT of the frontal bone is extremely rare, the majority of studies in the literature have been case reports [5–7]. The World Health Organization recognizes three distinct types of GCTs arising from the bone, tendon sheath, or soft tissue [8]. GCT most frequently occurs in the epiphyses of long bones and rarely occur in the orbit [9]. Radiographic features of GCT include an osteolytic lesion that is radiolucent and results in bony erosions with sharp margins on CT scan. MRI shows a

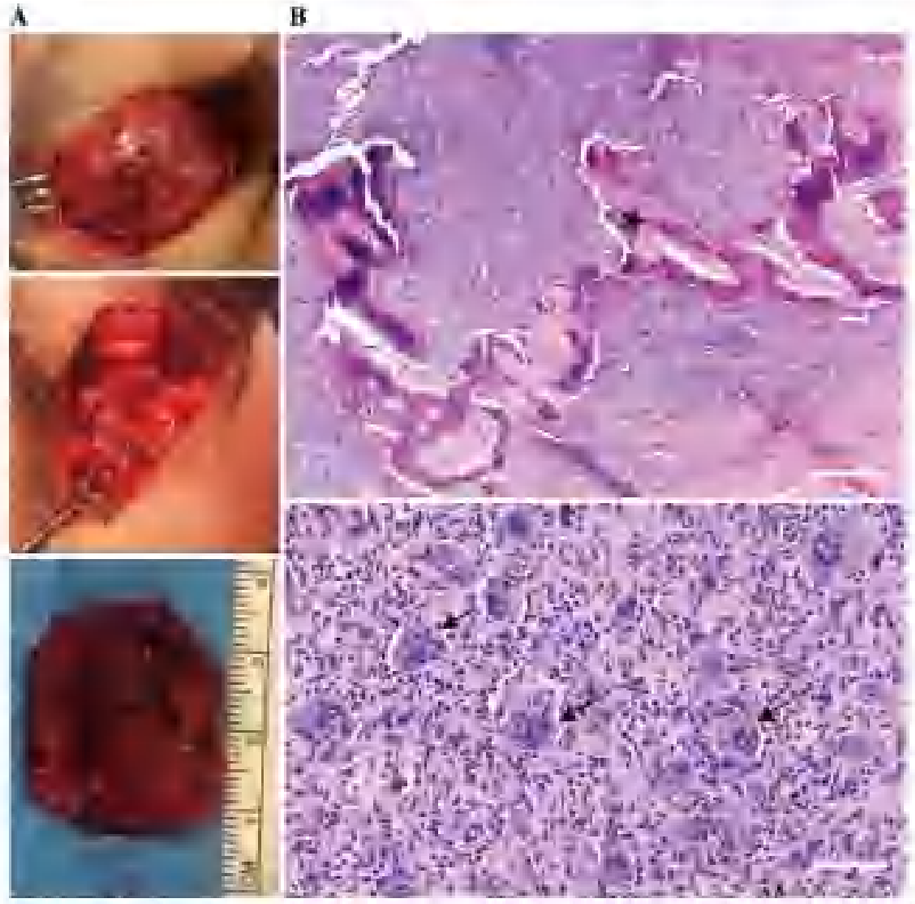

Fig. 3 Intraoperative photographs (**a**) highlight appearance of lesion (*top*) and the extent of surrounding bone destruction after excision (*middle*), and gross pathology of excised lesion is shown (*bottom*). Histologic analysis (**b**) at *low magnification* (*top*) reveals areas of reactive woven bone (*arrow*) and high magnification (*bottom*) shows multinucleated giant cells (*arrows*) scattered among mononuclear cells (H&E staining; *scale bars* are 200 μm *top* and 50 μm for *bottom*)

well-circumscribed lesion that exhibits hypointensity on T1-weighted images and hypointensity on T2-weighted images. Typically, the lesion enhances with contrast on both imaging modalities [10, 11]. Histologically, GCT arising from bone are composed of stromal mononuclear cells and giant cells whose histogenesis is controversial. The mononuclear cell represents the true neoplastic component, while the multinucleated giant cells have an osteoclast-like phenotype and express histocytic lineage markers. The histologic differential diagnosis of GCT include other processes in which multinucleated giant cells can be found, such as giant cell granuloma, "brown tumor" of hyperparathyroidism, non-ossifying fibroma, osteoblastoma, aneurysmal bone cyst, and Langerhans cell histiocytosis [12, 13]. While GCT is generally considered a benign tumor, it has the potential for malignant transformation [4, 9, 14]; therefore, careful observation is essential. The lesion often grows slowly and can cause significant bone destruction. The current treatment goal is for total surgical resection of the tumor without adjuvant radiation therapy, which has been shown to have the lowest recurrence rate. Indeed, Kamoshima et al. described a 2-year-old female patient with recurrent GCT of the frontal bone that underwent two partial surgical removals of the tumor with recurrence before total resection of the lesion, surrounding bone, and frontal lobe dura mater was curative [14]. The reported incidence in the literature of non-recurrence after total resection of a frontal bone lesion has been up to 30 months [15]. If total resection cannot be achieved, the combination of subtotal resection and radiation therapy shows a similar low recurrence. Other therapeutic strategies may lead to increased recurrence rates [16]. Continued long-term follow-up will be important in the ongoing management of our patient.

CONCLUSION

In summary, we present a rare case of a rapidly enlarging superotemporal orbital mass in a ten-year-old boy, which proved to be GCT of the frontal bone. While total surgical resection could not be achieved without a risk of added morbidity, gross resection, followed by close surveillance has resulted in no recurrence with 9 months of follow-up. Although rare, the ophthalmologist should be aware that GCT might present with orbital involvement.

ACKNOWLEDGEMENTS

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Compliance with Ethics Guidelines. This report is in full compliance with the Declaration of Helsinki and current Health Insurance Portability and Accountability Act regulations. Informed consent was obtained from the patient for being included in the study.

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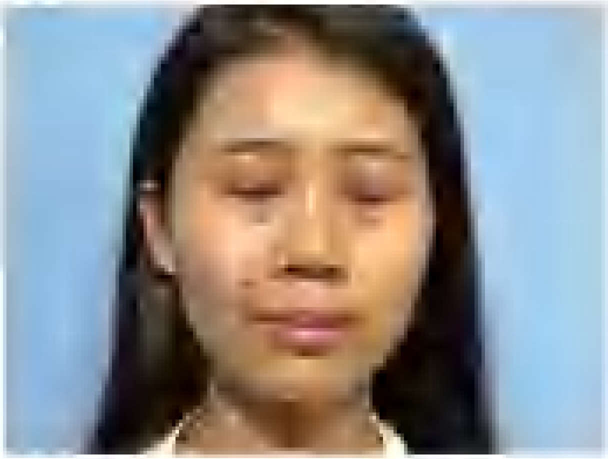

FIG. 1. [illegible]

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DISCUSSION

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A Case of the Blues—Colored Pencil Orbitopathy in an 18-Month-Old Boy

[illegible]

Abstract: Orbital penetrating injuries from pencils are rare. This report describes a case of penetrating orbital injury in a young child with a retained blue-colored pencil core foreign body, which led to rapid onset of orbital abscess requiring surgical drainage. Intraoperatively, orbital tissues were stained a bright blue color. Histopathological study of specimens also highlighted bright blue aggregates of foreign material infiltrating the orbital tissues. Cultures grew *Streptococcus mitis* and *Eikenella corrodens*, which are rare causes of orbital abscess. Unique properties of retained colored pencil core as compared to graphite pencil core are herein discussed. Due to differences in composition, colored pencil core foreign bodies may require more timely surgical intervention compared to uncolored graphite pencil core.

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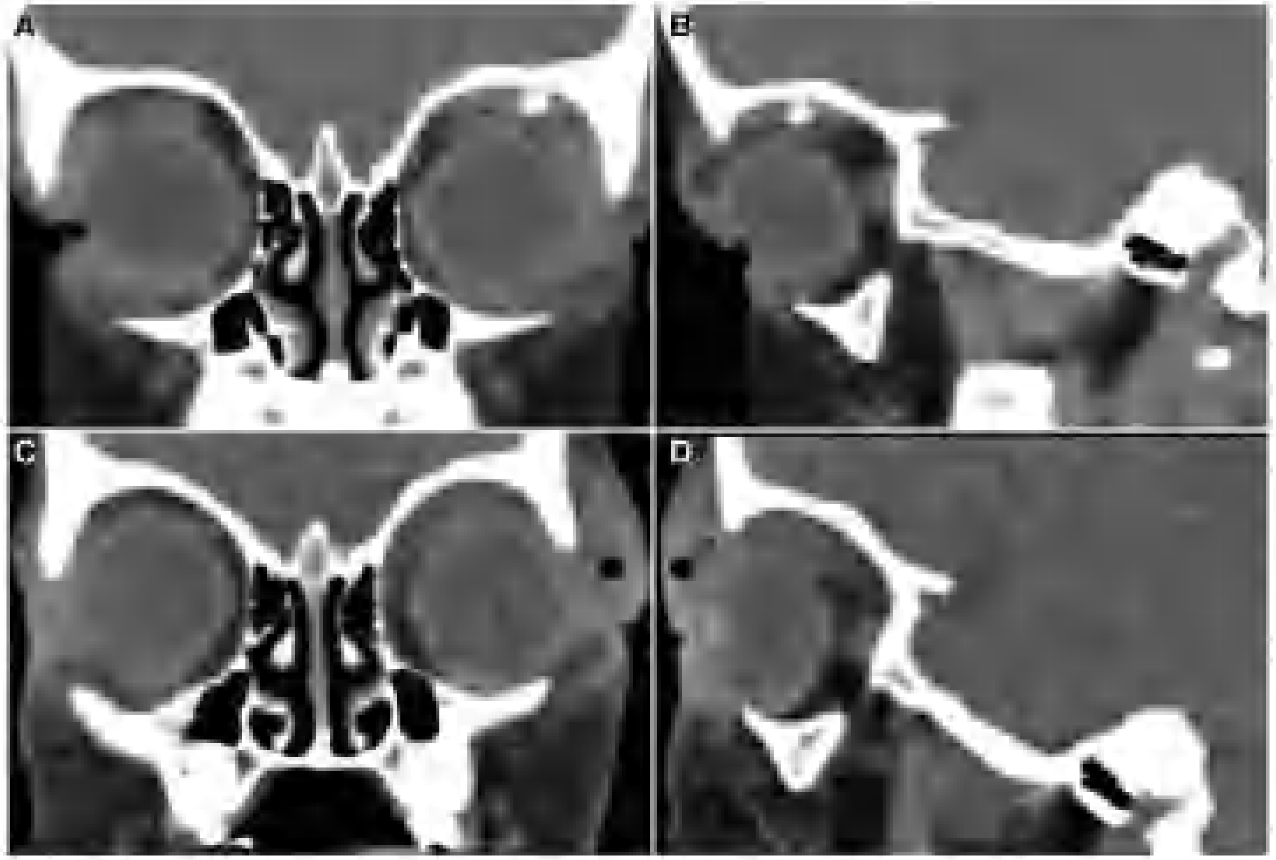

FIG. 1. **A, B**, [illegible] **C, D**, [illegible]

Orbital penetrating injuries from pencils are rare. [illegible]

CASE PRESENTATION

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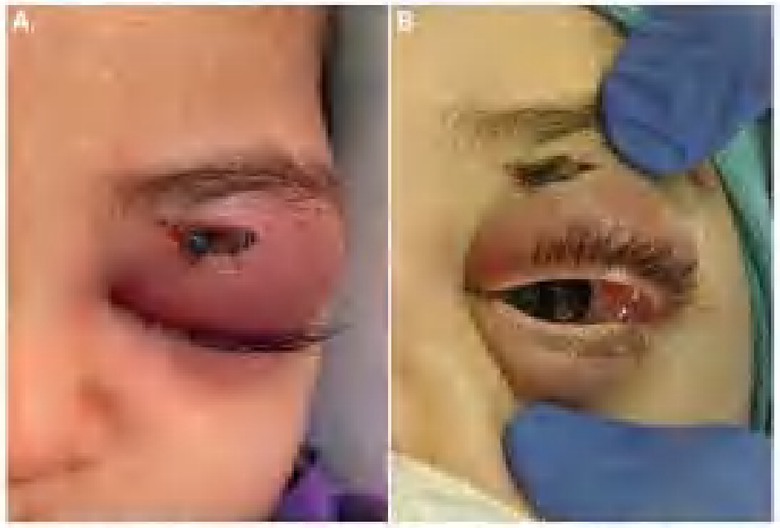

FIG. 2. **A**, Upper eyelid penetrating injury with periorbital edema and complete mechanical ptosis. **B**, Intraoperative exam under anesthesia reveals an intact globe.

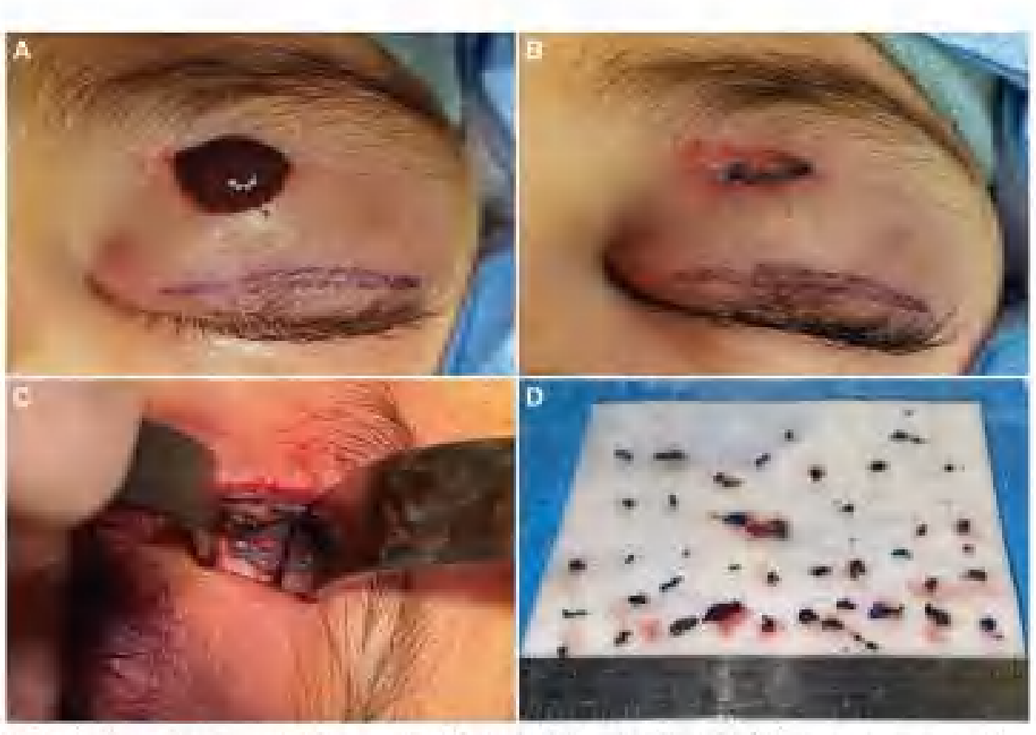

FIG. 3. **A**, Intraoperative drainage of thick, dark purple discharge. **B**, **C**, Blue-stained eyelid and orbital tissues after drainage of fluid. **D**, A portion of the piece-meal debridement of blue-colored orbital tissues.

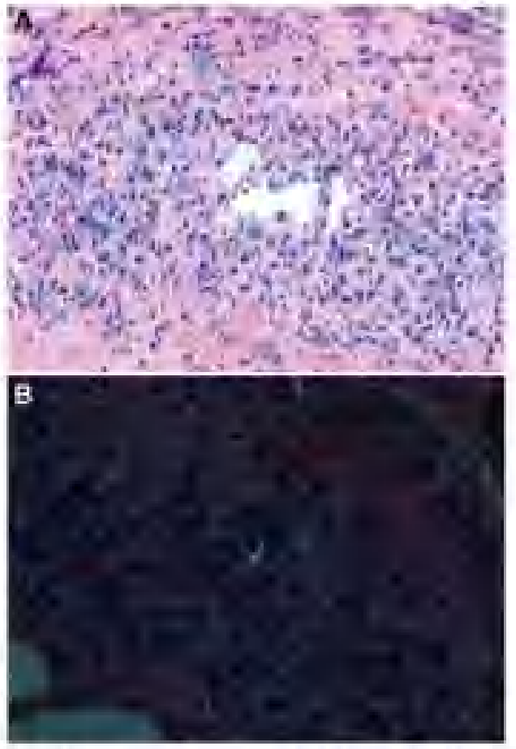

FIG. 4. **A**, H&E stain, 20×, evidence of neutrophil and epithelioid histiocytes with frequent aggregates of bright, turquoise blue, small, needle-like foreign material. **B**, Cross-polarization H&E stain, 20×. A fragment of blue foreign material demonstrating white birefringence, highlighting blue coloring.

The patient did well postoperatively on intravenous management until discontinuation and was eventually transitioned to oral amoxicillin-clavulanate and discharged home on postoperative day 7. Bacterial cultures grew *Staphylococcus aureus*, *Streptococcus viridis*, *Corynebacterium jeikeium*, and *Bacillus cereus* complex. At postoperative week 2 and after completion of antibiotic course, he had excellent ocular alignment of ptosis and no evidence of complications related to the injury.

DISCUSSION

Orbital penetrating injuries from pencils are rare.[1] Historical graphite pencil lead can lead to delayed granulomatous reaction from several weeks to several decades postinjury.[2,3] Because of differences in composition, colored pencil cores may behave differently than graphite pencil cores within tissues. Colored pencil core does not typically contain graphite and is often composed of pigment, cream, and binders such as talc, porcelain clay, metallic powders, and additives.[4,5] These colorants can penetrate the surrounding tissue and create an inflammatory reaction.[1]

Stitch and Tanzola described a similar case of tissue staining after colored pencil injury in a 4-year-old after red-colored pencil injury to the forehead, which led to a bright, artificially stable yellow-pigmented tattoo lesion.[1] They were not able to identify any solid colored pencil core foreign body on plain and computed tomography (CT) imaging, and the patient underwent surgical exploration with debridement of the yellow-colored tissue. Intraoperatively, they found that the yellow pigment was diffusely distributed throughout the tissue and not localized to a single foreign body. Histopathology revealed yellow-pigmented granulomatous inflammation with multinucleated giant cells and foreign body cells. Energy dispersive spectroscopy revealed the presence of cadmium and sulfur, which are components of yellow pigment.[1] Cadmium sulfide is a known carcinogen and can cause local tissue irritation and necrosis.[6] Although the patient's tissue was not sent for cadmium analysis, the yellow pigment was likely cadmium sulfide.

Our patient had a penetrating injury with a blue-colored pencil. Histopathology revealed blue-colored particles within the tissue. Energy dispersive spectroscopy revealed the presence of iron and sulfur, which are components of blue pigment.[4] Iron sulfide is a known carcinogen and can cause local tissue irritation and necrosis.[6] Although the patient's tissue was not sent for iron sulfide analysis, the blue pigment was likely iron sulfide.

Despite unanimous claims of colored pencil core toxicity, it is important to consider the physiologic temperature, duration of exposure, and breakdown of natural chromophores.[7] Although this is speculative, the lack of solid foreign body and the presence of fragmented material in smaller sizes prone to breakdown of the colored pigments within the tissues as a likely mechanism for inflammatory reaction and chronic granuloma.

Interestingly, despite these likely injury to the lacrimal gland, pre-existing *Staphylococcus aureus* and gram-negative bacterial cultures and *Aspergillus* species from fungal cultures. *Staphylococcus aureus* is typically found in normal human flora

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Outcomes on the Utilization of Lipodermoid Skin for Anterior Lamella Reconstruction in Severe Lipodermoids With Eyelid Coloboma: A Case Series

[illegible]

Abstract: Two young children with upper lid colobomas and associated lipodermoids underwent eyelid reconstruction using lipodermoid skin as an autograft with good cosmesis. We describe their presentation, surgical management, and clinical progress following reconstruction, demonstrating the suitability of this skin as an adequate graft avoiding the need for further skin graft harvesting in such cases.

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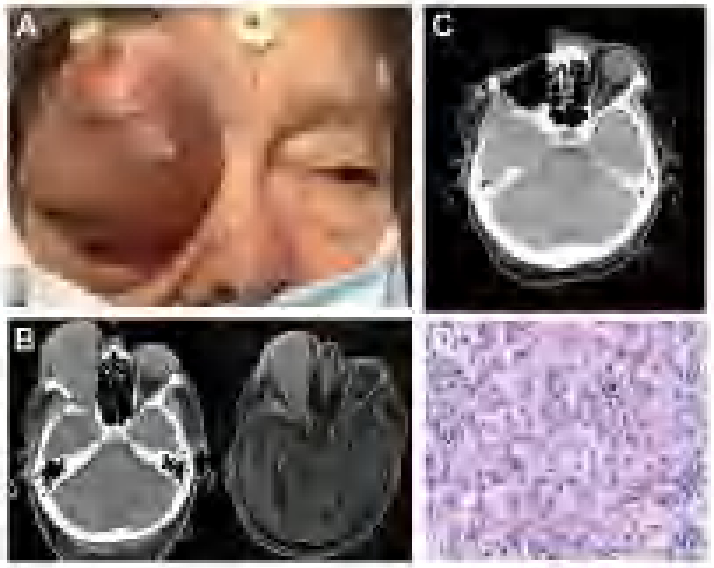
27. [illegible]
28. American Academy of Ophthalmology. AAO PPP Retina/Vitreous Committee, Hoskins Center for Quality Eye Care. Preferred Practice Pattern: Posterior Vitreous Detachment, Retinal Breaks, and Lattice Degeneration PPP 2019. October 2019 revision. [illegible] Accessed December 12, 2023.

Pictures & Perspectives



Anaplastic Meningioma of the Orbit

An 63-year-old woman presented with 2 months of progressive painful vision loss of the right eye. She had a previous World Health Organization (WHO) grade 1 right sphenoid wing meningioma, status postsurgical resection 2 years prior. Examination revealed a large orbital tumor and a nonformed, inferolaterally displaced globe (**A**). Imaging revealed a 7.5 cm × 3.8 cm × 4.2 cm intraorbital mass with intracranial extension along the temporal lobe and cavernous sinus (**B**). A right cranio-orbital craniotomy, orbital exenteration, and resection of the anterior/middle fossa tumor was performed (**C**). Histology revealed a WHO grade 3, anaplastic meningioma with frequent mitotic activity (**D**, circled). Given the patient's history and nature of meningiomas, the tumor origin was likely intracranial, primarily presenting with orbital involvement (Magnified version of Figure **A-D** is available online at www.aaojournal.org).

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Preserved vision without growth retardation after laparoscopic Roux-en-Y gastric bypass in a morbidly obese child with pseudotumor cerebri: 36-month follow-up

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Key words:
Adolescent
Severe obesity
Pseudotumor cerebri
Laparoscopic Roux-en-Y gastric bypass

Abstract A 12-year-old boy presented with a weight of 116 kg and a history of progressive visual loss associated with intractable pseudotumor cerebri requiring frontal subtemporal decompression. He underwent laparoscopic Roux-en-Y gastric bypass (RYGBP) 6 days postdecompression. At 36 months post-RYGBP, he has gained 5 cm since the time of surgery, his weight is 68.8 kg and 7.8% preoperative excess weight of 68.1 kg, and his visual acuity has improved with OD 20/100 preoperative, 20/200 and OS 20/70 (preoperative, 20/100). This case suggests that RYGBP can be performed safely and without stopping linear growth in carefully selected children.
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The childhood and adolescent obesity has increased at an alarming rate for the past 30 years, and it is now estimated that 15% of children are obese and an additional 15% are overweight [1,2]. Moreover, it has been shown that at least 50% of children older than 8 years who are obese will continue to be obese into adulthood, this risk increases with the age of the child [3]. More recently, it has been found that while only 5% of children with body mass index (BMI) below the 50th percentile become obese adults, 20% of children with a BMI between the 50th and 84th percentiles do and all children with a BMI above the 95th percentile become obese adults [4]. The epidemic of childhood obesity has correlated with a dramatic rise in the incidence of associated glucose intolerance and type 2 diabetes along with a broad range of comorbidities found in morbidly obese adults, including one of the less common comorbidities, pseudotumor cerebri (PTC) [5,6]. Treatment of PTC by weight loss surgery has been successful in adult series with resolution of persistent severe headache in all patients and dramatic reduction of cerebrospinal fluid pressure [7,8]. We report the 36-month follow-up after laparoscopic Roux-en-Y gastric bypass (RYGBP) in a 12-year-old morbidly obese boy who initially presented with progressive visual loss and papilledema. Despite bilateral optic nerve sheath decompression, his vision deteriorated. This case report suggests that obese morbidly obese children might benefit from weight reduction surgery. Yet linear growth is still possible after gastric bypass and has definitive use cutoffs alone should not

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dicate consideration for operative therapies in the morbidly obese child.

1. Case report

A morbidly obese 12-year-old white male presented with progressive visual impairment and headaches. Fluorescein fluorescein revealed multiple sprouting of acute optic nerve neovascularization with leakage consistent with papilledema. Magnetic resonance imaging and ventriculography with administration of contrast revealed no abnormalities. Lumbar puncture was performed to drain the cerebrospinal fluid pressure to 30 cm H_2O and showed normal cerebrospinal fluid analysis. Acetazolamide was started at 1 g/d and titrated to 4 g/d. Despite maximal medical therapy, the patient's vision continued to deteriorate. Subsequently, he was referred for bariatric surgery. After extensive nutritional, medical, psychological screening by a multidisciplinary bariatric team, the patient underwent RYGBP in December 2003 at 12 years 9 months of age. His preoperative BMI was 48 kg/m², and his weight and height were 125 kg and 161 cm. His father was a BMI of 47 kg/m² with a weight of 147 kg and 170 cm. His mother had a BMI of 42 kg/m² with a weight of 129 kg and height of 175 cm.

At operation, the patient had a small intraabdominal body habitus with moderate central visceral fat otherwise normal anatomy. An RYGBP was performed by creating a 15-mL gastric pouch, a 50-cm biliopancreatic limb, and a 150-cm Roux limb in an antecolic antegastric position using a previously described technique [9]. The total operative time for the procedure was 148 minutes, with an estimated blood loss of 20 mL. A gastrografin swallow performed on the first postoperative day demonstrated no evidence of leakage or obstruction. His diet was advanced to clear liquids, and he was discharged from the hospital on postoperative day number 3.

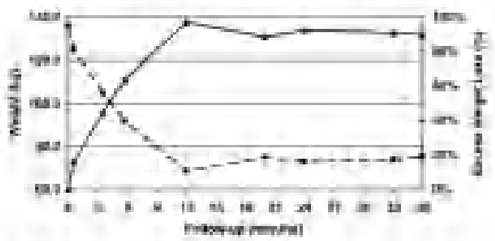

Fig. 1 Weight versus [illegible] over the 36 months after RYGBP in a 12-year-old child.

At 6 months, he had lost 47 kg (-34% excess weight loss), and at 12 month follow-up, he had lost 68 kg or 87% of his excess body weight loss (Fig. 1). His BMI was 24 kg/m². At 24-month follow-up, he had regained 4.7 kg from his nadir weight and was 4 cm taller than preoperatively, his BMI was 23 kg/m². At 36 months post-RYGBP, the weight was 68.8 kg (down nearly 60 kg) but he has grown 5 cm and his BMI remains 23 kg/m². Before surgery, he was at the 99th percentile for height, and 36 months after surgery, he was in the 50th percentile for height.

At 24-month follow-up ophthalmic examination showed visual acuity 20/100 OD and 20/70 OS; there was a left afferent pupillary defect. Extraocular motility and color examination were normal. Funduscopic examination revealed pale optic discs, macular retinal pigment epithelial changes and no epiretinal membranes; each of the findings was present preoperatively and consistent with changes of chronic papilledema. Visual fields were stable with residual central islands in both eyes.

He gained some [illegible] the first month [illegible] lost, reportedly [illegible] that he was having surgery. He reported eating only 1/2 cup of food at every meal. He denied that he was ever tempted to eat high-energy, high-fat foods although [illegible] has been exposed to them. He denied the presence of symptoms of depression, anxiety, oppositional behavior, or attention issues during psychological interview and testing. His IQ was reported in the borderline range for intellectual development. His [illegible] and grades in school have improved. Both of his parents have also undergone bariatric surgery at this time, and he will undergo abdominoplasty for excess skin.

2. Discussion

In this manuscript, we report on 2-year follow-up after RYGBP at a 12-year-old morbidly obese child with a history of PTC and papilledema. He achieved medical weight loss and the vision loss has become stable. At 2 year

knowledge, the patient is the youngest of any previously reported patients in the literature to undergo an RYGBP for morbid obesity and its comorbidities, and his age is below that recommended for obesity surgery in a recent consensus report of experts in adolescent obesity [10]. It is emphasized that this operation was performed as a last resort because of intractable PTC.

Pseudotumor cerebri is a rare disorder in which patients develop severe headaches, papilledema, and increased intracranial pressure without clinical, laboratory, or radiologic evidence of an intracranial space-occupying lesion. In our severely obese patient, the continuous episodes of headaches and papilledema were associated with high-opening pressures (>40 cm H_2O) on lumbar puncture and subsequent repeated symptomatic pressure [11]. Attempts to treat with medical therapy (acetazolamide) and repeated lumbar punctures did not provide successful clinical management of the elevated intracranial pressure.

Bariatric surgery has recently shown to be an effective treatment for PTC in severely obese adolescents. In the multicenter case series by Sugerman [12], Vanderbilt University had a preoperative diagnosis of PTC with previous severe headaches, which markedly improved the quality of their lives. These symptoms resolved in all patients in 1 year postoperative follow-up. Moreover, in a 6-patient group of 24 severely obese adults with PTC reported by the same author, all patients preoperatively had persistent severe headaches and magnetic brain imaging studies done with elevated cerebrospinal fluid pressures. All of them had fainting. After obesity surgery (23 patients had an RYGBP), all but one patient had complete resolution of headache and remission [7]. In obese patients with this condition, obesity surgery is the treatment of choice.

The National Institutes of Health Consensus Conference in 1991 concluded that a sufficient data set did not exist to provide recommendations for obesity surgery for children and adolescents [13]. In 2003, a group of surgeons and pediatricians specializing in the treatment of overweight and obese adolescents published a set of guidelines for bariatric surgery in severely overweight adolescents. They recommended the use of 35 as a threshold BMI and age 15 as the minimum for body-shaping recommendations. Medical and psychosocial maturation are factors that should potentially preclude earlier operative intervention [10].

The first large retrospective single-institution experience in adolescent obesity surgery was published by Mason and colleagues [14]. They demonstrated that vertical banded gastroplasty could be performed safely, with an operative mortality of 0%, a wound infection in a group of 47 patients younger than 21 years. They also showed that weight loss can be sustained.

More recently, Lawson and colleagues [15] reported outcomes in the Prospective Outcome Study (Roux-en-Y). They reviewed 30 RYGBP procedures carried out between the age of 13 and 21 in 3 centers. In a group of 20 patients followed up prospectively for 1 year, before operation, the average BMI dropped from 56.5 kg/m^2 to 32.8 kg/m^2, a 42% decrease. Moreover, serum markers of cardiovascular risk, including triglycerides and cholesterol, and fasting glucose and insulin demonstrated significant improvement. The results were performed with 14 laparoscopic cases and 3 laparoscopic converted to open procedures. There were no perioperative deaths, but 1 patient with 3 preoperative weight at 286 kg died 9 months after surgery from a cardiopulmonary arrest with sepsis.

Nguyen and colleagues [16] also reported their outcomes in 74 pediatric patients ages 13 to 17 who underwent laparoscopic adjustable gastric band surgery by a surgical group with significant adjustable banding experience and focus. Average preoperative BMI was 48 kg/m^2, and patients on average lost 61% of their excess weight within 2 years of surgery. All operations were completed laparoscopically, and there were no deaths. Band slippage occurred in 9 patients, 1 patient developed gastric perforation after laparoscopic repair of slip, and 1 patient required band removal because of intolerance after a slip. Symptomatic gallstones developed in 3 patients, and asymptomatic iron and vitamin D deficiency was found in a total of 17 patients. Adjustable band surgery represents a very promising strategy for weight loss in the pediatric population, though the FDA has not approved implantation of adjustable bands in pediatric populations outside of studies.

Any patient referred for bariatric surgery is but rarely meet criteria at a minimum according to the National

Table 1 Adolescent studies examining bariatric surgery for the last 5 years in the United States

Year	Author	*n*	Procedure (*n*)	Ages	Mean excess weight loss (follow-up interval)
1998	Nguyen *et al* [16]	74	Laparoscopic adjustable gastric banding	13–17	61% (2 y)
2003	Dolan and Sawers [18]	10	Laparoscopic adjustable gastric banding	15–17	70% (9 mo)
2003	Inge *et al* [19]	54	Laparoscopic adjustable gastric banding	16–18	47% (1 y)
2003	Alvarado [20]	30	Laparoscopic adjustable gastric banding	9–19	40% (1 y)
2004	Lawson *et al* [15]	30	Laparoscopic gastric bypass	13–21	37% (1 y) to 39% (3 y)
2004	Inge [21]	16	Laparoscopic Gl and open gastric bypass (2)	13–18	47% (1 y, 4)
2005	Sugerman *et al* [12]	3	Open gastric bypass (30) laparoscopic (3), open banding gastric bypass (1)	14–21	75%
2005	Alvarado *et al* [22]	9	Laparoscopic gastric bypass	12–19	50%

Institutes of Health guidelines. The BMI must be ≥35 kg/m^2 in grades with significant comorbid conditions; 40 kg/m^2 in grades without comorbid conditions. Additional necessary factors include patient compliance with follow-up and strong family support system, a clear understanding of the procedure to be performed, and realistic expectations of outcome and the patient's role in long-term success. All patients are sent for routine extensive psychological evaluation [17]. All children considered for weight loss surgery must have significant comorbidities. The decision to proceed with RYGBP in the child presented in this report was made only after meeting all of the above criteria and considering the severity of this child's progressive visual impairment and consultation with ophthalmology (Table 1).

A multidisciplinary and multispecialty consensus group recommendations are the implementation of obesity surgery in adolescents and specifically emphasized many divergent issues in children versus adolescents. This team appropriately cited the issue of patient group dynamics as surgery, the improved outcomes of behavioral therapy approaches to weight loss in children, and the known fact that a significant proportion of obese adolescents are not obese in adults. We agree with these main points that surgery should be reserved for those severely obese adolescents with significant comorbidities and only after careful consideration [18].

During the past 5 years this patient has had regular frequent follow-up with the surgeon and pediatric subspecialists as well as the psychologist and nutritionist and will continue to have multidisciplinary medical supervision. Long-term weight loss is ill-defined on compliance with eating regimen with dietary supplements and exercise regimens, all of which will continue to be supervised. He will likely continue to have major psychosocial adjustments to be passed through puberty and adhesions through school. It will also be very difficult to ascertain whether he will maintain access to health insurance in the long-term, which is very important for making sure that complications such as vitamin and mineral deficiencies are monitored and dealt with before they become major problems. Although there is much enthusiasm for this case adolescent's short-term weight loss and improvement in comorbidity, the long-term prospects remain guarded. This single case should not be interpreted as a signal to more aggressively open obesity surgery to younger adolescents and children.

In conclusion, this case highlights a successful outcome of one morbidly obese child with severe comorbidity who gained height during the 2 years after operation and appears that more children and adolescents may benefit from obesity surgery. It is emphasized that adolescents and children selected to undergo obesity surgery must be carefully chosen and monitored postoperatively by multidisciplinary teams, and the operations should only be performed in regional centers of excellence with the goal of enrolling all patients in targeted research.

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Floppy Eyelid Syndrome

Quantifying the Effect of Horizontal Tightening on Upper Eyelid Position

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Purpose: To evaluate the effect of horizontal upper eyelid tightening on upper eyelid position in patients with floppy eyelid syndrome.

Design: Prospective, noncomparative, interventional case series.

Participants: Eighteen patients with a clinical diagnosis of floppy eyelid syndrome.

Methods: Horizontal surgical tightening of the upper eyelid was performed by full-thickness wedge resection in 24 eyelids of 18 patients with floppy eyelid syndrome. Preoperative and postoperative upper eyelid position as measured by the margin reflex distance (MRD) was observed. Student's paired *t* test was used to analyze the change in upper eyelid position after horizontal tightening alone of floppy upper eyelids.

Main Outcome Measures: Change in upper eyelid MRD after surgery.

Results: Preoperative MRD ranged from +6.5 to 0.0 mm, with a mean of 1.9 mm (+1.3 mm standard deviation [SD]). Postoperative MRD ranged from 9.5 to 6.0 mm, with a mean of 7.3 mm (+1.4 mm). The change in MRD ranged from −3.5 to 2.5 mm, with a mean of 1.5 mm (±2.2 mm SD; $P = 0.001$).

Conclusions: Horizontal upper eyelid tightening alone generally results in secondary improvement in the ptosis associated with floppy eyelid syndrome. *Ophthalmology 2007;114:1932–1936 © 2007 by the American Academy of Ophthalmology*

Floppy eyelid syndrome (also known as [illegible] syndrome) is a condition characterized by an easily everted, floppy upper eyelid that opens during sleep causing abrasions and mechanical irritation, papillary conjunctivitis, and conjunctival keratinization of the upper palpebral conjunctiva.[1,2] Conservative treatment consists of topical lubricants, wearing a shield to prevent the upper eyelid from everting during sleep, and loss of body weight.[1] Dutton[3] described successful treatment of the condition by full-thickness eyelid shortening, and surgical procedures typically involve horizontal tightening of the upper eyelid.[1,3,4]

Some authors have reported an association of upper eyelid blepharoptosis with floppy eyelid syndrome, and some surgeons combine surgical correction of floppy eyelid syndrome with ptosis correction surgery.[5] However, there is little information available in the peer-reviewed literature regarding the change in eyelid margin position with horizontal tightening alone. The authors studied the change in upper eyelid position as measured by the margin reflex distance (MRD) after full-thickness wedge resection surgical treatment of floppy eyelid syndrome without concomitant ptosis correction surgery. The results of their series of cases are presented herein.

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Patients and Methods

This was a prospective study to which horizontal surgical tightening alone by modified full-thickness pentagonal wedge resection was performed in 24 eyelids of 18 patients with a clinical diagnosis of floppy eyelid syndrome of the upper eyelid. The diagnosis of floppy eyelid syndrome was made in each patient based on clinical features of excessive upper eyelid laxity with papillary conjunctival changes and corneal surface disease necessitating topical medical treatment. Associated features such as face-shaking, obese body habitus, and sleep apnea were noted when present. All patients seen in this study were provided within the acceptable standard of the community. No randomization was performed. The change in eyelid position was evaluated before and after surgery according to the authors' standard approach to the management of such cases. No drug-surgical interactions or other treatments were performed. Informed consent was obtained for each patient. Data were collected by the investigators in such a manner that subjects could not be identified directly or through identifiers linked to the subjects, in compliance with health insurance portability and accountability act guidelines. One surgeon (MMM, ADP, performed all operations. Each eyelid was anesthetized in the manner favored by the surgeon and had applied to it a drop of 0.5% proparacaine (Alcaine, Alcon Laboratories, Fort Worth, Texas). Jackson periorbital marks, eyelash clipping, [illegible] during surgery to the removal of body parts.

The primary end point was upper eyelid position. This was measured by MRD at least twice (mean). The MRD was defined as the distance in millimeters from the eyelid margin to the corneal light reflex, as previously described by Meyer and Beard.[6] Measurements were obtained to the closest 0.5 mm. Patients generally were examined after surgery at 1 week and 3 months. Patients with a referring general ophthalmologist were returned to that practitioner's care if they were stable at 3 months. In patients without a referring ophthalmologist, additional follow-up was scheduled at 6 months and 1 year. For the purposes of this study, the longest available follow-up MRD measurement was used to carry out Student's paired *t* test to determine the change in eyelid position after surgery.

Results

Twenty-four eyelids of 18 patients were included in the analysis (Table 1). Thirteen eyelids were right upper eyelids (54.2%) and 11 eyelids were left upper eyelids (45.8%). The mean age of the patients at the time of surgery was 57 years (range, 38–76 years; ±12 years standard deviation [SD]). Seventeen of the 18 patients were men (94.4%) and 1 was a woman (5.6%). The mean preoperative MRD was 1.9 mm (range, −0.5 to 4.0 mm; ±1.3 mm SD). The mean postoperative MRD was 3.2 mm (range, 0.5–6.0 mm; ±1.4 mm SD). The longest available postoperative MRD measurement ranged from 3 months to 12 months, with a mean of 4.8 months (±3.4 months SD). The upper eyelid position unchanged in 22 (91.6%) of 24 eyelids, was unchanged in 1 eyelid (4.2%), and worsened in 1 eyelid (4.2%). The mean change in MRD was statistically significant, with a mean difference of 1.3 mm (range, −0.5 to 2.5 mm; ±0.7 mm SD; $P < 0.001$, Student's paired *t* test; Figs 1–3). Although difficult to measure, eyelid fold prominence appeared to be improved qualitatively in most patients. Furthermore, all patients showed clinical improvement in their ocular surface problems. Two patients (representing 3 eyelids) missed their 3-month follow-up appointment because of unrelated medical problems. Additional follow-up was obtained at 6 to 12 months in these patients.

Table 1. Preoperative to Postoperative Change in Margin Reflex Distance 1

Patient No.	Gender	Eyelid No.	Age at Surgery (yrs)	Operative Eyelid	Margin Reflex Distance 1 (mm)						
					Preoperative	Postoperative					
						3 Mo	6 Mo	1 Yr	Longest Follow-up Time (mos)	Latest Measurement (mm)	Difference Postoperative–Preoperative
1	M	1	76	RUL	2.0	4.0	4.5		6.0	3.0	1.5
2	M	2	47	LUL	2.0	3.5			3.0	2.5	1.5
3	M	3	48	LUL	3.0	4.0			4.0	4.0	1.0
4	M	4	63	RUL	1.5	3.0			3.0	3.0	1.5
5	M	5	50	LUL	−0.5	0.5			4.0	0.5	1.0
6	M	6	69	RUL	2.0	2.0			3.0	2.0	2.0
7	M	7	48	RUL	1.5	3.0			4.0	3.0	1.5
8	M	8	61	RUL	2.0	3.0			3.0	3.0	1.0
9	M	9	76	RUL	2.5	3.0			3.0	3.0	0.5
		10	81	LUL	2.5	3.5			4.0	3.5	1.0
10	M	11	41	RUL	−1.5	1.5			3.0	1.5	−1.5
11	M	12	65	LUL	6.0	3.0		2.5	12.0	3.0	3.5
12	M	13	58	RUL	6.0			4.5	12.0	1.5	4.5
		14	54	LUL	6.0			4.5	12.0	1.5	4.5
13	M	15	45	RUL	4.0	5.5			3.0	5.5	1.5
14	F	16	64	RUL	6.5		4.5	2.5	12.0	4.5	1.5
15	M	17	50	RUL	2.0	4.0			3.0	4.0	2.0
		18	50	LUL	2.0	4.0			3.0	4.0	2.0
16	M	19	69	RUL	1.0	2.5			3.0	2.5	1.5
		20	69	LUL	2.0	3.5			3.0	3.5	1.5
17	M	21	66	RUL	3.0	4.0			3.0	4.0	1.0
		22	66	LUL	4.0	5.0			4.0	5.0	1.0
18	M	23	66	RUL	5.0	6.0			3.0	6.0	1.0
		24	66	LUL	4.0	6.0			3.0	6.0	2.0
Mean			57		1.9	3.6	2.5	3.9	4.6	3.2	1.3
Standard deviation			14		1.3	1.3	1.4	0.6	3.4	1.4	0.7

F = female; LUL = left upper eyelid; M = male; RUL = right upper eyelid.

Discussion

The cause of floppy eyelid syndrome is not clearly understood. Proposed theories have included an abnormality of the structure of the orbicularis oculi muscle, degeneration of collagenous connective tissue, and genetic collagen elastin disease abnormalities.[1,2,7,8] A 10-year review by Culbertson and Tseng[1] revealed that all affected patients slept face down, usually on the most severely affected eye.

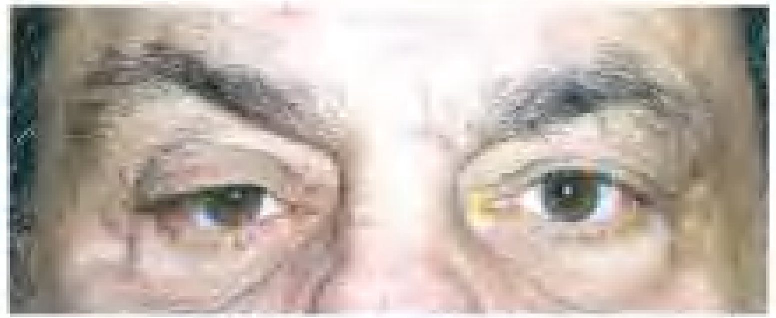

Figure 1. Preoperative photograph demonstrating eyelid and eyelash ptosis of the right upper eyelid in a patient with confirmed diagnosis of floppy eyelid syndrome.

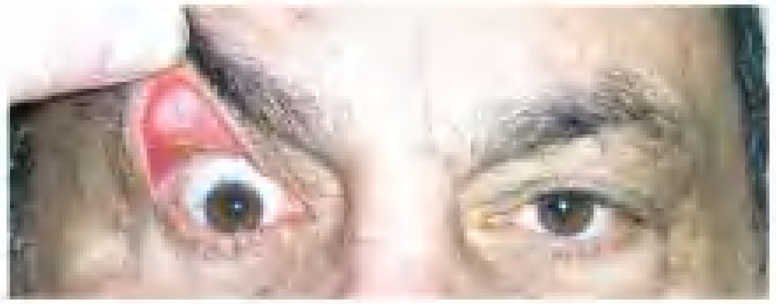

Figure 2. Preoperative photograph (same patient as in Fig 1) demonstrating easy eversion of the ptotic right upper eyelid with excessive horizontal laxity and tarsal erythema.

Figure 3. Intraoperative photograph (same patient as in Fig 1) demonstrating surgical markings of area to undergo full-thickness pentagonal wedge excision of the right upper eyelid.

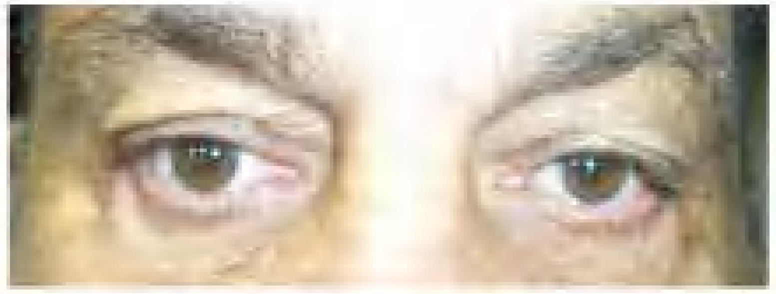

Figure 4. Postoperative photograph (same patient as in Fig 1) demonstrating improvement in eyelid and eyelash ptosis of the right upper eyelid after horizontal eyelid shortening alone without concomitant ptosis surgery.

[illegible] Although many studies focused on [illegible] inflammatory changes and tarsal collagen changes, more recent studies have suggested that decreased tarsal elastin may be more significant.[illegible]

Few reports have described the change in eyelid position preceding ptosis after surgical correction. In the current study, the authors found that horizontal upper eyelid tightening alone generally resulted in improvement of the ptosis associated with floppy eyelid syndrome. The upper eyelid position was found to be increased in 22 of 24 eyelids (91.6%), was unchanged in 1 eyelid (4.2%), and decreased in 1 eyelid (4.2%) after surgical correction by full-thickness wedge resection alone. The change in MRD was statistically significant, with a mean difference of 1.3 mm (range, –0.5 to 3.5 mm; SD, ±1.0 mm; $P<0.001$, Student's paired t test).

Common physical examination findings in floppy eyelid syndrome include a soft rubbery tarsus that can be folded on itself, eyelash ptosis with loss of parallel orientation, [illegible] and upper eyelid blepharoptosis.[illegible] The eyelid ptosis associated with floppy eyelid syndrome is not fully understood. It may be related to tarsal laxity alone, or possibly to [illegible] changes of the levator or Müller's muscle(s), or both, which are responsible for upper eyelid elevation. It may be wise to be alert for the coexistence of floppy eyelid syndrome when examining patients with ptosis.

Tightening of the upper eyelid may impart a mechanical advantage to the function of the upper eyelid elevators, allowing for increased effect from their efforts. The resting position of the eyelid is dependent on the [illegible] For example, upper eyelid ptosis can be seen after removal of large orbital [illegible] until the eyelid [illegible] Eyelid ptosis frequently associated with [illegible] is probably related to a similar phenomenon. Surgical horizontal shortening of the upper eyelid may prevent it from [illegible] in resting position, thereby causing it to sit higher on the globe. This may explain why upper eyelid elevation was seen even in patients without preoperative ptosis (MRD >3.0 mm). In fact, most patients without preoperative ptosis showed elevation of eyelid position. This implies that merely tightening a floppy eyelid horizontally improves levator function in patients with lax upper eyelids. The amount of elevation achieved was not correlated to the amount of tightening performed. However, the final resting position of the upper eyelid more likely relates to its conformation with the globe than to its absolute length.

The improvement in eyelid position with horizontal eyelid tightening in floppy eyelid syndrome is in contrast to the response of an eyelid without floppy eyelid syndrome to similar surgery (such as is commonly performed for excision of eyelid malignancies), in which the upper eyelid frequently becomes [illegible] ptotic [illegible] the eyelid is [illegible] between its 2 anchoring points (the medial and lateral canthal tendons). It generally is accepted that tightening an upper eyelid in patients with normal eyelid tone and aponeurotic ptosis leads to improved results and can be used to establish upper eyelid contour with aponeurotic ptosis surgery. In the current study, upper eyelid tightening [illegible] resulted in [illegible] quantifiable elevation of upper eyelid position and improvement in the ptosis [illegible] associated with floppy eyelid syndrome. Eyelash ptosis also was noted to be qualitatively improved.

Based on these results, the authors believe that unless the associated upper eyelid ptosis is particularly severe, it seems reasonable to perform surgical correction of floppy eyelid syndrome with horizontal tightening alone as an initial treatment strategy. A second surgery for ptosis correction may be performed through standard techniques if indicated or requested. If the preoperative ptosis is believed to be severe or if other signs of aponeurotic ptosis, such as high eyelid creases and increased ptosis on downgaze, are present, then it also may be reasonable to advance the levator [illegible] simultaneously in combination with upper eyelid horizontal shortening. In this study, however, all patients were pleased with the improvement from horizontal tightening alone, and no patient requested additional ptosis correction. It should be noted, however, that although improvement in eyelid position was noted in more than 92% of the patients in this study, the degree of improvement was variable, and [illegible] patients ([illegible] eyelids) nevertheless had postoperative MRD measurements that generally would be considered ptotic (less than 2.0 mm) by most standards.[illegible]

The limitations of this study must also be considered. The results are those of 2 different surgeons at different centers, both using full-thickness pentagonal wedge excision for treatment. Different surgeons may obtain different results, even with similar techniques. The degree of eyelid laxity was not graded. Therefore, it is uncertain whether the amount of eyelid [illegible] is related to the amount of tightening performed. This may be an area for future investigation. Some surgeons perform an upper eyelid lateral tarsal strip procedure to address a floppy eyelid. How an upper eyelid would respond to this technique is unclear, but the authors believe that the general mechanical principles may be similar. Ultimately, the decision for surgery and the type of surgery rests between the surgeon and patient, based on the surgeon's experience and an informed discussion.

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TABLE 1. Correlation of Age With Success of Nasolacrimal Duct Probing*

Age at Probing (y)	Number of Duct Probings		
	Total (n=)	Successful (n=)	Unsuccessful (%)
0 to 12	7	12	82
13 to 24	5	40	89
25 to 36	8	32	80
37 to 48	7	17	71
49 to 60	11	5	82

*$P = .001$ for all comparisons among age groups; chi-square analysis of variance.

TABLE 2. Correlation of Certain Factors With Success of Nasolacrimal Duct Probing

Preoperative Clinical Parameter	Correlation With Nasolacrimal Duct Probing
Age (mo)	$P = .0001$
Symptom grade 1 (epiphora + mucoid)	$P = .16$
Symptom grade 2 (mild mucoid discharge)	$P = .07$
Symptom grade 3 (daily recurrence)	$P = .02$
Swelling (lesion or cyst)	$P = .19$
Presence of mucoid discharge	$P = .05$
History of nasolacrimal duct probing	$P = .56$

*Chi-square analysis of variance.

nasolacrimal duct probing did not correlate with probing outcome (Table 2). Of all the preoperative clinical variables assessed, age and daily epiphora were associated with the highest rate of nasolacrimal duct probe failure.

The timing of nasolacrimal duct probing is controversial because some studies favor discontinuing high failure rates in older children.[1–3] Herein, the success of probing begins to substantially decline after age 2 years. Our determined probing success, which required complete rather than partial resolution of preoperative symptoms, also began a similar decline after age 2 years. This finding allowed for partial resolution of symptoms and may explain our different outcomes. We agree with Robb that late probing is optimum "in children older than 1 year, many surgeons stop nasolacrimal duct probing and proceed directly to alternate treatments of the nasolacrimal system. Because only 2 procedures were identified that can treat complete lacrimal probing with stenosis, we prefer to initially probe children older than 1 year. Increasing frequency of treating correlates with decreased probing success. Therefore, we may only treat lacrimal duct probing in children with daily tearing because these patients are at a higher risk for nasolacrimal duct probe failure and might require further treatment.

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Isolated Inferior Rectus Paresis Secondary to a Mesencephalic Cavernous Angioma

Andrew R. Harrison, MD, and Jonathan D. Wirtschafter, MD, FACS

PURPOSE: To report a case of recurrent binocular, vertical diplopia presenting as an isolated, unilateral inferior rectus paresis occurring in a patient with a mesencephalic trigeminal cavernous angioma.

METHOD: Case report. A 30-year-old man with recurrent vertical diplopia underwent neuro-ophthalmic examination, laboratory examination, pharmacologic testing, and magnetic resonance imaging and angiography.

RESULTS: Magnetic resonance imaging disclosed a lesion in the mesencephalon consistent with a cavernous angioma. Magnetic resonance angiography was negative.

CONCLUSIONS: Isolated inferior rectus paresis is a rare phenomenon. This unique case involved a patient with recurrent inferior rectus paresis secondary to a mesencephalic cavernous angioma. The disparity between the extent of the lesion and the neuro-ophthalmologic consequences is remarkable. (Am J Ophthalmol 1999; 127:617–619. © 1999 by Elsevier Science Inc. All rights reserved.)

THE OCULOMOTOR MUSCLES ORIGINATE IN A LIMITED portion of the ventral mesencephalon. Each muscle supplied by the oculomotor nerve is thought to be governed by subpopulations of cells, defining [illegible]

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FIGURE 1. Versions show left inferior rectus paresis. Note secondary overaction of right superior oblique and underaction of right inferior oblique.

with the exception of the levator palpebrae superioris muscles, which have a solitary midline subnucleus. Subnuclear demyelinating lesions are rare. We report a case of isolated inferior rectus pulse synchrony in a midbrain cavernous angioma.

A 30-year-old man was referred to the Neuro-ophthalmology Clinic at the University of Minnesota for evaluation of binocular vertical diplopia in left gaze that resolved spontaneously over 4 months. Six years before this examination, the patient had another episode that resolved in a similar fashion. Five months before his examination, he again noted binocular vertical diplopia in left gaze. He noted diplopia in primary gaze only when tired. He denied any blepharospasm. His ocular, neurologic, and systemic histories and reviews of systems were negative. He was taking no medications.

Visual acuity was 20/20 without correction. Pupils were equal, round, and briskly reactive to light, with no relative afferent pupillary defect. Duction of the right eye was normal. The left eye had a dramatic severe limitation of depression when the eye was adducted (Figure 1). In primary gaze, there were 4 prism diopters of left hypertropia. This increased with left gaze and with left head tilt. No blepharospasm or any sign of alternate representation of the third cranial nerve was present. Bilateral Maddox rod testing declared no vertical deviation. Pentagonal and ectophoria testing were negative. Cranial nerve testing and neurologic examination were otherwise unremarkable. Ophthalmoscopic findings were normal bilaterally. Lens-induced diplopia testing was performed and showed left inferior rectus paresis. Forced duction testing was normal. Acetylcholine receptor binding antibodies and thyroid stimulating immunoglobulin levels were normal.

Magnetic resonance imaging disclosed a round lesion in the left midbrain, impinging slightly on the midline. The mass had a core of hypointensity with a rim of hyperintensity on the T$_1$-weighted spoiled echo images (Figure 2). The lesion did not invisibly enhance with the administration of gadolinium. Magnetic resonance angiogram was negative. The diagnosis of cavernous angioma of the midbrain was made, and the patient was referred for neurosurgical evaluation. He elected to be managed with conservative observation.

Apart from focal neurologic deficits, other clinical presentations of cavernous angioma include seizures and headache. The intralesional bleeding rate is less than 1%. Occult hemorrhage-recurrence events frequently dwarf overt hemorrhage.

Isolated inferior rectus pulse without mechanical abnormalities is a profoundly rare phenomenon. The diagnosis of isolated inferior rectus paresis is based on evaluation of duction and versions. Ancillary clinical signs, such as the

FIGURE 2. T$_1$-weighted sagittal magnetic resonance image shows a 1-cm mass lesion of cross hatch with central heterogeneous signal surrounded by a hypointense ring in the tectum of the midbrain at the level of the superior colliculus.

Convergence-level lid apex and the presence of cyclodeviation, are of little help in diagnosing this condition. In our patient, the level lid apex and the profound torsion of downward deviation with lid in the abducted side. Isolated inferior rectus paresis has been described with cavernous angioma. Few reports exist in the literature, as thought to be caused by multiple etiologies.[1,2] The superior oblique overaction–underaction demyelinating and neurotonic disease. How the nerves were implicated in this case because of the marked asymmetry of the deviation. Cases of multiple cranial nerve dysfunction have been reported that cause superior oblique overaction paresis combined with underaction.[3] The present case suggests the clinical spectrum of binocular vertical diplopia in primary position to include isolated or multiple extraocular muscle involvement by the midbrain cavernous angioma.

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Orbital Chondrosarcoma Developing in a Patient With Paget Disease

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PURPOSE: To describe the radiologic, histopathologic, and cytogenetic features of an orbital chondrosarcoma developing in a patient with Paget disease.

METHODS: A 64-year-old woman presented with rapidly progressive proptosis of her right eye. Computed tomographic scans, histopathologic examination, and cytogenetic analysis were performed.

RESULTS: Computed tomographic scans disclosed osseous changes of the temporal and frontal bones, with areas of high density consistent with Paget disease. A soft-tissue tumor in the right lateral orbital wall was consistent with Paget sarcoma. On histology, a chondrosarcoma was diagnosed, which was confirmed by fluorescent in situ hybridization.

CONCLUSION: This is a unique case of orbital chondrosarcoma developing in a patient with Paget disease. (Am J Ophthalmol 1999;127:619–621. © 1999 by Elsevier Science Inc. All rights reserved.)

The [illegible] Paget disease is well recognized. The overall frequency of sarcomatous change is low (1% to 10%).

A 64-year-old woman with a 2-month history of progressive and painful proptosis of the right eye, restricted eye movements, and diplopia was referred to the Eye Hospital Rotterdam. Her local ophthalmologist found that she had a visual acuity of 20/30, 20/20, normal pupillary reflexes, and normal findings on ophthalmoscopy. Her medical history was [illegible]. Her initial complaint was RE, 2 mm Hg. A tumor in the right orbit was diagnosed. Upon referral, she had total loss of light perception in the right eye, proptosis that increased to 6 to 12 mm, and the globe was displaced medially and inferiorly. She had progressively severe pain accompanied with [illegible] numbness, corneal changes, and vascular compromise caused by compression of the temporal bone and the lacrimal gland area. A bony tumor was palpable.

The initial computed tomographic scan disclosed osseous changes of the entire skull, with [illegible] areas

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Supported [illegible]

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ORIGINAL INVESTIGATION

"Blue Scrub Lid Retraction": Changes in Eyelid Position on the Day of Surgery

[illegible]

Purpose: [illegible]

Methods: [illegible]

Results: [illegible]

Conclusions: [illegible]

[illegible]

E[illegible]

[illegible]

[illegible]

[illegible]

STATISTICAL ANALYSIS

[illegible]

RESULTS

[illegible]

METHODS

[illegible]

Eyelid and brow position measurements obtained from photos taken at the in-clinic consultation appointment, and on the immediate preoperative visit

	Margin-reflex distance 1		Margin-reflex distance 2		Brow-pupillary distance	
	OD	OS	OD	OS	OD	OS
Mean (SD)	1.2 mm (0.9)	1.1 mm (0.7)	4.9 mm (0.8)	4.7 mm (0.8)	17.8 mm (3.5)	18.0 mm (3.6)
Percentage with partial eyelid position change[a]	31.6%	26.3%	26.3%	21.1%	47.4%	36.8%
Mean (95% CI) absolute change[b]	1.0 (0.6)	1.1 (0.6)	0.6 (0.6)	0.8 (0.6)	1.2 (0.6)	1.5 (0.6)
Mean overall change[c]	0.0 (0.6)	−0.1 (0.6)[d]	0.1 (0.6)	0.0 (0.6)[d]	0.1 (0.6)	0.1 (0.6)

[a]Percentage of eyelids showing change greater than the 95% confidence interval for the corresponding measurement.
[b]Absolute value of change.
[c]Positive value indicates change in the direction of eyelid elevation.
[d]Negative value indicates change in the direction of eyelid retraction.

all eyelid measurements higher on the day of surgery. Eight patients had a lower MRD1 in both eyelids on the day of surgery, with a mean change in MRD1 of −1.0 mm for the OD and −1.0 mm for the OS. The largest negative change in MRD1 for a single patient was −1.7 mm for the right eyelid and −1.9 mm for the left eyelid.

MRD2 was also increased to a significant degree ($p < 0.001$ for both OD and OS) during the preoperative period in comparison with the in-clinic consultation. The mean increase in MRD2 was 0.8 mm for the right and 0.9 mm for the left eyelid. The percentage of eyelids with increased MRD2 was similar to that with increased MRD1: at 78.9% (30 of 38 eyelids) for MRD2 and 71.1% for MRD1. MRD2 and MRD1 were significantly correlated by Pearson correlation testing ($r = 0.483$, $p = 0.002$ and $r = 0.406$, $p = 0.04$).

Brow-pupillary distance was also measured for all subjects and demonstrated a mean change of 0.1 mm (and −1 mm for the right and OS, respectively; $p = 0.051$, brow-pupillary distance was not correlated to MRD1 as $r = 0.026$, $p = 0.958$ and $r = 0.173$, $p = 0.371$).

DISCUSSION

In this investigation, we demonstrated a higher MRD1 measurement on the day of surgery than in the clinic setting, for both surgical eyelids. The mean magnitude of MRD1 elevation seen in this study was about 1 mm, which is well within the range of eyelid elevation that stimulation of the Müller's muscle provides. Similarly, the MRD2 was increased in the interval surgery compared with in-clinic evaluation. This increase observed in MRD2 more significantly stretched to the contralateral eyelid in MRD1. The possible secondary (swallow) sympathetic innervation of Müller's muscle and the orbicularis muscle, the lower eyelid overlying the Müller's muscle, and their responsiveness to topical alpha-adrenergic stimulation. We postulate that the eyelid stretch and anxiety experienced by patients on the day of surgery may similarly stimulate Müller's muscle, affecting MRD1 and the relative increase in MRD2 over MRD1, and ultimately alter the preoperative exam.

Engagement of the frontalis muscle and the elevation of the eyebrows is often seen in patients with blepharoptosis as a form of compensation to aid in elevating the eyelid. As the results of established practice to maintain that measurements and surgical evaluation are performed with the relaxation of the frontalis muscle to minimize the impact of anterior elevation of the eyebrow and Müller's muscle. To facilitate, the clinician from the office to the ambulatory surgery, this measurement was performed with MRD1 to determine if patients were relaxed or tense during the initial evaluation. Although we did not find a significant difference in MRD1 between patients who were relaxed and those who were tense, the mean MRD1 was 0.7 mm higher in the tense group ($p = 0.077$) and the range of differences between the two groups was 0.477 to 0.902.

DISCUSSION

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eyelid position when measurements vary significantly between patient encounters. Targets of future investigations may include the inclusion of additional adrenergic markers and assessment of changes in surgical outcomes, in cases for which the surgical plan is made or altered on the basis of preoperative area findings.

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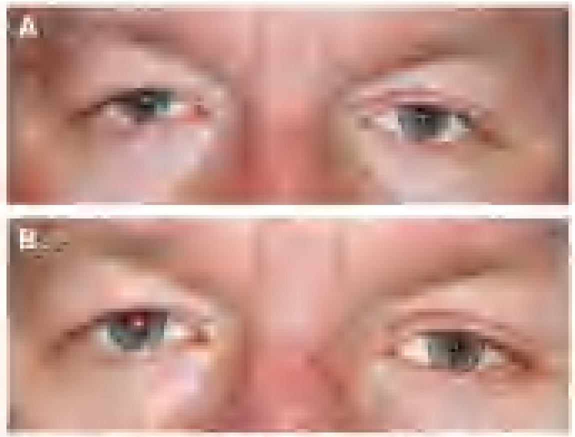
Reconstructive Surgery


ORIGINAL ARTICLE

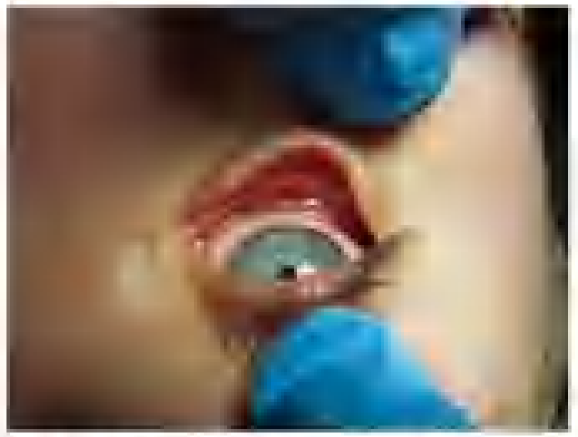
Use of DermaMatrix Graft in Oculoplastic Surgery

METHODS

RESULTS



DISCUSSION



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Case Report

Transport of patients with giant disfiguring cranial tumors from Africa to the US for collaborative multidisciplinary treatment

ABSTRACT

INTRODUCTION

we describe four patients with giant (>20 cm) disfiguring cranial tumors who were turned down for surgery at multiple international locations due to medical complexity and financial concerns. They were flown to be treated by a multidisciplinary surgical team including neurosurgeons, craniofacial reconstructive surgeons, and oculoplastic specialists. A cross-continental arrangement allowed the hospital and surgeons to complete their services free of charge, waiving the treatment costs, which ranged from $125,000 to $250,000.

CASE REPORTS

Case 1

A 28-year-old male from Ethiopia presented with a large bilateral mass measuring over 20 cm in its largest dimension arising from the frontal aspect of the left side of his head. The mass had grown rapidly over the previous 2 years, resulting in headaches, vomiting, and left-sided numbness.

Imaging studies

A catheter angiogram showed portions of the mass that were mildly to moderately vascular. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 24 cm × 20 cm × 18 cm extra-axial mass centered in the region of the left frontal bone [Figure 1]. The mass was partially solid, partially calcified, and partially cystic.

Operation

A bicoronal incision was made to the level of the zygoma and was carried down to the level of the tumor. The scalp flap was reflected forwards and backwards until we reached normal bone posteriorly and nasal bone anteriorly. Cutaneous and subcutaneous bleeding was controlled with bipolar electrocautery. Two holes were drilled through the skull on either side to normal dura and were connected posteriorly and anteriorly, crossing the sagittal sinus. The skull was cracked and lifted, along with the massive tumor mass, as one piece, weighing 17 lbs. Additional tumor was shaved out of the orbit and from the region of the sphenoid wing and temporal fossa. Substantial bleeding from the bone and dura was controlled, with 2 units blood lost in total. The scalp and skull were closed over two large Jackson-Pratt drains and a portion of the redundant scalp flap was resected. Intraoperative photographs are presented in Figure 2].

Pathological examination

Histopathological examination of the mass revealed a high-grade osteogenic sarcoma with chondroblastic features.

Postoperative course

The patient had no neurological deficits or serious skin-flap issues and returned to Ethiopia where he underwent limited

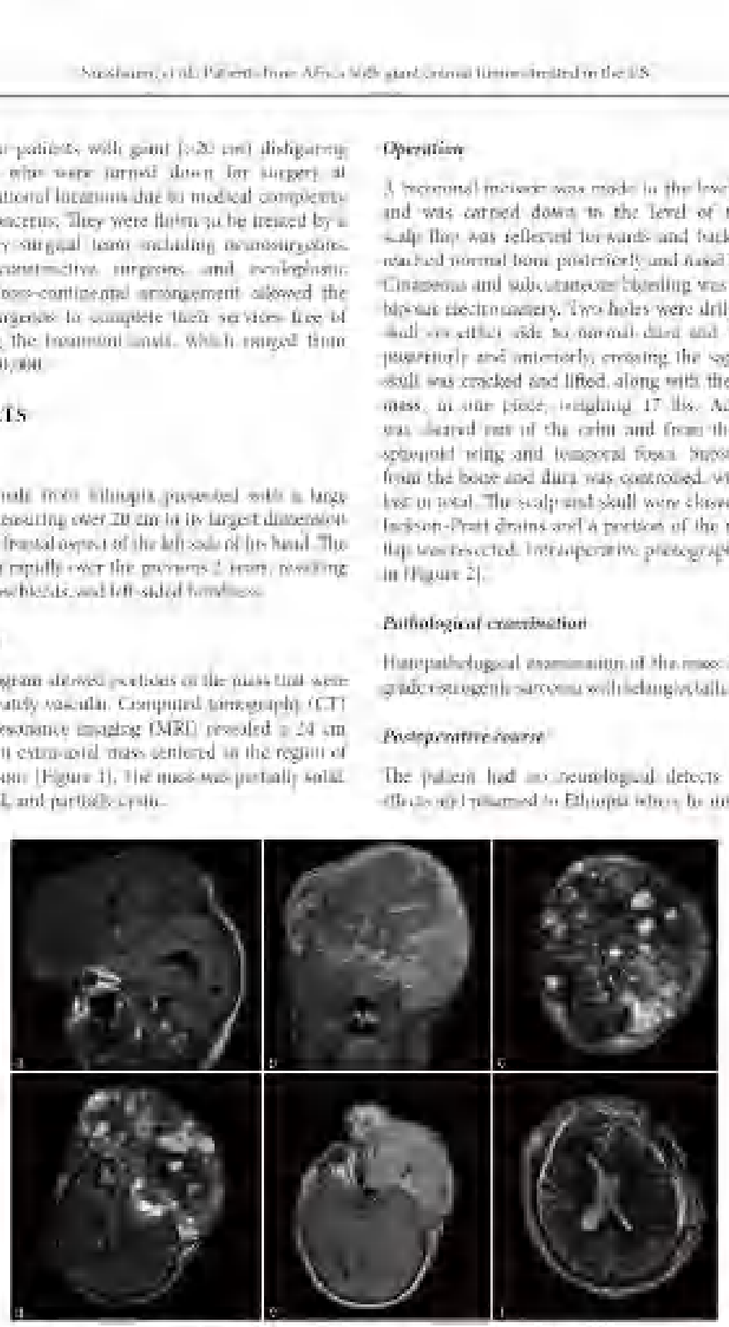

Figure 1: Preoperative radiographic images of disfiguring osteosarcoma tumor mass (Case 1). (a) Sagittal view T1-weighted MRI showing disfiguring tumor extending the left eye. (b) Postcontrast view, CT (c) and (d) Axial view, T2-weighted MRI showing well-defined enhancing nodules without invasion. (e) Axial view, CT (f) Axial view, T1-weighted MRI showing displacement of brain parenchyma.

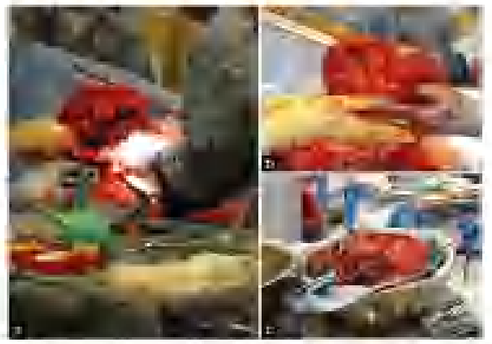

Figure 2: Intraoperative photographs showing (a) resection of the mass (b) removal of the mass with (c) the mass fully separated from the patient

treatment with chemotherapy but not radiation. At this time a positron emission tomography (PET) scan had shown the mass to be locally contained without remote spread.

Second surgery

The patient returned 11 months later with a recurrent tumor involving the nasal cavity and orbits. The largest axial dimensions of the anterior component measured 7 × 12 cm. The patient opted to undergo a second operation. The bicoronal incision from the previous surgery was reopened, and the scalp was reflected anteriorly, avoiding the tumor over the right orbital region. The tumor was resected bluntly with bipolar cautery. Once the tumor was resected, dural repair was placed. The same craniofacial reconstructive surgeon performed a nasal cranioplasty. The wound was closed with a Jackson-Pratt drain and nylon sutures, and the patient was taken to the recovery room in stable condition.

Third surgery

The patient returned 26 months later with another large recurrence of the tumor and opted for a third surgery. Before surgery, the patient underwent embolization of the right middle meningeal artery, with accessory meningeal artery and internal deep temporal artery, which were supplying the tumor. During surgery, the previous bicoronal incision was reopened. The scalp was reflected down to the underlying mesh. Tissues underlying the mesh and other anatomically located tumor tissue were aggressively removed. The frontal bone, which had been largely replaced by tumor, was removed externally, down to the orbital rims. The orbital rims were removed, and orbits were decompressed aggressively to the optic and cavernous canals. The sphenoid wing was drilled down bilaterally, as

a bur blow completely exposed with the tumor on the right side. Surgery continued down into the pterygopalatine fossa and then came down to the midline over the floor of the region of the ethmoid sinuses, which were completely filled with tumor tissue.

The patient experienced severe blood loss and intraoperative coagulopathy. This was addressed with repeated Factor VII. Some tumor remained in the ethmoid sinus and behind the maxilla on the left side. This was not removed due to the significant blood loss that had already occurred. The craniofacial reconstructive surgeon used the existing titanium graft from the previous cranioplasty to reconstruct the defect.

The patient was treated with additional courses of chemotherapy, but after returning to Ethiopia, he succumbed to his disease 9 months later.

Case 2

A 28-year-old female from Ethiopia presented with a giant skull-based tumor with a massive intracranial component, disturbing her facial anatomy and right eye.

Imaging studies

Diagnostic angiography, CT, and MRI revealed a giant, moderately hypervascular, multilobulated, and peripherally calcified cystic mass lesion which appeared to arise from the skull base and occupy the entire nasal cavity, ethmoid sinus, and ipsilateral sinus regions [Figure 3]. The intracranial component of the tumor obliterated the olfactory fossa, bilaterally invaded the cavernous sinuses, and caused extensive elevation and splaying of the internal carotid arteries, anterior cerebral arteries, optic chiasm, and bifrontal optic nerves. The mass measured approximately 10 cm × 9 cm × 11 cm. There was no evidence of edema or gliotic reaction in the adjacent brain parenchyma.

Operation

The patient underwent resection of the tumor through a craniofacial translocal approach. A bicoronal incision was carried down, preserving the galeal layer for possible use as a graft layer. An incision was made over the face and nose to expose the front of the tumor. We broke through the thin bony shell and entered the multiloculated cystic tumor cavity. Fluid was drained and the operating microscope was brought into the field. This allowed us to work circumferentially to remove the entire solid tumor components all the way back to the intracranial/intradural tumor dura. This left a massive cavity measuring over 15 cm in diameter. All soft tissue were removed and bone was drilled down. The lateral wall of the tumor with orbital adherence was left in place to avoid orbital problems. Bone was then drilled off the medial

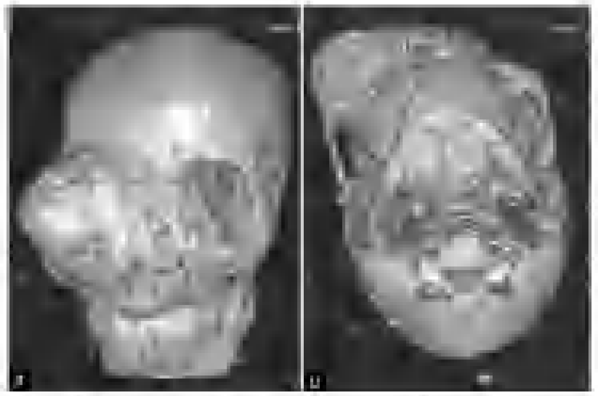

Figure 5: Preoperative radiographic images of deforming cranial tumors (Case 2). (a) Anteroposterior view CT showing the fibrous tissue deforming the right eye. (b) Axial view CT.

wall to decompress the lesion. The dura was never entered. Calvarial bone grafts were harvested by taking a large frontal parasagittal craniotomy.

A craniofacial reconstructive surgeon with the help of an oculoplastic specialist completed a complex reconstruction. We used the bone grafts to reconstruct a new orbit and mid-face. Repair of the skull bone and scalp was undertaken in a second surgery by our craniofacial/plastic surgeon.

Pathological examination

Histopathological examination demonstrated an ossifying fibroma with a proliferation of plump spindle cells, mostly hypocellular, with focal hypercellular areas. Production of woven bone was seen intermittently with the spindle cells. The spindle cells showed focal areas of storiform arrangement with focal osteoblastic rimming. The final diagnosis was fibrous dysplasia.

Postoperative course

The patient remained neurologically and physically stable throughout the follow-up period, with the exception of increasing headaches and occasional [illegible]. Follow-up PET and MRI at 1 month and 10 months postoperative were stable and showed no evidence of tumor growth. The patient has been followed for 10 years with mild interval progression of bony changes but no clear evidence of tumor regrowth. During this time, she underwent one additional delayed cosmetic procedure for her left eye.

Case 3

A 29-year-old man presented with extensive bone and soft-tissue changes related to a large plexiform neurofibroma involving the left temporal region, underlying bone, and dura. He had no neurological deficit but did have worsening headaches. The patient traveled from Ethiopia for surgical repair.

Imaging studies

CT scan of the brain including bone windows and thin cut imaging through the temporal bones demonstrated extensive bony erosion with scalloping of the bone edges compatible with the long-standing presence of the left temporal mass which itself involved the subcutaneous tissue, temporalis muscle, and dura. There was no appreciable intradural extension of the lesion. These findings were confirmed on MRI, which revealed the heterogeneously enhancing mass involving the soft tissue, bone, and dura of the left temporal region. Diagnostic angiography revealed enlargement of the superficial temporal and middle meningeal arteries which were embolized with polyvinyl alcohol the day before surgery.

Operation

A single-stage operation was carried out. Our craniofacial team resected a large amount of redundant soft tissue and skin overlying the relatively hypervascular mass. The tumor was removed en bloc, and thickened underlying dura was also resected. The underlying bone was severely thinned, and titanium cranioplasty was used for reconstruction.

Pathological examination

Pathological examination was compatible with a plexiform neurofibroma.

Postoperative course

Postoperatively, the patient did well without new deficits. After 3 months recovery and removal of all sutures, the patient was able to return home. Six-month followup was carried out remotely, and the patient was doing well without regrowth of tumor or new deficits. The patient was offered a second surgery to correct cosmetic appearance, but was happy with the result and declined to return.

Case 4

A 44-year-old woman from Nigeria presented with worsening headaches and balance difficulties.

Imaging studies

The patient traveled to our center where MRI revealed a 5 cm mass lesion involving the cerebellopontine angle with overlying bony hyperostosis. CT scan with bone windows demonstrated the marked hyperostosis resulting in deformity

of the overlying skull, which was well hidden by the patient's hair on physical examination. There was marked deformity of the cerebellum and brainstem by the extra-axial mass which displaced the basilar artery and extended out along the internal auditory canal.

Operation

The patient underwent retrosigmoid craniotomy with resection of the tumor. At the time of surgery, the majority of the tumor was removed, but a small amount was left due to adherence to the basilar artery. The bony hyperostosis was aggressively drilled away, and titanium mesh was utilized to cover the defect.

Pathological examination

Pathological examination demonstrated a meningioma.

Postoperative course

The patient tolerated this procedure well, though she developed partial fourth cranial nerve palsy after the surgery. Otherwise, she suffered no new deficits. She returned home 6 weeks after surgery, and followup imaging at 18 months was stable. Her fourth cranial nerve palsy had fully resolved.

DISCUSSION

Here, we demonstrate the successful treatment of giant skull deforming tumors in 4 patients from Africa by a multidisciplinary team. Giant skull deforming tumors are exceptionally rare with limited cases reported in recent history.[illegible] Since these tumors develop over the course of several years,[illegible] they usually occur in patients with lack access to medical care or otherwise resist treatment during the early stages of tumor development.[illegible] The majority of recent cases have been meningiomas[illegible] but cases of glioblastoma,[illegible] squamous cell carcinoma,[illegible] and osteosarcoma or ossifying fibroma, as seen here, have also been reported.

Common risks and symptoms associated with giant skull deforming tumors include headaches,[illegible] cognitive and neurological impairment,[illegible] and ulceration and subsequent infection of the scalp.[illegible] However, some patients experience little to no symptoms beyond the skull protrusion itself,[illegible] which may contribute to the delay in seeking treatment. Surgical complications include damage to existing brain structures and hemorrhage.[illegible] As we experienced, the resection of highly vascular tumors can lead to substantial blood loss and must be anticipated and monitored during the procedure. In addition, reconstruction of the skull or facial structures adds a major challenge, necessitating consultation and careful planning with plastic surgeons.[illegible]

Reported methods of reconstruction include the use of myocutaneous skin flap, resection,[illegible] bone reconstruction with methyl methacrylate,[illegible] or dural onlay reconstruction with pericranium,[illegible] lyophilized dura,[illegible] or titanium mesh as described here. The use of myocutaneous skin flap reposition represents an important technique to provide tissue coverage following resection of complex tumors. Importantly, when employing this approach, the flap should consist of sufficient subcutaneous tissue and vascularity to ensure it receives ample blood supply.[illegible] In our experience, these giant tumors often led to tissue expansion, leaving more than enough skin to provide tissue coverage and often necessitating resection of redundant tissue at the conclusion of the procedure.

Due to the complexity and rarity of giant skull deforming tumors, each procedure must be planned and performed on a case-by-case basis. Imaging studies should be undertaken to help establish the extent of the tumor and guide surgical resection. As we do in all cases, the goals of surgery balanced maximal safe surgical resection with a desire to avoid permanent neurological injury or disability. Although we knew that the only chance of achieving cure in these cases might be the initial surgery (given the barriers to having the patients return to the US for repeat operations), we also felt that a permanent disability would be an unacceptable complication, particularly for individuals returning to countries with limited medical and social support resources. Three of our patients had been "home-bound" for years before surgery due to the disfiguring nature of their tumors. In these cases, it was hoped that simply restoring a "near-normal" cosmetic result would allow the patients to re-enter society, radically improving their quality of life.

Giant skull deforming tumors are exceptionally rare and there is no definitive consensus on treatment practices, particularly for patients from countries with such limited medical resources. Historically, neurosurgeons have traveled to areas in sub-Saharan Africa, Latin America, and the Caribbean to fund neurosurgical [illegible], where an estimated 22 million additional neurosurgical procedures are needed for patients.[illegible] However, for challenging tumors like these that require a multidisciplinary team of specialists, care is facilitated by bringing patients to an area where such resources already concentrated. The highly specialized nature of modern neurosurgery requires the collaboration of many practitioners to address the multiple aspects of these unique cases. These multidisciplinary teams must include physicians from different subspecialties, including cranial surgery, tumor resection, craniofacial reconstruction, and oculoplastic surgery. Complete surgical resection and skull reconstruction are feasible in these patients, but chances of hemorrhage and difficulty of skull reconstruction require a skilled, multidisciplinary team of clinicians.

Interestingly and unexpectedly, our provision of care to these patients resulted both positive and negative responses by the

lay community in the Twin Cities. Treatment costs for the patients described here ranged from $125,000 to $275,000. The cross-continental agreement allowed the surgeons and hospital to offer their services free of charge to the patient. When word of the surgeries was made public by the local media,[17] much of the Twin Cities community responded positively, while others found it unfair to provide free care to noncitizens when there are US citizens who cannot afford treatment. Thus, the hospital has become averse to future ambitious endeavors because of risk of negative media attention.

CONCLUSION

Giant disfiguring cranial tumors are extremely rare, primarily occurring in patients who are unable or unwilling to access care during the early stages of tumor development. Resection of such large masses can lead to substantial blood loss, and reconstruction of the impaired skull region and facial features requires precise management. Here, we show the successful treatment of four giant disfiguring cranial tumors by a multidisciplinary team. With proper curation and resources to send patients to a center able to provide excellent care, simultaneous surgical resection and craniofacial reconstruction by a multidisciplinary surgical team are a viable treatment option for these rare cases.

Acknowledgments

The authors acknowledge Superior Medical Experts for research and drafting assistance.

Declaration of patient consent

Patients consent not required as patients' identities were not disclosed or compromised.

Financial support and sponsorship

[illegible]

Conflicts of interest

[illegible]

REFERENCES

[illegible]

[illegible]

Necrobiotic Xanthogranuloma With Predominant Periorbital Involvement

[illegible]

Abstract: We present an unusual case of necrobiotic xanthogranuloma with periorbital involvement. [illegible]

[illegible]

CASE REPORT

[illegible]

Histopathology: [illegible]

DISCUSSION

[illegible]

[illegible]

DOI: [illegible]

Ophthal Plast Reconstr Surg, Vol. 26, No. 6, 2010

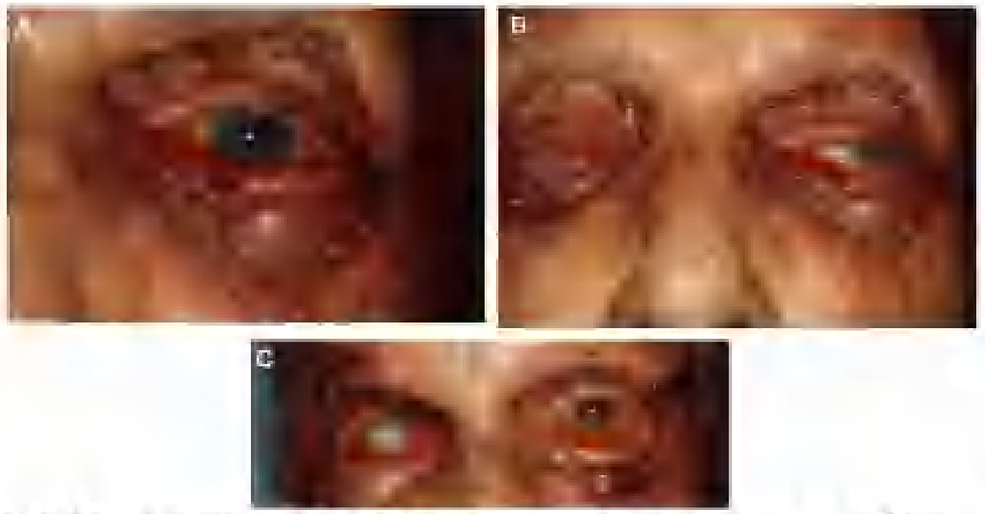

FIG. 1. A, Bilateral, periorbital yellow purple-like skin lesions with erosion through the dermis and surrounding edema. B, Inferior scleral exposure due to lagophthalmos. C, Corneal ulcer and chemosis.

Though multiple histopathologic and involvement of the lung, heart, kidney, intestine, ovary, larynx, pharynx, and skeletal muscle,[1,2,4,7] skin lesions of the trunk and extremities are often the initial presentation in 65% of cases, which are later followed by periorbital involvement. The hematologic manifestations are characterized by the triad paraproteinemia, 80% of which are of the immunoglobulin G (IgG) kappa or lambda light-chain type, hemorrhagic diathesis of the paraproteinemia, and blood dyscrasias may reveal hematologic malignancies such as multiple myeloma, chronic lymphocytic leukemia, and non-Hodgkin or Hodgkin lymphoma in up to one-third of PNG.[2]

Patients with NXG may demonstrate hematologic abnormalities including normocytic, normochromic anemia, leukocytosis, hypergammaglobulinemia, cryoglobulinemia, and paraproteinuria.[2,10] Initial investigations should therefore include complete blood count, erythrocyte sedimentation rate, urinalysis, serum protein electrophoresis, analysis of urine for Bence-Jones proteins, and skeletal survey. Based on the above findings, some clinicians have performed bone and echocardiography on all patients diagnosed with NXG.[10]

While the etiology is unknown, several theories of pathogenesis exist. One is that the formation of serum immunoglobulin-lipid complexes that deposit in the skin leads to a giant cell foreign body reaction.[1] Other hypotheses imply that the paraproteinemia exists a secondary proliferation of macrophages with receptors for the Fc portion of IgG or that paraproteins of NXG bind to hyaluronic receptors of fibrocytes, inducing granuloma formation.

Multiple treatment regimens for NXG have been tried and have met with variable success. Chemotherapy has shown to benefit some patients, both with and without adjunctive radiation therapy. Chemotherapeutic agents used have included cyclophosphamide, chlorambucil, azathioprine, melphalan, prednisone, and prednisolone.[1,2,4,10,11] Chan et al[11] found a good response to high-dose pulsed oral dexamethasone at a dose of 32 mg twice, followed by a maintenance dexamethasone regimen of 20 mg, at a cost of chemotherapy-resistant NXG. Surgical excision is generally not recommended because lesions recur within 6 months to 1 year in 42% of cases. Furthermore, the recurrent lesion is more than half of the cases larger than the original. Mechanical ptosis and inflammation should therefore not be worsening of the condition in certain reported cases.[2,10] Overall, despite of the diagnostic biopsy, surgical management is discouraged. These patients are at lifelong risk of developing a hematologic malignancy and require lifelong follow-up for earliest possible detection.

CONCLUSION

NXG is a disease with a variable clinical spectrum often involving ocular adnexa. The potential for an associated malignancy to undergo malignant transformation is relatively high, implying regular follow-ups for early detection. Treatment with chemotherapeutic agents with or without radiation have intermittent efficacy. The literature suggests that surgical debulking may lead to a recurrence of higher severity than the initial lesion and should therefore be avoided if possible. Exposure keratopathy and immunity positive corneal infiltrates were complicating factors in the current case.

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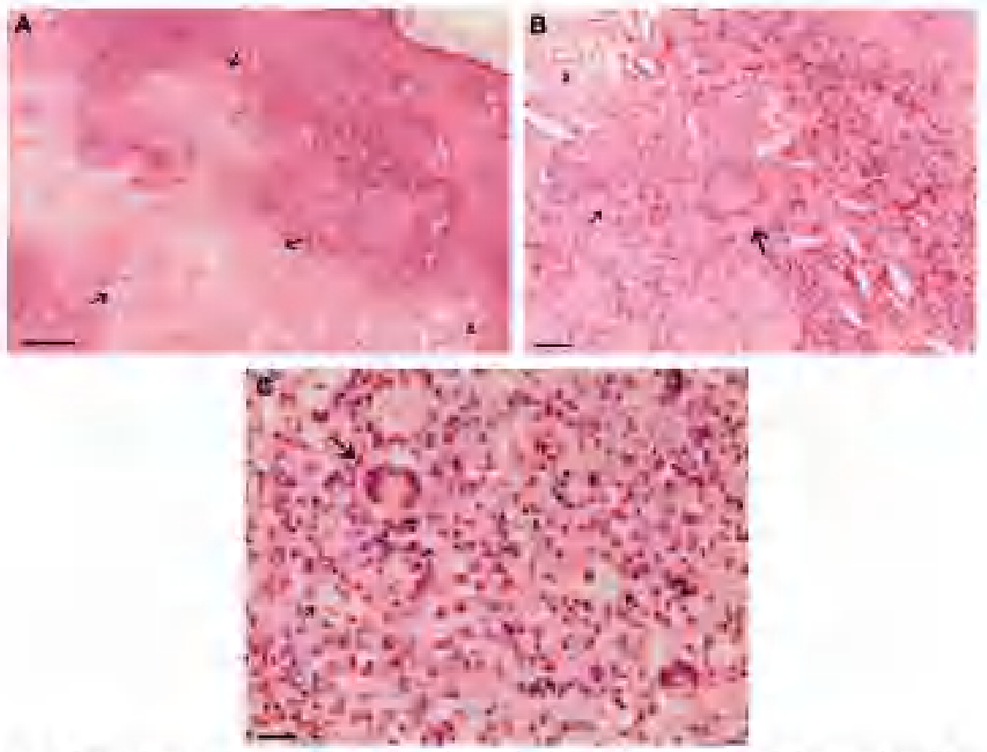

FIG. 2. A, Sheets of pleomorphic neoplastic tumor cells within the dermis. Multiple clear spaces in vertical orientation (arrows). Hematoxylin-eosin, ×50. B, Higher power in the dermis showing giant cells (large arrow) and mononuclear histiocytes with adjacent cytoplasmic vacuoles (small arrows) and mucoid cytoplasmic inclusions (arrowheads). Hematoxylin-eosin, ×200. C, High-power view of tumor cells demonstrating bizarre giant cell nuclei (arrow) against a background of loose mononuclear and small neurotic hematoxylin, ×400.

Deep Penetrating Orbitocerebral Steel Spring Injury With Minimal Sequelae: A Case Report

Matthew T. Nolte, M.D., Shreyas P. Kinare, M.D., Dennis Bartley, D.O., and Arsenio P. Lee, M.D., J.D.

Abstract: The authors report a penetrating orbitocerebral steel mattress spring injury without permanent ophthalmic or neurologic sequelae. A 44-year-old female mattress factory worker sustained an injury to her right orbit in a high-velocity projectile foreign body. Imaging revealed a metallic spring in the right orbit traversing the optic nerve.

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and superior orbital fissure and bridging in the temporal lobe of the brain. Cerebral angiography demonstrated the steel rod around, but not damaging, the middle cerebral artery and other vessels. With a combined craniotomy and frontal orbitotomy, the spring was removed in one piece counterclockwise rotation. Postoperatively, the patient had mild left-sided weakness that resolved after several weeks. Ocular examination was normal, including full extraocular movements and a visual acuity of 20/20 in each eye. The authors theorize that the spiral shape and counterclockwise unscrewing allowed the projectile to follow a path of least resistance penetrating deeply and exiting around but not injuring, vital structures. A right craniofacial approach was effective in removing the spring.

CASE PRESENTATION

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DISCUSSION

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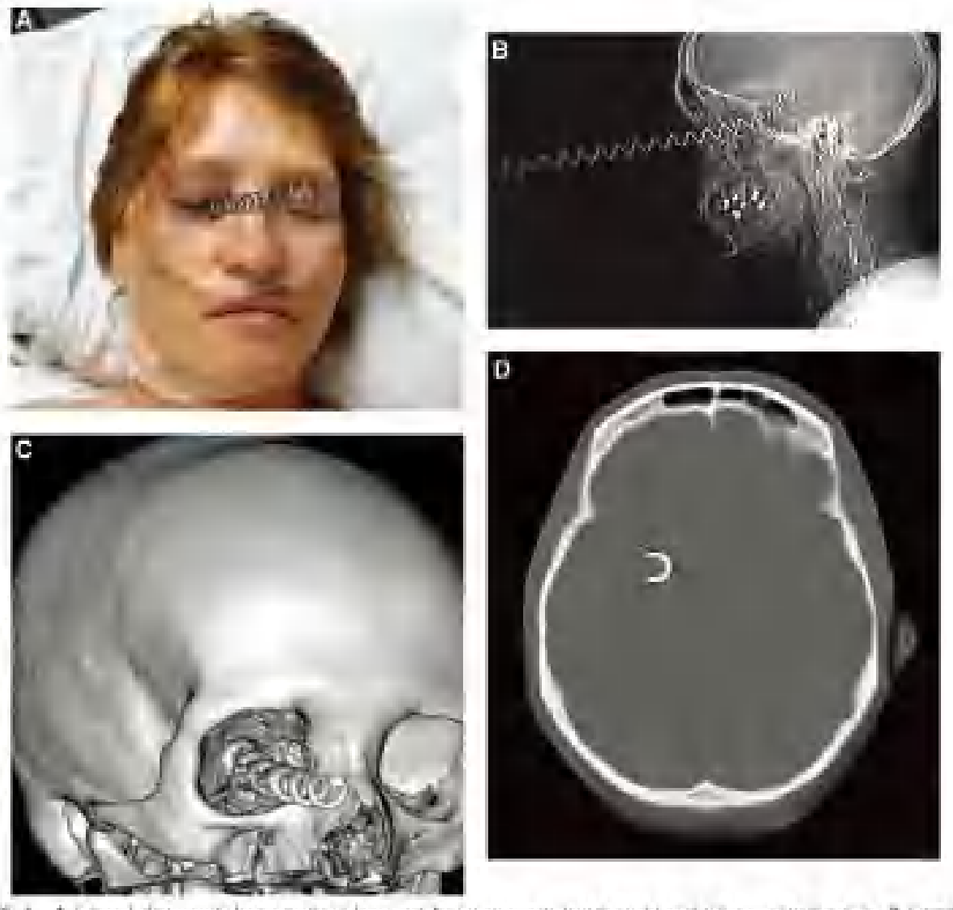

FIG. 1. A, External photograph demonstrating a large metallic spring penetrating the right orbit inferonasal to the globe. B, Lateral skull film depicting the spring penetrating through the orbit and into the brain. C, Three-dimensional volumetric reconstruction showing the spring penetrating through the orbit and into the superior orbital fissure. D, Axial CT scan showing deep penetration of the metallic spring in the brain.

may take a straight path despite decreasing its velocity in that path unless they are influenced by intrinsic forces such as dense tissue or bone.[7] Moreover, the plasticity of a spring may allow it to conform slightly as it penetrates. Alternatively, the axis rotation of a rod through tissue may cause lesser amounts of tissue damage to occur during its penetration. As such, the spring in our patient may have taken the path of least resistance, sparing vital structures such as the optic nerve or major arteries. Further investigation is needed to explain the torsional ballistics of rigid rods through human tissues.

The combined craniotomy and orbitotomy approach may have also contributed to the positive outcome. Direct visualization during removal may have prevented excessive intracranial or intraorbital bleeding and spared adjacent soft tissue trauma during spring extraction. Additionally, these approaches afforded the opportunity to close fistulous subdural defects that

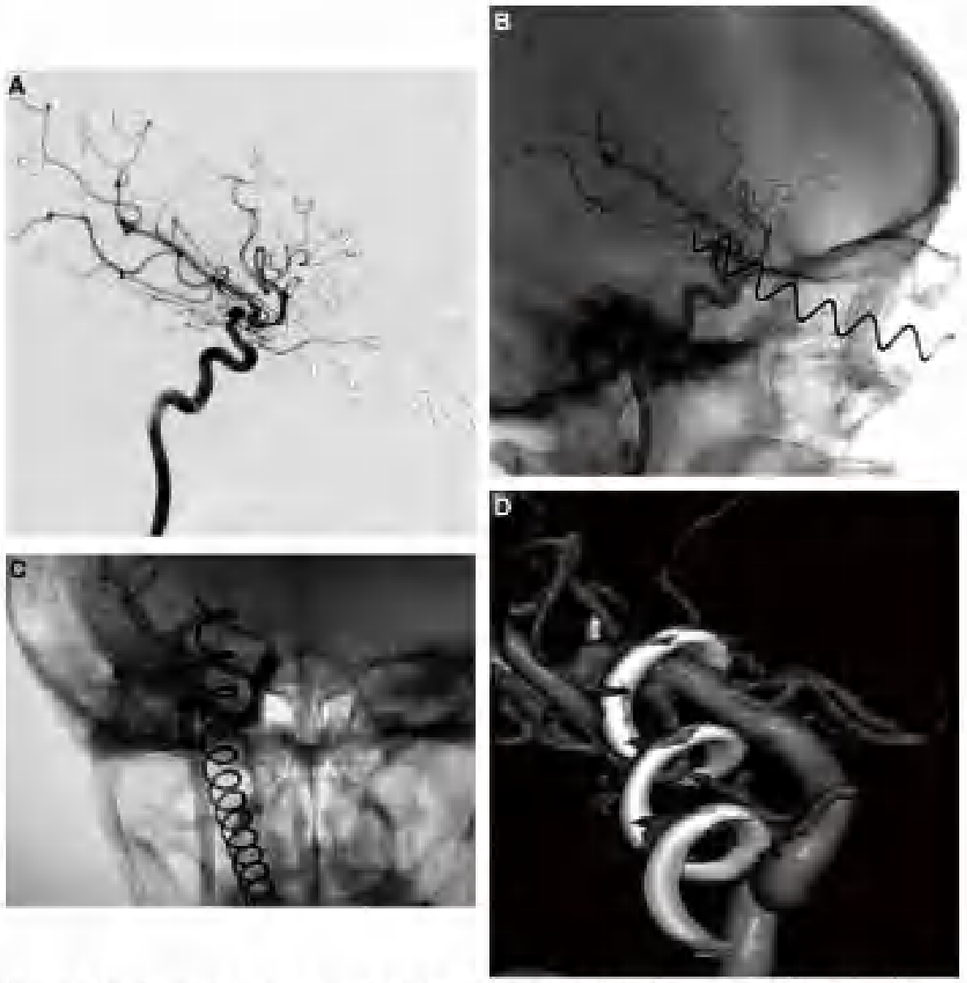

FIG. 2. Imaging with contrast injection in the right internal carotid artery demonstrating intracranial penetration of the metallic spring without injury to the right intracranial internal carotid artery, ophthalmic artery, and the proximal middle cerebral artery (M1 segment). A, Lateral view of digital subtraction cerebral angiogram. B, Lateral view of cerebral angiogram. C, Frontal view of cerebral angiogram. D, Three-dimensional volumetric reconstruction.

the specifics on the optic nerve and fit of eyewear are taken in this case, further investigation and education surrounding the best ways to prevent injury with proper protective eyewear are paramount.

CONCLUSION

A deep orbitocerebral penetrating injury with a steel spring may be rare. A multidisciplinary and combined neurosurgical and orbital specialty approach, using careful counterclockwise rotation with direct visualization, achieved an excellent outcome.

ACKNOWLEDGMENTS

The authors thank Heather Hudson for her skilled technical assistance.

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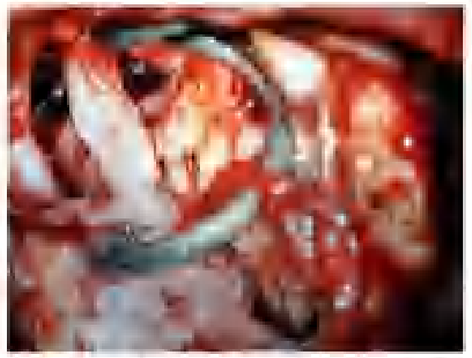

FIG. 1. [illegible] intraoperative photograph of right frontal craniotomy [illegible] the metal spring [illegible] against the right cerebral [illegible] cortex [illegible] to the [illegible].

[illegible]
[illegible]
[illegible]
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[illegible]
[illegible]

Orbital Lymphoma Presenting With Choroidal Detachments

Mark S. Hartwell, MD, Sandy A. Barbe, D.O., F.A.C.O.S.,*† Ronald Fontanesi, M.D., F.R.C.P.(C),‡ and Hugh McKenna, M.D., F.R.C.P.(C)§*

Abstract: This report describes a case of orbital B-cell lymphoma of extranodal marginal cell type with atypical clinical and radiographic features. The patient presented with choroidal effusion and optic disk swelling of the right eye. A CT scan revealed an intraconal mass surrounding the optic nerve and indenting the globe. A right orbitotomy with biopsy of the mass was performed. Histologic and immunohistochemical analysis confirmed a diagnosis of extranodal marginal cell B-cell lymphoma. This is the first case of primary orbital lym-

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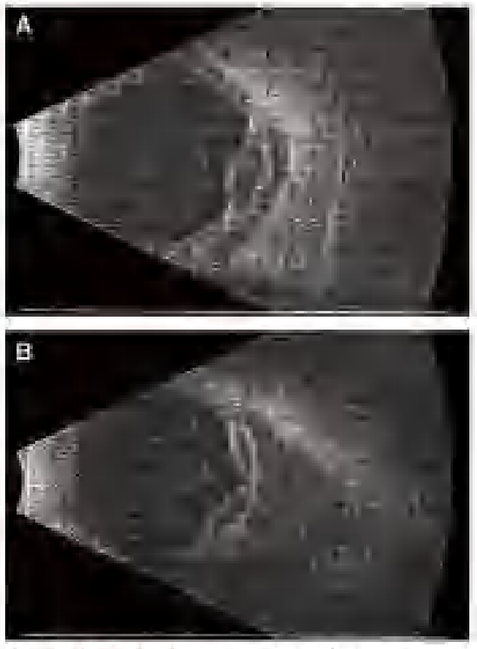


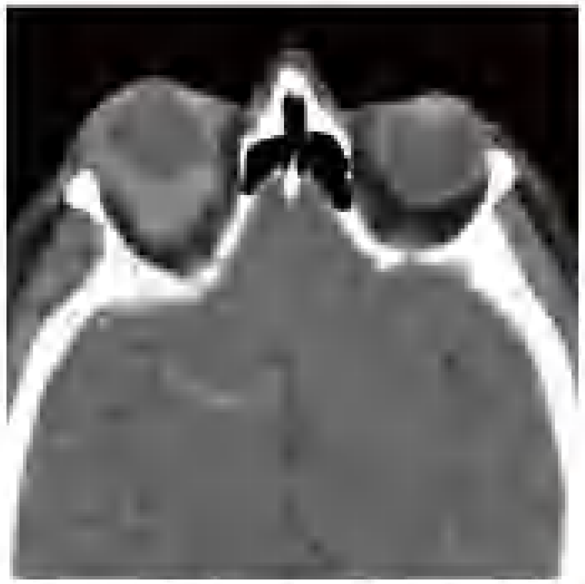
FIG. 3. A, Peripheral ultrasonic B-scan ultrasonogram showing a smooth, thick choroidal/pars [illegible] effusion that appeared to [illegible] consistent with choroidal detachment. A low reflectivity [illegible] was noted adjacent to the globe. B, Peripheral transverse B-scan ultrasonogram showing [illegible] producing a scalloped appearance that is characteristic of choroidal detachments.

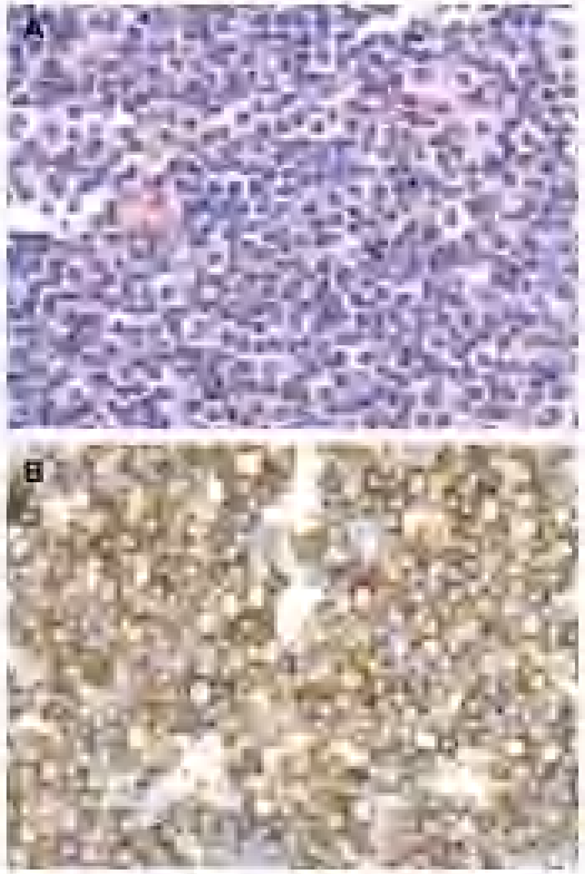
phoma presenting with choroidal effusion described in the literature.

Ocular adnexal lymphoma constitutes [illegible] of all [illegible] and primarily involves the orbital [illegible] and [illegible] [illegible]. Typical presenting signs and [illegible] include [illegible] proptosis associated with [illegible] and limitation of extraocular movement. The [illegible] tumor tends to grow [illegible] orbital margins without bony destruction or infiltration. We document a case of orbital lymphoma presenting [illegible] with choroidal effusion and optic disk swelling.

CASE PRESENTATION

A 71 year old man was referred for [illegible] evaluation 2 months after right cataract surgery complicated by [illegible] hemorrhage. The patient was on [illegible] latanoprost/timolol, [illegible] ophthalmic solution, [illegible] and [illegible]. Initial C.A. [illegible] was 1.4 in the right eye, which had been stable 4 months prior to the surgery, when he was noted to have high intraocular pressure (34 mm Hg) in the right eye. At the time postoperatively was hypotony present. On presentation, the patient's visual acuity was counting fingers at [illegible] and 20/25 in the [illegible] [illegible] pressures were 21 mm Hg in both eyes. Anterior segment examination of the right eye revealed a posterior chamber intraocular lens





DISCUSSION

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REFERENCES

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Delayed Orbital Hematoma After Lateral Canthoplasty

[illegible]

CASE PRESENTATION

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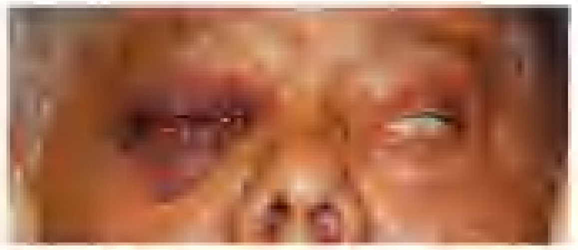

FIG. 1. Photograph taken on presentation with retrobulbar hemorrhage after glaucoma surgery, demonstrating periocular ecchymosis and subconjunctival hemorrhage.

[illegible]

DISCUSSION

[illegible]

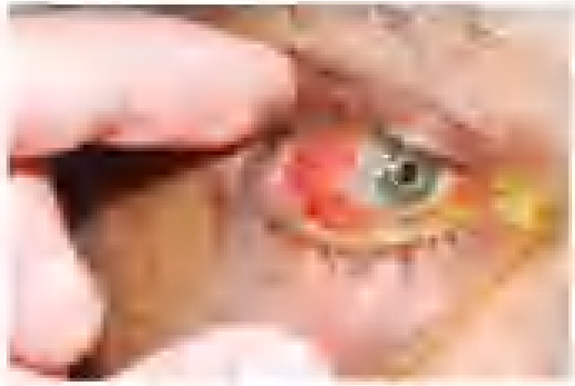

FIG. 3. Photograph taken 18 days after lateral canthotomy and inferior cantholysis, demonstrating subsequent recurrent hemorrhage with lateral canthal hematoma and canthal dehiscence.

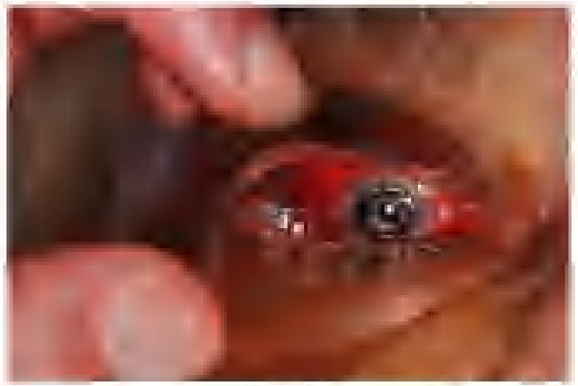

FIG. 4. Photograph taken 5 weeks after presentation with lateral canthal hematoma, showing response to conservative treatment with granulation tissue noted in the lateral canthus.

[illegible]

[illegible]

REFERENCES

[illegible]

A Caruncular Choristoma Presenting as an Eyelid Mass in an Infant

[illegible]

Abstract: A 7-week-old patient presented for evaluation of a congenital eyelid mass. Following surgical excision of the lesion, histopathologic diagnosis of caruncular choristoma was made. To the authors' knowledge, this is the first report of caruncular tissue presenting as an external eyelid mass.

A [illegible]

[illegible]

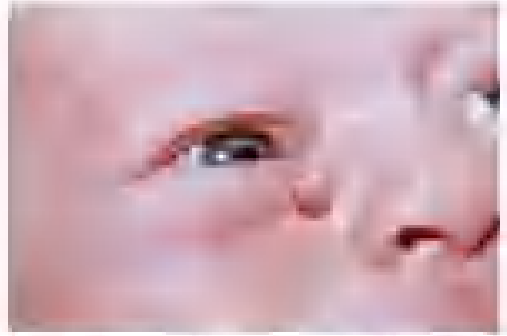

FIG. 1. External photograph obtained at 7 weeks of age demonstrating small, pedunculated, 5 × 6-mm mass [illegible] the right medial canthus.

[illegible]

FIG. 2. [illegible] stratified squamous epithelium [illegible] were identified within the lesion. [illegible] (hematoxylin-eosin stain, [illegible]).

FIG. 3. [illegible]

[illegible]

DISCUSSION

[illegible]

REFERENCES

[illegible]

The Importance of Keeping the Chin Up in Graves Orbitopathy

[illegible]

Abstract: [illegible]

A [illegible]

FIG. 1. [illegible]

FIG. 3. A CT-scan showing the enlarged inferior rectus muscles, more pronounced at the right side.

[illegible]

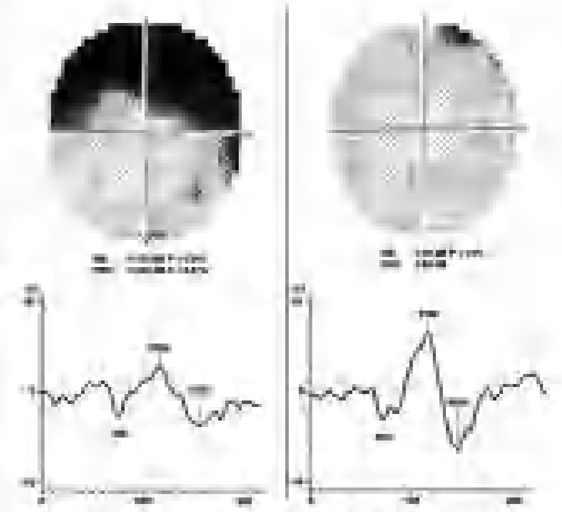

FIG. 2. Visual fields (top) and pVEPs for check size [illegible] from the right eye when measured in "primary position" (left) and when measured in chin lift (right).

DISCUSSION

[illegible]

FIG. 4. The patient positioned in chin lift at the [illegible]

Ophthal Plast Reconstr Surg Vol. 28, No. 8, 2012

Abstract: Oncocytic carcinoma (OC) is a rare, and although its occurrence in the lacrimal gland has been documented, clinical and histologic data are lacking. The authors report the first case of OCA of the lacrimal gland synchronously present in a patient with neurofibromatosis (NF). An 87-year-old man affected by type 1 NF presented with a 2-year history of left proptosis and ptosis. Orbital CT scan showed a mass in the lacrimal gland fossa infiltrating the globe, lateral rectus muscle, and bone. An incisional biopsy revealed a primary high-grade malignancy, and the patient underwent orbital exenteration followed by postoperative adjunctive radiotherapy. Six months after the operation, the patient was alive, without evidence of recurrence or metastatic disease. OCA is a high-grade neoplasm with infiltrative growth pattern and tendency to recur and metastasize. Its occurrence in association with NF has not been documented before, but clinicians should be aware of this possibility when evaluating proptosis in NF patients. Radical surgical excision, followed by adjunctive radiotherapy, is considered the treatment of choice, but the prognosis remains guarded.

Oncocytic carcinoma (OC) is an uncommon high-grade malignant neoplasm composed by monomorphic and pleomorphic oncocytic cells. Occurrence of OC in the lacrimal gland was rarely documented in the literature.[1–3] To the best of our knowledge, this is the first case of OCA of the lacrimal gland synchronously present and reproducible through biopsies with the typical cutaneous lesions associated with neurofibromatosis (NF).

CASE REPORT

An 87-year-old man presented with a 2-year history of slowly progressive, painless proptosis and ptosis of the left eye. He had a 17-year history of NF, mental retardation, and spinal deformities that were unaffected by a low-grade astrocytoma of cerebellar vermis and other relevant medical conditions. He had undergone multiple plexiform neurofibroma surgical resections of the left orbit and face at 10 years of age and a left parotidectomy for facial nerve palsy at 20 years of age. He was also affected by hypertension, diabetes mellitus, and chronic obstructive pulmonary disease. He had no family history of NF. Ophthalmic examination revealed 4 mm of left proptosis and grade 2 eye ptosis. The extraocular motility was normal, although there was a restriction in the left eye. Slit-lamp examination revealed a normal anterior segment, and no abnormalities were found in the left eye. Fundoscopic examination was unremarkable. Computed tomography (CT) scan showed a homogeneous, moderately enhancing mass located in the left lacrimal fossa with diffuse involvement of the ipsilateral orbital and extraocular muscles as well as the lateral orbital wall (Fig. 1). Left maxillary sinus opacification was also evident. Six months after the operation, the patient was alive, without evidence of recurrence or metastatic disease. OCA is a high-grade neoplasm with infiltrative growth pattern and tendency to recur and metastasize. Its occurrence in association with NF has not been documented before, but clinicians should be aware of this possibility when evaluating proptosis in NF patients. Radical surgical excision, followed by adjunctive radiotherapy, is considered the treatment of choice, but the prognosis remains guarded.

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Oncocytic Carcinoma of the Lacrimal Gland in a Patient With Neurofibromatosis

Giuseppe P. Bonavolontà, M.D.,*
Giulio Strianese, M.D.,†
and Luca Lanzetta, M.D.‡

FIG. 1. Preoperative appearance of the lacrimal gland mass displacing the globe medially. Multiple neurofibromata are visible on the face.

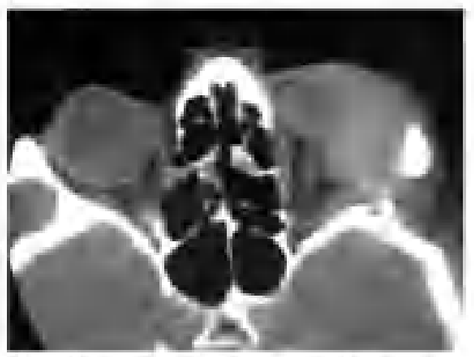

FIG. 2. Postoperative CT scan showing a well-defined mass with polypoid lesions infiltrating the lateral wall of the globe, lateral rectus muscle, and lateral bone.

DISCUSSION

OCA is characterized by a malignant proliferation of the cells that constitute the adenomatous epithelium. It may occur de novo but more frequently originates from malignant transformation of a benign oncocytoma. A salient clinical feature is a long-standing asymptomatic mass that may grow fast in response to transformation to an OCA. Histologic criteria that characterize oncocytic tumors are the massive accumulation of oncocytic cells as readings by hematoxylin-eosin stains and PTAH, but the diagnosis is undoubtedly confirmed by electron microscopy or immunohistochemistry. Cytological and phenotypic atypia associated with an infiltrative growth pattern differentiate the malignant tumors.[1] Differential diagnosis includes metastatic neoplasms or adenocarcinoma of the salivary glands. Clinically, oncocytoma and oncocytic tumors of the lacrimal gland are rare, representing less than 1% of all neoplasms.[2] In the salivary glands, oncocytomas occur more frequently in the parotid gland, where they represent less than 5% of all neoplastic lesions.[3] The occurrence of OCA in the lacrimal gland was described for the first time in the English literature in 1965 by Rapoport and Font.[1] An electron microscopy and DNA content performed on tumor tissue was not available. Numerous cases of "oncocytic" adenocarcinoma were described in the following years, but clinical information was usually missing. In all only 4 cases of OCA of the lacrimal gland were reported in the literature from 1965 to 1995.[1–4] The first case of the Italian literature in 1965,[5] including another case reported by Rigdon et al.,[1] is common. It appears that the diagnosis of OCA, as in the present literature, has been based merely on histological examination. Unfortunately, immunohistochemical and molecular information were not available in any of the reports. The treatment of malignant lacrimal gland tumors is poorly documented, mainly because of their rarity. Because of their aggressive behavior, they are usually treated with radical surgical excision, followed by adjunctive radiotherapy.[4] Chemotherapy is rarely used as a first line of treatment. The role of systemic chemotherapy is unknown. Its occurrence in association with tumors of the orbit is a controversial argument in the case of malignant tumors' presentation followed by radiation therapy was made.

To our best of our knowledge, this is the first case of OCA of the lacrimal gland synchronously present and reported in the English literature in a patient affected by NF. NF is a recognized risk factor for the development of malignant peripheral nerve sheath tumors, but it may also give rise to other tumors, including epithelial tumors arising from lacrimal gland. Lacrimal gland tumors are rarely clinically encountered in patients with NF. Clinicians should be aware of this possibility when evaluating proptosis in NF patients.[5]

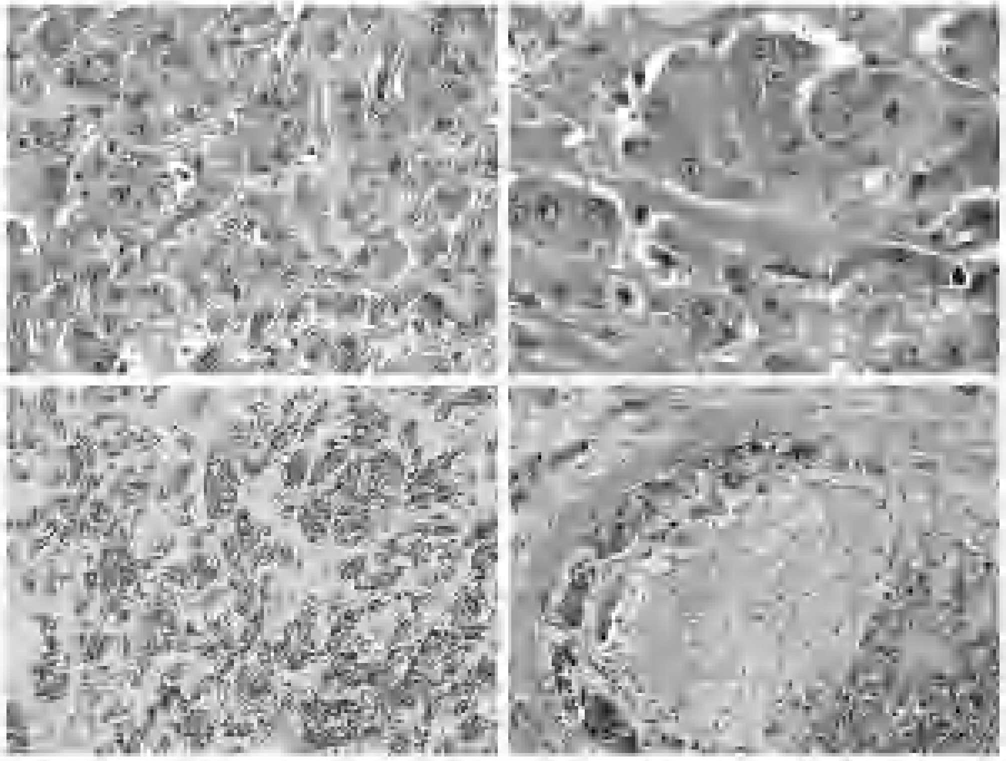

FIG. [illegible]

REFERENCES

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Ptosis and Ophthalmoplegia Associated With Epidermolysis Bullosa Simplex-Muscular Dystrophy

[illegible]

Abstract: The association of epidermolysis bullosa simplex and muscular dystrophy (EBS-MD) has rarely been discussed in ophthalmology literature. This case report offers a brief summary of epidermolysis bullosa and describes what is known about EBS-MD. The case reviews a patient with EBS-MD who presented with ptosis and ophthalmoplegia, suggesting that these may be complications of EBS-MD.

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CASE REPORT

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COMMENT

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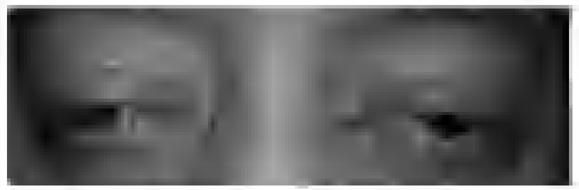

FIG. [illegible]

FIG. [illegible]

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REFERENCES

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Abobotulinum Toxin A (Dysport) and Botulinum Toxin Type A (Botox) for Purposeful Induction of Eyelid Ptosis

[illegible]

Abstract: [illegible]

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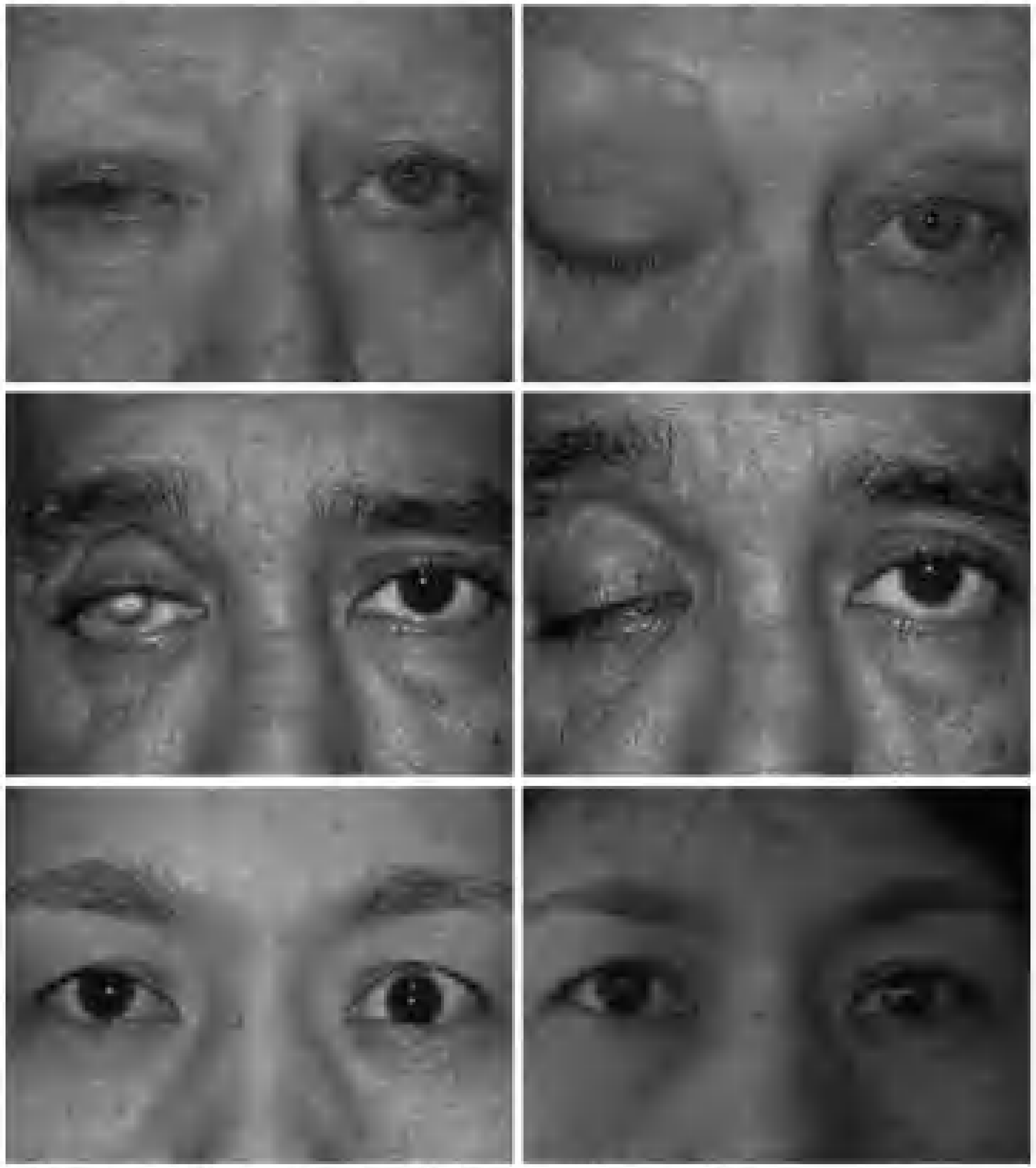

FIG. 1. Preprocedure and postprocedure photograph for each patient—1, 2, and 3 as described.

toxin A for functional corneal protection in two cases and botulinum toxin type A for facial symmetry after Bell's palsy in one patient. The first case is a 75-year-old female with a nonhealing corneal erosion in her right eye secondary to epithelial basement membrane corneal dystrophy who underwent injection of 24 units of abobotulinum toxin A to the right Muller's muscle and levator palpebrae superioris to induce a protective ptosis. The second case is a 40-year-old male with corneal decompensation in the right eye after penetrating keratoplasty who underwent similar injection at both sites. The third case is a 46-year-old Asian female with history of Bell's palsty affecting her right side and causing mild left eyelid retraction who was injected 3 units of botulinum toxin type A to her Muller's muscle for lid positioning. Chemodenervation is used in these cases to purposefully induce ptosis by careful injection to Muller's muscle and the levator palpebrae superioris for functional and cosmetic purposes.

E[illegible]

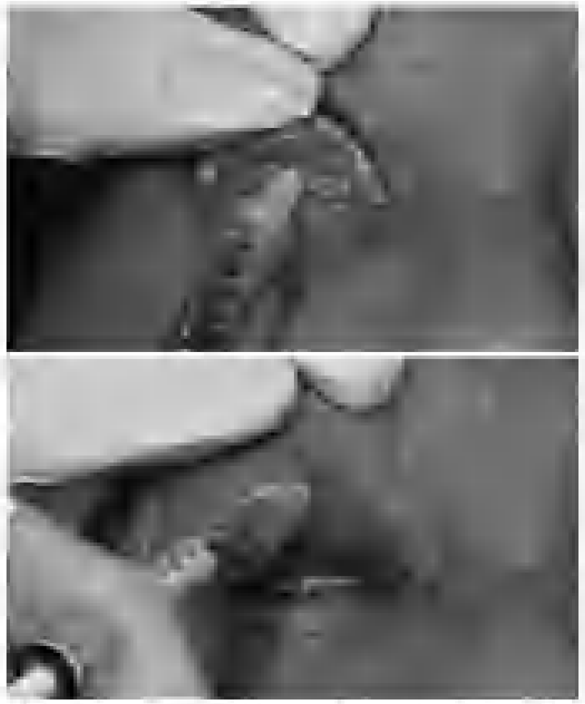

FIG. 2. [illegible]

REFERENCES

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Eyelid Basal Cell Carcinoma Developing in an Epidermoid Cyst: A Previously Unreported Event

[illegible]

Abstract: [illegible]

[illegible]

DOI: [illegible]

one of which harbored a basal cell carcinoma arising from its orthokeratinizing squamous cell lining. Focal openings indicated that the cysts represented follicular infundibular ectasias. BER-EP4-positive immunostaining confirmed the basal cell nature of the neoplasm. This is the first example in the eyelid of an epidermoid cyst displaying malignant transformation. No matter how innocent they may appear, all small cystic or noncystic eyelid lesions should be submitted for pathologic evaluation.

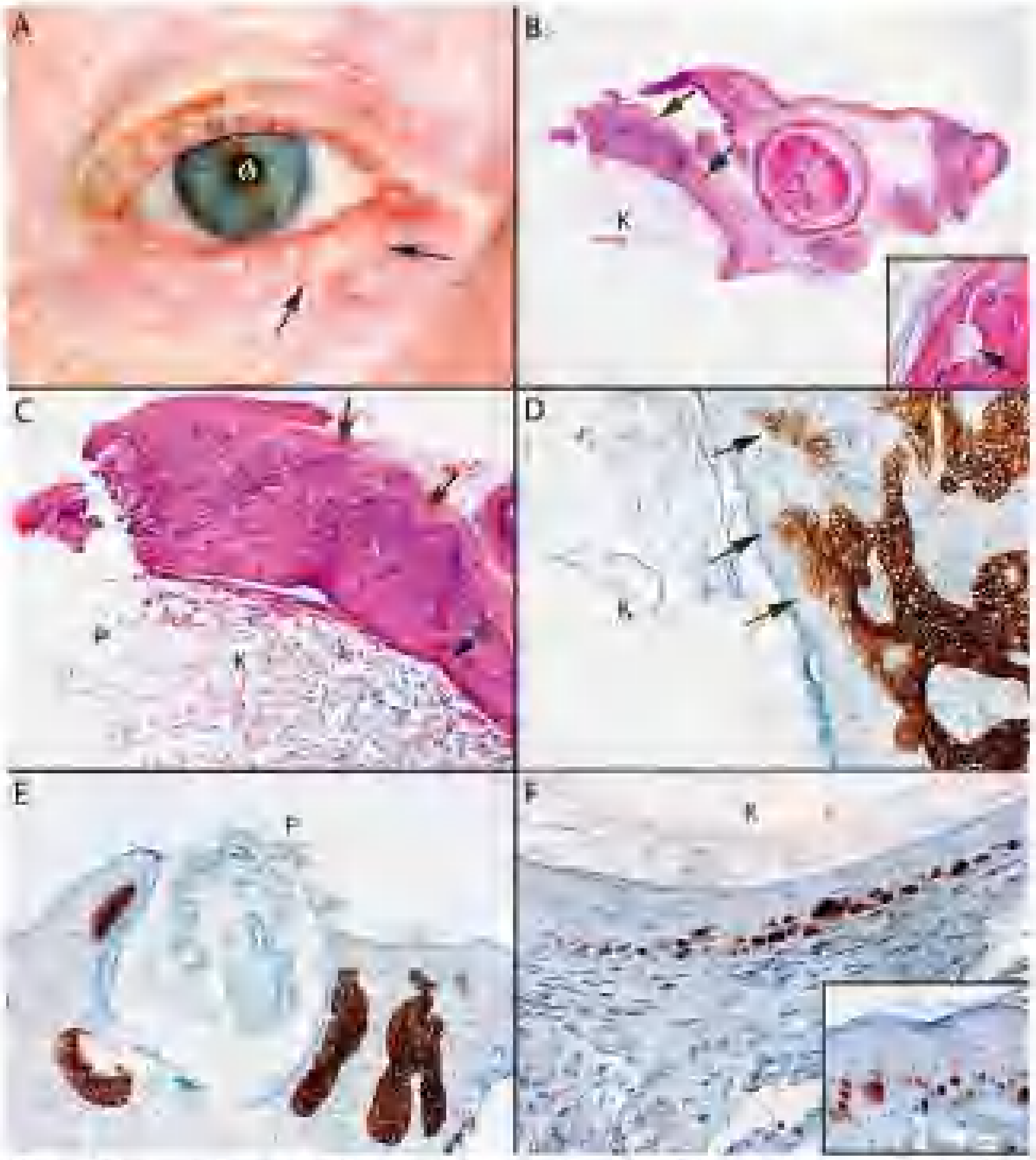
E[illegible]

CASE REPORT

[illegible]

DISCUSSION

[illegible]



Eyelid basal cell carcinoma arising in an epidermoid cyst. A, [illegible]

REFERENCES

1. [illegible]
2. [illegible]
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7. [illegible]
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9. [illegible]

Primary Orbital Manifestation of Hodgkin Lymphoma in a 3-Year-Old Child

Andrew R. Thompson, M.D.[1], Hongyuan Liu, M.D.[2], Alfred Marcus Lewis, M.D.[3], John C. Dynan, M.D.[4], and Matthew S. Ater, M.D.[5]

Abstract: Hodgkin lymphoma is exceedingly rare in children, as is primary orbital manifestation of systemic Hodgkin lymphoma in any age category. The authors describe the clinicopathologic manifestations of a rare case of systemic Hodgkin lymphoma with primary orbital manifestation in a 3-year-old boy with histologically proven Hodgkin lymphoma who moved voluntarily. After an initial biopsy and tumor debulking, followed by systemic workup, the diagnosis of stage IV A Hodgkin lymphoma was made. He underwent treatment with 4 cycles of adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide, followed by involved field radiation. He has been followed at regular intervals for 4.5 years. Scans have shown resolution of all MRI, and blood tests have remained normal. To the best of the authors' knowledge, this is the youngest patient with primary orbital manifestation of Hodgkin lymphoma reported in the English literature.

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Hodgkin lymphoma is rare in children (only 7% of reported patients with lymphoma are younger than 10 years of age). Most cases of clinical manifestation of Hodgkin disease (HD) have been described in systemic disease or in immunocompromised individuals. There are few cases in the English literature of primary orbital presentation of Hodgkin disease in otherwise healthy individuals, presumably more typical of the histologic type classification of Hodgkin disease.[1] The youngest reported case in the English literature is that of an 11-year-old boy.[2] We report a case of primary orbital manifestation of Hodgkin lymphoma in a 3-year-old boy. To our knowledge, this is the youngest patient to have primary orbital manifestation of Hodgkin lymphoma reported in the English literature.

CASE REPORT

A 3-year-old black boy [illegible] of unknown duration of swelling of the right upper eyelid. His patient's parents denied any history of prior redness or swelling, and denied any episodes of trauma or prematurity. He had been treated with 2 different antibiotics over the previous 2 weeks, and no relieved. [illegible]

On physical examination, the patient's head was appealing [illegible]. There was obvious swelling of the right upper eyelid, sufficient to cause ptosis of [illegible] (Fig. 1). His visual acuity was 20/30 bilaterally using Allen figures. He had no relative [illegible]. [illegible] were all within normal limits. There was no anterior segment and funduscopic abnormalities were noted bilaterally.

CT demonstrated a soft tissue mass in the right superior orbital [illegible] (Fig. 2). An incisional biopsy did not reveal [illegible]. The tumor was [illegible] and [illegible] were positive. Ultimately, there was [illegible] consistent with [illegible]. Bone marrow biopsy [illegible] of Hodgkin lymphoma.

CT scan of the chest revealed [illegible] and [illegible] lymph nodes, right supraclavicular lymph node and [illegible]. PET scan of the chest revealed a left paraspinal soft tissue mass with intermediate metabolic [illegible] hypermetabolic. Abdominal CT [illegible] enhancing lymphadenopathy in the level of the lower pole of the right kidney. There were diffuse increased uptake in the distal bone and skeletal [illegible] with a focal [illegible] (PET scan [illegible] activity in the right neck and mediastinal, left supraclavicular and pelvic areas. Cervical lymph node biopsy revealed

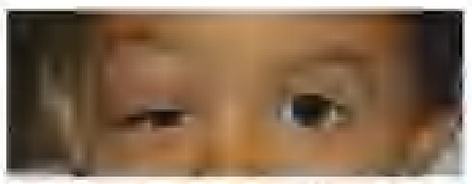

FIG. 1. A 3-year-old boy with a [illegible] of swelling of the right upper eyelid.

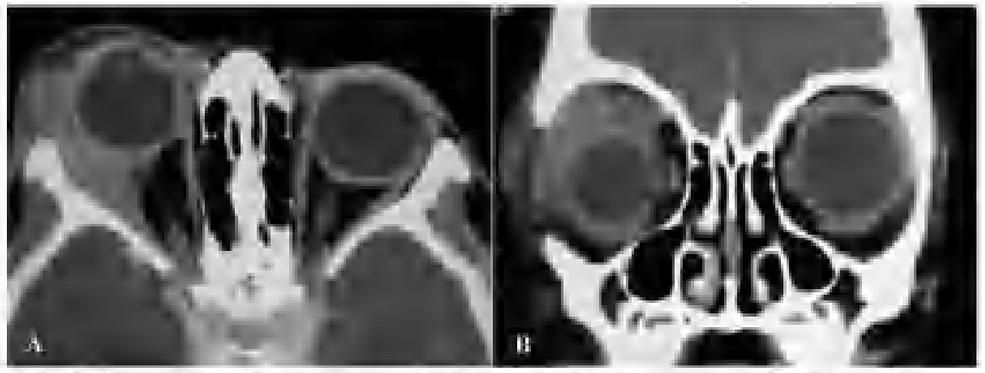

FIG. 2. A CT scan of the head showing a homogeneous right supramaxillary soft tissue mass in coronal (A) and coronal (B) views.

similar findings of [illegible] and hyperplasia. The final diagnosis of Hodgkin lymphoma, nodular sclerosis, [illegible] number positive were negative.

A bone marrow biopsy was [illegible] with mesenchymal cells. The main focus of imaging and [illegible] was [illegible]. Treatment included [illegible] with 4 cycles of adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide chemotherapy. The patient also received [illegible] to the orbit, face, and neck [illegible] with [illegible] and [illegible]. He has been followed with [illegible] examinations, imaging of involved areas, and whole-body PET scanning. Six years after treatment, he has had [illegible] and has been [illegible] normal. Dental complications from the orbital mass [illegible] required [illegible] and [illegible]. After clinical surgery, [illegible] was [illegible] 20/30 [illegible] and 20/20 in the left.

DISCUSSION

Nearly [illegible] of patients [illegible] with [illegible] and [illegible] lymphadenopathy. Nearly [illegible]

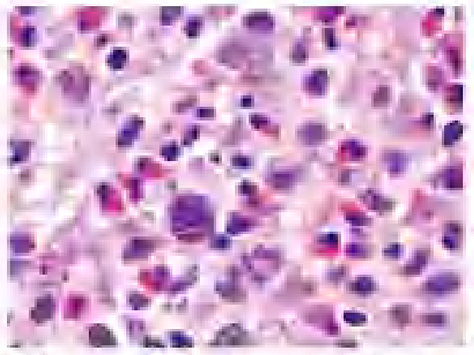

FIG. 3. [illegible] shown [illegible] shows a [illegible] Reed-Sternberg cell.

[illegible] Hodgkin lymphoma, while accounting for [illegible] of all systemic lymphomas in adults, is exceedingly rare in childhood. Hodgkin lymphoma has a bimodal age distribution with the first peak being seen between the ages of 15 and 20 years and the second peak occurring in the sixth decade. Hodgkin lymphoma is very rarely diagnosed in children less than 5 years of age. The most common presentation of Hodgkin lymphoma in children includes asymptomatic cervical or supraclavicular lymphadenopathy. Other common presentations include mediastinal adenopathy resulting in [illegible] pleural [illegible] effusion. Primary disease sites are typically supradiaphragmatic. Constitutional symptoms are present in approximately [illegible] of children and include fevers, night sweats, and weight loss. Primary orbital manifestations of Hodgkin lymphoma are extraordinarily rare.

Pertinent laboratory findings of Hodgkin disease include eosinophilia, leukocytosis, lymphopenia, normocytic anemia, and normocytosis. Lymph node biopsy revealing the characteristic multinucleated Reed-Sternberg cells is diagnostic. There are 4 histologic subtypes of Hodgkin disease: lymphocyte predominance, nodular sclerosis, lymphocyte depletion, and mixed cellularity, accounting for [illegible] of pediatric cases are of the nodular sclerosing or mixed cellularity subtypes. Following diagnosis, thorax radiography and pelvic imaging in addition to PET scan are the standard procedures for staging and planning treatment.

Treatment for Hodgkin lymphoma in children is a balance between maximizing survival and minimizing treatment-related toxicity. Treatment protocol is long and can be intensive. Current protocols typically involve combinations of chemotherapeutic agents. In pediatric patients with bulky tumors and B-type symptoms, involved field radiation is also implemented. Chemotherapy-only protocols are [illegible] high-dose regimens with [illegible] relapse rates in [illegible] of children with localized disease and in [illegible] of children with advanced disease within 5 years of diagnosis. Salvage rates for relapse range from [illegible] and [illegible] for childhood Hodgkin disease, respectively.[illegible]

To the best of our knowledge, our case represents the youngest, otherwise healthy, individual with primary orbital manifestation of Hodgkin lymphoma reported in the English literature. Distinguishing benign inflammatory lesions from less common, but lethal, disease is imperative. A high degree of clinical suspicion for lymphoproliferative malignancy is necessary when treating an orbital mass in all age groups.

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Primary Diffuse Large B-Cell Lymphoma of the Frontal Sinus

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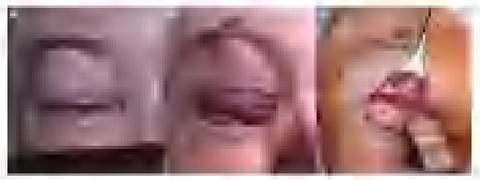

FIG. 1. Frontal presentation (A) in way of surgery (B), revealed expansile, rapid consumption of tissue, with severe comminuted swelling and hemorrhagic edema. Orbital exploration (C) revealed a firm, greyish, calcified tumor invading the superior orbit.

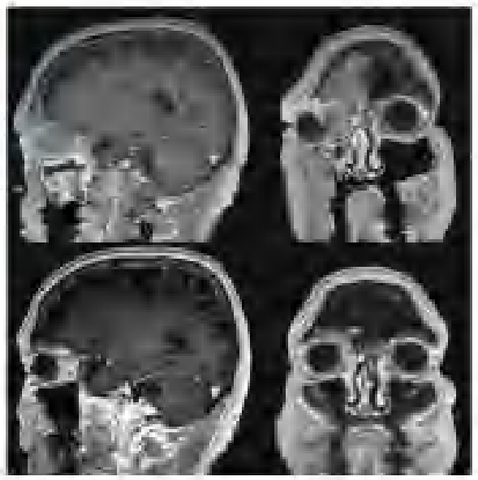

FIG. 2. Post-contrast axial magnetic resonance imaging (top) showed a large, expansile mass originating from the right frontal sinus into the superior extraconal space, with encasement of multiple extraocular muscles and the optic nerve. Post-treatment imaging (bottom) demonstrated complete metabolic response.

A 10-year-old male presented with a complaint of right upper eyelid swelling and 1 month of progressive binocular diplopia. Examination was notable for right eye vision of 20/70, asymptomatic sensory exotropia, presence of 4 mm, complete pupils, proptosis, chemosis, and conjunctival injection (Fig. 1A). Slit lamp and dilated examination were otherwise normal. CT demonstrated a large, homogenous, expansile mass extending from the right frontal apex into the superior extraconal orbit. He was scheduled for surgery and placed on a preoperative prednisone taper. In the intervening month, his asymptomatic rapid progression of disease with severe periorbital edema and hemorrhagic chemosis (Fig. 1B). He underwent right anterior orbitotomy and frontal sinus exploration. Final administration and sensitivity pansinusitis. Orbital exploration revealed a firm, grey-tan colored tumor invading the superior orbit (Fig. 1C). Histopathology revealed CD20 positive diffuse large B-cell lymphoma with MYC gene rearrangement. Staging work-up including MRI (Fig. 2, top) revealed an intracranial extension of lesion size, with encasement of the right superior, medial, and lateral rectus muscles, superior oblique muscle, and optic nerve. He was diagnosed with stage IV diffuse large B-cell lymphoma of the frontal sinus and right orbit. He completed 3 cycles of

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Case report

Erotic asphyxiation: May have you seeing double

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ABSTRACT

Purpose: If not recognized and treated promptly, nontraumatic orbital subperiosteal hemorrhage (NTSOH) can have serious sequelae including compressive optic neuropathy and permanent vision loss. The following case establishes erotic asphyxiation as a cause of NTSOH.

Observations: A 29 year-old patient presented with diplopia and periorbital edema and ecchymosis. Complete ophthalmologic exam showed exotropic neuropathy. Computed tomography of the orbits revealed a subperiosteal fluid collection in the right orbit. The patient had no risk factors for NTSOH, but after detailed questioning she admitted to participating in erotic asphyxiation prior to the onset of her symptoms. She was observed and subsequently lost to follow up.

Conclusions and Importance: To the authors' knowledge, erotic asphyxiation as a cause of orbital subperiosteal hemorrhage has not been previously reported. Lack of knowledge about erotic asphyxiation amongst healthcare providers may contribute to hesitance to directly question patients about the practice. Clinicians should be aware of erotic asphyxiation as a potential cause of orbital subperiosteal hemorrhage.

1. Introduction

Erotic asphyxiation involves production of cerebral hypoxia for sexual pleasure. The authors report a case of nontraumatic orbital subperiosteal hemorrhage (NTSOH) following erotic asphyxiation in a patient with no other risk factors. The etiology of the hemorrhage was revealed only after thorough questioning. To the authors' knowledge, this is the first report of erotic asphyxiation as a cause of orbital subperiosteal hematoma.

2. Case report

A 29 year-old female presented with progressively worsening binocular diplopia, right-sided periorbital edema and ecchymosis, and a pressure sensation behind her right eye. There was moderate edema and ecchymosis of the right upper eyelid with associated mechanical ptosis and mild proptosis (Fig. 1). Right globe elevation was limited, and there was a small angle right hypertropia in primary gaze. Uncorrected visual acuity was 20/20 and color vision was full in both eyes. The pupils reacted normally with no relative afferent pupillary defect. Posterior segment examination revealed no optic nerve or retinal pathology.

Computed tomography of the orbits was performed revealing a superomedial subperiosteal fluid collection in the right orbit measuring approximately 2.1 × 0.6 cm and displacing the globe inferolaterally (Fig. 2).

The patient did not have any significant past medical history. She denied use of anticoagulants, history of periorbital trauma, recent vomiting, weightlifting, or other activities causing increased

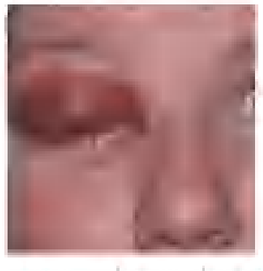

Fig. 1. Clinical photograph showing exotropia, ptosis and periorbital edema of the right eye with associated erythema of lower and mid eyelid.

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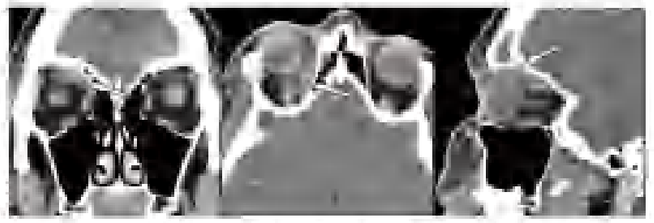

Fig. 2. Computed tomography (CT) of the orbits revealed a superomedial subperiosteal fluid collection in the right orbit measuring approximately 2.1 × 0.6 cm and displacing the globe inferolaterally.

[illegible] pressure. She denied any trauma to the eye and reported the presence of right sided visual symptoms during isometric activity (e.g. [illegible]) and denied any [illegible] pressure [illegible] the carotid arteries. There was no sign or evidence to the contrary when the presenting ocular examination [illegible] and dental exam [illegible] were [illegible].

Given the grave [illegible] of orbital compartment syndrome, the decision was made to [illegible] She was appropriately lost to follow up. [illegible] a patient to [illegible] was [illegible]. The report describes [illegible] [illegible] that could [illegible] [illegible].

3. Discussion

Asphyxiation is the [illegible] of [illegible] caused by [illegible] for the purpose of arousing or enhancing sexual pleasure.[1] Strangulation, suffocation, chest or neck compression, and inhalation of volatile solvents are methods used to induce hypoxia.

Although the prevalence of autoerotic asphyxiation is difficult to quantify due to its secretive nature, the incidence of autoerotic deaths in Western countries is estimated to be 0.5 deaths per million people per year.[2] Of these, 70–80% are due to autoerotic asphyxia by hanging, and an additional 10–30% are related to asphyxia by use of plastic bags or chemicals.[3] The actual prevalence of autoerotic asphyxiation is likely much higher than these statistics suggest as they do not include the incidents that erotic death or the insurance scandal that are mentally labeled as suicide.[2,4]

Autoerotic practices have been documented for over 200 years, and the vast majority of individuals involved in North America are young, white men.[2] Further questioning in circumstances may reveal accompanying practices used to enhance sexual pleasure including cross-dressing and rectal or genital foreign body insertion.[2,4] Several asphyxial mechanisms have been [illegible] as a mechanism of injury in other demographics as cases have been reported across all age groups and socioeconomic classes and regardless of marital status.[2]

NTSOH has been reported in a number of situations. The most common etiology is related to a sudden increase in cranial venous pressure, which occurs in situations such as vomiting, childbirth, or constipation.[5] Other predisposing factors include bleeding disorders, sinus infections, or the use of general anesthesia.[6] A case of a NTSOH in a young, healthy patient after a yoga headstand maneuver has also been reported.[7] The bleeding in NTSOH is thought to originate from small veins coursing across the subperiosteal space between the orbital bone and periorbita.[8] Common presenting symptoms include proptosis, globe displacement, eyelid edema, periorbital pain, nausea and vomiting, and diplopia.[5–8] If not recognized and treated promptly, orbital subperiosteal hematoma can cause compressive optic neuropathy and permanent vision loss. Surgical drainage is indicated for patients with acute optic nerve compression or to confirm an uncertain diagnosis.[5]

Although orbital subperiosteal hemorrhage have been attributed to other nontraumatic causes, to our knowledge, erotic asphyxiation as a cause of orbital subperiosteal hematoma has not been previously reported. Our patient was a young female who presented to the emergency department with diplopia, periorbital ecchymosis, and pain and was found to have an orbital subperiosteal hematoma in the absence of trauma or obvious non-traumatic risk factors. Upon further questioning, the patient revealed that she had participated in autoerotic asphyxiation by means of strangulation, two days prior to her presentation, around the time of onset of her symptoms.

4. Conclusions

Many healthcare professionals lack knowledge of the unusual, secretive practice of erotic asphyxiation and its prevalence. This contributes to hesitance to directly question patients and in turn may delay recognition and treatment of complications resulting from the practice. This case report establishes erotic asphyxiation as a cause of orbital subperiosteal hemorrhage.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Acknowledgements and disclosures

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Conflict of interest

The following authors have no financial disclosures: CSH, ARH, TJB, AM.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Nodular Lymphocyte Predominant Hodgkin Lymphoma Presenting With Unilateral Orbital Involvement

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Abstract: A 40-year-old white woman presented to her general ophthalmologist for swelling of the left upper eyelid that began approximately 4 months before. CT scan of the orbits with and without contrast demonstrated homogenous enhancement of the left lacrimal gland. Examination was notable for left hypoglobus and proptosis. The patient underwent left lateral orbitotomy with biopsy of the mass and frozen section analysis showed lymphoid infiltrates. Subsequent histopathologic diagnosis was consistent with nodular lymphocyte predominant Hodgkin lymphoma, a rare subtype of Hodgkin lymphoma that has only rarely been reported previously in the orbit. The authors review the case and the relevant literature.

CASE REPORT

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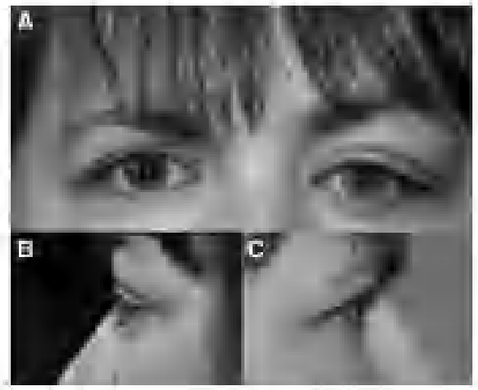

FIG. 1. **A**, External photograph. The dilated and irregular right pupil is evident and suggestive trauma. On the **left**, there is left upper eyelid redness, proptosis, and hypotropia. **B**, **C**, The left side in profile (**B**) shows proptosis relative to the right side (**C**).

DISCUSSION

Ocular and visual adnexal lymphoma can occur both in association with disseminated systemic disease. Although HL accounts for nearly 30% of all lymphomas, orbital involvement is unusual. Lymphoma affecting the orbit and eyelid adnexa is commonly B-cell non-Hodgkin lymphoma.[1] Non-Hodgkin lymphoma most commonly manifests with mucosa-associated lymphoid tissue (MALT) lymphoma, often presents as primary ocular adnexal disease.[2] Ophthalmologic manifestations of HL are nonspecific and rarely ocular adnexal disease can be involved during the natural course of the disease. Isolated ocular adnexal involvement by NLPHL is not common.[3] However, HL seldom presents with ocular adnexal involvement as an initial finding.[4] More commonly, the orbital location involved in HL is the setting of known advanced, systemic disease.[5] Although uncommon, there are reports of ocular adnexal involvement in classical HL.[6–8] Importantly, HL is known to be associated with Epstein-Barr virus, NLPHL and classical Hodgkin lymphoma, which are considered due to their differences in clinical appearance, behavior, and immunophenotypic features.[9] While cases of classical Hodgkin lymphoma involving the orbit have been previously reported, orbital involvement by NLPHL is not. Levy et al.[10] reported a series of 563 patients with lymphoma involving the ocular adnexa diagnosed between 1993 and 2005. Of these 563 patients, only 1 was found to have classical Hodgkin lymphoma. No cases of NLPHL were identified. Upon review of the literature, the authors only identified 1 published report of orbital involvement in NLPHL.

Akbar et al.[1] described a 48-year-old woman who presented with bilateral upper eyelid swelling who was found to have painless, multinodular palpable masses on both upper eyelids and mild left blepharoptosis with an S-shaped contour. The masses were mobile with retraction of the upper eyelids. However, the rest of the ocular examination was unremarkable. MRI of orbits showed signal abnormalities at the region of the lacrimal gland hypointense on T1 weighted images and hyperintense on T2 weighted images. Histopathologic evaluation of tissue from an incisional biopsy demonstrated lymphocyte predominant cells. The patient was referred to a hematologist for systemic evaluation. CT scans of the chest and abdomen showed bilateral axillary, inguinal, paraaortic, paracaval, and bilateral internal iliac lymphadenopathy. Excisional biopsy of an axillary node was performed and histopathologic and immunohistochemical examination was consistent NLPHL. Bone marrow biopsy was negative for NLPHL, and a diagnosis of Ann Arbor Clinical Stage III-A HL was made. After 6 cycles of adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy, the patient's ocular findings resolved and she had been in remission for 3 years at the time of the publication by Akbar et al.[1]

The case demonstrates that NLPHL can present in the orbit as a sign of systemic disease with unilateral involvement. Furthermore, in contrast to the case published by Akbar et al.,[1] orbital and ocular adnexal findings may manifest as proptosis, hypotropia, and upper eyelid fullness rather than multiple

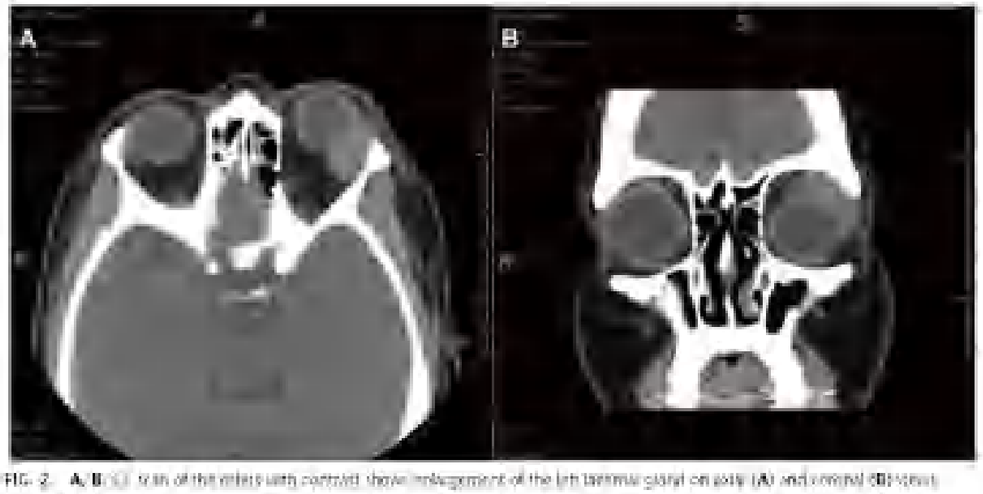

FIG. 2. **A**, **B**, (**A**) With all the orbits with contrast, there is enlargement of the left lacrimal gland on axial (**A**) and coronal (**B**) views.

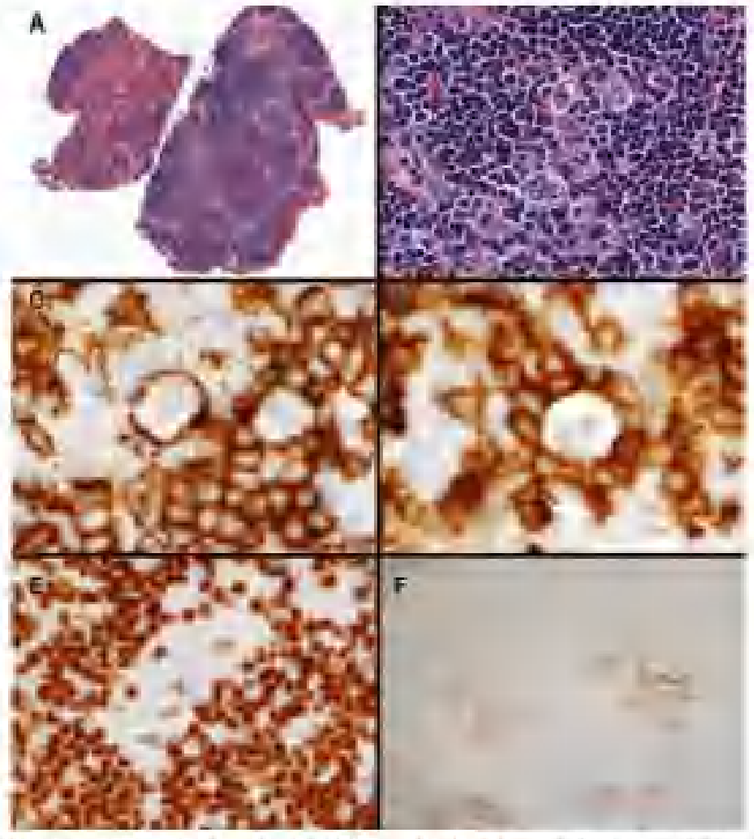

FIG. 3. **A**, H & E stain demonstrating a nodular infiltrate (×1). **B**, "Lymphocyte predominant" (LP) cells on H & E stain (×40). **C**, CD20 positive LP cells (×100 oil immersion). **D**, LP cell with CD3-positive T-cell rosette (×100 oil immersion). **E**, EMA/PAS-3 immunostaining of LP cells, surrounded by small B-cells showing mostly interfollicular positivity (×50 oil immersion). **F**, Expanded and elongated follicular dendritic cell meshworks demonstrated by CD21 staining (×40).

upper eyelid masses. The clinician, as well as the pathologist must remain aware of lymphoma in the differential diagnosis for lacrimal gland enlargement. Incisional biopsy with fresh tissue evaluation for lymphoma remains effective and efficient should the tumor measure.

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Upper Face and Orbit "Degloving" Dog Bite Injury

[redacted]

Abstract: A 70-year-old woman who attempted suicide by intravenous heroin was bitten on unknown time period with her 3 pet dachshunds chewed her upper face and bilateral periorbital areas including all 4 eyelids, both lacrimal glands, all of the conjunctiva from both eyes, the extraocular orbital muscles on the left side only, and anterior orbital fat from both sides. A subtotal exenteration was performed on the left orbit and a temporoparietal fascia-pericranium flap was used to reconstruct the right orbit and lacrimal mucosa, replacing both the bulbar and palpebral conjunctiva. To the authors' knowledge, this is the first report of such extensive orbital injuries from dog bites.

CASE REPORT

[redacted]

DISCUSSION

[redacted]

[redacted]

A, Preoperative injury. B, Debris of conjunctiva and lacrimal gland. C, Immediate postoperative result with split-thickness skin graft over remainder of defect. E, Two months postoperatively.

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Browlifting as an Alternative Procedure for Apraxia of Eyelid Opening

[illegible]

Abstract: Essential blepharospasm is an idiopathic disorder that consists of spontaneous, spasmodic, and involuntary eyelid closure in the absence of ocular disease. Some patients develop an inability to open their eyelids in the absence of orbicularis spasms. These patients have essential blepharospasm combined with apraxia of eyelid opening. Botulinum toxin injections are the treatment of choice for blepharospasm but results may be insufficient, especially in cases associated with apraxia. Apraxia can be treated surgically by levator aponeurosis advancement, frontalis suspension, and upper myectomy. The authors report the first browlift using polypropylene suture to manage eyelid apraxia associated with blepharospasm as an alternative and minimally invasive procedure.

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CASE REPORT

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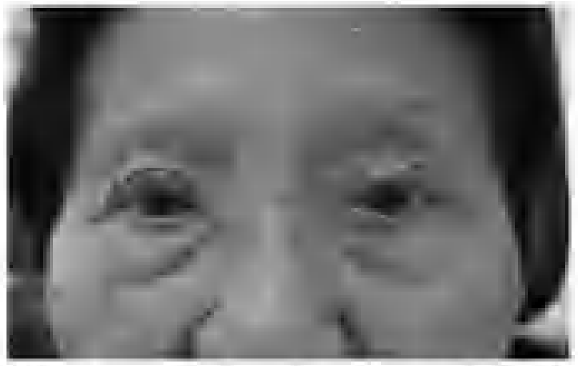

FIG. 1. A 7?-year-old Asian woman with blepharospasm and secondary eyelid apraxia.

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DISCUSSION

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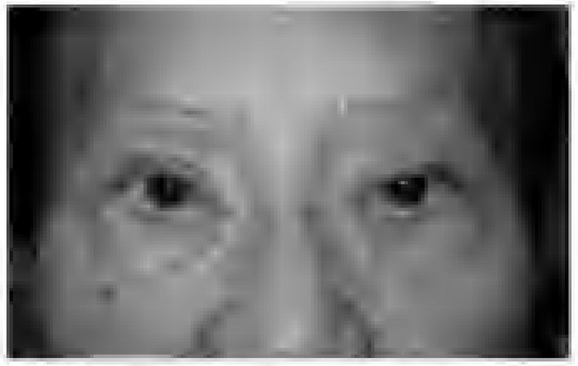

FIG. 2. Six months after browlifting, the patient reported no recurrence of [illegible]

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REFERENCES

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Bulbar Conjunctival Autograft With Rectus Muscle Transeyelid Traction Suture for Diplopia Due to Bulbar Conjunctival Scarring

[illegible]

Abstract: Cases of bulbar conjunctival fibrosis from pterygium surgery, strabismus surgery, trauma, chemical exposure, and inflammatory conditions can be difficult to manage. Despite surgical approaches entailing autografts, amniotic membranes, and antimetabolites, preventing postoperative scarring and contracture can be difficult, particularly in patients with susceptibility to scarring. The authors present a case of a 39-year-old man with diplopia secondary to subconjunctival scarring and fibrosis after multiple pterygium surgeries. The authors describe a unique surgical approach using a medial rectus transeyelid traction suture as a means of preventing postoperative conjunctival graft contracture and functional disability.

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CASE REPORT

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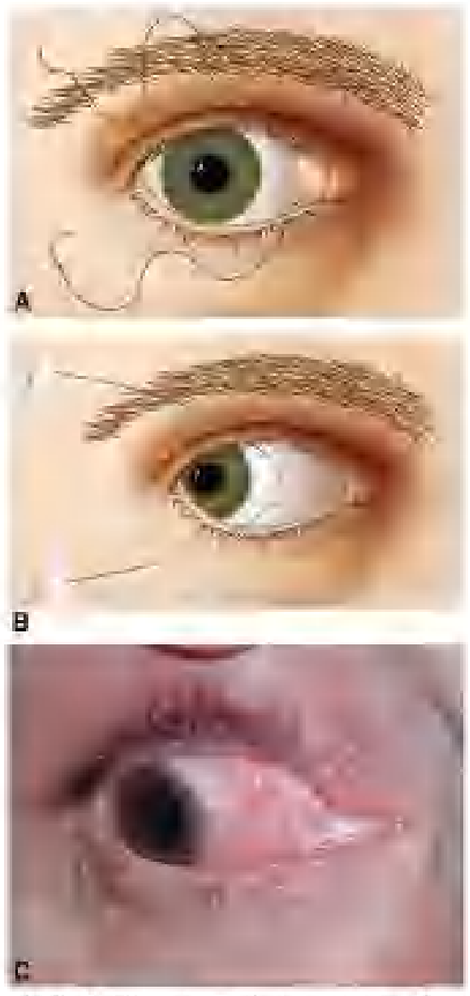


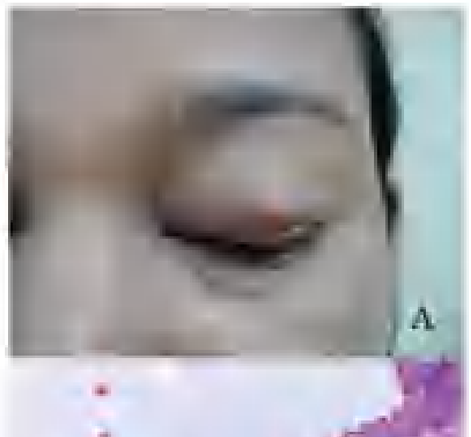
A, Sketch demonstrating area of excision and the 6-0 nylon suture placed underneath the medial rectus muscle insertion. B, Sketch demonstrating the needle suture passed through the sclera and conjunctiva, and brought out through the lateral preseptal fornix. C, Postoperative view of the patient showing the superior scleral and conjunctival autograft in place with 7-0 chromic sutures. The lateral scleral suture has been taped to the temporal skin with a traction of tension and abduction. D, Postoperative view, the scleral conjunctival autograft has healed with minimal globe retraction on abduction.

a thin-walled cystic nodule containing a creamy substance. Histopathology identified acanthosis of the abscess simplex was further characterized by the absence of a family history and involvement of only one lesion. Steatocystoma is a cystic lesion that is very rare in dermatology practice but that has been reported rarely on the eyelid. Its clinical appearance is indistinguishable from other cystic lesions of the periorbital area and it should be considered in the differential diagnosis of eyelid lesions.

A variety of benign and malignant lesions of the eyelids can affect the eyelid. The lesions we frequently encounter are eyelid inflammations, namely, chalazion, blepharitis, and pyogenic granuloma, and inclusion cysts. Sometimes, these common lesions may present with atypical features and mimic more malignant lesions, such as basal cell carcinoma, sebaceous carcinoma, or squamous cell carcinoma.[1] We report a case with a nodular lesion of the upper eyelid that was diagnosed as steatocystoma simplex.

CASE REPORT

A 47-year-old woman presented with a recurrent nodular lesion of 1-year duration with mild pain of the left upper eyelid (Fig. 1A). She had undergone excision once in the previous 5 years without supportive pathologic reports. The lesion enlarged insidiously and was cystic in consistency.



A, Photograph showing a normal lesion on the left upper eyelid. B, Micrograph of the cyst shows an irregularly corrugated lumen and sebaceous units attached to the wall of the cyst (hematoxylin-eosin, ×100).

DISCUSSION

REFERENCES

1. [illegible]
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Schwannoma of the Lower Eyelid in a 13-Year-Old Girl

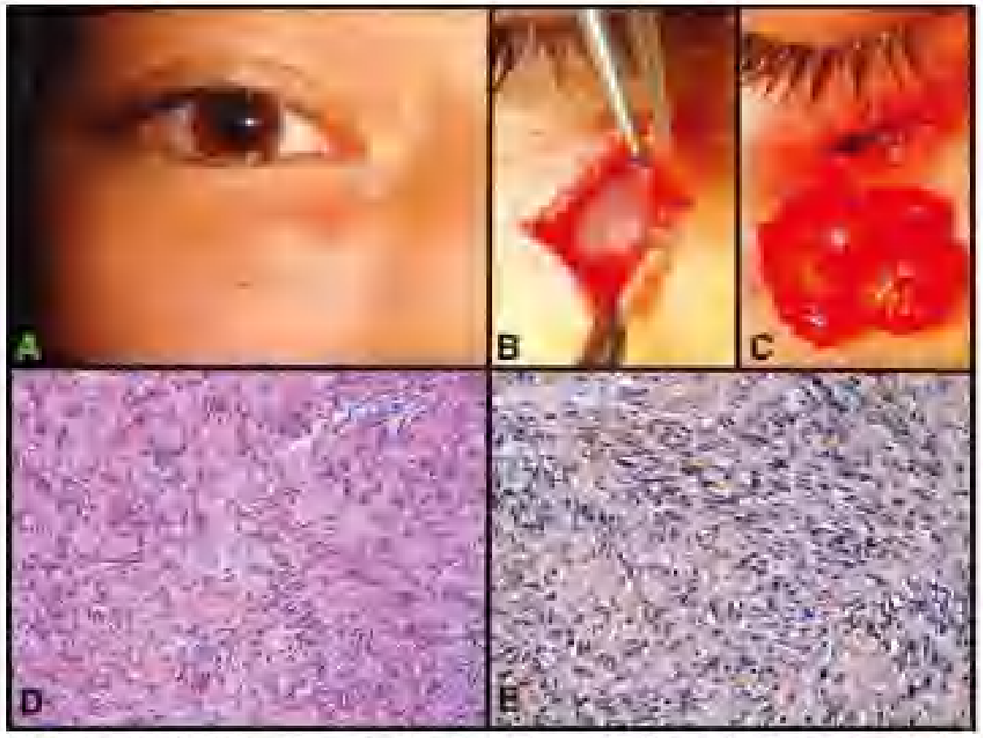
[illegible]

Abstract: A 13-year-old girl presented with a history of a slowly enlarged, painless right lower eyelid mass of 2 years' duration. Excisional biopsy revealed the characteristic histopathologic features of a schwannoma. After complete excision, there was no recurrence at 1-year follow-up. Schwannoma is a rare eyelid tumor, appearing sporadically and as a solitary lesion, which should be considered in the differential diagnosis of eyelid masses or thickening.

CASE REPORT

DISCUSSION

CONCLUSION



A, Round lower eyelid mass in a 13-year-old girl. B, Lesion seen with a smooth capsule beneath the skin and muscularis. C, Gross appearance of the lesion (color online) after complete excision through a skin incision. D, Spindle cells arranged as a palisading tumor in an Antoni A area (hematoxylin-eosin, ×40). E, S-100 positivity in spindle cells (×200).

DISCUSSION

CONCLUSION

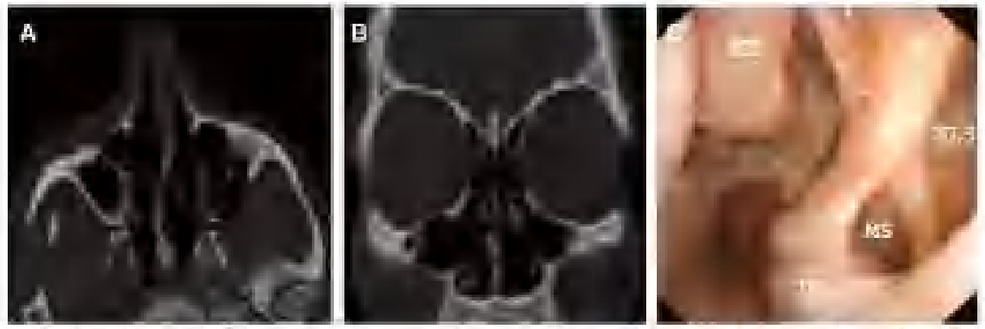


FIG. 2. Case 1. A, Axial CT shows marsupialization and enlargement of both dacryocystoceles. B, Coronal CT shows bilateral wide middle meatal antrostomy. C, During left nasal endoscopy, note the permeability of the nasolacrimal duct and maxillary sinus.

dacryocystitis.[7] Malfunction of nasolacrimal duct can also be silent, thus predisposing to the formation of a congenital dacryocystocele in rare cases.[8] An enlargement of the nasolacrimal duct, so-called dacryocystocele, with dilatation of the membranous duct (the passage after an obstruction of the proximal valve of Rosenmüller) and distal stenosis (Hasner) part of the normal drainage system.[1] There are few reported cases of enlarged nasolacrimal ducts with an average diameter of 14 mm in the series by Rhemtulla and Meyer[9] and 16 mm in the case reported by Schlegel and Stephens.[10] CT in our first case had a left nasolacrimal duct of 17 mm, whereas the second case had a duct of 16 mm of diameter.

The pathogenesis of dacryocystocele remains unclear. As reported,[1] it may form as the result of distal obstruction within the nasolacrimal system (both proximally and distally), which leads to an increased intraductal pressure enough to cause dilation of the nasolacrimal duct by a bone remodeling process. This chronic enlargement of the lacrimal system results in obstruction of the normal drainage of the maxillary sinus, leading to the development of sinusoidal and chronic sinusitis, as demonstrated by our cases.

Multidisciplinary surgical treatment was successful in both patients. The first case was treated with lacrimal endoscopic sinus surgery, with marsupialization of both dacryocystoceles. The marsupialization technique is a procedure that involves excising a portion of the cystic wall and suturing the remaining mucosa to the surrounding tissue, thus creating a permanent opening.[11] The second patient underwent endonasal dacryocystorhinostomy with Jones tube. Both approaches were effective, the first was directed toward relief of airway obstruction and nasal obstruction with diseases of epiphora, whereas the second was developed to resolve epiphora in the absence of lacrimal sac and canaliculi.[12]

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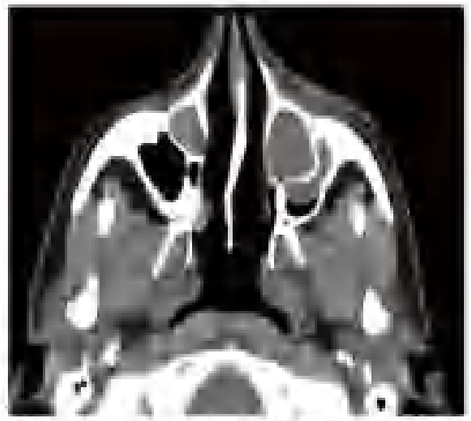

FIG. 1. Case 1. A 46-year-old woman. Preoperative axial CT shows dacryocystocele of both nasolacrimal ducts 20 mm diameter, on the left and 17 mm diameter on the right.

CASE REPORT

We evaluated a 76-year-old woman with a long-standing history of chronic sinusitis symptoms and recurrent left dacryocystitis, without epiphora. Examination revealed the lateral nasolacrimal groove tumefaction and a left medial canthal fistula. Nasal endoscopy showed left nasolacrimal duct mucocele. Nasal endoscopy showed left nasolacrimal duct mucocele. Computed tomography (CT) scan revealed a bilateral nasolacrimal duct dilatation (Fig. 1). Bilateral dacryocystocele, opening widely both canaliculi sometimes in the nose cavity. Complete resolution of the symptoms was achieved in the 24-month follow-up scan CT (Fig. 2A, B) and nasal endoscopy (Fig. 2C) also showed the improvement.

We also evaluated the 46-year-old brother for chronic dacryocystitis and left epiphora. His medical history revealed right nasal epiphora that had resolved after external dacryocystorhinostomy performed during childhood. Nasal endoscopy and nasal CT (Fig. 3A, B) showed a left dacryocystocele in the nasolacrimal maxillary transition. Examination revealed bilateral lacrimal puncta agenesis (Fig. 3C) and a left medial canthal fistula. Under general anesthesia, endonasal dacryocystorhinostomy with Jones tube (19 mm) was performed. Cytocultive, pus for cytology and dacryocystitis were observed. At the 24-month follow-up visit, the surgery remained patent on CT.

DISCUSSION

Embryologically, the lacrimal system develops from a thickening of epithelium within a groove between the frontal nasal process and the adjacent maxillary swellings. The epithelium invaginates to the underlying mesenchyme and forms an epithelial cord. Many progressive canalicular. As it develops the duct is situated in bone during ossification of the maxilla. Failure the canalization of [illegible]

Congenital absence of lacrimal puncta may be associated [illegible]

Surgical Treatment of Familial Dacryocystocele and Lacrimal Puncta Agenesis

[illegible]

Abstract: Bilateral agenesis of the lacrimal puncta and enlargement of the nasolacrimal canal are rare anatomic variants. The authors present 2 familial cases: a 76-year-old woman with bilateral dacryocystocele and lacrimal puncta agenesis and her 46-year-old brother, who had a long history of epiphora and recurrent dacryocystitis, and also had bilateral lacrimal puncta agenesis and a left dacryocystocele. The authors report the endoscopic, CT, and MRI findings, and describe the surgical treatments, by endoscopic dacryocystorhinostomy in the first case, and conjunctivodacryocystorhinostomy with Jones tube in the second case. At 24 months after surgery, both patients' symptoms were improved.

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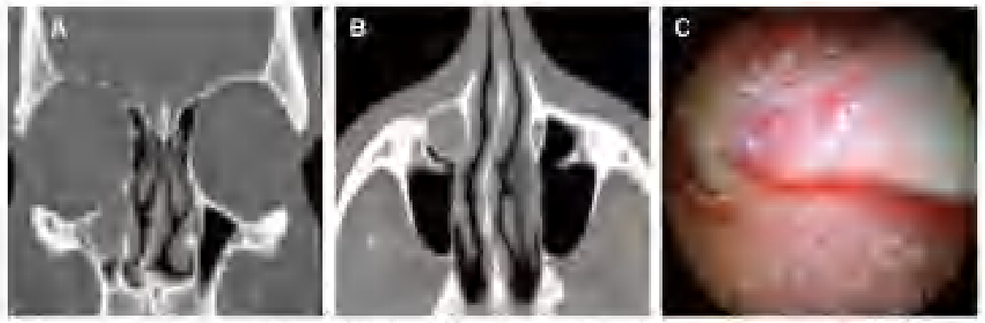

FIG. 3. Case 2. A 46-year-old man. A, Coronal CT shows enlargement of the left nasolacrimal duct (19 mm in diameter). B, Axial CT shows left maxillary mucinous cystic. C, Left lacrimal puncta agenesis.

Transorbital Puncture of the Cavernous Sinus to Treat a Dural Carotid-Cavernous Sinus Fistula

Kieran Smith, M.B.B.Ch., M.R.C.Ophth.[1]
Peter J. Mitchell, M.B.B.S., M.Med., F.R.A.N.Z.C.R.[1]
and Alan R. Hoffan, M.B.B.S., F.R.A.N.Z.C.R.[2]

Abstract: A 35-year old woman presented with left ocular injection, proptosis, and reduced vision. Cerebral angiography demonstrated a dural carotid-cavernous fistula supplied by bilateral and external carotid branches. Following endovascular embolization, the external carotid supply was obliterated. A residual lesion supplied by a branch of the ophthalmic artery and draining to the ophthalmic vein persisted in progressive glaucoma. Compartmentalization of the cavernous sinus precluded access to the fistula via the cerebral venous system. Attempted transfemoral embolization via the ophthalmic artery was not achieved. The superior ophthalmic vein was partially thrombosed and an attempt at its surgical isolation was unsuccessful. In this patient, transorbital puncture of the cavernous sinus performed complete obliteration of the fistula and resulted in prompt resolution of symptoms.

Transorbital puncture of the cavernous sinus for the treatment of carotid-cavernous sinus fistula (CCF) is rarely performed and, to our knowledge, has not been described in the ophthalmic literature.[1]

CASE REPORT

A 35-year-old woman presented with a 6-year history of left proptosis. Visual function had reduced to the left hand quadrant was full, with a left relative afferent pupillary defect. A left exotropia, fixed upgaze restriction, and conjunctival chemosis were present. Intraocular pressures were 14 mm Hg (OD) and 27 mm Hg (OS).

Cerebral angiography demonstrated a left flamm type D CCF with arterial feeders from the internal carotid artery and accessory meningeal artery bilaterally. Transvenous embolization of the anterior cavernous sinus via the inferior petrosal sinus was not possible because of venous occlusion. Occlusion of the cavernous sinus via the inferior ophthalmic vein was partially successful, leaving the ophthalmic vein partially thrombosed and an enlarged, progressive orbital fistula manifested from glaucoma necessary in medical management.

Transorbital puncture of the cavernous sinus was performed under general anesthesia. Using real-time digital subtraction angiography and roadmap fluoroscopy, a 20-gauge Chiba needle was advanced via the inferolateral orbit into the cavernous sinus via the superior orbital fissure (Fig. 2). The inner metal stylet was removed, leaving a coaxial plastic sheath, and the cavernous sinus catheterized with a microguidewire (Boston Scientific, Watertown, MA). A 5-F-A-2 coil (Cook, Bloomington, IN) and 4 mm Guglielmi detachable coils (Boston Scientific) were placed, with complete fistula obliteration confirmed on DSA angiography (Fig. 3A, B). No catheter was used subsequently.

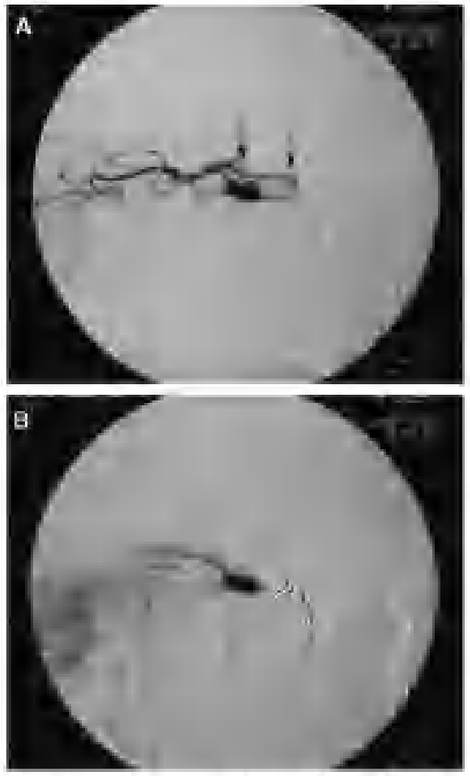

FIG. 1. Lateral view, arterial (A) and late (B) phase ophthalmic artery angiogram. Tortuous arterial supply of the orbital fistula, following intravenous embolization, is the posterior recurrent meningeal branch of the ophthalmic artery (arrow) arising at an acute angle 2 mm from the internal carotid artery. The late phase shows the fistula draining anteriorly to the ophthalmic veins. The orbital veins are severely congested but optic nerve perfusion (ophthalmic vein) is still maintained (arrow).

No procedural complications occurred. Visual acuity returned to 20/20 with complete resolution of fistula symptoms and signs. Fistula findings were maintained over 1 years' follow-up.

DISCUSSION

Endovascular embolization is the established treatment for dural CCF. Through anesthesia, transvenous access can be approached via the cerebral venous system (the superior ophthalmic vein and the petrosal sinus). Alternatively,

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Reprint requests to [illegible]

FIG. 2. Catheter (Angiocath, Becton Dickinson Infusion Therapy Systems, Inc., UT, USA) positioned in position (Angiocath) tips and a reservoir dye (Mamac, Cook Australia, Queensland, Australia) just prior to removal the inner metal needle. Tip to the lateral orbital puncture site is demonstrated.

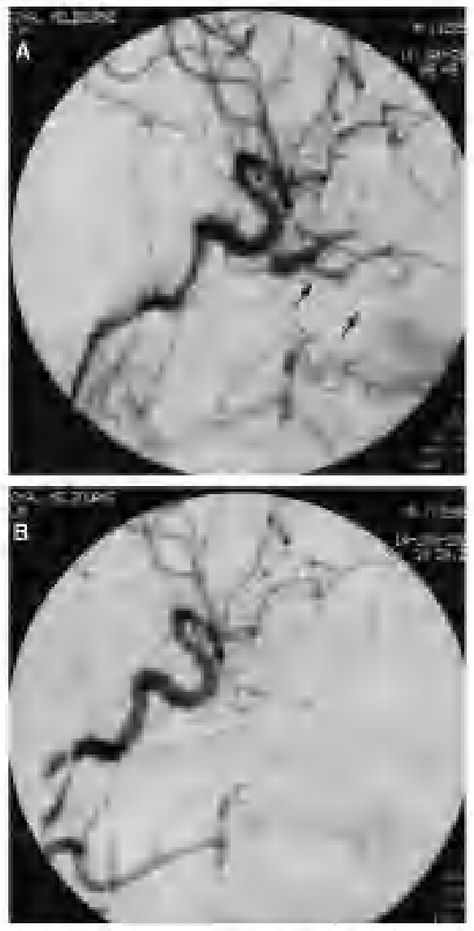

FIG. 3. A. Lateral view (common carotid artery) angiogram showing the catheter tip in relation to the cavernous sinus, superior ophthalmic vein and external carotid artery. The arrows indicate the line of the catheter. B. After delivery of 4 fine platinum coils, the fistula no longer identified.

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Pituitary Macroadenoma Presenting With Brow Mass and Acromegaly

Chantal M. Van Wijk, M.D.,* Lisa A. Kunkel, M.D.† and Andrew R. Harvey, M.D.*

Abstract: A 62-year-old woman presented with a brow mass and acromegaly. Biopsy of the lesion showed fibrous dysplasia. Radiologic imaging revealed a pituitary macroadenoma. The patient underwent transsphenoidal pituitary resection and radiation treatment, followed by medical management of acromegaly.

Pituitary tumors account for 10% to 15% of all primary intracranial tumors.[1] They are usually associated with symptoms due to local compression or hormonal hypersecretion. Typically women are affected more frequently than men. Growth hormone (GH)-secreting tumors account for 20% of secreting pituitary tumors, of which 75% are macroadenomas.[2] Presentation of pituitary tumors is pathophysiologic or usually related to visual field loss from compression of the optic chiasm. Other associated symptoms develop as for hormonal hypersecretion, such as galactorrhea, infertility, or loss of libido. An ophthalmologist often is consulted first.

We present an atypical case of a patient with a pituitary macroadenoma who presented with a brow mass and acromegaly.

CASE REPORT

A 62-year-old white woman was referred by her general ophthalmologist for evaluation of a right brow mass. The patient had first noticed the lump 2 years prior to examination. The mass was not painful or inflamed, but had significantly changed in appearance. Her medical history was significant for hypercholesterolemia, back problems, and the recent removal of a benign epidermoid cyst on her left forearm. She had no known drug allergies. On review of systems, she noted enlargement of her feet from size 10 to a size 11 over the past 2 years. She also was receiving eyeglasses for her diplopia. She had no family history of cancer.

Her visual acuity was 20/25 OD, 20/20 OS. Her pupils, confrontational visual fields, and ocular motility were grossly normal. Slit-lamp examination was also unremarkable. There was a firm, nontender mass located in the right superolateral orbital rim just anterior to the lateral eyebrow that was fixed and immobile (Fig. 1A). She also had bilateral hands and feet, consistent with acromegaly (Fig. 1B).

A biopsy of the brow lesion was performed using an eyelid crease technique. The mass was noticed at the superolateral orbital rim and was discovered to be a bony lesion. The periosteum was incised, and a dental burr was used to thin out the bony lesion, which ultimately revealed a fibrous dysplasia. CT and MRI showed a pituitary macroadenoma measuring 2.5 × 2.1 × 1.6 cm that involved the sella, clivus, and sphenoid bone extensions (sinus and skeleton) (Fig. 1C).

A, Right lateral brow mass (arrow). B, Acromegaly with enlargement of hands, nose, and jaw. C, MRI was performed to demonstrate the pituitary macroadenoma.

The patient was referred to neurological and endocrinologic evaluation. Laboratory values revealed elevated levels of GH of 162 ng/ml (normal, 0–5) and insulin-like growth

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Ectopic Meningioma Anterior to the Lacrimal Gland Fossa

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Abstract: A 46-year-old man reported a slowly growing tumor on the lateral edge of his left upper eyelid. The lesion was short but noticeable on palpation. A neoplasm of the lacrimal gland was suspected. CT showed a lobular calcified lesion at the left upper eyelid. Resection of the tumor was performed, which was located just behind the orbital septum and in front of the lacrimal gland. Anatomopathologic investigation of the excised specimen with immunohistochemistry revealed a benign meningioma of a meningothelioendothelial type, containing multiple bone elements. An ectopic orbital meningioma is rare, and this is the first case of a benign mixed neoplasm of this locus. Therefore, it should be included in the differential diagnosis of a lacrimal gland tumor.

Primary and secondary meningiomas of the orbit may be confused with other lacrimal gland neoplasms.[1] Most often they are easily identified by their characteristic features.[2] Apart from these, only rarely do ectopic orbital meningiomas occur. We report a case of a benign mixed meningioma of the left upper eyelid, which was easily removed by an upper blepharotomy and an extraconal approach.

CASE REPORT

A 46-year-old man was referred with a painless tumor presenting in the left upper eyelid during the past 3 years (Fig. 1A). Medical history was unremarkable except for hypertension. He was taking antihypertensive medication. Visual acuity was 20/20 OU. Slit-lamp examination revealed normal anterior segments. A firm mass was palpable under the left upper eyelid. It was also visible when the excessively exhibited mass located at the external edge of the lacrimal gland without appearance of involvement of the adjacent orbital structures (Fig. 1B). Pressure dolorosa was absent and proptosis.

A superior temporal approach revealed a well-encapsulated, lobulated mass within the preaponeurotic fat pad anterior to the orbital part of the lacrimal gland. The tumor was excised under loupe vision and removed (Fig. 1C).

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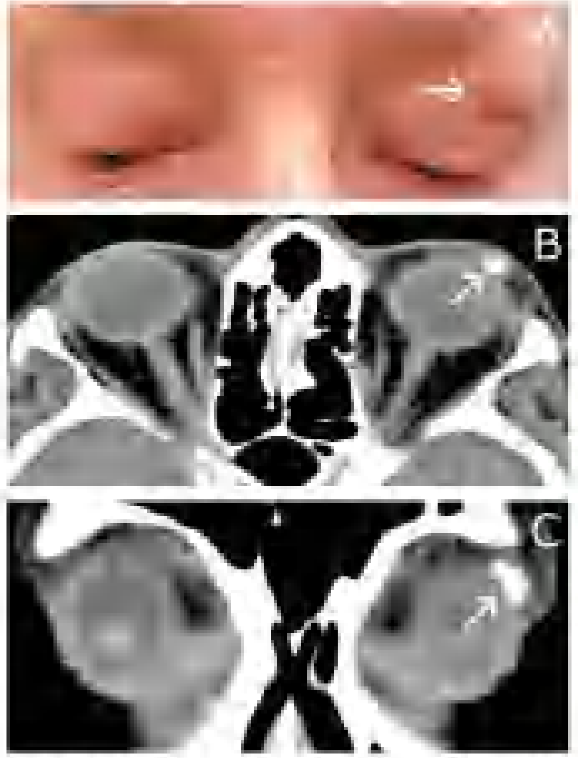

FIG. 1. A, Clinical appearance of tumor protruding through left upper eyelid (arrow). B, Axial CT shows a calcified mass (arrow) at the lateral edge of left eye without signs of bony or skin infiltration. C, Coronal view shows tumor (arrow).

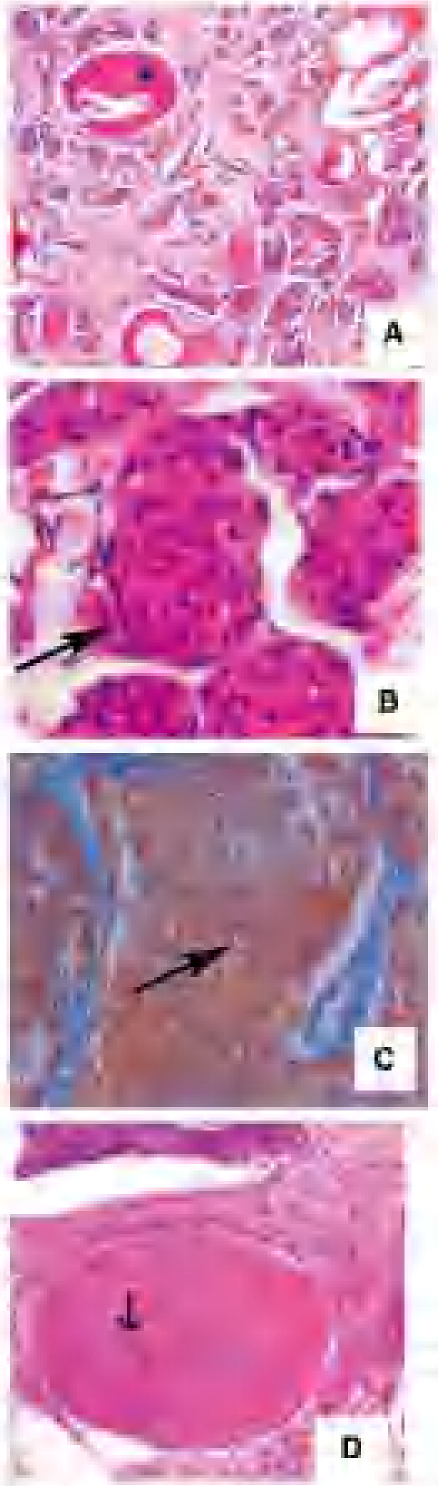

FIG. 2. A, [illegible] staining of the specimen shows [illegible] meningioma and areas of osseous metaplasia (asterisk) (×20). B, High magnification of the tumoral cell aggregates (arrow) (hematoxylin-eosin, ×400). C, High-magnification epithelial membrane antigen stain of tumoral cells (arrow) (×400). D, Magnification of osseous metaplasia (arrow) [illegible] ectopic meningioma (×200).

[illegible]

DISCUSSION

[illegible]

REFERENCES

[illegible]

Orbital Leiomyoma: Histopathologic and Immunohistochemical Findings of a Rare Tumor

[illegible]

Abstract. A [illegible]-year-old man was referred for evaluation of a right orbital hemangioma. Ophthalmologic examination was unremarkable except for [illegible] of proptosis OD. CT revealed a [illegible] lesion with evidence of growth from [illegible] within a year. The tumor did not compromise other orbital structures. An excisional biopsy was performed. On the basis of the histopathologic and immunohistochemical findings, the diagnosis of orbital leiomyoma was established. Orbital leiomyoma is a slow-growing tumor that can be located anywhere in the orbit. Posterior tumors are believed to originate from smooth muscle cells of vessel walls; anterior lesions may arise from the capsulopalpebral or Müller muscle. Although there are no unique features that help the radiologist to exclude other benign lesions of the orbit, the histopathologic diagnosis using immunohistochemical markers is usually straightforward. Attention to the cytologic features that exclude the malignant variant is of utmost relevance for proper diagnosis and patient counseling.

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CASE REPORT

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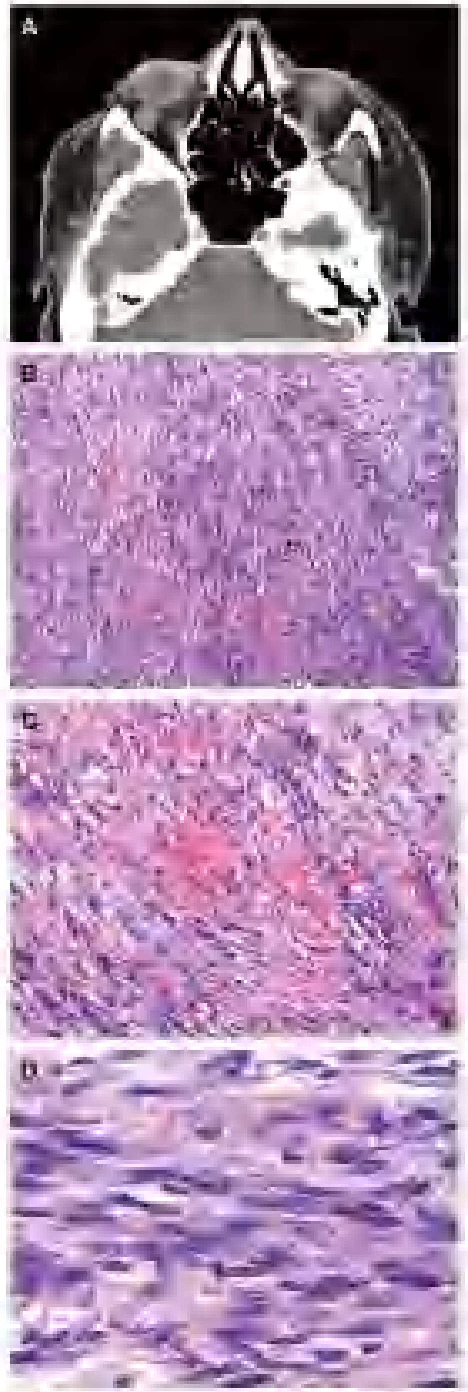
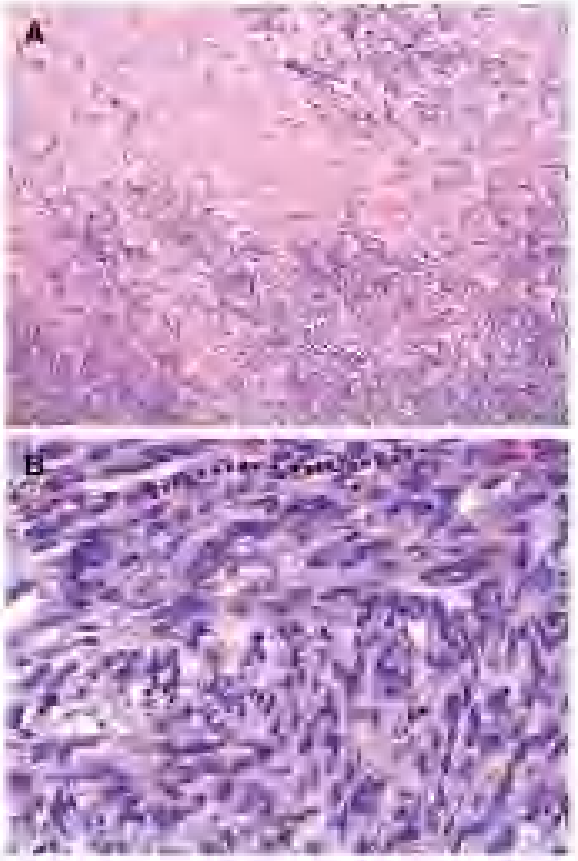
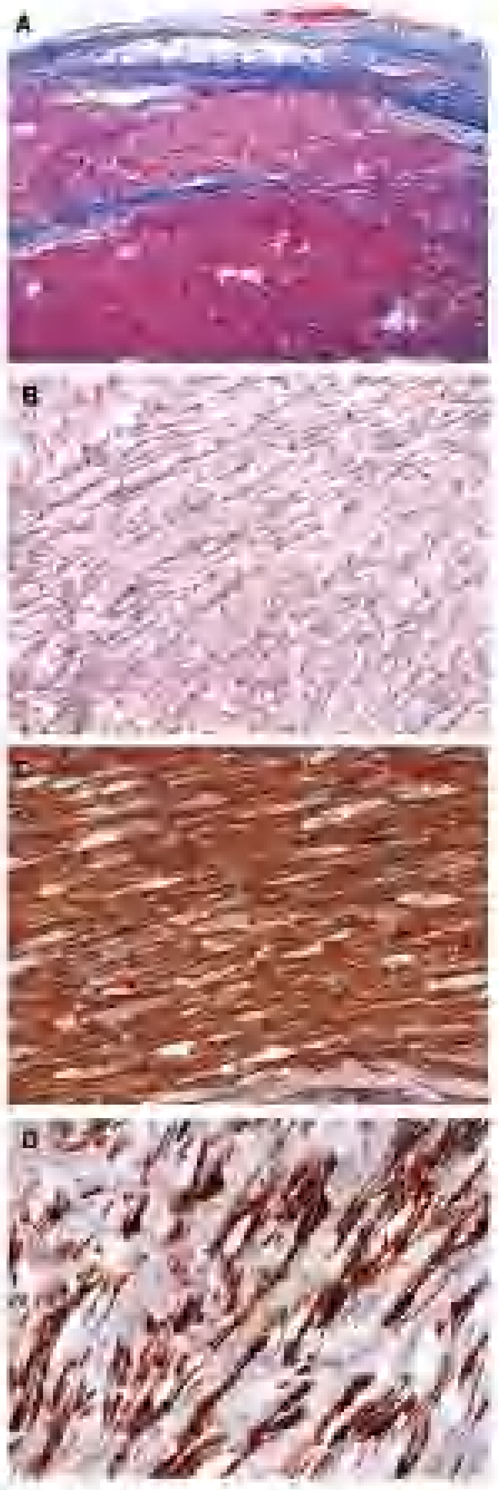


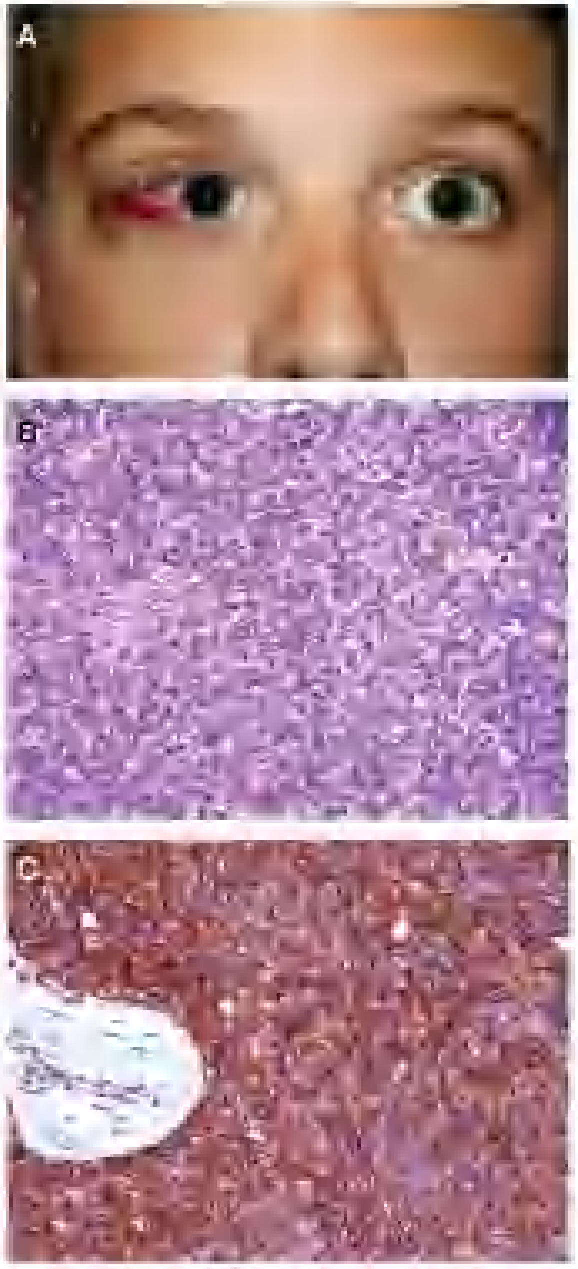


DISCUSSION



REFERENCES

Ewing Sarcoma Presenting as a Subconjunctival Mass



CASE REPORT

DISCUSSION

REFERENCES

Primary Cutaneous Anaplastic Large Cell Lymphoma of the Medial Canthus and Orbit

CASE REPORT

FIG. 1. The patient before (A) and after (B) radiotherapy.

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DISCUSSION

[illegible]

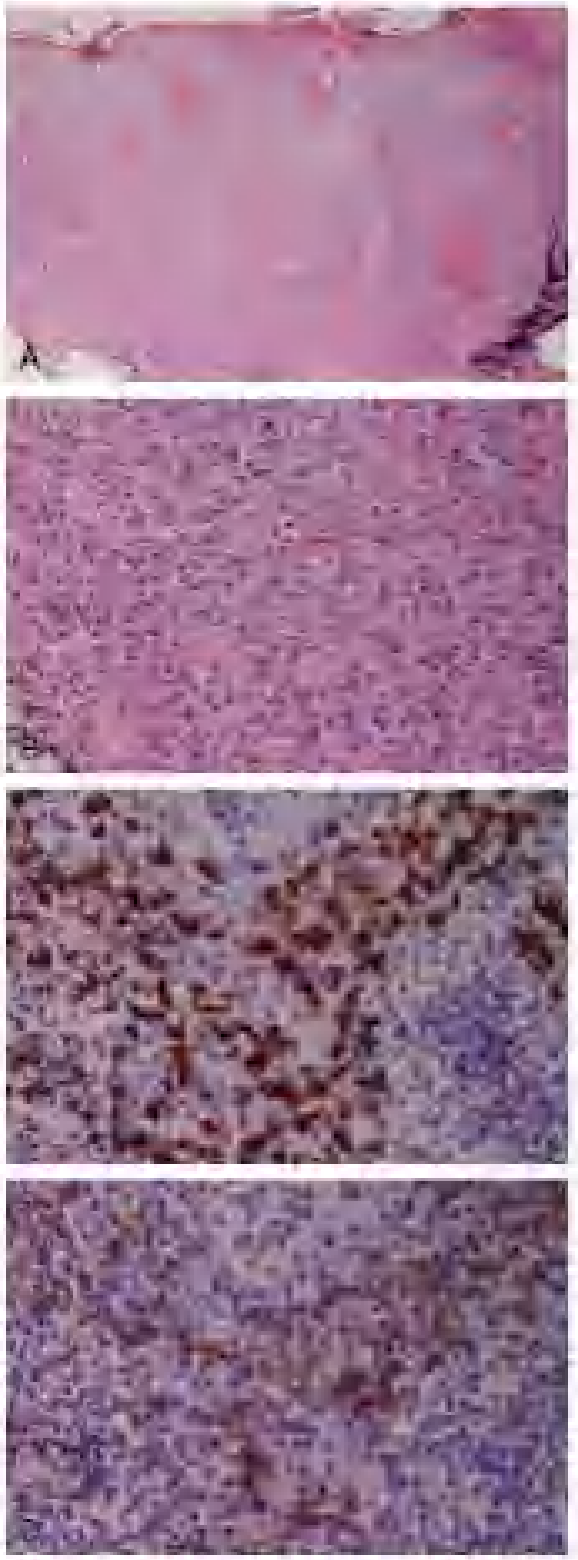

FIG. 2. [illegible]

FIG. 3. [illegible]

[illegible]

REFERENCES

[illegible]

Idiopathic Sclerosing Orbital Inflammation: Two Cases Presenting With Paresthesia

[illegible]

Abstract: The authors report 2 patients with idiopathic sclerosing inflammation of the orbit who presented with periorbital paresthesia in the trigeminal nerve distribution. The diagnosis in both cases was confirmed with biopsy and both patients responded to corticosteroid treatment. Although periorbital paresthesia is usually a sign of malignancy, these cases illustrate that it may also occur in patients with sclerosing orbital inflammation.

[illegible]

CASE REPORTS

Case 1. [illegible]

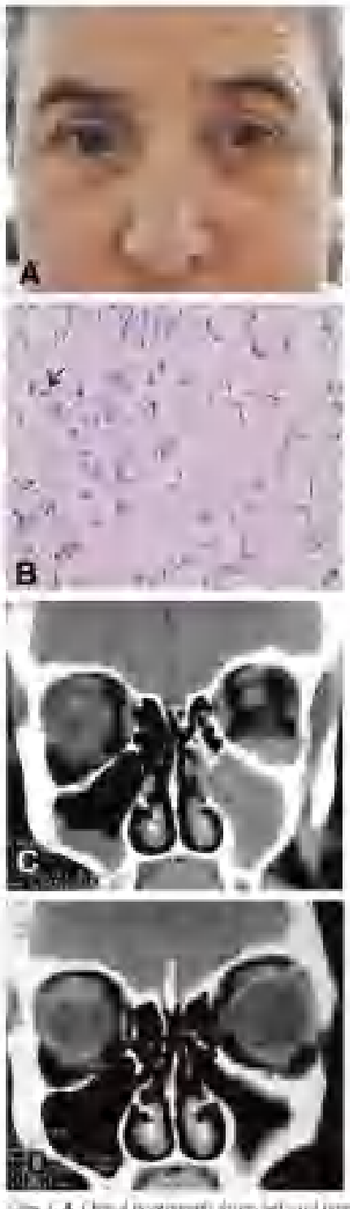

FIG. 1. Case 1. A, Clinical photograph shows left canal proptosis with ptosis of the right eyelid. B, Photomicrograph of orbital biopsy specimen (Periodic acid–Schiff stain, ×100) shows a dense lymphocytic and eosinophilic (arrow) cellular infiltrate. C, CT (posteroanterior) demonstrates a left inferior orbital mass with involvement of the inferior rectus muscle together with left maxillary sinus opacification. D, CT following treatment with intravenous methylprednisolone bolus shows near complete resolution of the disease.

Three of the cases with ongoing low-grade systemic symptoms following chronic inflammation characterized by T-lymphocytes and a chronic inflammatory cell infiltrate adjacent with a Sjögren's syndrome (Fig. 3B). Special stains for mycobacterium (AFB), parasite, acid-fast BBE and fungus (periodic acid–Schiff) were negative. Through the maxillary sinus Associate Hospital, the biological stage of the cyst separates needle-like with the same pattern.[4] The cyst is treated with orbital floor corticosteroid injections (1 mm intravenous methylprednisolone, 40 mg/ml, initially, and 3 doses). The symptoms and signs resolved 1 week after the first administration of intravenous methylprednisolone. The patient was noted on imaging (Fig. 1D). Two months after the last injection the intraorbital symptoms (Fig. 1).

Case 2. A 30-year-old white woman presented with a 3-month history of swelling and redness of the right upper eyelid associated with severe periorbital pain. Two and a months later the presented with the right frontal and maxillary sinus. On examination, visual acuity was 20/20 OU. Exophthalmometry of the right proptosis with 2 mm of inferonasal globe displacement was noted (Fig. 2A). Right limitation of right eye elevation. Sensation was diminished over the distribution of the ophthalmic, supraorbital, lacrimal, and supratrochlear branches of the trigeminal nerve, with intact corneal sensation. CT revealed a homogeneous soft tissue opacification from the lacrimal bone along the lateral wall (Fig. 2B) and through the inferior orbital fissure (Fig. 2C).

Biopsy via a lateral eyelid crease incision confirmed chronic orbital inflammation (Fig. 2D). The patient was treated with intravenous injection of methylprednisolone sodium 40 mg/ml (2 doses a week) apart with little response. She was then started on oral prednisone 20 mg/m which she ingested daily with complete resolution of symptoms and signs within a few weeks. She remains on a tapering dose of prednisone.

DISCUSSION

Necrotizing idiopathic orbital inflammation is an uncommon subtype of idiopathic orbital inflammation that usually manifests with painful proptosis. Optic pain, visual loss, and restriction of eye movements are other common findings. Eye motility disturbances are rare, with only 2 cases previously reported in the literature.[1] In fact, motility dysfunction is unusual in orbital disease. Rose and Wright[1] in a review of their entire experience found an incidence of motility defects in 15% patients. However, anesthetic sensory loss due to eye patients was seen in only 6 (6%) of patients. While malignancies such as adenoid cystic carcinoma and squamous cell carcinoma are known to cause sensory disturbance through perineural spread, Rose and Wright found that 25% of their cases with sensory loss were secondary to dental inflammatory disease. Periorbital anesthesia has also been reported in association with fungal rhinosinusitis.[5] The primary loss of sensation may be subtle, while inflammation is more likely resulting in mechanical entrapment of the nerves and the presence of symptoms and signs following steroid treatment support this theory. In addition to explaining the loss of sensation, Rose and Wright[1] have also noted the lack of correlation between disease duration and visual acuity. Hence, in summary, diseases showed by means of the present for sclerosing idiopathic orbital inflammation is present with sensation due to involvement of sensory nerves.

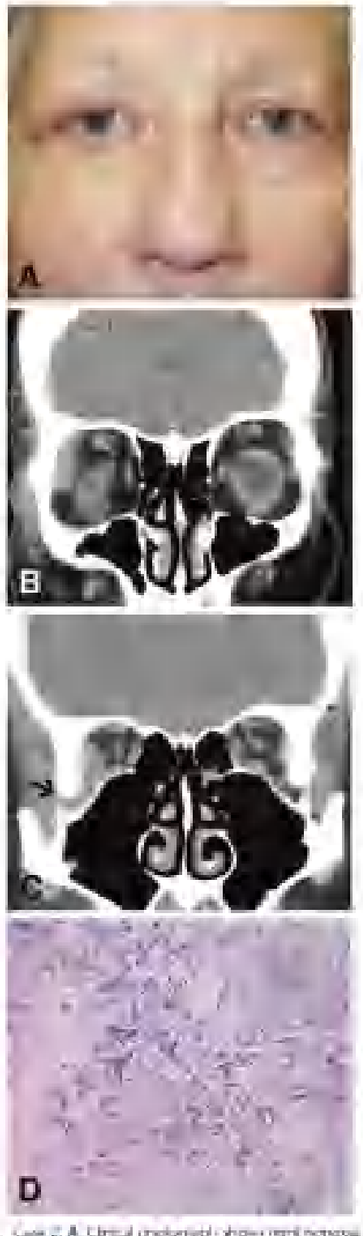

FIG. 2. Case 2. A, Clinical photograph shows right periorbital proptosis. B and C, CT shows an orbital mass occupying the right sinus with (B) and extending through the inferior orbital fissure (C) (arrow). D, Photomicrograph of orbital biopsy specimen showing inflammation with atrophic, elongated lacrimal glandular cells (hematoxylin-eosin, ×100).

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Exaggerated Postsurgical Inflammation in a Patient With Insufficiently Treated Addison Disease

[illegible], M.D.,* Nicolas J. Zhang, M.D.,†
Yan H. Nan, M.D.,‡ Ping Hou, M.D.,§
and Frederick T. Jordan, M.D.,¶

Abstract: **A patient with Addison disease developed fever, pain, and marked orbital inflammation 3 days after evisceration in the setting of perforated corneal ulcer. He was treated for presumed orbital cellulitis without improvement. Increasing the corticosteroid dose for his Addison disease resulted in complete resolution of the inflammation.**

Patients with Addison disease have reduced cortisol production. A patient with predominantly treated Addison disease who underwent evisceration in the setting of bacterial keratitis with perforation developed exaggerated postoperative inflammation that mimicked orbital cellulitis.

CASE REPORT

A 40-year-old man developed an ulcer within a contact lens that perforated OS. Perforation developed 5 days later despite topical fortified vancomycin and tobramycin and aggressive topical cultures. His ocular history OS included congenital cataract, amblyopia, glaucoma requiring Ahmed valve implant, and penetrating keratoplasty. He had also undergone 17 years prior his medical history included Addison disease. His medications included oral dexamethasone and fludrocortisone.

Examination OS revealed hand motions acuity, a purulent corneal ulcer, flat anterior chamber, corneal hypopyon, and marked conjunctival injection. Evisceration with removal of the Ahmed valve was performed. Abundant amoeba were seen in Gram's stained smears of the corneal

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[illegible] has no financial interest in the products or companies described in this article.
[illegible] presented at the Annual Meeting of the American Society of Ophthalmic Plastic and Reconstructive Surgery, Boston, Massachusetts, October 4, 2008.

[illegible], Ophthalmology Associates, [illegible], Bethesda, Maryland 20814, [illegible]

DOI: 10.1097/IOP.0b013e3181956ee1

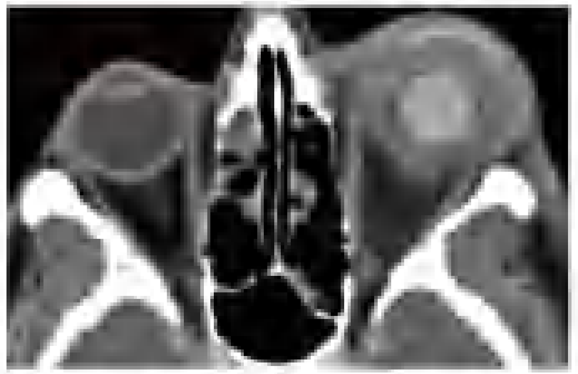
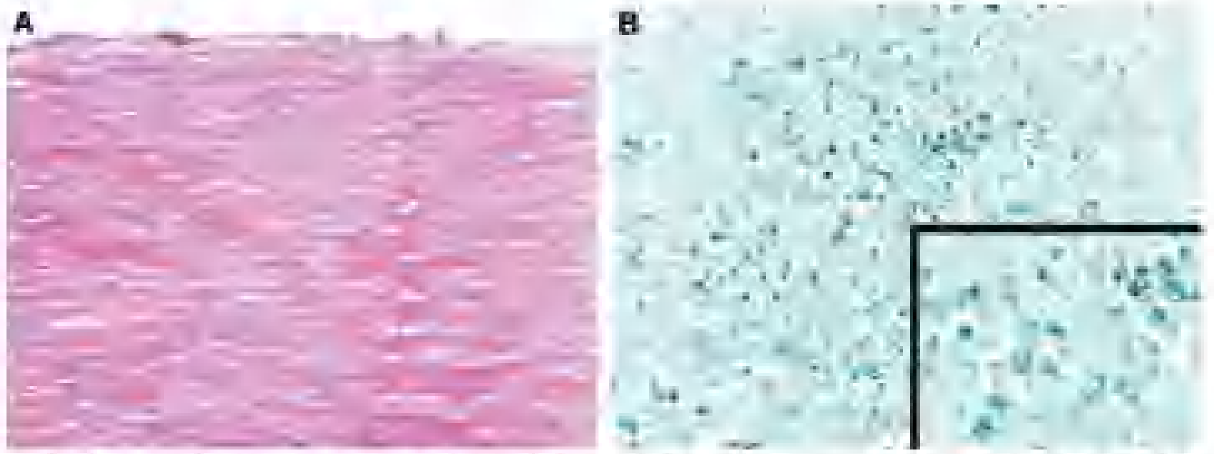


FIG. 1. Axial CT demonstrated soft tissue swelling involving the anterior orbit and eyelids. No abscess is evident.

DISCUSSION

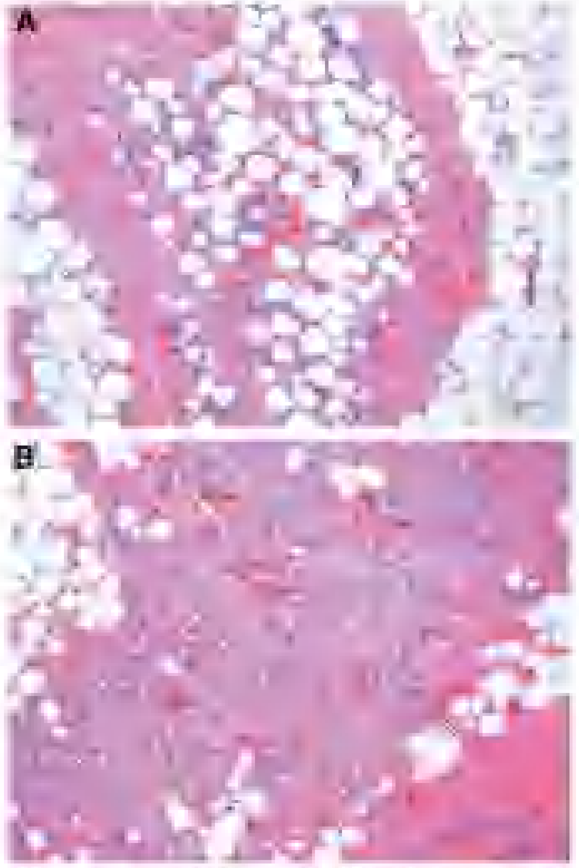
REFERENCES



Histologic Features of Mesotherapy-induced Orbital Fat Inflammation

Abstract: A 67-year-old man developed acute orbital inflammation after receiving cosmetic mesotherapy (Lipo-Dissolve) to the inferior orbital fat compartments. The injection was intended to cause lipolysis and shrinkage of fat lobules with subsequent cosmetic improvement. Injection of a mixture of bile salts, phospholipid, and alcohol preservative bilaterally in inferior orbital fat lobules led to an acute inflammatory reaction characterized histologically 12 days later by mild lymphocytic infiltration, fat necrosis, and fibrosis in the target areas. Benign proliferation of peripheral nerve trunks consistent with a traumatic neuroma was also noted histologically on one side. Inflammation including fat necrosis and traumatic neuroma are all possible consequences of mesotherapy.

CASE REPORT



Orbital Abscesses Caused by *Fusobacterium necrophorum*

Thomas Mills, M.D., Douglas Libby, M.D.
Bharat Majethia, M.D., and Robert J. Goldberg, M.D.

Abstract: The authors describe 2 cases of young men who presented with pansinusitis and *Fusobacterium necrophorum* orbital abscesses. The first patient had a complicated clinical course including epidural abscess formation and meningitis. He underwent surgical evacuation of the abscesses and sinus drainage and required long-term broad spectrum antibiotic therapy with full recovery. The second patient had a clinical course complicated by *F. necrophorum* septicemia. He required surgical evacuation of the abscess, sinus drainage, and long-term broad-spectrum antibiotic therapy and has remained asymptomatic since. *F. necrophorum* may be emerging as an increasingly prevalent pathogen in orbital abscesses and can portend a more aggressive clinical course where early surgical intervention may be prudent.

Orbital cellulitis and abscess often occur in children and young adults as a result of spread of infection from adjacent paranasal sinuses. Although *Staphylococcus* and *Streptococcus* species are most commonly implicated as responsible pathogens, *Fusobacterium necrophorum* has been increasingly recognized as an important pathogen in orbital abscesses and can portend a more aggressive clinical course. Although rare, *F. necrophorum* is the most frequently isolated species of the *Fusobacterium* genus and is a gram-negative, anaerobic bacillus that normally resides in the oropharynx, gastrointestinal tract, and female genital tract. It is the principal species associated with Lemierre's syndrome, which is the constellation of anaerobic sepsis, internal jugular vein thrombosis, and septic emboli arising from infections of the head and neck.[1] We present 2 cases of orbital abscesses caused by *F. necrophorum*.

CASE REPORTS

Case 1. An 18-year-old man presented with 24 hours of right periorbital swelling and pain preceded by 2 weeks of fever, myalgias, and malaise. He had received a course of antibiotics 2 days before presentation. On examination, he had moderate right upper eyelid swelling and edema, hyperemia, 2 mm of proptosis, and 50% restriction of ocular motility in all gazes. His visual acuity was 20/20 OU, and he had no relative afferent pupillary defect. CT scan revealed complete opacification of the ethmoid sinuses, sphenoid and maxillary sinuses with right lateral epidural abscess and right orbital subperiosteal abscess (Fig. 1A, B).

He was initially treated with intravenous vancomycin and ceftriaxone, and clindamycin. On day 2 he acutely developed new onset right periorbital chemosis and lethargy and underwent emergent evacuation of the right lateral epidural abscess, right orbital drainage via an external ethmoidectomy, and right maxillary antrostomy and ethmoidectomy (Fig. 1C). Postoperatively, the patient developed worsening right periorbital swelling and was found to have a right orbital subperiosteal abscess. He underwent repeat drainage of the right orbital abscess via a lateral orbitotomy. Cultures grew *F. necrophorum*, *Streptococcus milleri*, and *Peptostreptococcus*. He was treated with 6 weeks of intravenous ceftriaxone and metronidazole followed by 6 weeks of oral amoxicillin-clavulanate. He had complete resolution of his symptoms and remained asymptomatic at 6 months follow-up.

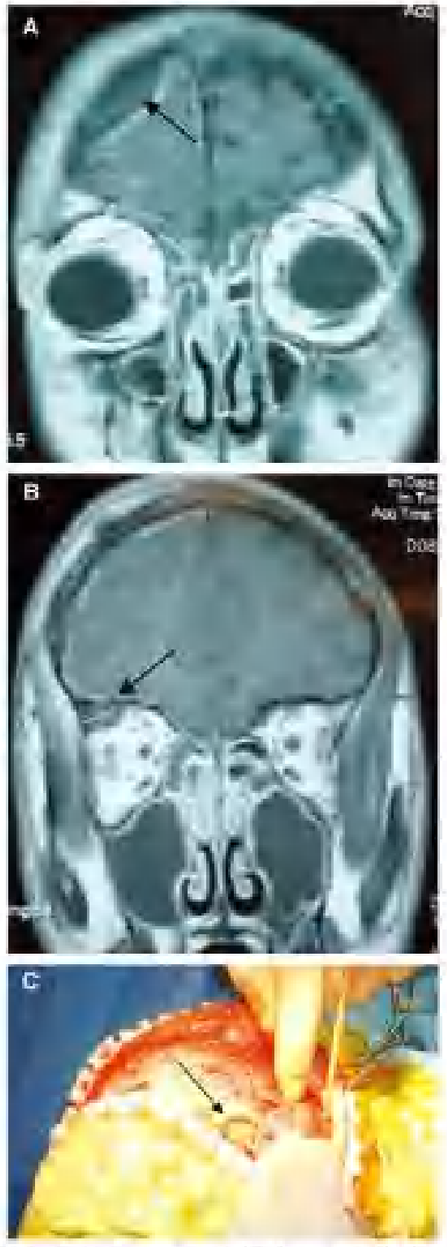


FIG. 1. Case 1. Contrast-enhanced CT demonstrates (**A**) a 30 mm × 11 mm epidural abscess (arrow) in the right frontal region and (**B**) a 11 mm × 16 mm abscess (arrow) in the right lateral ethmoid orbit with complete opacification of the paranasal sinuses. (**C**) Intraoperative drainage of the epidural abscess (arrow).

Case 2. A 20-year-old man presented with 2 days of left periorbital swelling and pain. He had been treated with 2 weeks of oral antibiotics for sinusitis. On examination, he had moderate left upper eyelid swelling and edema, hyperemia, 4 mm of proptosis, and 50% restriction of ocular motility in all gazes. His visual acuity was 20/20 OU, and he had no relative afferent pupillary defect. CT scan revealed complete opacification of the ethmoid sinuses, sphenoid and maxillary sinuses with a left lateral epidural abscess and left orbital subperiosteal abscess (Fig. 2A–C).

He was initially treated with intravenous vancomycin and ceftriaxone. On hospital day 4 he acutely developed worsening left periorbital swelling and pain. He underwent repeat CT scan, which revealed worsening left periorbital cellulitis and a new left orbital subperiosteal abscess. He underwent repeat drainage of the left orbital abscess via a lateral orbitotomy. Cultures grew *F. necrophorum*, *Streptococcus milleri*, and *Peptostreptococcus*. He was treated with 6 weeks of intravenous ceftriaxone and metronidazole followed by 6 weeks of oral amoxicillin-clavulanate. He had complete resolution of his symptoms and remained asymptomatic at 6 months follow-up.

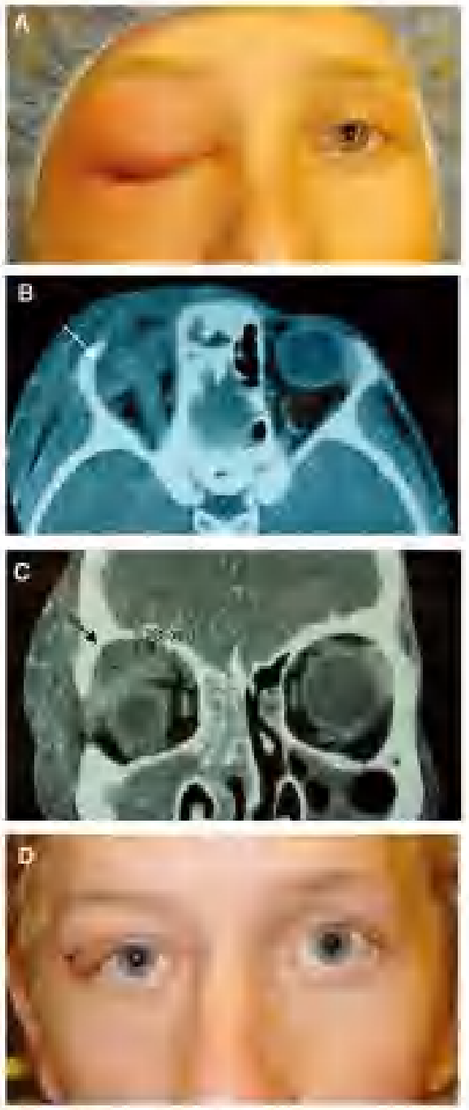


FIG. 2. Case 2. (**A**) A 20-year-old man on presentation with right orbital cellulitis. (**B**) Axial and (**C**) coronal CT of the right superolateral intraconal orbital abscess (arrow); 10 mm in greatest dimension. (**D**) Two weeks after drainage of orbital abscess with marked resolution of orbital cellulitis.

DISCUSSION

Necrobacillosis remains a controversial diagnosis as a consequence of its association with systemic and severe infection and the presence of pathogenic strains of *Fusobacterium* that are unusually resistant. The case reports demonstrate that early aggressive surgical intervention and long-term broad-spectrum antibiotic therapy with the specific organisms—*Fusobacterium*—may result in successful treatment of this potentially serious infection. The pathogenic mechanisms behind this disease process could not be clearly established from a combination of clinical findings and imaging in the case of orbital abscesses, but likely contributed to the patient's symptoms.

The findings are similar to previous reports in the literature, but early CT scan findings are variable. Possible differential diagnoses include orbital cellulitis, bacterial abscess, and fungal infection. Unrecognized orbital abscess can lead to severe visual loss and the ability to accurately identify and treat this condition is crucial.[2–4] The indications for and long-term effects of corticosteroids in orbital cellulitis remain controversial.[5–7] The indications for and long-term effects of corticosteroids in orbital cellulitis remain controversial.[5–7]

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Osteogenesis With Hematopoiesis Simulating Infection in a Hydroxyapatite Orbital Implant

David B. Jordan, M.D., Nicole J. Ballinger, M.D.,*† Suzanne Rootman, M.D.,‡ and Ron C. Paxton, M.D.‡*

Abstract: A 28-year-old woman underwent secondary orbital implant surgery with placement of a hydroxyapatite implant. Over the next 7 years she underwent 3 drilling procedures. She began having copious discharge 1 year after the last drilling procedure. She was seen on numerous occasions with culture discharge unresponsive to a variety of topical and oral antibiotics. Clinically, with the conjunctiva diffusely inflamed, the implant eroded to touch, and the presence of a granulomatous granuloma, implant infection was suspected and the implant subsequently removed. Histopathologic assessment revealed widespread lamellar bone formation, including focal areas of contact with adjacent extramedullary hematopoiesis. There was no evidence of an inflammatory process or infection. Postoperatively, the patient's symptoms and signs resolved. Extramedullary hematopoiesis within hydroxyapatite implants is rare. Presence of orbital implant infection is also rare. Osteogenesis with extramedullary hematopoiesis simulating implant infection has not previously been reported.

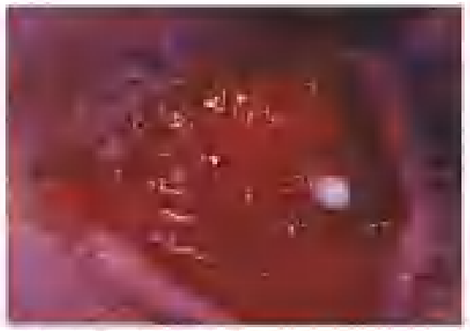

FIG. 1. Diffuse inflammation of conjunctiva, with purulent discharge and a fungoid granuloma involving a perforation site (inset).

CASE REPORT

A 28-year-old woman underwent secondary orbital implant surgery with an HA implant by primary socket modality. Over the next 7 years, 3 drilling procedures were performed to placate for an inadvertent peg and sleeve peg system. Twelve months after her last drilling procedure, she began experiencing purulent discharge from the socket. Despite numerous courses of topical and oral antibiotics, the socket discharge persisted and was accompanied by conjunctival discharge at times and socket tenderness. On examination, the socket and peripheral conjunctiva were grossly diffuse with purulent socket discharge. Granuloma in the fornix and a prosthesis granuloma were identified overlying hydroxyapatite socket (Fig. 1). The implant was found to touch through the most inferior aspect of the socket at the time of removal, but no gross soft tissue dehiscence was noted. Postoperatively, the discharge resolved, the socket inflammation cleared, and the patient's symptoms resolved. Histopathologic examination revealed widespread lamellar bone formation, including focal areas of mature formation with active extramedullary hematopoiesis in addition to immature osteoid (Fig. 2). Gram, fluorescein, acid fast, and periodic acid–Schiff stains for microorganisms were negative. Special mucin stains for mucormycosis were negative.

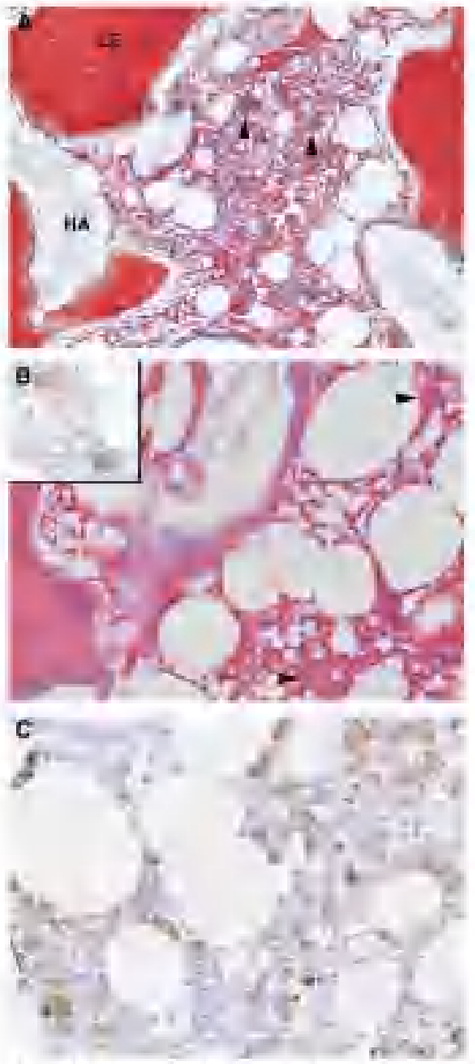

FIG. 2. A, Implant showing material with active intramedullary hematopoiesis including megakaryocytes (arrowheads) surrounded by lamellar bone (LB) and dissolved hydroxyapatite (HA) (Movat, ×200). B, High-power view of extramedullary hematopoiesis demonstrating megakaryocytes (arrowheads), hemosiderin (arrow), and RBCs. The inset shows positive cytoplasmic staining with factor VIII related antigen (arrowheads) of megakaryocytes (×400). C, Extramedullary hematopoiesis with granulocytic precursors showing positivity for myeloperoxidase (×400).

DISCUSSION

HA orbital implants are commonly used in ophthalmic socket surgery. Infection with implantation is also not unusual because implant removal is often required to resolve problems.[1] Early signs and symptoms of implant infection include chronic conjunctival conjunctivitis inflammation, but are nonspecific as patients with an implant may commonly have these findings.[2] Persistent discharge and conjunctival inflammation despite multiple drops should raise suspicion of an implant infection.[3] Treatment options, granulomas, and observation on extrusion of the implant also should alert the clinician to possible implant infection.[4]

In the present case, implant infection was suspected clinically as the case had all the characteristic features.[1] Interestingly, investigations and, particularly, culture and histopathology

case reported by Sires and Bendel[1] and in the rabbit model of Low et al.[2] The presence of bone has been attributed to an osteoinductive effect of HA.[3] Two possible explanations by which bone may form in HA implants were postulated by Group et al.[3]: dedifferentiation of circulating monocytes or monocytic metaplasia of fibrocytes that migrate in the implant. Of 6 patients who underwent HA implant removal by other authors at 5, 7, 8, 8, 10, and 16 months that were found to have bone formation, only one had any clinical symptoms that may potentially have been attributed to the bone formation.[4–7] The implant was from a 70-year-old woman who had undergone enucleation.[6] Eight months later she had intractable pain and the HA implant was removed. Unfortunately, the authors did not state whether the patient's symptoms resolved, how extensive the bone formation was, or whether there was any bone exposure. It is therefore difficult to attribute the intractable pain to the bone formation. In 10 of 13 patients we previously reported who underwent HA implant removal because of signs and symptoms suggestive of implant infection, bone formation (without hematopoiesis) was documented.[5] In each case histopathologically, there was either acute or chronic inflammatory cells found with or without the presence of bacterial colonies or bacterial organisms.[5] In our patient, with extensive bone formation and hematopoiesis, suppurative discharge was the main symptom with implant tenderness being less significant. Clinically, she appeared to have an implant infection, but histopathologically there were no signs of implant infection, just the myeloerythroid hematopoiesis.

In summary, the most serious complication of porous implants is infection and implant removal is often required as treatment.[1–7] Recurrent discharge, pyogenic granuloma formation, and breakdown of the implant are hallmarks of an infected implant.[1–7] The present case indicates that these symptoms and signs also may be hallmarks of osteogenesis with extramedullary hematopoiesis in the implant. Alternatively, they may represent coincidental findings unrelated to the symptomatology. To our knowledge, implant removal is the only known treatment.

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Possible role of frankincense in the treatment of benign essential blepharospasm

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Keywords:
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ABSTRACT

Purpose: To report case series of benign essential blepharospasm (BEB) symptom relief in the setting of regular topical frankincense usage.

Observations: The patients reported underwent botulinum toxin (BT) injections of botulinum toxin (BT) injection appointments before and after the onset of regular frankincense usage and (2) partial regression of symptoms. After starting frankincense, patient 1 decreased the frequency of her BT injections from 3–4 every 12+ months, eventually stopping BT injections altogether. Patient 2 decreased her BT appointments from every 3–4 months to approximately every 8 months after starting frankincense. Both patients had previously tried multiple additional treatments for their BEB symptoms which did not yield improvement; both patients reported significant improvement in their symptoms secondary to topical frankincense oil.

Conclusions and Importance: Frankincense is a natural product of Boswellia trees. It has been used generally for its anti-inflammatory properties for many years in multiple countries. We report two cases of individuals with long-standing, debilitating benign essential blepharospasm achieving significant symptom relief after beginning regular usage of topical frankincense essential oil. The natural oil offers an organic and effective treatment option for this chronic, progressive condition.

1. Introduction

Benign essential blepharospasm (BEB) is a facial dystonia characterized by involuntary contraction of the orbicularis oculi. Oral medications for BEB include benzodiazepines, anticholinergics, anticonvulsants, and dopaminergics, but these therapies generally lack long-term effectiveness and result in significant side effects. Surgical myectomy is generally recommended for those who do not respond well to medical therapy. To date, the most effective therapy for BEB is botulinum toxin (BT) injections, but a recent Cochrane review indicates that the effect begins to wear off after 10.1 weeks. Most patients receive injection approximately every 12 weeks or 4–5 times per year. A non-invasive therapy for BEB or increasing the time between injections could improve quality of life among patients with BEB.

Frankincense is a natural gum resin derived from Boswellia trees and has been used in rheumatoid arthritis, ulcerative colitis, Crohn's disease, multiple sclerosis, and other inflammatory conditions. It has also been used among patients with Parkinson disease, a condition characterized by dystonic movements. We report the novel use of topical frankincense oil for the treatment of BEB.

2. Case report

A 72-year-old woman noted a three-year history of progressive light sensitivity, dry eyes, and eyelid spasms. Her visual acuity was 20/20 each eye. The rest of her efferent and afferent examination was unremarkable. She was diagnosed with BEB and treated with 50 units of BT injections and artificial tears. She received a total of 50 units of onabotulinumtoxinA along the upper and lower medial and lateral eyelids as well as the lateral canthal region. The patient received repeat injections 3 and 5 months later then was lost to follow-up for 4 years.

She resumed BT injections in May 2007 due to worsening of symptoms and consistently scheduled injections every 3–4 months. In 2009, she began using topical frankincense essential oil on all four eyelids daily. After approximately one year, she experienced improvement in symptoms and decreased her BT injection frequency to every 12 months before stopping altogether in September 2010. She did not receive BT again before her death in September 2015.

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3. Case report 2

[illegible]

4. Discussion

[illegible] Mice experiments suggest boswellic acids may reduce brain damage secondary to stroke, enhance learning and memory in Alzheimer's disease, and improve motor symptoms in Parkinson's disease. The proposed mechanisms involve reducing DNA oxidative damage and free radical formation, increasing acetylcholine levels in the brain, and decreasing acetylcholinesterase and [illegible] levels in the brain respectively. Last, frankincense has beneficial effects [illegible] multiple sclerosis via decreasing IL-17 production, neuropathic pain via TRPV1 downregulation, and anxiety through reduction of corticosterone levels.

The mechanism of action of frankincense in BEB is unclear. The effect may relate to the improvement in dystonic movements in Parkinson disease treated with frankincense. In a randomized, double-masked, placebo-controlled crossover study, anticholinergic and antimuscarinic therapies showed significant benefit to some of the subjects with BEB. In mouse models, frankincense has been shown to exhibit antimuscarinic properties, and this may explain the improvement among our patients. Alternatively, both patients could have experienced a placebo-like effect or enjoyed spontaneous improvement. However, Castelbuono and Miller noted that spontaneous improvement typically occurs within the first 5 years of symptom onset, whereas our patients had symptoms for 9 and 20 years respectively before improvement of their BEB symptoms.

BT is well-established as the treatment of choice for BEB. The recommended starting dose for BT injections in this specific context is 1.25–5 units/injection site, which can subsequently be increased in future appointments depending on response. It remains common practice to limit the dosing to <100 units. The patients in this case series received 2.5–5 units per injection site. They never exceeded more than 5 units per injection site or 50 units for their total dosing. Most patients receive injections every 12 weeks, and it should be noted that Case 1 was atypical in that she received injections every 5-8 months.

Frankincense is non-toxic and has displayed an impressive safety profile. Multiple clinical trials yielded no long-term, irreversible adverse effects. The most prevalent side effects that have been noted are nausea and gastrointestinal upset. No severe drug interactions have been noted.

It is important to acknowledge this case series does not establish clear causation between regular periorbital frankincense usage and BEB symptom relief, warranting further study. A prospective trial of frankincense in the treatment of BEB would be helpful.

5. Conclusion

Frankincense is a natural product of Boswellia trees and has been used for its anti-inflammatory properties in multiple disease states. These cases suggest daily topical frankincense essential oil may improve signs and symptoms of benign essential blepharospasm, and further study is warranted.

Patient consent

Informed consent for research was obtained from both patients.

Acknowledgements and disclosures

The authors report no disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare no conflict of interest.

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Brief Reports

Retrobulbar Hemorrhage Nine Days after Cosmetic Blepharoplasty Resulting in Permanent Visual Loss

[illegible]

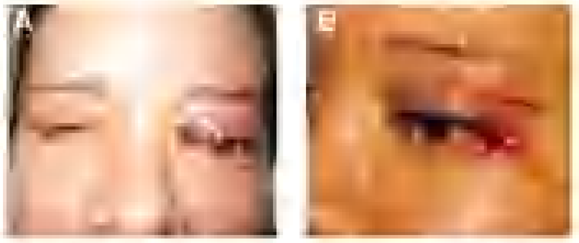

FIG. 1. A, [illegible] B, [illegible]

Abstract: A healthy 45-year-old man had a retrobulbar hemorrhage 9 days after cosmetic upper eyelid blepharoplasty that resulted in permanent visual loss. After performing a left lateral canthotomy and cantholysis, intraocular pressure returned to normal and vision improved from no light perception to 20/40; however, the patient did have permanent visual field loss. To our knowledge, this is the longest period of time after blepharoplasty that a retrobulbar hemorrhage occurred. Ophthalmologists should have a heightened level of suspicion 1 to 2 weeks after surgery.

R[illegible]

CASE REPORT

[illegible]

[illegible]

DOI: [illegible]

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DISCUSSION

[illegible]

FIG. 2. A, Axial CT [illegible] B, Coronal [illegible]

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REFERENCES

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Cavernous Sinus/Orbital Apex Syndrome Associated With Indwelling Orbital Catheter Use

Timothy Lai, M.D.* and John D. Ng, M.D.†

Abstract: A 46-year-old man with a history of right orbital fractures and blindness underwent simultaneous fracture repair and enucleation with orbital implantation. During surgery, an orbital catheter was placed for administering local anesthesia to control postoperative pain. After administration of local anesthesia through the catheter on postoperative day 1, the patient had development of a complete ptosis, total ophthalmoplegia, mydriasis, vision loss from 20/20 to NLP, and hypesthesia of the V1 and V2 trigeminal nerve distribution. Intraocular pressures and dilated funduscopic examination were normal. There was no evidence of central nervous system effects or respiratory depression. After 4 hours of observation, the vision, sensation, motility, ptosis, and pupil response all returned to normal. Although rare, contralateral cavernous sinus/orbital apex syndrome may occur with indwelling orbital catheter administration of local anesthetic in an orbit with fractures.

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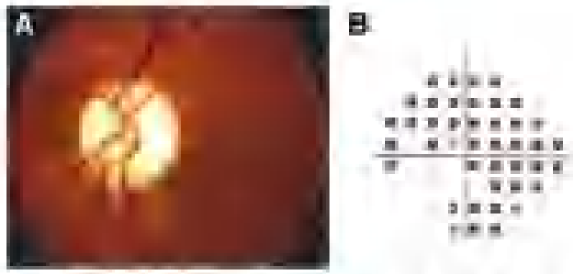

FIG. 3. A, Optic disc photo [illegible] B, Humphrey visual field [illegible]

BRIEF REPORTS

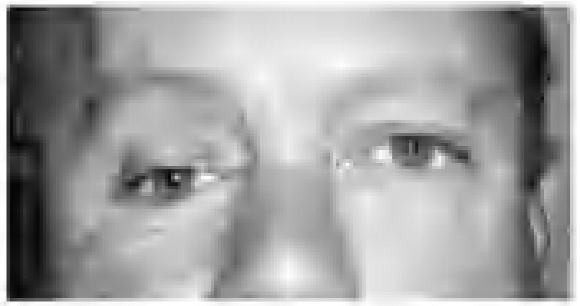

FIG. 1. Patient [illegible]

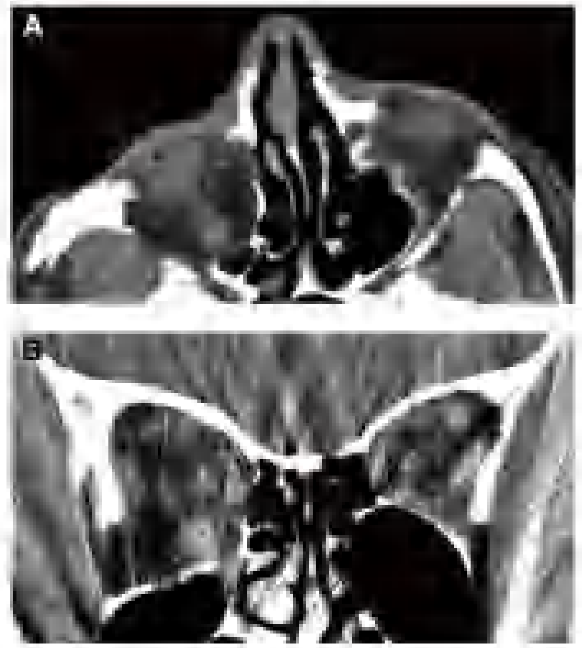

FIG. 2. A, Axial and B, coronal CT [illegible]

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CASE REPORT

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DISCUSSION

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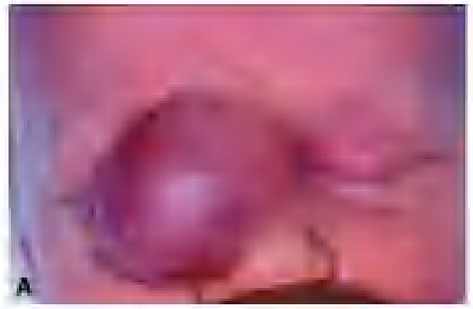

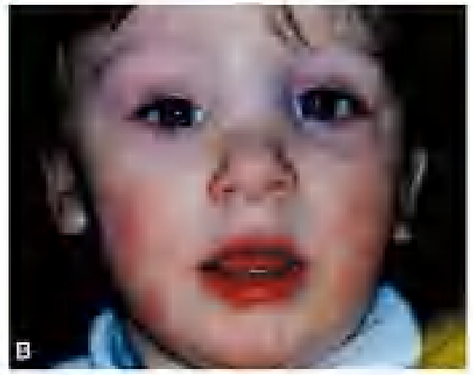

FIG. 1. A, Two-day-old infant presenting with anterior cranial encephalocele. B, Three years after surgery, with excellent orbital symmetry and normal neurologic development.

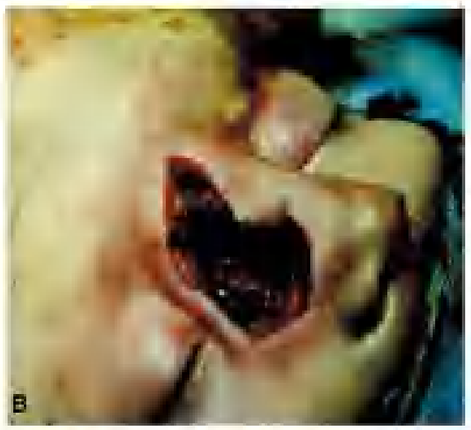

FIG. 3. A, Transcranial view of meningoencephalocele. The defective neural tissue is dissected and the dural and bone defects are repaired. B, Anterior view. Redundant skin and the mass are resected from the medial canthal and orbital area with rejuvenating of the medial canthal tendon.

pillary approach are necessary in avoiding visual impairment and aesthetic complications (Fig. 1, Fig. 2, and Fig. 3).

CASE REPORT

An 11-day-old boy presented with a mass in the medial canthus of the right inferior extending medial to the glabella and inferior to the nasal bone. The mass caused nasal airway obstruction and tended to be reflected inferiorly during bottle-feeding. It measured 35 mm vertically and 29 mm horizontally. He

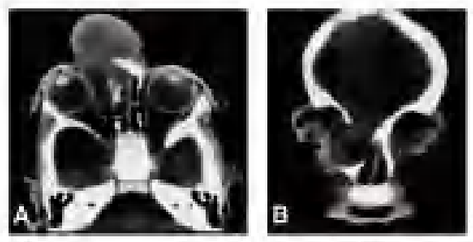

FIG. 2. Preoperative axial (A) and coronal (B) CT scans show orbital defect with defective neural tissue herniation.

fluxed and followed objects well with both eyes. Extraocular movements were full and conjugate. Vertical palpebral width and horizontal fissure were symmetrical at 9 mm and 11 mm, respectively. Medial to medial canthal distance was 34 mm on the right and 31 mm on the left. There was 1 mm of right exophthalmos with symmetric globe elongation. Cycloplegic retinoscopy revealed a −2.00 sphere with axis of +100 at 180 degrees OD. The examination was otherwise normal.

CT revealed a meningoencephalocele herniating through a defect in the cribriform plate and right fronto-ethmoid sinuses. The contents of the sac appeared to be neural tissue from the normal brain tissue to such an extent that the ipsilateral middle cranial fossa was also empty.

Reconstructive surgery was undertaken to prevent nasal airway obstruction, amblyopia, and the psychological trauma of a severely disfigured deformity. A frontal craniotomy was performed by osteotomies with transection of the primitive herniating neural tissue and dural repair of the dural defect. Full-thickness calvarial bone graft was used to repair the

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Juvenile Dermatomyositis Presenting With Periorbital Edema

[illegible], M.D., and [illegible], M.D.

Abstract: Juvenile dermatomyositis is a rare disease that affects the skin and muscles. It often presents with a classic heliotrope eyelid rash. We present a case of juvenile dermatomyositis presenting with significant bilateral periorbital edema, with its complete resolution after systemic antiinflammatory therapy.

A [illegible]

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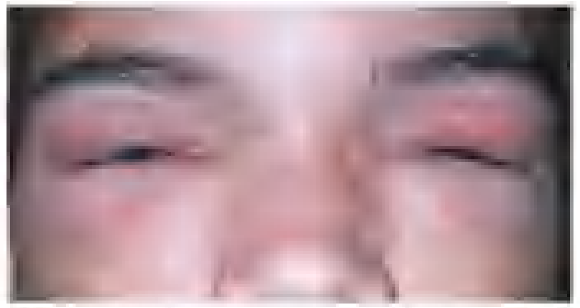

FIG. 1. Significant bilateral periorbital edema with overlying heliotrope rash, characteristic of dermatomyositis.

FIG. 3. Hematoxylin and eosin stain at ×5 magnification. **A,** Right eyelid biopsy shows nonspecific inflammation. **B,** Right sternocleidomastoid muscle biopsy shows marked inflammatory infiltrate consisting of lymphocytes and macrophages. Also note the variation in muscle fiber sizes.

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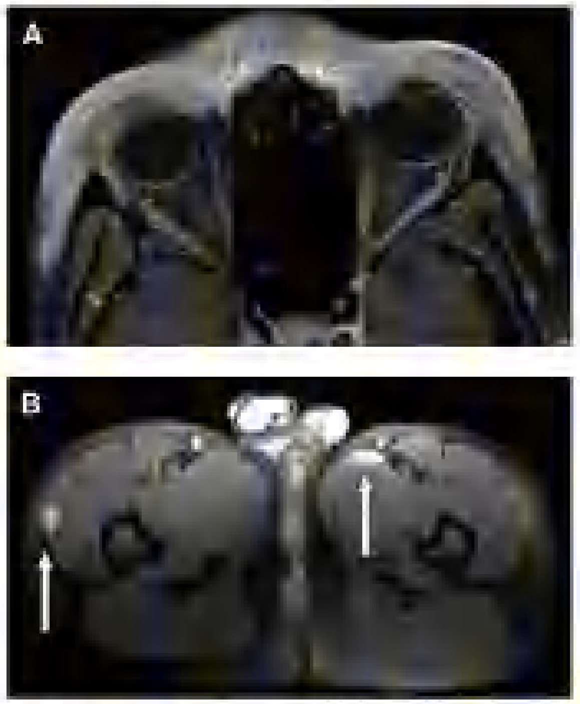

FIG. 2. **A,** Orbital MRI illustrates prominent bilateral preseptal soft tissue swelling. **B,** Lower extremity MRI shows scattered foci of inflammation in thigh muscles (arrows).

DISCUSSION

[illegible]

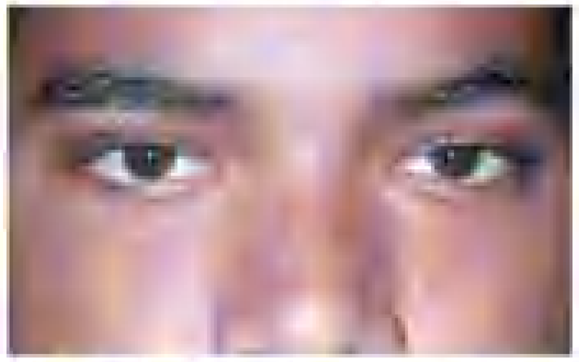

FIG. 4. Resolution of periorbital edema after systemic treatment for juvenile dermatomyositis.

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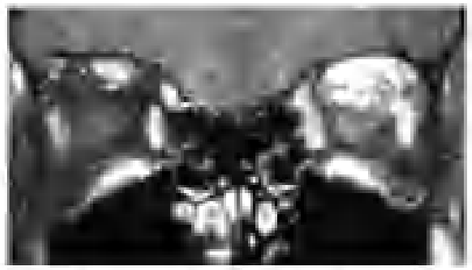

FIG. 1. Coronal contrast-enhanced MRI with left superolateral enhancing mass (white arrow) in orbit and normal right orbit.

CyberKnife Radiosurgery and Rituximab in the Successful Management of Sclerosing Idiopathic Orbital Inflammatory Disease

Alexander V. Ho, M.D., Mark J. Kleinberg, M.D.,*
H. James Williams, M.D., and
Daniel W. Kozelsky, M.D.†*

Abstract: A 26-year-old man presented with cranium-invasive idiopathic orbital inflammatory disease. After a poor initial response to oral steroids, an orbital biopsy confirmed the diagnosis. A pauci-cellular lymphocytic infiltrate with areas of fibrosis was seen to replace normal tissue. With the development of exposure keratopathy and diplopia associated with eyelid retraction, lagophthalmos, and decreased motility, increasing doses of steroids and periocular steroid injections were instituted without effect. On the basis of successful treatment of malignant lymphocytic tissue, it was treated with CyberKnife radiosurgery and rituximab. This resulted in symptom resolution with improved eyelid closure and motility. Eighteen months after treatment, he is essentially symptom-free, with almost complete radiographic regression of the disease process.

Sclerosing idiopathic orbital inflammatory disease (SIOID) refers to a unique group of disorders that present with extensive fibrosis and dense lymphocytic infiltrate. Successful long-term treatment is challenging. Recent findings suggest that some cases may be responsive to radiotherapy and rituximab.[1] We report a case of sclerosing SIOID successfully treated with CyberKnife radiosurgery and rituximab.

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FIG. 1. Coronal contrast-enhanced MRI with left superolateral enhancing mass (white arrow) in orbit and normal right orbit.

CASE REPORT

A 26-year-old man initially presented with a 2-year history of worsening left orbital pain, proptosis, diplopia, and blurring vision. His ophthalmic history included an uncomplicated cataract surgery in the left eye. His medical history was unremarkable. He had no known systemic disease. MRI demonstrated an enhancing left superolateral orbital mass, and computed tomography (CT) revealed a bony erosion of the lateral orbital wall (Fig. 1). Complete physical examination was normal. Blood studies, including complete blood count, serum chemistry, and angiotensin-converting enzyme level, were within normal limits. Chest radiography was also normal. Initial treatment was with oral prednisone 60 mg daily for 10 days. Treatment failure resulted in referral to an ophthalmologist. Repeat CT showed further orbital soft tissue involvement. MRI showed a mass lesion with heterogeneous enhancement and restricted diffusion. An open biopsy specimen was obtained through lateral orbitotomy. Tissue showed a pauci-cellular inflammatory infiltrate with plasma cells and lymphocytes. Immunohistochemical staining revealed a polyclonal population of lymphocytes with normal kappa and lambda light chain ratios. Flow cytometry revealed a mixed population of T lymphocytes and plasma cells. Tissue culture was negative for fungal and acid-fast bacilli organisms. The histological findings were consistent with a diagnosis of SIOID (Fig. 2). After surgery, sclerosing disease resulted in left upper eyelid retraction. There was no appreciable symptomatic improvement after treatment with prednisone, methotrexate, and azathioprine.

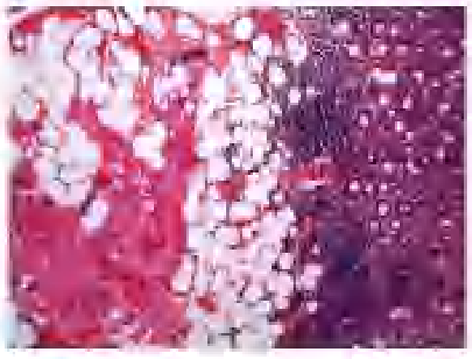

FIG. 2. Biopsy specimen from the left orbit demonstrating a polymorphous inflammatory infiltrate with a histiocytoid cellular matrix, the lacrimal gland tissue, and dense fibrous tissue containing scattered chronic inflammatory cells (hematoxylin and eosin stain, magnification ×100).

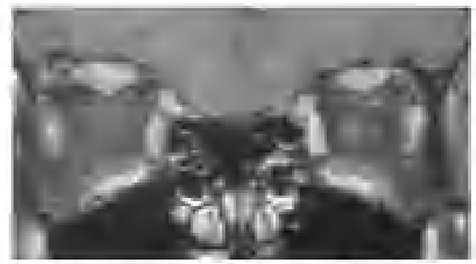

FIG. 3. Coronal contrast-enhanced MRI with improvement in left superolateral orbital mass obtained after CyberKnife and rituximab treatment.

It is impossible to determine if CytoRich is responsible for some of the effect because drug was administered sequentially. The patient did not have symptomatic improvement with supraorbital Cox electrical stimulation (CyberKnife) and botox injections. It is possible that there is a synergistic effect with the combination therapy. Randomized, prospective studies will need to be performed to evaluate the effect of CytoRich alone, botox, combination therapy, and/or the known combinations.

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Thyroid Eye Disease Presenting After Cosmetic Botulinum Toxin Injections

Andrew R. Harrison, M.D.[1], and
Jonathan P. Dingeldein, M.D.[2]

Abstract: **A 55-year-old woman with left periorbital swelling 4 days after botulinum toxin injection in the lateral canthal area presented after noticing left eye prominence. Physical examination demonstrated proptosis and eyelid retraction. Computed tomography of the orbits confirmed extraocular muscle enlargement consistent with thyroid eye disease. In this case, the patient had development of proptosis after receiving botulinum toxin injections. Although the proptosis may represent progression of the patients' thyroid eye disease, it is worthwhile to consider botulinum toxin as a possible cause given its widespread use.**

Thyroid eye disease (TED) is the most common cause for unilateral or bilateral proptosis in adults.[1] Previous studies have reported the induction of proptosis by medications such as corticosteroids and isoproterenol and the precipitation of TED after organ surgery.[2–4] The cosmetic use of botulinum toxin (BTX) has grown during the past decade as the result of the relatively low risk of side effects. Common periorbital adverse effects include ptosis, diplopia, and lagophthalmos.[5] We present a patient who had periorbital swelling after BTX injection. The case report suggests the onset of the disease directly after the injections. Other studies have drawn proposed the association of TED after injection of potential triggers and surgery.[2–4] The proposed mechanism may simply represent the patient with TED coincidentally developing concurrently at the time of her BTX injections. Alternate possibilities include that the paralysis of the lateral rectus muscle by the BTX injection induced ophthalmoplegia that activated previously undiagnosed disease. Whether or not the proposed association is true, the patient is encouraged by the presence of BTX diseases similar to this. Also due to the prevalence of thyroid disease, it serves as a potential cause to consider BTX injection complications.

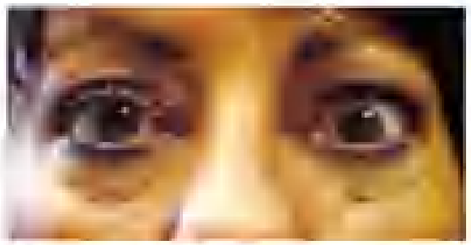

FIG. 1. Patient with left upper eyelid protraction and mild proptosis.

CASE REPORT

A 55-year-old white woman with a history of generalized myasthenia gravis (MG) presented to the Ophthalmology and Oculoplastic Clinic with a left periorbital swelling. Twelve years before presentation, she was diagnosed with Graves' hyperthyroidism and treated with radioactive iodine. She was evaluated for Graves' ophthalmopathy and found to have normal visual acuity, no lid retraction, and normal thyroid function testing. She had history of walking up to several days after the onset of her MG symptoms. She had received botulinum toxin injections for her MG symptoms. She developed periorbital swelling 4 days after injection. The BTX injected for her facial cosmetic areas. The swelling involved the upper eyelid, and the initial presumptive diagnosis of eyelid blepharoptosis revealed asymmetric proptosis (right = 20 mm; left = 24 mm) on applanation. Pupils and extraocular motility were normal. Fundus examination showed normal optic nerves and retinas. Computed tomography of the orbits revealed enlarged extraocular muscles (Fig. 2). Serologic testing revealed elevated thyroid-stimulating immunoglobulin (TSI) (>500 IU/L; normal, <140 IU/L) and thyroid peroxidase antibody (>1,000 IU/mL; normal, <35 IU/mL). Thyroid function tests were normal. She denied subjective symptoms of dysthyroidism (Fig. 3).

DISCUSSION

Thyroid eye disease has an incidence of 1 in 1,000 in the United States and is a leading cause of unilateral and bilateral proptosis during the adult years. In 50% of patients with TED, the ocular symptoms precede the onset of the systemic disease by as much as 10 years.[1] Common signs include eyelid retraction, proptosis, and diplopia. The most common TED-related symptoms were a sensation of dryness (>50%) and ocular pain (>40%). Approximately 10% of patients with TED have optic neuropathy.[1]

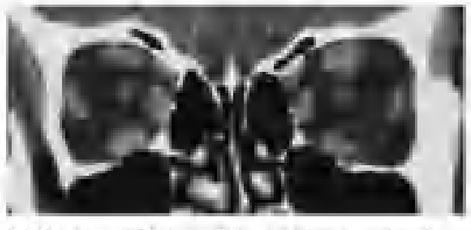

FIG. 2. Coronal CT demonstrates extraocular muscle enlargement.

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The exact cause of TED remains unknown; however, it is generally considered an autoimmune disease and the interplay of several mediators, including an expansion, seem to cause fibroblasts and fibrocytes response.[6]

Reasons given for the possible increase in the number of appearances of Graves ophthalmic indications as a side-effect to cosmetic facial injection and treatment of thyroid. Side effects are common. BTX injection is made more by paralysis of the ocular muscles, ptosis, and diplopia.[7] In our patient, her symptoms were evident within 4 days after injection. BTX injection are limited cardiac effects.

We are aware of previous reports of TED in conjunction with patients with recently performed other BTX injections. The time course suggests the onset of the disease directly after the injections. Other studies have drawn proposed the association of TED after injection of potential triggers and surgery.[2–4] The proposed mechanism may simply represent the patient with TED coincidentally developing concurrently at the time of her BTX injections. Alternate possibilities include that the paralysis of the lateral rectus muscle by the BTX injection induced ophthalmoplegia that activated previously undiagnosed disease. Whether or not the proposed association is true, the patient is encouraged by the presence of BTX diseases similar to this. Also due to the prevalence of thyroid disease, it serves as a potential cause to consider BTX injection complications.

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Orbital Cysts Lined With Both Stratified Squamous and Columnar Epithelia: A Late Complication of Silicone Implants

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Leonard E. K. Ang, F.R.C.S., F.A.C.S.(Ophth.),
Chee-Teck Chin, A.B.O., D.O.M.S., Elizabeth S. T. Chan, D.O., F.R.C.P.(Lond.), F.R.C.S., F.A.C.S., and
Sean-Thiak Chin, F.R.C.S.(Edin.)

Abstract: **Two patients presented with orbital cysts 2 and 7 years after orbital blowout fracture repair with silicone plate implants. The orbital cysts caused significant exophthalmos and restriction in ocular motility. Surgical excision revealed thick-walled cysts that were displacing the globe and encapsulating the silicone implant. On histopathologic examination, the cysts were lined with both stratified squamous and ciliated columnar (respiratory) epithelia. We propose that squamous and respiratory epithelial cells may have been deposited during surgery from the conjunctival and sinus epithelia, respectively. This case series illustrates that although an uncommon complication, epithelium-lined implant cysts may develop several years after orbital fracture repair with a silicone implant. A transconjunctival surgical approach is a possible risk factor.**

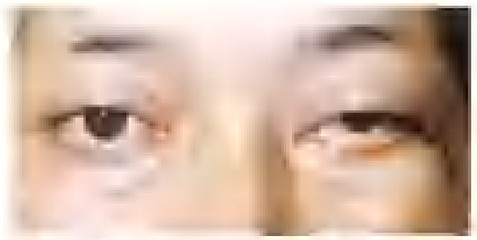

FIG. 3. Patient 1 had a mass over the left medial orbit, roughly symmetrical and about the same size as the right.

The implantation of silicone plates during orbital fracture repair has been associated with the subsequent formation of epithelium-lined implant cysts.[1–4] We report two patients who developed cysts with cystic wall lined by both stratified squamous and columnar epithelia several years after orbital fracture repair. Our findings suggest that only limited squamous and columnar epithelia lining the orbital cavity may be implanted during surgery. This case series illustrates that although an uncommon complication, epithelium-lined implant cysts may develop several years after orbital fracture repair with a silicone implant. A transconjunctival surgical approach is a possible risk factor.

CASE REPORTS

Case 1. A 36-year-old man had undergone left facial trauma and fracture of the left orbital floor. Radiographic report and surgical notes 2 years after orbital floor fracture repair did not note plate implantation. Examination of the left upper eyelid revealed a hyperplastic, 1 cm × 1 cm pink mass, with normal overlying skin. There was proptosis and a large, firm mass along the floor of the left orbit (Fig. 1).

CT showed a left orbital extraconal cystic lesion measuring 4.6 cm × 3.4 cm × 3.0 cm (volume, 24 cm³) at the inferior orbital rim. The cyst was well defined with thick, regular, smooth wall and was in close relation to the surrounding bone and compressing the adjacent globe. The cyst wall was lined by both columnar epithelium and stratified squamous epithelium (Fig. 2).

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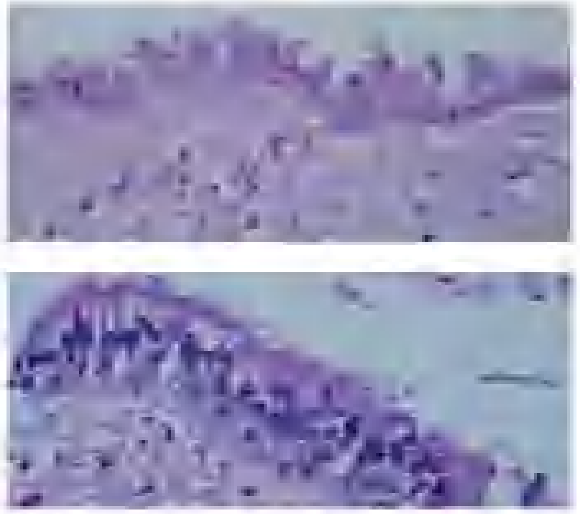

FIG. 2. Histopathology of the cyst wall from patient 1 (hematoxylin and eosin stain; magnification, ×400). The cyst was lined by stratified squamous epithelium (top) and ciliated columnar epithelium (bottom).

Case 2. [illegible]

[illegible]

DISCUSSION

[illegible]

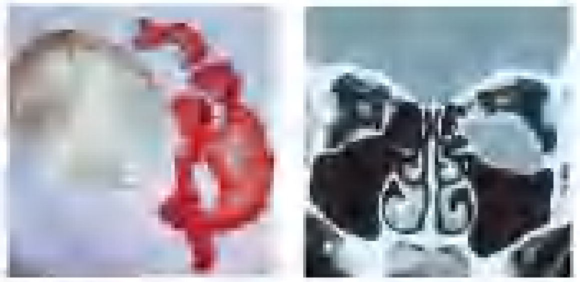

FIG. 3. Left, The intact orbital cyst and silicone plate removed from patient 2 during orbitotomy. Right, Coronal CT of patient 2 demonstrating a soft-tissue mass arising from the inferomedial aspect of the left orbit.

[illegible]

ACKNOWLEDGMENTS

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Lymphoplasmacytic Lymphoma Isolated to an Extraocular Muscle

[illegible]

Abstract: A 44-year-old woman presented with a 1-month history of right-sided tearing, redness, and chronic headache. Clinical examination was notable for 4-mm proptosis and decreased visual acuity OD. Orbital CT demonstrated isolated enlargement of the right lateral rectus. Surgical biopsy was undertaken after an unsuccessful trial of oral steroids. Histopathology and immunophenotyping demonstrated a lymphoplasmacytic lymphoma. External beam radiation induced regression of the lymphoma with decreased proptosis and improved visual acuity.

[illegible]

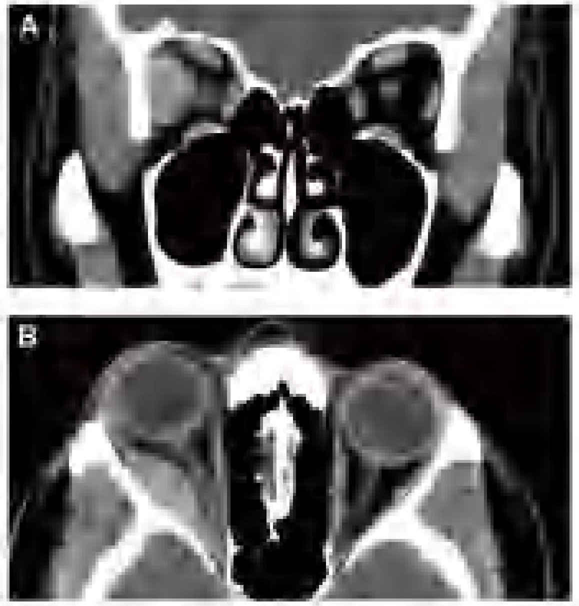

FIG. 1. A, Axial and B, coronal orbital CT images demonstrating isolated enlargement of the right lateral rectus muscle. Axial image depicts lack of distal tendinous insertion involvement.

CASE REPORT

[illegible]

[illegible]

FIG. 2. Photomicrograph shows both lymphocytic and plasmacytic infiltrate within striated muscle (hematoxylin and eosin stain; magnification, ×20).

[illegible]

DISCUSSION

[illegible]

REFERENCES

[illegible]

Large, Rapidly Growing Pilomatrixoma of the Upper Eyelid

Valentin Huerva, M.D., Ph.D., M. Carmen Sanchez, M.D., and Julio Asenjo, M.D.

Abstract: **A 41-year-old woman presented with a rapidly growing mass on her upper left eyelid that had first appeared 3 months earlier. The mass was dark red in color, alternating with whitish pseudocyst formations, and measured 3 cm long with a 1-cm base presenting. The rapid growth had caused a mechanical ptosis and bleeding as the result of erosion of the skin covering the tumor. The initial clinical diagnosis suggested a malignant lesion or vascular tumor; excisional biopsy was performed. The eyelid crease was approached for incision and resection as for a blepharoplasty. Pathologic examination yielded a diagnosis of giant pilomatrixoma. Pilomatrixomas are rare in adults and rarely attain such a large size. After 1 year of follow-up, no recurrence of the tumor has been observed.**

Pilomatrixoma [illegible]

[illegible]

Accepted for publication [illegible]

DOI: [illegible]

FIG. 1. Large tumor at the superior sulcus of the upper left eyelid measuring 3 cm long, < 1 cm base with dark-red coloring, alternating with whitish pseudocyst formations. Rapid growth caused mechanical ptosis and bleeding as the result of erosion of the skin covering the tumor.

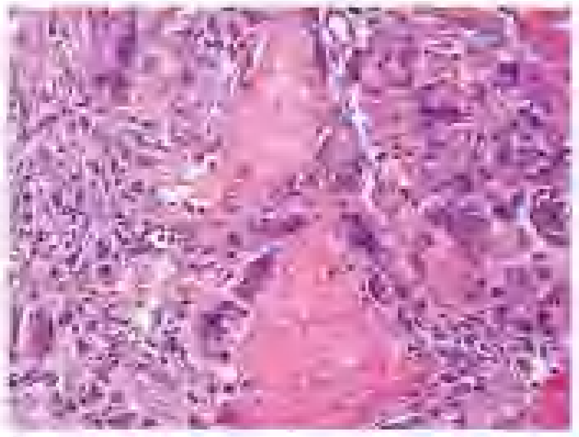

FIG. 2. Histopathology demonstrating characteristic ghost cells of pilomatrixoma and numerous foreign body giant cells in its surroundings. There is an absence of atypical mitotic figures and necrosis (hematoxylin and eosin stain).

[illegible]

CASE REPORT

[illegible]

DISCUSSION

[illegible]

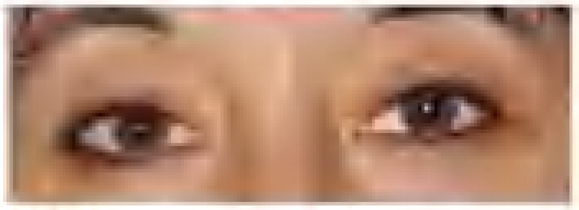

FIG. 3. One month after excision, the patient has a symmetrical eyelid crease with a small scar [illegible]

The differential diagnosis of pilomatrixoma in children includes congenital dermoid cyst, sebaceous epidermal inclusion cyst, chalazion, juvenile xanthogranuloma, vascular tumor, and rhabdomyosarcoma.[1–3] In adults, a red-blue discoloration should be differentiated from a large epidermoid cyst, which is freely movable, painless, and covered by intact epidermis with diffuse homogeneous yellow coloration when lifted with forceps. Dermoid cysts appear in children and in young adults. The overlying skin, with normal appearance, is easily movable over the lesion. Cavernous vascular tumors are frequent haemangiomas in the periorbital region. They have a rock-hard texture, with red-blue coloration and very slow growth. The differential diagnosis in adults also includes rare, benign hair follicle-derived eyelid tumors such as trichoepithelioma, trichilemmoma, trichoblastoma, and inverted follicular keratosis, which is approximately 65% of the cases the diagnosis is histologic, without any clear preventive clinicopathologic correlation.[4,5,7]

In conclusion, we present a new case of large, rapidly growing pilomatrixoma in an adult. Accurate diagnosis was possible after histologic examination. A large red-blue mass with rapid growth in the upper eyelids and eyebrows in adults may suggest a pilomatrixoma. Its excision, taking advantage of the eyelid crease, leads to an excellent cosmetic result.

ACKNOWLEDGMENTS

The authors thank Dr. R. M. Egido, Pathology Department, University Hospital Arnau de Vilanova, for histopathologic consultation.

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Intravascular Lymphoma Presenting as an Orbital Mass Lesion: A Case Report

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ORIGINAL ARTICLE

Intravascular Lymphoma Presenting as an Orbital Mass Lesion: A Case Report

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ABSTRACT

We describe a case of intravascular lymphoma that presented as an orbital mass lesion. A 77-year-old female presented with longstanding fatigue and one-month of diplopia. Magnetic resonance imaging (MRI) revealed a frontal lobe brain lesion and a right orbital mass. Brain biopsy was interpreted as anaplastic oligodendroglioma. Orbital biopsy revealed intravascular lymphoma. On review of brain histopathology the diagnosis was revised to CNS intravascular lymphoma. To the best of our knowledge, this case represents the first report of intravascular lymphoma presenting as an orbital mass lesion.

KEYWORDS: Orbital Lymphoma, Vitreoretinal

INTRODUCTION

Intravascular lymphoma (IVL) is a rare, large B-cell non-Hodgkin's lymphoma (Pluot and Tapparone, 1959; Wick et al., 1996) characterized by growth of neoplastic cells within lumina of small blood vessels. Intravascular lymphoma commonly presents with cutaneous and/or central nervous system symptoms. A previous case series described intraocular involvement presenting with reduced visual acuity (Elner et al., 1986). We report a case of IVL presenting as an orbital mass.

Case Report

A 77-year-old woman complained of chronic malaise and diplopia for 4 weeks. Medical history was significant for breast cancer 34 years prior and a 4-month history of pituitary adenoma. One month prior to our evaluation she underwent brain biopsy of a right fronto-temporal lesion at an outside institution that was interpreted as anaplastic oligodendroglioma (Figure 1).

Examination revealed visual acuities of 20/40 OD and 20/50 OS. The right pupil was 1mm larger than the left and poorly reactive with an afferent pupillary defect. Slit-lamp examination revealed marked nuclear sclerosis. External examination showed ptosis of the right upper lid. One millimeter of proptosis was noted OD.

Magnetic resonance imaging and computed tomography scans demonstrated a right superotemporal intraconal mass between the superior and lateral rectus muscles that enhanced with gadolinium (Figure 2). There was no bony destruction and the lesion abutted to the globe.

Superior transconjunctival orbital exploration was performed under general anesthesia. Dissection into sub-Tenon's space revealed a large intraconal mass. Multiple biopsies were obtained and sent for pathologic evaluation. The orbital fat and lacrimal gland

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appeared histologically unremarkable. A small focus of vascular prominence contained intraluminal cells with high nuclear to cytoplasmic ratios and occasional prominent nucleoli (Figure 3). A panel of immunoperoxidase stains confirmed the histologic suspicion of IVL. The atypical intravascular cells expressed CD45, CD20, and CD6, but not CD3 or CD10 or CD30. CD34 and CD31 stains highlighted the endothelial cells confirming the intravascular location of the neoplastic cells (Figure 4). On review of the brain histopathology from an outside institution, the diagnosis of this lesion was revised to CNS intravascular lymphoma.

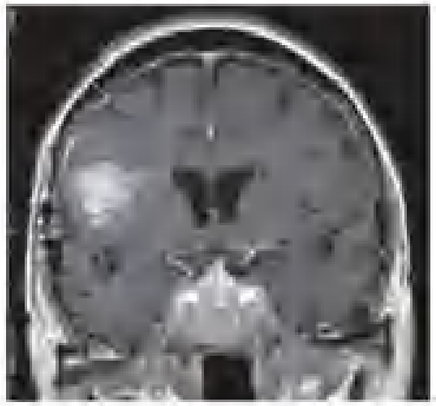

FIGURE 1

FIGURE 2

COMMENT

Intravascular lymphoma is a rare extranodal large B-cell non-Hodgkin's lymphoma, characterized by widespread intravascular proliferation of neoplastic cells. The tumor predominantly affects middle-aged to older patients, without predilection for either sex (Ferreri et al., 2004). Clinical presentation is heterogeneous, making diagnosis elusive. Half of IVL cases are diagnosed at autopsy, where involvement of the brain is followed in frequency by involvement of the bony marrow, adrenal, prostate, and kidney. Symptoms result from ischemic end-organ dysfunction secondary to microvascular occlusion. The most common presentations are cutaneous lesions involving the trunk and lower legs and/or non-specific neurological manifestations. Diagnosis is histological, based on biopsy of presenting lesions (Gill et al., 2005). The reason for confinement of neoplastic cells

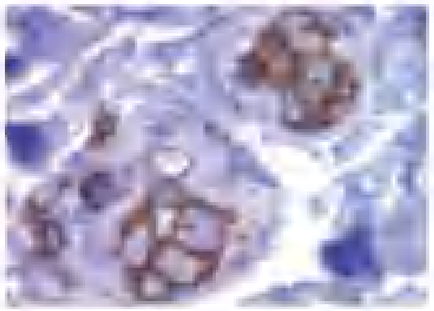

FIGURE 4

FIGURE 3

within vascular lumina is unknown but may involve abnormalities of adhesion molecule expression (Jalkanen et al., 1989; Kanda et al., 1999; Ponzoni et al., 2000).

Histologically, intravascular lymphoma is composed of neoplastic lymphocytes with large vesicular nuclei, prominent nucleoli, and scant basophilic cytoplasm. Immunohistochemical analysis typically identifies the lymphocytes as B-cells. T-cell, histiocytic, and NK-cell variants have been described, but are exceedingly rare (Wu et al., 2005). The cells are found embedded within a network of fibrin, forming thrombi in lumina of small vessels.

Treatment of intravascular lymphoma consists of anthracycline-based (CHOP) chemotherapy with or without radiotherapy. Despite aggressive therapy, prognosis is poor. Following the diagnosis of IVL, our patient was offered a palliative regimen of radiation and rituximab. Unfortunately, the patient deteriorated rapidly and died less than one month following diagnosis.

Although lymphomas comprise 6 to 8% of all orbital tumors (Bardenstein, 2005) and almost all histologic types of lymphoma have been described in the orbit, we could not find any previous reports of orbital IVL.

Declaration of interest: Supported in part by Research to Prevent Blindness (NY, NY) and the Lions and Lionesses of Minnesota. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Incidence of Ocular Injury in Visually Asymptomatic Orbital Fractures

[illegible]

Purpose: [illegible]
Methods: [illegible]
Results: [illegible]
Conclusion: [illegible]

[illegible]

METHODS

[illegible]

[illegible]

TABLE 1. Number of patients with varying severity of ocular injury in both symptomatic and asymptomatic cohorts

Injury severity	Asymptomatic	Symptomatic	Total
No injury	29	3	32
Mild	23	35	58
Moderate	10	—	10
Severe	0	0	0
Total	62	38	100

RESULTS

DISCUSSION

TABLE 2. Number of patients with varying severity of injury and corresponding visual acuity

Snellen	No injury	Mild injury	Moderate injury	Severe injury	Total
20/20 or better	29	58	0	0	87
20/30–20/80	3	0	7	0	10
20/100 or worse	0	0	3	0	3
Total	32	58	10	0	100

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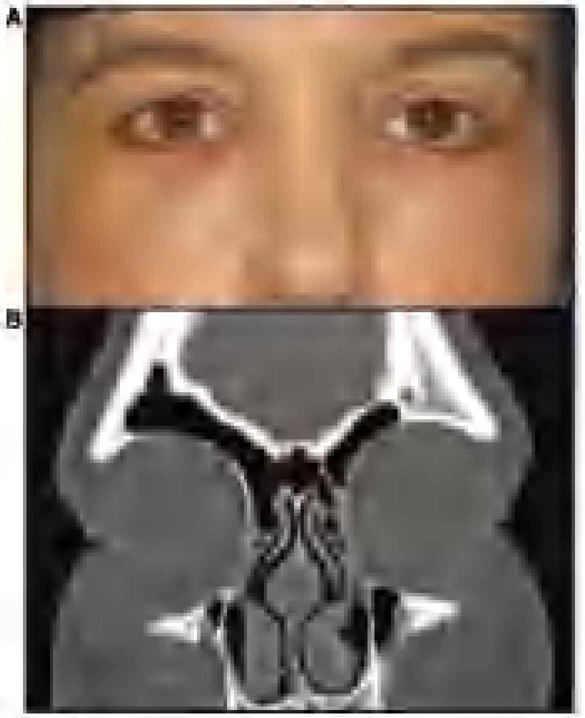

FIG. 2. A, Initial presentation. (B) coronal CT shows soft tissue density material extending from cheek to inferior periorbital region.

1 year of chronic bilateral periorbital swelling (Fig. 2). She had cosmetic Restylane (Medicis Aesthetics Inc., Scottsdale, AZ) injection 4 years prior. Ophthalmologic examination was otherwise normal. MRI showed hyperintensity in fat-suppressed T2-weighted images located in the subcutaneous plane. [illegible]

CASE 3

A 39-year-old woman with medical history of [illegible] presented with 1 year of periocular swelling (Fig. 3) and an otherwise normal examination. She had Restylane injections to the cheeks and eyelids 9 years prior. [illegible] Surgical biopsy revealed [illegible] amorphous material infiltrating the muscle and subcutaneous tissue without inflammation. [illegible] consistent with HA. Injection with hyaluronidase resolved the swelling.

DISCUSSION

HA gels such as Juvederm and Restylane are commonly used materials for facial volume augmentation. Both products are marketed as having a temporary effect. There have been case reports of [illegible] HA [illegible] years after injection. Foreign body inflammatory reactions have been described as long as [illegible] years after injection. [illegible] has been reported. [illegible]

[illegible]

In summary, the authors present the most comprehensive series to date of [illegible] HA which appeared to migrate [illegible] tissue in the periocular region. Awareness of this potential complication is important to avoid a delay in diagnosis and unnecessary testing.

REFERENCES

[illegible]

Granulocytic Sarcoma of the Orbit Presenting as a Fulminant Orbitopathy in an Adult With Acute Myeloid Leukemia

[illegible], Andrew R. Harrison, M.D., J. Douglas Cameron, M.D., M.B.A., and Ali Mokhtarzadeh, M.D.

Abstract: A 64-year-old woman with relapsed acute myelogenous leukemia (AML) undergoing salvage chemotherapy developed rapid onset of right-sided ophthalmoplegia, proptosis, optic neuropathy, and vision loss from 20/30 to hand motions over a 3-hour period on day 4 of her treatment. CT scan of her orbits revealed a superolateral orbital mass and periocular edema. She underwent immediate canthotomy and cantholysis, and lateral orbitotomy with debulking of the mass later the same day. The histopathology was consistent with aggregates of myeloid blasts. Her vision recovered to 20/20 on postoperative day 1. Orbital granulocytic sarcoma is a rare condition often concurrent with AML, typically in the pediatric population and rarely in adults. Presentation as a fulminant orbitopathy with rapidly progressive optic neuropathy and vision loss over several hours has not been previously reported.

[illegible]

Granulocytic sarcoma (GS) is an uncommon, localized tumor composed of malignant cells of myeloid origin occurring at extramedullary sites other than the bone marrow. Orbital GS typically presents in children although [illegible] the adult population. GS can represent a complication of [illegible] syndromes, in particular acute myelogenous leukemia (AML). The authors present an unusual manifestation of orbital GS as a fulminant orbital process in a 64-year-old woman with AML presenting with [illegible] rapid proptosis and [illegible] optic neuropathy and vision loss [illegible] over several hours. This report is in full compliance with the Declaration of Helsinki and United States Health Insurance Portability and Accountability Act regulations.

CASE REPORT

A 64-year-old woman with relapsed AML undergoing salvage chemotherapy [illegible]

[illegible]

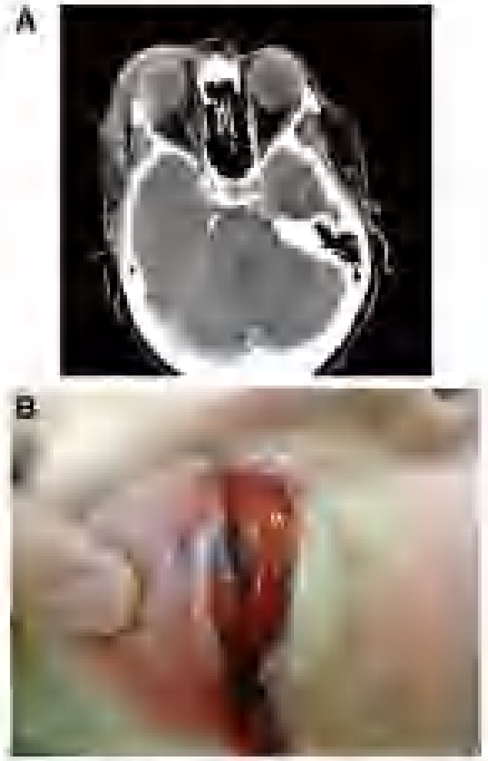

FIG. 1. A, Axial cut from CT demonstrating proptosis of OD and mass in the extraconal superolateral orbit. B, External photograph of OD after lateral canthotomy and [illegible] cantholysis demonstrating proptosis and significant chemosis. The chemosis was not hemorrhagic prior to the procedure.

Her vision recovered to 20/20 on postoperative day 1 [illegible] She [illegible] expired 1 month following the episode. There was complete resolution of all abnormal orbital findings during this period.

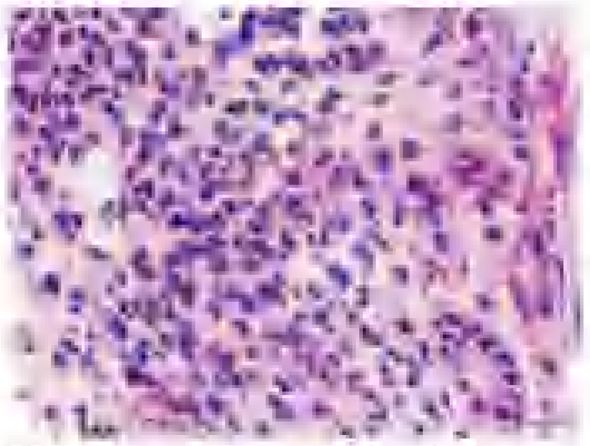

FIG. 2. [illegible]

DISCUSSION

[illegible]

CONCLUSION

[illegible]

REFERENCES

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[illegible]

Development of Herpes Zoster Ophthalmicus in an Immunocompetent Pediatric Patient Following Facial Trauma

[illegible]

Abstract: Herpes zoster ophthalmicus (HZO) is a [illegible] infection caused by reactivation of latent varicella zoster virus in the dorsal root ganglia of the ophthalmic division of the trigeminal nerve. Although a rare diagnosis in an otherwise healthy, vaccinated pediatric patient, this entity may occur with increasing frequency among those with preceding trauma, particularly in the month prior to presentation. Herein, we highlight a case of HZO in a vaccinated, immunocompetent adolescent in the setting of recent facial trauma.

[illegible]

[illegible]

CASE PRESENTATION

[illegible]

DISCUSSION

[illegible]

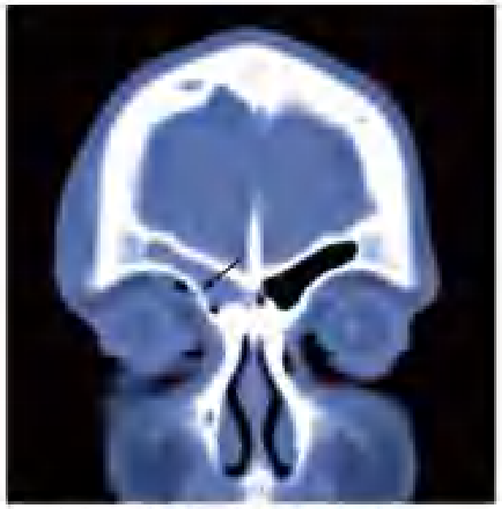

FIG. 1. CT imaging of the brain revealed subtle, nondisplaced orbital roof fracture (arrow) with frontal sinus hemorrhage in addition to subperiosteal hemorrhage and gas collection in the right superomedial extraconal space; there was no evidence of extraocular muscle entrapment.

against varicella than those who were unvaccinated.[2] Notably, one patient had received his first dose of the varicella vaccine at age 1 year and second dose at age 5 years. Moreover, he denied a history of chickenpox and had no known exposure to varicella aside from vaccination. In this setting, either wild-type varicella—from exposure to an individual with a mild, undiagnosed case of varicella—or vaccine-associated varicella may represent a potential source of HZO.

Mechanical trauma is another risk factor that has been implicated in the pathogenesis of herpes zoster following cryosurgery, rhytidectomy, and massage as well as oculoplastic, midface, brain and spinal procedures. In these cases, localized sensory precedes herpes zoster eruptions at the site of traumatized dermatomes.[3] Physical trauma sustained within the preceding 6 months and the preceding 1 month has been associated with an 8-fold and 12-fold increased risk, respectively, of development of herpes zoster at the same site.[4] Recent minor life stress has been correlated with an increased risk of zoster at the location of injury, but not elsewhere.[5] Trauma may mediate reactivation of VZV via localized activation, inflammatory stimulation, and focal hyperemia involving dorsal root ganglia.[3] We posit that the chronology and location of our patient's recent injury point to a traumatic mechanism affecting his subsequent HZO outbreak. Transpiring 3 weeks prior to presentation, the trauma involved the orbital roof and was associated with hemorrhage and gas localization in the superomedial extraconal space. The trauma and ensuing inflammation occurred in close proximity to the supratrochlear notch and supraorbital foramen, where branches of the frontal nerve—which itself is the largest branch of the ophthalmic nerve—exit the skull and provide sensory innervation to the skin of the upper eyelid, forehead, and superior scalp.[6] Thus, it is possible that traumatic stimulation of these nerves may have triggered the patient's reactivation of latent varicella-zoster at these dermatomes.

Herein, we highlight a case of HZO in a vaccinated, immunocompetent adolescent in the setting of recent facial trauma. Although a rare diagnosis in an otherwise healthy pediatric patient, this entity may occur with increasing frequency among those with prevailing trauma, particularly in the aftermath of contact sports, interpersonal violence, and motor vehicle accidents. Moreover, it underscores the importance of maintaining a high index of suspicion for HZO in patients with a history of varicella vaccination.

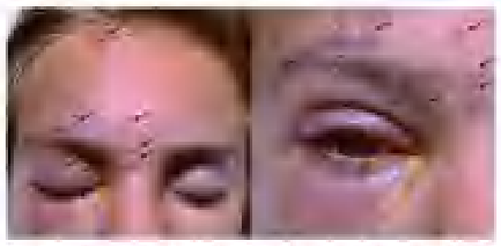

FIG. 2. External exam demonstrates prominent vesicles (arrows) on an erythematous base in V1 distribution and right supratarsal laceration status post repair (left panel), as well as periorbital erythema and edema, injection, and diffuse injection (right panel).

1. [illegible]
2. [illegible]
3. [illegible]
4. [illegible]
5. [illegible]
6. [illegible]
7. [illegible]
8. [illegible]

Aspiration as a Novel Technique to Address Facial and Periocular Myiasis

Jonathon E. Li, M.D., Julie O. Mehta, M.P.H., Margaret C. Pfeifle, M.D., Shweta S. Clark, M.D., and Jessica R. C. Ruby, M.D.

Abstract: Suction aspiration, which has not yet been described in the treatment for myiasis in the periorbital and facial regions, was used to achieve rapid resolution of maggot burden in a 78-year-old patient who presented with a large ulcerated squamous cell carcinoma of the face. This technique also facilitated submission of parasite samples for further analysis. Suction aspiration had no complications, such as significant residual ruptured maggots in the wound or eye injury. Suction aspiration is a safe and efficient technique to reduce maggot burden that has advantages over classic ophthalmic treatments, especially near the eyes and airway.

Myiasis is a parasitic infestation by the larval form (commonly affecting animals). Multiple methods have been described to treat the condition in the periorbital surgical cavity, including "[illegible] ointment, intravenous ivermectin, [illegible] of the wound," topical ivermectin, and [illegible] observation until self-resolution. Direct manual removal with forceps can be painful for the patient and is time-consuming, especially when there is a severe disease burden. Iatrogenic debridement can also cause accidental rupture of the maggots, which increases the risk of leaving portions of the larvae behind. This has been noted to [illegible]

Application for myiasis of a squamous cell carcinoma lesion. A: Multiple myiasis located within a squamous cell carcinoma lesion. B: Aspiration technique: feeder suction tip connected to vial suction. C: Collection of larvae in aspiration container.

[illegible] topical steroid ointment, fungicidal topical cleansing agents, or [illegible] can be used to improve the efficacy of forceps removal. However, these methods are suboptimal in many ways. Antiparasitic therapy, either as primary component or as side effects associated with systemic treatment, physical debridement is the [illegible] for [illegible] myiasis.[1]

Case reports have presented suction aspiration as a technique for myiasis in other locations.[2] [illegible] reported the first application of suction aspiration for myiasis of nasal mucosa, which [illegible] with minimal patient burden. The collection and evaluation of parasitic fauna is important with [illegible] and cultured in the series of the Occupational Health

CASE PRESENTATION

[illegible] 78-year-old male patient with [illegible] presented with [illegible]

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-.

Blepharophimosis Syndrome

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Continuing Education Activity

Blepharophimosis syndrome (BPES), which stands for blepharophimosis, ptosis, epicanthus inverse syndrome, is a rare genetic disorder primarily affecting eyelid development, resulting in a distinct facial appearance. The syndrome is characterized by:

- Telecanthus: Increased distance between the inner corners of the eyes
- Ptosis: Drooping of the upper eyelid
- Epicanthus inversus: Upward fold of skin near the inner corner of the eye

These features define BPES. The disruption of the development of the eyelid and associated tissues during embryogenesis is the cause of the structural abnormalities observed in BPES. The severity and subtype of BPES can vary, with some individuals experiencing significant visual impairment from ptosis, whereas others may have cosmetic concerns. The condition is restricted to the structural flaws that are present from birth and does not tend to spread. However, ptosis can lead to other issues, including amblyopia, if left untreated, which emphasizes the need for early detection and surgery. BPES is classified into 2 types.

The 4 traditional clinical signs—telecanthus, epicanthus inversus, ptosis, and blepharophimosis—are present in every form. Type I is linked to early ovarian failure. Only the traditional facial traits define type II. If left untreated, these characteristics are linked to a high amblyopia risk. Early surgical intervention is necessary for both types to ensure normal development of eyesight. This activity reviews the clinical presentation, assessment, treatment, and management of BPES, emphasizing the role of an interprofessional healthcare team—including endocrinologists, genetic counselors, and other medical professionals—in optimizing patient care and outcomes.

Objectives:

- Assess the typical physical examination findings associated with blepharophimosis syndrome.
- Apply best practices for the treatment and management of blepharophimosis syndrome.
- Implement recommended treatment considerations for patients with blepharophimosis syndrome who have additional systemic complications, including premature ovarian insufficiency.
- Collaborate with healthcare professionals and implement interprofessional team strategies to improve care, treatment outcomes, and management of patients with blepharophimosis syndrome.

Access free multiple choice questions on this topic.

Introduction

Blepharophimosis syndrome (BPES) is a relatively rare genetic condition that primarily affects eyelid formation and results in a distinctive facial appearance present at birth.[1] This condition was first described by Komoto in 1921.[2] The condition is characterized by the existence of a reduced horizontal opening of the eyelid (blepharophimosis), drooping of the upper eyelid (ptosis), increased distance between the inner corners of the eyes (telecanthus), and an upward fold of skin near the inner corner of the eye, where the medial eyelid skin fold appears more prominent in the lower eyelid, extending across the canthus and tapering into the upper eyelid (epicanthus inversus).[3] These congenital features define the syndrome, hence the

acronym BPES (see **Image.** Male Child with Blepharophimosis Syndrome).[4]

Blepharophimosis syndrome is an autosomal dominant disease affecting the eyelids and mid-face structures. These characteristics significantly impact the patient's vision and facial appearance. BPES can also be associated with additional systemic defects, specifically premature ovarian insufficiency in females, resulting in BPES type I.[5] Most cases are caused by mutations in *FOXL2* on chromosome 3q23.

The structural defects observed in BPES are caused by the interruption of the development of the eyelid and related tissues during embryogenesis. The course of BPES is contingent upon the specific subtype and severity, resulting in varying outcomes. Some persons may encounter substantial visual impairment caused by ptosis, whereas others may be concerned with cosmetic issues. The condition has no propensity for dissemination but remains limited to the congenital structural defects. Nevertheless, if ptosis is not addressed, subsequent complications such as amblyopia may result, underscoring the importance of prompt detection and surgery.

There are 2 main types of BPES. Each type harbors the 4 classic clinical signs—blepharophimosis, ptosis, epicanthus inversus, and telecanthus. Type I is associated with premature ovarian insufficiency, whereas type II is characterized by the classic facial features alone. These features are associated with a high incidence of amblyopia if not correctly managed. Both types require surgical treatment early in life for normal vision development (see **Image.** Male Child After Surgery for Blepharophimosis Syndrome).

Etiology

BPES is mainly caused by mutations in *FOXL2*, which is crucial for the development of eyelids and ovarian follicles. This gene encodes a forkhead family transcription factor that plays a vital role in controlling gene expression throughout embryonic development.[6] Pathogenic mutations disrupt the normal functioning of FOXL2, resulting in the observable characteristics of BPES.

The genetic cause of BPES was discovered in 2001 through genetic sequencing of 7 families affected by BPES.[7] Pathogenic mutations in *FOXL2* on chromosome 3q23 are responsible for BPES. *FOXL2* encodes a forkhead transcription factor of 376 amino acids, which contain a tract of 14 alanine residues. To date, over 100 unique *FOXL2* mutations have been identified in BPES families.[8] The exact function of FOXL2 is unknown.[9] Still, expression studies have shown that FOXL2 is expressed in the mesenchyme of developing fetal eyelids and the granulosa cells of fetal and adult ovaries.[7]

The 2 types of BPES are phenotypically indistinguishable but can be determined through genetic testing. Mutations that truncate FOXL2 before the polyalanine tract result in type I BPES. Mutations that expand the polyalanine tract result in type II BPES.[10] BPES can be caused by various types of mutations including missense, nonsense, or frameshift mutations.[11][12] These mutations can result in a loss-of-function or dominant-negative effect.[13] In individuals with type I BPES, the genetic abnormalities not only impact the formation of eyelids but also interfere with the functioning of the ovaries, resulting in premature ovarian insufficiency in affected females. Type II BPES is characterized by ocular manifestations without concurrent ovarian dysfunction.[14]

Epidemiology

BPES is a rare disorder, occurring in approximately 1 of 50,000 newborns.[15] Although type I BPES affects both males and females, the specific risk of early ovarian insufficiency is exclusive to females. The syndrome has been observed in several ethnic groups globally, without any notable geographical or ethnic inclination observed. Most cases of BPES are familial via an autosomal dominant pattern. However, spontaneous mutations may occur. Within affected families, BPES generally shows complete penetrance but exhibits varying expressivity, implying that the degree of eyelid abnormalities and related symptoms can greatly differ, even among individuals within the same family.

Up to 75% of affected individuals have a *FOXL2* mutation.[15] Approximately 64% of cases occur in women.[16] Type I has 100% penetrance and is transmitted primarily through males due to females developing premature ovarian insufficiency and reduced fertility. Type II has 96.5% penetrance and is transmitted through males and females.[17][16] The incidence of strabismus in BPES is 20 to 27%.[18] Development of amblyopia from ptosis or strabismus is between

39% and 56%.[17] Refractive error is common and as high as 94%, with simple hyperopia being the most common etiology.[15]

Pathophysiology

The underlying mechanism of BPES revolves around the interference with typical eyelid and face formation caused by abnormalities in *FOXL2*. The eyelid abnormalities, such as blepharophimosis, ptosis, and epicanthus inversus, occur due to the hindered differentiation and migration of the mesenchymal tissues that shape the eyelids during embryonic development. The most frequently observed characteristics are constricted palpebral fissures, drooping eyelids, and telecanthus. Type I BPES is characterized by a *FOXL2* mutation, which causes ovarian dysfunction and disrupts the process of folliculogenesis, leading to early ovarian insufficiency.

Eyelid morphogenesis is a complex process involving the coordinated movement of neural crest-derived periocular mesenchymal cells during embryonic development. These cells form eyelid structures, including the levator palpebrae superioris, smooth muscle, and tarsus.[19]

In congenital ptosis, the levator palpebrae superioris muscle is maldeveloped, resulting in a droopy upper eyelid. Genes associated with congenital ptosis include *ZFH4* and *FOXL2*. Mutations in *FOXL2* disrupt actin gene expression in the smooth muscle cells of periocular mesenchyma. This disruption results in severe hypoplasia of the levator palpebrae superioris and other craniofacial defects, causing blepharophimosis, ptosis, and epicanthus inversus.[19][20]

The *FOXL2* transcription factor is crucial in sexual development and ovarian function. The expression of *FOXL2* is the highest in granulosa cells of the ovary, and it plays a vital role in folliculogenesis, hormone signaling, cell regulation, proliferation, and apoptosis. In the absence of FOXL2, primary follicle formation in the ovaries is disrupted, and the number of follicles recruited during fetal ovarian development is depleted. The decreased number of follicles formed during ovarian development causes premature ovarian insufficiency and sequelae of reduced estrogen.[9][21]

Histopathology

In cases of BPES, histopathological analysis of tissue indicates the presence of undeveloped or dysplastic levator palpebrae muscles, which are responsible for raising the eyelids.[22] Abnormalities may also be observed in the connective tissue components of the eyelids, such as the tarsus and orbicularis oculi muscle.[23] In instances involving concurrent premature ovarian insufficiency, an examination of the ovaries by biopsy may uncover a diminished quantity of follicles and other indications that are in line with ovarian dysgenesis.[24] Nevertheless, histopathology is not commonly employed for diagnosing BPES, as the primary methods used are clinical and genetic.

History and Physical

The evaluation of a patient with BPES typically starts with the observations of ocular abnormalities shortly after birth. There may be a hereditary pattern of comparable facial characteristics or a history of early menopause in female relatives. The physical examination reveals the characteristic manifestations of the syndrome, including blepharophimosis (narrowed eyelid fissures), ptosis (drooping of the upper eyelids), telecanthus (increased distance between the inner corners of the eyes), and epicanthus inversus (an upward fold of skin near the inner corner of the eye). These findings are typically bilateral and symmetrical.

Females with type I BPES may show signs of premature ovarian insufficiency, such as irregular menstrual periods or secondary amenorrhea, during adolescence or early adulthood. The degree of ptosis might vary, with certain patients encountering substantial visual blockage requiring prompt surgical intervention.

The diagnosis of BPES is mainly clinical (see **Image.** Male Child with Blepharophimosis Syndrome). Physical examination findings include:

- Blepharophimosis: A horizontal shortening of the palpebral fissure. The average horizontal palpebral fissure measures 25 to 30 mm, but in BPES, it measures 20 to 22 mm.[25]
- Ptosis: Upper eyelid droopiness develops from bilateral dysplasia of the levator palpebral superioris muscle, resulting in poor levator function and bilateral ptosis.[26][27]

- Epicanthus inversus: A skin fold arising from the medial lower eyelid and running inward and upward to the upper eyelid. This feature is always bilateral, the caruncle and plica semilunaris beneath have a hypoplastic appearance.[28]
- Telecanthus: The bony walls of the orbit are unaffected in BPES. The medial canthal tendons are elongated, which causes a widened intercanthal distance with normal interpupillary distance.[29]

There are 2 clinical types of BPES:

- Type I BPES is characterized by blepharophimosis, ptosis, epicanthus inversus, telecanthus, and premature ovarian insufficiency.
- Type II BPES is characterized by the same classic 4 findings without premature ovarian insufficiency.

Numerous other coexisting malformations and compensatory responses have been reported. Craniofacial malformations include thin and short upper eyelid skin with a margin that has an S-shape, whereas the lower margin has a downward concavity, with or without slight ectropion.[30][31]

Abnormalities of the lacrimal drainage apparatus include lateral displacement of the lower punctum, canaliculi stenosis, and elongation of the horizontal canaliculi.[32][33] Other ophthalmic manifestations include strabismus, microphthalmos, and optic disc coloboma.[34] Facial abnormalities include wide and flattened nasal bridges and anteverted ears.[16]

Individuals compensate for ptosis by adopting a chin-up head position and constantly contracting their frontalis muscles. The eyebrows can become more prominent and arched, giving patients a continually surprised look.[2]

Evaluation

The assessment of BPES involves a combination of clinical examination and genetic testing. Diagnosis is typically made by observing distinctive facial characteristics and confirmed through genetic testing that identifies pathogenic mutations in *FOXL2*.[35] *FOXL2* sequencing is considered the most reliable method for diagnosis.[36] Procedures such as chromosomal microarray analysis or karyotyping might be used to detect significant deletions or chromosomal rearrangements affecting 3q23.[37]

In addition to genetic testing, a thorough ophthalmologic evaluation is essential, involving the measurement of palpebral fissure length, evaluation of ptosis severity, and examination of levator palpebrae muscle functionality. Visual acuity should also be evaluated to identify any associated conditions such as amblyopia. Endocrine assessment may be required in females, especially those with type I BPES, to determine ovarian function.[38]

Individuals with the characteristic features of BPES can undergo gene-targeted testing to detect mutations in *FOXL2*.[39] If no variant is detected, comprehensive genomic testing can be conducted to detect deletions or duplications in the *FOXL2* region. In some cases, cytogenetic testing is completed to further evaluate for balanced translocations or other interruptions of the *FOXL2* region.[8][40]

Female individuals with type I BPES develop primary ovarian insufficiency, manifesting as pubertal delay, primary amenorrhea, secondary amenorrhea, or oligomenorrhea. Endocrinologic laboratory testing can aid in diagnosis, with elevated levels of follicle-stimulating and luteinizing hormones and decreased serum concentrations of estrogen and progesterone. Transvaginal ultrasound with antral follicular count can assess ovarian reserve and aid discussions regarding poor fertility.[41]

Treatment / Management

The management of BPES involves multiple disciplines, including ophthalmology, genetics, and, in the case of type I BPES, endocrinology. The main objectives of treatment are to enhance visual function and address aesthetic considerations. Treatment goals include surgical eyelid repair to promote normal visual development, improve cosmesis, alleviate neck strain from chin-up posture, and address primary ovarian insufficiency and infertility in females with type I BPES. Initial management involves a pediatric ophthalmologist assessing for amblyopia, strabismus, and refractive error. Referral to an oculoplastic surgeon should be made to evaluate the degree of ptosis, blepharophimosis, and epicanthus inversus (see **Image.** Male Child After Surgery for Blepharophimosis Syndrome).[42]

Surgical correction is the primary treatment for eyelid abnormalities. Ptosis correction is frequently necessary to prevent or treat amblyopia. Frontalis sling surgery, a procedure that uses a suspensory device to raise the eyelid, is

commonly employed. Medial canthoplasty is a surgical procedure that can repair telecanthus by repositioning the inner corners of the eyelids to a more typical position. Traditionally, eyelid correction was performed as a 2-stage surgery at 3 to 5 years of age. A medial canthoplasty using the Mustarde technique or double-opposing z-plasty to repair epicanthus inversus and telecanthus is followed by frontalis suspension for ptosis repair 6 to 12 months later. Performing ptosis correction and medial canthoplasty simultaneously could lead to tension between tightened vertical and horizontal tissues, potentially reducing the effectiveness of the procedures if done separately.[42][43]

Some surgeons argue that medial canthus reconstruction can worsen ptosis and should be addressed first. Other surgeons recommend repairing ptosis first due to the high incidence of amblyopia and then performing medial canthus repair at a later age when the face has grown. Recent reports have described successful outcomes with single-stage surgery combining medial canthoplasty and ptosis repair for a select group of individuals. Additional studies are required to assess the outcomes of single-stage versus two-stage repair.[44]

In general, the following surgical recommendations are made:

- If the central visual axis is unobstructed, surgical repair can wait until 3 to 5 years.
- If the central visual axis is obscured, but the vertical interpalpebral fissure height is more than 2 mm, either single-stage or two-stage repair is associated with satisfactory outcomes.[45]
- If the central visual axis is obscured, and the vertical interpalpebral fissure height is less than 2 mm, a two-stage repair should be pursued as early as possible, involving ptosis repair first to prevent amblyopia, followed by medial canthoplasty.[17]

Females who inherit BPES from the paternal parent are more likely to have type I disease and should be referred to a clinical geneticist to discuss the nature of the disease, its mode of inheritance, and the fertility implications of the genetic disorder.[46] Women should be informed of the risk of premature ovarian insufficiency and referred to a pediatric or reproductive endocrinologist and gynecologist to monitor ovarian status. Hormone

replacement therapy is recommended to address early ovarian insufficiency and to prevent the long-term consequences of estrogen deprivation, such as osteoporosis and cardiovascular disease. Young women may consider fertility preservation alternatives, such as oocyte or embryo cryopreservation, before the decrease of ovarian function.[47][48] The American Society for Reproductive Medicine and the International Menopause Society recommend estrogen replacement therapy for women with primary ovarian insufficiency.[49] Hormone replacement therapy under the guidance of an endocrinologist and gynecologist is reasonable for maintaining normal bone mineral density. The options for women who wish to pursue parenthood include adoption, foster parenthood, embryo donation, egg donation, and cryopreservation.[50][46]

Genetic counseling is a process that involves providing individuals and families with information about genetic conditions, inheritance patterns, and the risks of passing on genetic disorders. The goal is to assist individuals in making informed decisions about family planning.[51] Affected families are advised to undergo genetic counseling to discuss inheritance patterns, the likelihood of passing on the condition to their children, and available reproductive choices. Families with known *FOXL2* mutations can access prenatal genetic testing and preimplantation genetic diagnosis.[52]

Differential Diagnosis

Most patients with BPES have a clear family history, but de novo mutations are possible.[53] If eyelid findings are present without a clear family history, it is important to consider other conditions that include ptosis and blepharophimosis as major characteristic features—NR2F2-associated 46, XX sex reversal 5, the Say-Barber-Biesecker variant of Ohdo syndrome, congenital ptosis, ptosis with external ophthalmoplegia, Noonan syndrome, Marden-Walker syndrome, Schwartz Jampel syndrome, Waardenburg syndrome, Williams syndrome, trisomy 18, cerebro-oculo-facial-digital syndrome, Dubowitz syndrome, and Smith-Lemli-Opitz syndrome.[54][55]

Conditions such as congenital ptosis [56] caused by isolated levator muscle failure must be distinguished from BPES, in which ptosis is a component of a more comprehensive syndrome. Waardenburg syndrome [57] is defined by the presence of dystopia canthorum (abnormally wide-set eyes), which can sometimes be mistaken for BPES. Nevertheless, Waardenburg syndrome

encompasses hearing impairment and abnormalities in pigmentation, whereas these characteristics are not present in BPES. Individuals with Noonan syndrome [58] may exhibit ptosis (drooping of the upper eyelid) and hypertelorism (increased distance between the eyes), along with other characteristics such as below average height, congenital cardiac abnormalities, and delays in development. Apert syndrome [59] can be distinguished from BPES by the presence of syndactyly (fusion of fingers and toes), severe skull malformations, and craniofacial anomalies.

Staging

BPES does not adhere to a conventional stage scheme, as shown in oncological conditions. Nevertheless, it is possible to categorize it according to the kind (type I or type II) and the severity of symptoms, specifically in terms of their effect on vision and ovarian function. The classification assists in directing the care strategy, especially in females, where timely recognition of type I BPES is crucial for treating premature ovarian insufficiency.[60]

Prognosis

The outlook for individuals with BPES is typically favorable with proper care. Timely surgical intervention for ptosis can effectively avoid the development of amblyopia and enhance visual results (see **Image.** Male Child After Surgery for Blepharophimosis Syndrome). Cosmetic surgery has the potential to significantly improve the physical appearance and psychological well-being of individuals who undergo it.[61] The reproductive prognosis of females with type I BPES depends on the timing and severity of ovarian insufficiency. Early identification and intervention can alleviate certain detrimental consequences linked to early ovarian insufficiency. Patients require a multidisciplinary approach and coordination of care across many specialties. The prognosis is excellent when medical and surgical management is addressed early in life. Depending on the severity of the disorder, surgical treatment can require multiple stages, but outcomes are very successful. Patients with BPES have an average lifespan.

Complications

The primary complications of BPES result from untreated ptosis, which can cause amblyopia by blocking the visual axis during crucial stages of visual development. Possible surgical consequences may involve the occurrence of either under- or overcorrection of the condition. Ptosis, asymmetry, and scarring are present. Type I BPES is associated with problems such as infertility, osteoporosis, and cardiovascular disease, all resulting from prolonged estrogen deficiency due to premature ovarian insufficiency. Females with typical facial features and concomitant infertility may also experience psychological challenges, such as low self-esteem and social difficulties. Complications can occur after surgical repair. Early popular techniques, such as the Mustarde technique and z-epicanthoplasty, had major incidences of severe scarring. Other techniques, such as the Y-to-V technique and medial epicanthoplasty with skin redraping, have been developed to improve cosmetic outcomes.[62]

Many organic and inorganic materials are used for frontalis sling suspension to treat congenital ptosis surgically. Alloplastic materials include braided polyester sutures, polypropylene sutures, expanded polytetrafluoroethylene, and silastic bands. Placing foreign material in the tissue can result in granulomatous formation, infection, or extrusion.[63]

Homografts, such as autogenous fascia lata, are associated with longer recovery time and a second potential site of infection. Overcorrection of congenital ptosis can result in lagophthalmos and cause corneal complications.

Deterrence and Patient Education

Education for individuals and families affected by BPES should prioritize the significance of early identification and intervention to mitigate visual problems. Educating parents about the signs of amblyopia and the importance of regular ophthalmologic monitoring is essential. For females with type I BPES, it is crucial to provide early information to about the risks of premature ovarian insufficiency and the available alternatives for fertility preservation. Genetic counseling is essential for delivering precise information regarding the pattern of inheritance, potential dangers to future offspring, and the range of available reproductive options.

Families must understand the need for lifelong monitoring of vision into adulthood. Surgery is almost always necessary early in life to prevent

amblyopia, and it may be required again later in adulthood for cosmetic reconstruction if desired.

Families and patients should know that multiple methods exist to lift the eyelid and repair ptosis. The operation should be personalized to the patient's needs. When considering any procedure, a do-nothing option should be explained to the family and patient. Adolescence can be a challenging time for female patients, and support from a multidisciplinary team of healthcare providers is necessary. Genetic testing also involves different approaches. Females should discuss infertility and family planning with a genetic counselor

Pearls and Other Issues

BPES should be considered a possible diagnosis in infants who display the distinctive combination of blepharophimosis, ptosis, telecanthus, and epicanthus inversus. The diagnosis can be confirmed through genetic testing for *FOXL2* mutations. Prompt surgical surgery for ptosis is essential to prevent the development of amblyopia. Regular ophthalmologic surveillance is essential to assess the progress of visual development and determine whether further surgical interventions are required. Genetic counseling and reproductive alternatives, such as prenatal diagnosis and preimplantation genetic diagnosis, should be considered in families with a hereditary predisposition to BPES.

Enhancing Healthcare Team Outcomes

Management of BPES is complex and requires a multidisciplinary approach including a pediatric ophthalmologist, oculoplastic surgeon, pediatrician, endocrinologist, gynecologist, nurses, and genetic counselor. Ophthalmologists play a critical role in educating fellow clinicians and healthcare professionals about the risk of amblyopia and its visual implications if unrecognized.

Genetic information is complex, and genetic counselors are essential in educating families and patients on test results. The decision to pursue genetic testing is very personal, particularly for female patients. FOXL2 gene mutation analysis is primarily used to identify future fertility status. Genetic counselors can lead one-on-one counseling to families regarding unexpected test results and discussions regarding reproductive choices. The Clinical Genetics Society recommends postponing genetic testing for disorders with purely reproductive implications until the individual has reached an age or level of maturity where they can fully understand the impact of the test and make an informed decision about whether to proceed with testing.[64]

Endocrinologists and gynecologists are critical in the interprofessional approach to treating these patients. Individuals with type 1 BPES should be referred to an endocrinologist to address ovarian insufficiency and administer suitable hormonal therapy. Regular interprofessional meetings can facilitate the coordination of care and enhance patient outcomes. Low estrogen levels at a young age increase the risk of osteoporosis, heart disease, and depression. Women with premature ovarian failure cannot get pregnant naturally but can carry a pregnancy with in vitro fertilization with donor oocytes. Patients should be referred to a gynecologist or infertility specialist to discuss reproductive treatments. Ensuring patients understand reproductive biology and therapeutic options can help them cope with this emotionally distressing condition.

Involving patients and their families in decision-making is crucial, particularly when it comes to surgical alternatives and genetic counseling. Providing the family with information about the ailment and treatment alternatives facilitates the ability to make well-informed decisions and improves compliance with treatment regimens.

BPES raises ethical concerns related to fertility preservation and the possibility of doing preimplantation genetic diagnosis in families with identified FOXL2 mutations. These discussions should be approached with sensitivity while respecting the patient's right to make decisions about their health and considering their cultural views.

By providing comprehensive care that addresses the physical and psychological elements of BPES, healthcare professionals can significantly enhance the quality of life for individuals affected by this condition. To uphold a superior level of care, it is advisable to engage in regular training and stay updated on the most recent guidelines and surgical methods.

Review Questions

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Figures

Male Child with Blepharophimosis Syndrome. The image shows the classic findings of blepharophimosis, ptosis, and epicanthus inverus in each eye, and telecanthus. Contributed by A Harrison, MD

Male Child After Surgery for Blepharophimosis Syndrome. The image shows a male patient 3 weeks after surgical repair of blepharophimosis syndrome. Ptosis repair is performed by frontalis suspension, and telecanthus repair is performed by transnasal wiring. Contributed by A Harrison, MD

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Head & Face Medicine

RESEARCH Open Access

Orbital volume changes during growth and development in human children assessed using cone beam computed tomography

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Abstract

Objectives: To measure growth-related changes in orbital volume from childhood to the late teenage years using cone-beam computed tomography (CBCT) scans.

Methods: This retrospective cohort study involved 46 (24 male, 41 female) healthy Caucasian children (ages 6–18 years) with existing serial craniofacial CBCT scans. CBCT scans were available for 292 orbits. Each orbit was transformed into a closed space with well-defined boundaries and orbital volume was measured using manual segmentation. A novel statistical analysis was applied to extract the maximum amount of longitudinal information from the data. Intra- and inter-operator correlation coefficients were calculated from duplicate segmentations on a random subset (10%) of the sample.

Results: Orbital volume increased at a rate of 1–3% annually until the late teenage years. Intra- and inter-operator segmentation reliability measurements were > 99%.

Conclusions: Orbital volume increases by 1–3% per year throughout childhood continuing until the late teenage years. The annual increase is large enough to be clinically relevant as it may lead to less than optimal long-term surgical outcomes when reconstructive surgery for the pediatric anophthalmic socket is required.

Keywords: Orbit, Craniofacial, Growth and development, Cone Beam Computed Tomography, CBCT, Segmentation, Human

Introduction

A number of genetic, developmental, and pathological conditions affect orbital development, often necessitating surgical intervention at an early age. Despite the development of techniques and materials aimed at improving outcomes of orbital implantation, fundamental knowledge on the rate and timing of orbital growth in humans is scarce. Depending on the source, the orbit is reported to reach maturity between 7 and 15 years of age [1–4]. Studies attempting to model orbital volume changes in childhood have faced measurement and statistical challenges [5, 6]. The only conclusion that can be confidently drawn from the available literature is the broad generalization that orbital volume changes very slowly during childhood and adolescence, if at all.

Where regulation permits, orthodontists are increasingly using cone-beam computed tomography (CBCT) scans as the preferred imaging for diagnosis and treatment planning [7]. CBCT was introduced into the US market in the early 2000s and early adopters of this technology have now accumulated databases of serial craniofacial CBCT scans in healthy individuals. One advantage

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of utilizing a large CBCT database is the availability of multiple scans for each subject. This allows characterization of changes in the orbit of a single subject over time, in a longitudinal fashion. The complicating factor is the imperfect longitudinal character of the data. Scans are acquired based on clinical need rather than research purposes. For this reason, the resulting datasets are irregular and may consist of varying numbers of serial scans per individual and no consistency in the time elapsed between successive scans.

The purpose of this study was to measure changes in orbital volume from childhood to the late teenage years using serial CBCT scans of healthy individuals. To do this, we developed a protocol to segment and measure orbital volume on CBCT scans and developed unique statistical tools to extract the maximum amount of information from the longitudinal dataset. Clinically, this information can be used to help determine optimal timing for pediatric orbital and lacrimal surgery where bone is removed or implants are placed, as well as in the management of the anophthalmic socket.

Materials and methods

Study population

This retrospective cohort study was approved at the oversight level by the Institutional Review Board at the University of Minnesota (STUDY00002026). All methods were performed in accordance with the relevant guidelines and regulations. All subjects included in the study or their legal guardian had provided informed consent for the use of orthodontic records for research purposes. The study cohort consisted of patients who had undergone orthodontic treatment at the University of Minnesota, and had pre- and post-treatment CBCT scans taken as part of orthodontic treatment. The radiographic records of an orthodontic patient typically consist of pre-, post-, and, occasionally, mid-treatment scans, used for diagnosis and treatment planning and outcome evaluation. This ensured the availability of a large database of CBCT scans from healthy individuals regardless of their craniofacial characteristics or the details of the treatment they received.

In order for a subject to be included, all of the following inclusion criteria had to be met: (1) The subject is Caucasian, (2) Age between 6 and 18 years on the day the initial scan was acquired, (3) At least two existing full field-of-view CBCT scans, and (4) All CBCT scans acquired on the same scanner with identical acquisition parameters to ensure consistent image quality across timepoints. Subjects were excluded if they met one or more of the following criteria: (1) History of craniofacial trauma, surgery, or pathology, (2) Craniofacial anomalies (e.g. cleft lip/palate), (3) Interval between successive scans less than 12 months, (4) Treatment with orthopedic appliances including headgear or functional appliances, (5) Previous or planned orthognathic surgery, (6) CBCT scans corrupted by motion artifact or poor image quality. The final study population consisted of 46 patients (24 male, 41 female) aged 6–18 years all of whom were treated with fixed orthodontic appliances (braces) between the years 2012 and 2017. The sex and age distributions are summarized in Table 1. These patients had 3 serial CBCT scans, 10 patients had 3 serial scans, and 32 patients had 2 serial scans. In total, our sample consisted of 246 CBCT scans imaging 292 orbits.

All CBCT scans were full field-of-view (17 × 23 cm) scans acquired at 120 kV and 18.54 mAs with a pulsed scan time of 8.9 s using an iCAT Next Generation scanner (Imaging Sciences International, Hatfield, PA, USA). The scan data were reconstructed with a voxel size of 0.3 mm^3. All scans were fully deidentified prior to use in this study.

Data collection

Data collection was performed using digital imaging and communications in medicine (DICOM) volumes. A total of three software programs were used at different stages of our workflow: Dolphin Imaging software (version 11.7; Dolphin Imaging & Management Solutions, Chatsworth, CA, USA) for anonymization of each scan, 3D Slicer (version 4.10.1, [illegible]) for segmenting the orbital bones and connecting artificial boundaries to turn each orbit into a closed object, and SmartPaint (version 1.5.1, [illegible]) for final segmentation of the orbital cavity

Table 1 Age and sex distribution of CBCT scans

Characteristic	Number of Scans
Sex (# Participants, % Sex)	
Female	27
Male	
Race (# Participants, % Age)	
Age 7	4
Age 8	3
Age 9	7
Age 10	3
Age 11	3
Age 12	3
Age 13	3
Age 14	4
Age 15	3
Age 16	3
Age 17	4
Age 18	3

and volume measurement. All steps of data collection were performed by a single operator (K.A.S.).

A detailed, step-by-step description of the protocol is provided in the Supplemental Materials. In brief, all scans were oriented using Dolphin Imaging Software. Scans were then imported into 3D Slicer, where they were cropped into right and left orbits. To transform the orbit into a closed space, we developed rules for establishing artificial boundaries where openings exist (Table 2). A virtual surface was generated for the anterior boundary in several steps using various Slicer modules. First, orbital bones were segmented using hysteresis thresholding and the orbital rim was manually outlined with fiducial markers in the Segment Editor. Next, the resulting markup list was used to generate a 3D surface using Delaunay Triangulation in the Markups-to-Model module. Finally, the Volume crop with model module was used to set the intensity of all voxels contained within the 3D mesh nodes to zero.

Segmentation of the orbital cavity and volume measurement was performed using SmartPaint. This software allows users to manually "paint" areas of an image using a 3D brush that, instead of an isodistance-based fill, effectively labels voxels according to Euclidean distance to the midpoint of the brush and the intensity values of the image. The remaining artificial boundaries were manually delineated by approximating a convex path between adjacent bones. In other words, the boundaries were filled until the segmentation was a smooth continuation of the orbit's natural contours as viewed from all three orthogonal perspectives. Once the segmentation was completed, the SmartPaint software automatically calculated the volume by counting the number of labeled voxels. A 3D rendering of the model is shown in Fig. 1.

Reliability study

To evaluate the reproducibility of measurements, we evaluated both intra-operator and inter-operator reliability. To assess intra-operator reliability, CBCT scans of a randomly selected subset of 30% (30 orbits) were re-analyzed by a single operator (K.A.S.), who repeated all steps of the data collection scheme after a four week washout period. To evaluate inter-operator reliability, a second operator (C.S.H.) completed the measurements. The second operator was first calibrated with a two-day session using training materials (i.e. a step-by-step guide describing the data collection protocol) and by performing the protocol on 10 orbits not used elsewhere in the study. A four-week washout period followed. Then, both operators repeated all data collection steps on 30 randomly selected orbits. Both operators worked independently. Operators could reference the training materials while performing replications. Intraclass and interclass correlation coefficients were calculated to quantify the reproducibility of this protocol.

Table 2 Operating [illegible] for virtual cavity enclosure in orbital segmentation and data measurement

Opening	Rule for generating boundary
Anterior aperture	3D surface generated from fiducials placed along the margin of the orbital rim
Optic canal	Diagonal – line passing between the most posterior point on the lateral wall of the orbit and the most posterior point on the medial wall of the orbit (as viewed in three orthogonal slice planes)
Inferior orbital fissure	Manually delineated – convex path of varying orientation to approximate the natural curvature between hysteresis-based 3D interfaces in SmartPaint
Superior orbital fissure	Manually delineated – convex path of varying orientation to approximate the natural curvature between hysteresis-based 3D interfaces in SmartPaint
Nasolacrimal canal	Manually delineated – convex path of varying orientation to approximate the natural curvature between hysteresis-based 3D interfaces in SmartPaint
Ethmoidal sinus	Hard tissue boundary and portions delineated manually – manual delineation of bony perimeter
Sphenoidal sinus	Hard tissue boundary and portions delineated manually – manual delineation of bony perimeter

Statistical analysis

All statistical analyses were conducted using Stata (version 14.2; StataCorp, College Station, TX, USA). To address the challenges of estimating orbital growth from an unbalanced panel of scans, we adapted a technique from the real estate finance literature. Specifically, we constructed a "Weighted Repeat Scan" (WRS) index. From a statistical perspective, our approach is identical to that described in Case & Shiller [11], which formed the basis for the well-known Case-Shiller House Price Index. The approach relies on pairs of observations (i.e., scans) to estimate the growth rate between scans.

We began by assigning each scan an age, based on the age of the patient at the time of the scan. To do so, we divided the age of the patient in years by 365.25 and rounded the quotient to the nearest integer. For example, a scan of a patient aged 10 years and 7 months would be classified as the scan of an 11 year old. Because of this data set's maximum of the age range, we reclassified the three scans of 19 year olds with the scans of the 18 year olds. We also averaged the volume measurements of left and right orbits for each patient at each

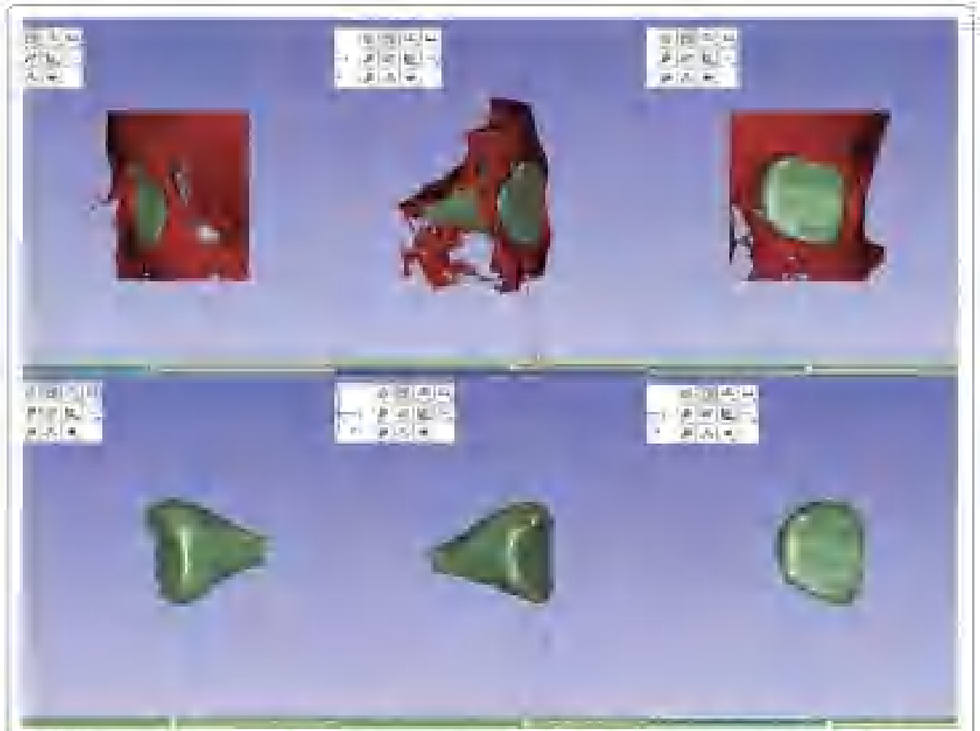

Fig. 1 3D rendering of the segmented orbital cavity (green) and orbital bones (red), viewed in 3D Slicer (coronal, sagittal, and frontal views)

point in time. The volume measure we employed is therefore the average of the measured volume of the patient's left and right orbits.

For any two consecutive scans of the same individual i, we computed

$$growth_{i,k} = \ln(volume_{i,k}) - \ln(volume_{i,j}) \quad (1)$$

where $volume_{i,k}$ is the volume of individual i's orbit at age k in mm^3, $volume_{i,j}$ is the volume of individual i's orbit at age j, and $k > j$.

The WRS index was constructed using a three-step process. In the first step, we estimated the regression

$$growth_{i,k} = \sum_{t=12} \gamma_t D_{i,t} + \varepsilon_{i,k} \quad (2)$$

using an ordinary least squares (OLS) regression, where $D_{i,t}$ can take one of three variables: 1 if $k = t$, −1 if $j = t$, and 0 otherwise.

In the second step, we took the residuals from the first step, squared them, and estimated the OLS regression

$$\varepsilon^2_{i,k} = \alpha + \beta(k - j) + v_{i,k} \quad (3)$$

We then re-estimated the first regression using a weighted least squared (WLS) regression, where the square root of the fitted values from the second regression – $\sqrt{\hat{\varepsilon}^2_{i,k}}$ – are the regression weights. A WRS index produces a log growth index, which can then be converted into levels by exponentiating and multiplying by the average volume in the base year. Any year can be chosen as the base year for the purposes of the empirical analysis. We selected age 12 years because it was near the middle of the distribution, both in terms of ages and number of scans.

We tested for statistical significance of the coefficients estimated in the third step of the analysis using a two-sided t-test, implicitly testing whether the coefficient was different from that of the base year. The coefficients and standard errors are summarized in Table 3. Standard errors are clustered by patient. Clustering the standard errors in this way accounts for the possibility that the

Table 3 Coefficient Estimates

	Coefficient estimate		
Age	Pooled	Female	Male
age 7	0.1611*	-0.0826**	-0.0391
	(0.0715)	(0.0396)	(0.0738)
age 8	0.1103**	-0.0928***	-0.0875***
	(0.0424)	(0.0248)	(0.0328)
age 9	-0.0616***	-0.0612***	-0.0550***
	(0.0144)	(0.0102)	(0.0192)
age 10	-0.0324**	0.0010	-0.0264*
	(0.0125)	(0.0075)	(0.0149)
age 11	-0.0468***	-0.0155	-0.0513***
	(0.0145)	(0.0098)	(0.0181)
age 12	-	-	-
Base year			
age 13	0.0659	0.0341	0.0810
	(0.0554)	(0.0316)	(0.0729)
age 14	0.0445***	0.0429***	0.0537
	(0.0123)	(0.0160)	(0.0357)
age 15	0.0930***	0.0897***	0.0948***
	(0.0139)	(0.0091)	(0.0133)
age 16	0.0847***	0.0870***	0.0857
	(0.0132)	(0.0076)	(0.0259)
age 17	0.0778***	0.0468***	0.1117***
	(0.0119)	(0.0052)	(0.0228)
age 18	0.0808***	0.0712***	0.1084***
	(0.0135)	(0.0062)	(0.0273)
Observations	81	54	27
R-squared	0.754	0.770	0.884

Standard errors (clustered by patient in parentheses). Significance (significance from a two-sided t-test) is indicated as follows: *p<0.05, **p<0.01, ***p<0.001

errors may be correlated across the scans of a single patient.

Finally, a dependent t-test was used to analyze the difference between the average volume of the right and left orbits.

Results

The changes in orbital volume over the course of growth and development are shown in Fig. 2. Figure 2 A shows orbital volume plotted against age pooling measurements from males and females and right and left orbits. Figure 2B and D show orbital volume plotted against age for females and males, respectively, and Fig. 2 C shows changes in orbital volume plotted against age for males and females. In general, orbital volume increased until the late teen years, with an approximate growth rate of 1–2% per year. The index for the male subsample was less smooth than that of the female subsample, which may be due in part to the smaller number of scans. Figure 2 C illustrates the fact that for both sexes the orbital volume continued to increase well into the teens, with the increase more pronounced among males.

Results of the replicability study are depicted in the Bland-Altman plots shown in Fig. 2E, F. The intraclass correlation coefficient was 0.985. The interclass correlation coefficient was 0.909.

In both the pooled group and in each of the male and female subsamples, the coefficient estimates for 8 year olds are smaller than zero, indicating that the average volume among these groups is smaller than those of 12 year olds (the base year), with the difference being statistically distinguishable ($P<0.001$) from zero at the 99.9% level (Table 3). Similarly, in all three columns, the coefficient estimates for 17 year olds is larger than zero, indicating that the average volume among these groups are larger than those of the 12 year olds. Here again, for all three groups (pooled, females and males), the coefficients are statistically distinguishable ($P<0.01$) from zero at the 99.9% level.

A statistically significant difference was found between the right and left orbital volumes, with the average volume of the right orbit approximately 0.5% larger than the left orbit ($p<0.05$).

Discussion

This study aimed at generating findings with direct applicability to surgeons placing orbital implants. Proper reconstruction of orbital volume is critical in the management of the anophthalmic socket [9, 10]. For this reason, we chose to measure orbital volume as the single outcome since it is ultimately the variable of greatest clinical interest. The results suggest that changes in orbital volume continue until the late teen years, with an approximate growth rate of 1–2% per year. The finding that the growth rate is slow does not mean that these results are insignificant. Over years, even gradual increases can result in clinically relevant changes that may impact the long-term outcome of eye replacement procedures. The fact that orbital volume was found to increase into the late teen years challenges conventional notions of "maturity" and suggests that we may not yet know its ultimate endpoint. Our results corroborate findings of other long-term studies suggesting that orbital growth does not, as is often taught, end after adolescence, but instead slows to a low basal rate. Many of these studies assessed differences in bony orbital measurements between young and old adults and demonstrated continued growth and remodeling of the craniofacial skeleton throughout adulthood [11–13]. These bony changes manifest as a clockwise angular rotation of the bony orbit, with the forehead moving anteriorly and inferiorly

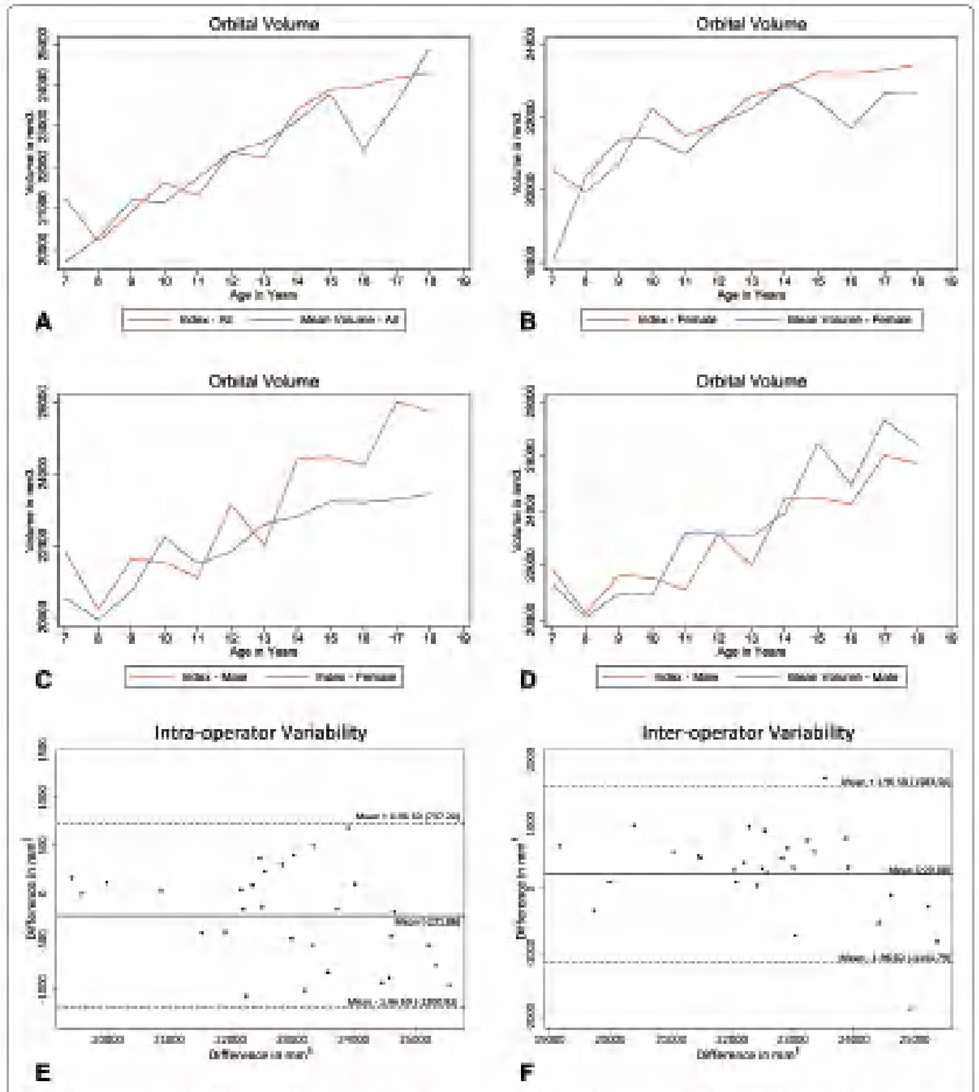

Fig. 2 Changes in orbital volume as a function of age for the various subgroups and replications. Age 12 is the baseline year. **A** Simple Average vs. Index (pooling males and females, right and left orbits). **B** Simple average vs. Index, females only (pooling right and left orbits). **C** Simple average vs. Index, males only (pooling right and left orbits). **D** Index, Males and females only (pooling right and left orbits). **E** Bland-Altman plot showing the differences in repeat volume measurements on 30 orbits by a single operator. **F** Bland-Altman plot showing the differences in volume measurements on 30 orbits by two operators

and the authors' manual anatomic landmarks. Overall results from prior studies suggest that periods of bony remodeling persist throughout adulthood and may contribute to continued changes in orbital volume during adulthood [11–13].

Interestingly, the volume of the right orbit was on average about 0.6% larger than the volume of the left orbit ($P<0.05$). This finding is in contrast with previous studies, notably Bentley et al. [2] and Swanepoel and Lombard [10], failing to find a significant difference. The aforementioned authors proceeded to use averaged data from their left and right orbits to develop their growth curves. Both studies used an independent t-test to test for equivalence between right and left sides. Implicitly, their approach tested whether the difference between the average right orbit and the average left orbit was zero. In contrast, we tested whether the average difference between right orbit and left orbit was zero. In the context of an individual patient, we believe the latter, within-individual test is more appropriate. We also considered the ratio of volumes between right and left orbit rather than the simple difference. In fact, we reanalyzed the raw data provided in Bentley et al. [2] using our approach and found that the volume of the right orbit was larger than that of the left orbit. Specifically, we found that the mean difference in volume between an individual's right orbit and left orbit is positive ($P<0.01$), and the ratio between the volume of an individual's right orbit and that individual's left orbit is greater than one ($P<0.01$). In both cases, this difference persists even when controlling for sex in an OLS regression specification with heteroskedasticity-robust standard errors ($P=0.01$ and $P<0.01$, respectively). Since these studies were purely cross-sectional and thus relied on differences in average orbital volume to model orbital growth, this finding may have some relevance.

To our knowledge, this is the first study to use CBCT datasets to study age-related changes in orbital volume. Multiple challenges had to be overcome to generate interpretable data for this study. Orbital anatomy, with its thin bones and numerous openings with undefined boundaries, low growth rates, and image noise meant that great attention was needed to confidently detect very small changes in orbital volume. Following the technique of numerous studies, [11–13] we used manual segmentation to segment and measure orbital volume. The major difference between our segmentation protocol and others is in how the orbital boundaries are defined. We developed a scheme to transform each orbit into an ovoid space with well-defined boundaries in all panels in axes. The product generating a robust barrier seal the orbital aperture. Our method for delineating the orbital volume – by constructing a boundary based on anatomical landmarks, is most similar to Ioannou et al., 2018 [12]. Whereas virtual boundaries could not be created due to an inability to accurately segment the thin ethmoid bones, rules were made to guide users in intuitively delineating the limits of the orbital cavity.

There is a large body of literature describing various protocols for measuring orbital volume with computed tomography (CT) [11–13] and MRI [14, 15]. While CBCT is capable of obtaining submillimeter resolution with isotropic voxels with far lower doses than conventional CT, it also posed unique challenges. These challenges – which include the lack of correspondence between grayscale values and actual Hounsfield Units and poorer image quality resulting from scatter, artifacts and undersampling – precluded many of the time-saving automation steps used in protocols developed for conventional CT. These challenges exist at the time rather than numerical, since the fine resolution of CBCT images successfully minimizes error due to partial-volume effects.

The use of the WRS approach represents a second methodological contribution of this paper. While the WRS methodology was adapted from a very different context – the creation of a real estate index – from a statistical perspective, the underlying problems in our dataset mirror those for which the methodology was developed. In both contexts, observations appear at irregular intervals: houses sell only periodically and CBCT scans are taken when necessary for clinical purposes rather than at regular intervals. In both contexts, there is substantial heterogeneity across individuals which must be controlled for: each house has unique characteristics just as each patient's skull is distinct. The methodology controls for time-invariant features of individuals by relying on changes within individual over time, rather than looking across individuals. Finally, what in financial economics is termed a "return" is mathematically equivalent to a growth rate. Given all these features, the WRS methodology is well-suited for use in this context.

The described methodology for utilization of CBCT databases available through dental departments can help orbital and facial surgeons better understand the growth of the pediatric orbit. This can, with future studies, help guide timing and implant selection for anophthalmic socket procedures, orbital trauma reconstruction, and facial surgery. For our study, we chose to measure a single outcome (volume), but future studies can focus on finer details and patterns of orbital growth. In particular, determining the mechanism of childhood orbital volume expansion, and whether it involves bone deposition or resorption, would be helpful in order to evaluate the similarities and differences between orbital changes during childhood and the bony remodeling that occurs during adulthood.

Conclusions

Orbital volume increases by 1–2% per year throughout childhood continuing until the late teenage years. This annual increase is large enough to be clinically relevant, as it may lead to less-than-optimal long-term surgical outcomes when reconstructive surgery for the pediatric anophthalmic socket is required.

Supplementary information

The online version contains supplementary material available at [illegible]

Additional file 1.

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Author's contributions

[illegible] All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

[illegible] All methods were performed in accordance with the relevant guidelines and regulations. All patients included in the study, or their legal guardians, provided informed consent for the use of radiographic scans for research purposes.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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Abbreviations and Acronyms:
OCT = optical coherence tomography; **ONH** = optic nerve head; **RNF** = retinal nerve fiber.

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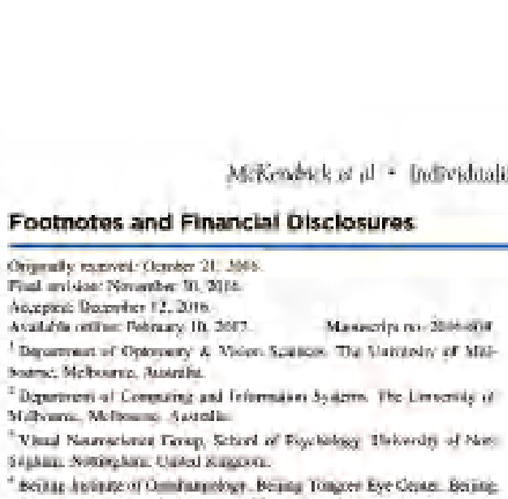
Pictures & Perspectives



Malignant Orbital Melanoma Associated with Oculodermal Melanocytosis

A 30-year-old man diagnosed in childhood with right oculodermal melanocytosis (Nevus of Ota) (Fig 1A), presented with overnight onset of proptosis, ophthalmoplegia, and pain. En suite, T1-weighted magnetic resonance imaging with gadolinium demonstrates a large heterogeneously enhancing predominantly intraconal mass, abutting the temporal bone dura through a bony defect in the lateral orbital wall (Fig 1B). Ocular examination revealed no axial mass. Lateral orbitotomy (Fig 1C) and biopsy revealed pigmented melanoma cells infiltrating orbital tissue with perineural and perivascular invasion (Fig 1D). Orbital malignant melanoma associated with Nevus of Ota has rarely been reported. Tumor hemorrhage presumably instigated his rapid onset symptoms.

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Clinical challenges

The glue that holds the situation together

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In keeping with the format of a clinical pathologic conference, the abstract and key words appear at the end of the article.

1. Case report

A 48-year-old Hispanic man presented with a fluctuating mass in his left upper eyelid for several years. He noticed the lesion increased in size when he leaned forward, and he experienced pain and pressure around his left eye when bending down or lying flat. Reported visual changes or pain with eye movement. His past medical history was remarkable only for hypertension.

Visual acuity was 20/20 in each eye. Motility and confrontational visual fields were full. Margin reflex distances 1 and 2 were 4.5 mm and 6 mm in each eye, respectively. Exophthalmometry demonstrated 2 mm of relative enophthalmos in the left eye. Slight hollowing of the left lateral superior sulcus suggested left enophthalmos rather than right exophthalmos. There was some fullness at the medial aspect of the left upper eyelid that increased with Valsalva maneuver (Fig. 1). The increased fullness produced inferior and lateral globe displacement. Slit lamp and dilated fundus examinations were unremarkable.

What are the considerations in an adult with a distensible mass in the orbit? What is the significance of the Valsalva maneuver? What initial imaging would you recommend?

2. Comments by Andrew R. Harrison, MD

A chronic distensible mass in an adult typically represents a vascular malformation of the orbit. Other differential considerations for an orbital mass includes venolymphatic malformation, arteriovenous malformation, cavernous hemangioma, schwannoma, neurofibroma, lymphoma, and orbital metastasis. It is important to determine the flow characteristics of these lesions and their connection to the deeper orbital venous system. A lesion that shows increased size with Valsalva maneuver suggests connection with the venous drainage of the orbit. At this point, orbital imaging is indicated, and I would obtain magnetic resonance imaging of the orbit with gadolinium. Having the patient Valsalva during the scan will increase the size of the lesion. This also can be accomplished by having the scan performed with the patient's head in a dependent position.

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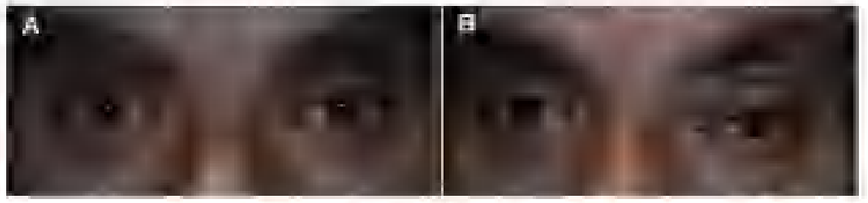

Fig. 1 – A: Frontal photograph demonstrating fullness of the left superomedial orbit (A) that increases in size with Valsalva maneuver (B).

3. Case report (continued)

Contrast-enhanced magnetic resonance imaging demonstrated a 2.1 × 2.5 × 1.5 cm complex lesion in the left superomedial orbit, wrapped between the superior oblique and medial rectus muscles, and above the medial central tendon. No intraconal extension was noted. The mass was T2-hyperintense with central enhancement and had a layering fluid-fluid level (Fig. 2), possibly representing prior hemorrhage. The orbital contents were otherwise unremarkable. Magnetic resonance angiography demonstrated normal intracranial arterial vasculature and did not demonstrate any flow-related enhancement within the lesion to suggest a significant arterial component.

Does this alter your differential diagnosis? How do you distinguish this from a venolymphatic malformation? How would you proceed?

4. Comments by Dr. Harrison (continued)

The magnetic resonance imaging results are consistent with a low-flow venous malformation of the orbit. Orbital venolymphatic malformations are isolated from the normal orbital vascular system and are not affected by postural changes. The venolymphatic malformation would show absence of

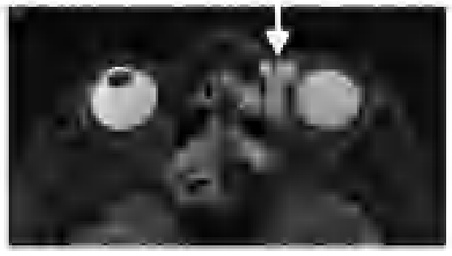

Fig. 2 – Axial T2-weighted magnetic resonance imaging demonstrating a T2-hyperintense, contrast-enhancing mass of the left orbit with fluid-fluid level (arrow), possibly representing prior hemorrhage.

enhancement in the lymphatic component. If the patient is asymptomatic, these lesions may be observed. For patients with pain or visual compromise, the lesion may be excised surgically. The use of preoperative embolization with glue has greatly improved the safety of surgical resection owing to improved hemostasis.

5. Case report (continued)

The clinical and radiographic findings were consistent with a low-flow, venous malformation of the orbit—a orbital varix. After discussing options with the patient, including observation, he elected surgical excision because of discomfort, orbital pressure, and disfigurement. A multidisciplinary approach was performed in collaboration with interventional radiology in a 2-step approach fluoroscopic mapping, gluing, and surgical excision. The lesion was approached surgically through an eyelid crease incision. Once exposed, the lesion was directly cannulated, and the outflow channels were defined under direct fluoroscopy. Real-time mapping showed no high-flow vessels or abnormal communication with the superior ophthalmic vein or cavernous sinus. The lesion was then gently flushed with sucrose 10% dextrose and water (D5W) then filled with a 3:1 mixture of n-butyl-cyanoacrylate (NBCA) and iodinated contrast, occluding the lesion. Once solidified, the vascular malformation was directly excised.

Histopathologic evaluation of the lesion confirmed a vascular malformation with thrombosis and capillary endothelial hyperplasia (Fig. 3). The patient's recovery was uneventful, and his symptoms were relieved. At 6-year follow-up, he remains well without recurrence.

6. Discussion

Vascular malformations of the orbit comprise a spectrum of entities that are primarily classified by their flow dynamics. To differentiate these clinically, examination techniques include palpation, ocular auscultation, and observation during Valsalva maneuver. Useful imaging modalities include Doppler ultrasound, computed tomography, and magnetic resonance imaging, including magnetic resonance angiography.

Orbital varix is a historical term for a low-flow vascular malformation of the venous system with dysplastic vessels and normal endothelial turnover. They are often distensible

Fig. 3 – Stained section showing numerous abnormal blood vessels, slit-like vascular channels, fibroadipose tissue, and nerve bundles. Many of the blood vessels contain organizing thrombi (large arrow) and some are forming papillary endothelial hyperplasia (small arrow) (hematoxylin & eosin [H&E], original magnification: ×10).

and increase in size with Valsalva venous pressure. Depending on the location of the lesion, they can present as intermittent unilateral edema of a diffuse mass, often causing orbital pain or functional deficits secondary to elevated orbital pressure. They may also cause vasodilatation at rest, diplopia, or ecchymosis from spontaneous orbital hemorrhage.

Observation is typically recommended for asymptomatic orbital varices. Indications for treatment include pain, impaired ocular function, or disfigurement. Options for treatment include various modalities of vascular occlusion with or without surgical excision. [redacted] Although each has theoretical advantages, combining NBCA embolization with excision has become the preferred approach. NBCA belongs to a family of polymers with adhesive properties, including ethyl-2-cyanoacrylate (Super Glue and 2-octyl cyanoacrylate (DERMABOND) that have a long track record of successful use with minimal morbidity. [redacted] NCBA polymerizes on contact with ionic compounds, effectively occluding the venous malformation.

Without adjuvant NBCA, surgical excision of orbital varices is fraught with complications. These dysplastic, friable vessels bleed easily, have undefined surgical margins, and may be intricately associated with—or directly infiltrating—delicate and important orbital structures. When combined with excision, embolization decreases surgical risks by decreasing bleeding and facilitating more complete excision while avoiding undesirable complications of NBCA embolization alone, such as granulomatous inflammation, necrosis, and edema. [redacted] There are several series of patients who underwent successful NBCA embolization with subsequent surgical resection without postoperative complication.

Vision loss is a potential complication via retrograde flow of embolic material into a feeding artery, although careful preoperative and intraoperative planning and patient selection help minimize this risk. The ideal lesions suited for this approach is an extensive, "low-outflow" venous lesion, which has minimal or no early drainage through normal venous outflow. Conversely, those lesions that drain early and supply widely during vascular maneuver and angiographic imaging. Additionally, careful mapping of venous outflow under direct fluoroscopic guidance can identify drainage patterns into the superior ophthalmic vein and cavernous sinus. When present, these can be manually compressed to minimize inadvertent migration of the cyanoacrylate glue into vital venous channels. If direct compression is not possible, initial gluing may be performed to block the outflow, and subsequent injections of the lesion can be facilitated, decreasing the risk of disseminating embolic material. [redacted] Despite adequate embolization and extensive excision, lesions may recur in younger patients possibly secondary to incomplete embolization or recanalization.

In conclusion, this patient who presented with a distensible vascular malformation of the orbit causing pain and disfigurement posed a clinical challenge. His findings were consistent with a low-flow venous malformation—an orbital varix. When treatment is indicated, for pain, functional deficit, or cosmetic disfigurement, our preferred approach is a multidisciplinary excision with direct NBCA embolization, followed by immediate surgical excision. This approach has the advantage of minimizing intraoperative bleeding, facilitating more thorough and safe excision, and avoiding risks inherent in other treatment modalities. Although this technique is still evolving, it provides orbital surgeons with a demonstrated effective approach to these challenging cases.

7. Disclosures

The author reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

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Keywords
orbital varix
orbital vascular malformation
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ABSTRACT

A 48-year-old man presented with a longstanding left upper eyelid mass that increased in size when bending forward. The mass was associated with exophthalmos and slowly increased in size with Valsalva maneuver. Magnetic resonance imaging and arteriography demonstrated a vascular malformation without an abnormal arterial component. Because of his increasing pain, the vascular malformation was excised in a multidisciplinary approach involving intraoperative fluoroscopic mapping, cyanoacrylate embolization, and surgical excision. Histopathology was consistent with a benign vascular malformation. Clinically, this was a low-flow, distensible venous malformation—or orbital varix.