Treacher Collins Syndrome

Billie Wicks

Sanford USD Medical Center School of Radiologic

Technology December 19th, 2019

Treacher Collins Syndrome

I. Introduction

Thesis: TCS is a rare craniofacial development disorder. This condition affects the way the face develops which would include the malformation of the cheekbones, jaw, ear and eyelids

II. Discussion

A. History
    a. Edward Treacher Collins
    b. Adolphe Franceschetti and David Klein

B. Genetic and Random mutations

C. Pathologic Characteristics

D. Effects

E. Diagnosis
    a. Ultrasonography
    b. MRI/ CT
    c. Xray

F. Treatment
    a. Reconstructive surgery
    b. Bone grafting
    c. New avenues

III. Conclusion

Objectives

At the conclusion of this paper, the audience will be able to:

1. Identify the causes of Treacher Collins Syndrome and whom it affects
2. Recognize the physical characteristics and issues that can arise
3. Understand how and when TCS is diagnosed
4. Compare old and new avenues on how to manage this syndrome

Treacher Collins Syndrome

"There is no greater disability in society than the inability to see a person as more," Robert M. Hensel. Treacher Collins Syndrome (TCS) is a rare craniofacial development disorder that occurs in 1:50,000 live births. TCS can be caused by genetic or random mutations. More than 130 distinct mandibulofacial mutations have been identified. [1] This condition affects the development of the facial structures. This would include the malformation of the cheekbones, jaw, ears and eyelids. The symptoms of Treacher Collins Syndrome can vary depending on the severity of the condition.

History

The first case of this syndrome was described in 1900 by an ophthalmologist, or eye doctor, by the name of Edward Treacher Collins. Edward Collins was an English ophthalmologist in London and was the first to describe the features of a foreshortened mandible and the downslanting of the eyes. He classified this as Treacher Collins Syndrome. However, the first extensive review was done by Adolphe Franceschetti and David Klein in 1949. These ophthalmologists specialized in genetics. They described the same physical traits but used the term mandibulofacial dysostosis to classify this condition. Because of this, the condition can also be known as Franceshetti-Klein syndrome.[2]

Genetic and Hereditary Mutations

Treacher Collins Syndrome, or TCS, is a congenital condition of the mutation of the gene known as TCOF1. Random mutations make up 60% of TCS cases, while the other 40% of cases are hereditary or genetically inherited. This mutation causes an abnormality of the craniofacial bones which include the maxilla, mandible, eye sockets, and ears.[1] A major cause of this mutation is the apoptosis that occurs within the neuroepithelium inside the embryo. This occurs during the early embryonic stage. Apoptosis is the process of cells going through a variety of changes that lead to the termination of the cell. Neuroepithelium cannot survive this process.[2] When neuroepithelium does not generate properly, hypoplasia, or underdevelopment of the cranioskeletal elements occur.[1]

The tissues that are affected originate from the maxillary and mandibular first pharyngeal arches and the second hyoid pharyngeal arch (Fig.1). These develop in the fourth week of gestation. These give rise to the structures of the head and neck. The first and second pharyngeal arches contain many cranial crest nerves, which form cartilage, bone, and connective tissue of the face and head. These cranial crest cells derive from neuroepithelium. Neuroepithelium is a type of epithelium which contains sensory nerve endings that can be found in locations such as the retina, inner ear and nasal membranes. With the gene mutation of TCOF1, the migration of the cranial crest cells are reduced by a quarter of the normal migration. Therefore, 25% of the cranial crest cells never make it to the epidermis where development occurs.[2]

The gene TCOF1 encodes a nucleolar phosphoprotein which is known as Treacle. To understand the full pathology of this disease, one must understand the importance of Treacle, the protein encoded by the TCOF1 gene. This protein has an important role in the mutation of ribosomes, as well as the development of the neural crest cells.[1] Neural crest cells are precursors to the craniofacial soft tissue and bone. Treacle is important for spatiotemporal regulation of ribosome biogenesis. When mutation of this gene takes place, it results in deficient biogenesis. This results in neuroepithelial apoptosis occurring and a large amount of neural crest cell deaths. General cardiac skeletal hypoplasia occurs due to generation of insufficient neural crest cells.[1] This leads to the cartilage and bone never getting the chance to develop properly.

Neural crest cells make up the branchial arches. Haploinsufficiency of the TCOF1 gene will cause mutations. Any region that derives from these branches, such as the eyes, ears, mandible and palate are also affected. Studies have shown that mandibular hypoplasia and external ear malformations are associated together because they both originate from the first and second branchial arches during embryonic development.[3]

Pathological Characteristics

When the tissue and craniofacial bones fail to develop properly the consequences can affect the overall well-being of a person. These life-long implications include both biological and psychological problems, as well as physical properties. The physical properties of an individual

suffering from TCS include underdeveloped facial bones, small jaw and chin, eyes slanting downwards, and unusually formed ears (Fig 2).[2]

Studies have shown that 77% of patients have external ear deformities that include rotation of the outer ear tissue and disproportionate structures.[3] The external ear abnormalities include absent, small and/or rotated ears, as well as stenosis or a constricted external auditory canal, or EAC. This can cause delayed speech development, but typically it does not result in hearing loss. Frequent ear infections are common because of the abnormal size and shape of the outer ear. The EAC, on average, extends 2.5 cm from the tympanic membrane, which separates the canal from the middle ear structures: the malleus, incus and stapes. Middle ear abnormalities usually include ankylosis, hypoplasia, or overall absence of the auditory ossicles. However, the inner ear structures remain normal and usually function properly. [4]

Hearing loss can occur in 40-50% of individuals because of the middle ear anomalies. This is attributed to the malformation of the auditory ossicles and the overall hypoplasia of these structures.[4] Radiographic analysis , usually magnetic resonance imaging (MRI), of the middle ear has concluded that most patients have irregular or completely absent auditory ossicles, as well as unnecessary fusions between the malleus and incus. In most cases, the stapes and oval window are also absent. The malleus, incus, and stapes or, auditory ossicles, transmit vibrations throughout the middle ear to the cochlea where it is converted into sound. Fusions between the malleus and incus inhibit the vibration of sound waves which causes acoustic complications.[1]

A collaborative study was conducted by the Department of Craniofacial Surgery Center, Plastic Surgery Hospital, Academy of Medical Sciences, and Peking Union Medical College in Beijing, China. The study was done in regard to TCS patients affected with ear deformities. The desired outcome was to assess the ear volumes of TCS patients with 3D imaging. A control group of 39 individuals, aged and gender matched, were compared to the same criteria of 36 individuals with TCS who had no surgical history. Both groups underwent CT scans that included the entire skull. The results from this study showed a 50% reduction in external ear volume of the TCS patients than the control group. With reduced external ear volume, less sound is transmitted. Other findings included the mandibular morphology of these groups. The left

mandibular body length was 21.4% shorter among patients with TCS and 29.7% shorter on the right compared to the control group. Also, the mandibular rami heights were decreased by 32.8% on the left and 33.2% decreased on the right. Mandibular hypoplasia can cause severe functional impairment. Impairment can include abnormal positioning of the tongue and a small oral cavity. Because of these problems, breathing difficulties can occur during birth and during sleep. [3]

Hypoplasia of the zygomatic bone and mandible, depending on severity, can cause respiratory and feeding difficulties due to the abnormal deformities (Fig. 3).This is caused by the down slanting palpebral fissures as well as malar hypoplasia, micrognathia, and abnormalities of the ears. Micrognathia and retrognathia affect the temporomandibular joints and muscles of the jaw by causing difficulties opening and closing the jaw joint.[4] Less common abnormalities can occur including cleft palate, unilateral or bilateral choanal stenosis or atresia. Choanal stenosis or atresia is the narrowing or blockage of the nasal airway by tissue. Newborns that suffer from TCS usually require airway management due to the narrowing of the airway along with the extreme shortening of the mandible. This can also cause glossoptosis to obstruct the airway of an infant. Glossoptosis is the downward displacement or retraction of the tongue. Because of this, many infants can suffer from sleep apnea, which can lead to neonatal death. Sleep apnea is a condition where breathing continually starts and stops. This occurs because the airway is partially obstructed. [4]

The other physical characteristics of Treacher Collins Syndrome, such as hypoplasia of the mandible and zygoma, lead to dental malocclusion. These malocclusions are widely spaced teeth and a reduction in the number of teeth. It is also very common for the palate to be abnormally high and the zygomatic arches to be completely absent.[1] Of the individuals who suffer from TCS, 60% have reported dental anomalies. These include enamel opacities, tooth agenesis and ectopic eruption of the maxillary first molars. Tooth agenesis is the incomplete formation of one or more teeth. Ectopic eruption is when the molar intercepts a primary tooth's position, which eventually leads to a foreshortened arch and inadequate space for more tooth formation. This eventually causes issues as an adult when eating certain types of food.[4]

Patients experience many different ophthalmologic problems with TCS. Some that have been documented include down slanting palpebral fissures, absent medial lower lid eyelashes, lower lid lacrimal deformity, epiphora or excessive watering of the eye, and although it is uncommon, vision impairment that requires treatment.[5] Coloboma of the lower eyelids can result in corneal exposure. Coloboma is when a piece of the eyelid is missing because of development malfunctions. Other vision impairments that can take place are anisometropia and strabismus, or double vision. Anisometropia is when the two eyes have unequal refractive power; for example, a patient could suffer from nearsightedness and farsightedness.[4]

Although the main physical characteristics of Treacher Collins Syndrome are facial deformities, other functions of the body can be altered. Mild development delay of the digestive and cardiac systems sometimes can occur due to the pathogenic variations of the TCOF1 gene; however, this is not seen in all TCS patients.[4]

The major problems that arise at birth or before are usually breathing or airway complications and tongue obstructions. Later issues include hearing loss, speech problems and ophthalmology concerns. These characteristics lead to learning impairment, low self-esteem and minimal social interactions.

Emotional Effects

Not only do TCS patients have physical challenges, the syndrome also comes with emotional and social difficulties for both the patients and their caregivers. It is important for patients, families, caregivers and bystanders to understand the diagnosis as well as the treatment for these individuals.[6]

Intellectual disabilities are not commonly associated with TCS; however, if a patient suffers from hearing loss, this can contribute to a learning disability. Speech problems that are typically seen are dominated by abnormal resonance due to the restriction of the nasal passages and oropharynx. Articulation errors are also seen in TCS patients. This is attributed to the malocclusion with anterior open bite, retroglossal and overall abnormal oral anatomy.[5] Caregivers state that, on average, individuals start to notice their own condition at a mean age of 3.3 years. At the ages of 3 and 4, children start noticing the difference in their facial features in

comparison to others. Many patients experience social anxiety and seclusion. Caregivers report their children having negative emotions. These ongoing experiences lead to aggression instead of adaptive coping.[6]

Diagnosis

Tests used to diagnose TCS may include physical examination, genetic testing, and obtaining medical history. Besides noticing the obvious physical features, xray, ultrasonography, CT and MRI are other ways to demonstrate and observe the internal bone structures of patients. Radiography is used to confirm the results that are seen first hand, as well as help with surgical reconstruction.

Ultrasonography

A person can be diagnosed even before birth because of the ability of ultrasonography. This is the preferred method because no radiation is involved. Ultrasonography is the process of using high frequency sound waves to create an image. It is widely used in obstetrical settings due to its ability to recognize fetal appearances (Fig. 6). Recent improvements over the decades have provided clear diagnoses for Treacher Collins Syndrome with 3D and 4D ultrasonography.[7]

Since the onset of TCS abnormalities occur during embryonic development, the first detection is found with ultrasound. Usually a combination of magnetic resonance imaging, or MRI, and ultrasound is used to further diagnose the severity in vitro and verify the true condition.[1] Prenatal ultrasonographers follow their clinical protocols for diagnosis of any prenatal condition. Once a conclusion is made, it affects the care plan throughout the rest of the pregnancy.

TCS is most often found in utero, or before birth. Diagnosing in utero is crucial for prevention of worsening symptoms. Early detection helps the efficiency of the invasive and prolonged treatment conditions. Prenatal ultrasonography diagnosis is possible because of the ability to detect abnormalities of the face, ears and limbs.[2]

MRI

Magnetic Resonance Imaging, or MRI, is used to diagnose many cases of TCS in utero and postnatal (Fig 7). It is mainly used to show defects of the middle ear and hemifacial anomalies. This is also a preferred method of diagnosis over computed tomography (CT) because radiation is not involved for the mother or child. MRI uses a magnetic field and radio waves to form an image.[8] It is deemed safe when used at strengths of 3T or less, but of course, exposure time, gradient field switching, and power deposition must be considered.[9]

Ultrasound is the first choice to detect TCS, but MRI is generally used when a detailed image is needed for reconstruction or further diagnosis. Ultrasound may show shadows that can be perceived as an anomaly, but in fact are not. In utero, MRI is used to rule out or confirm findings that are discovered in the ultrasound. During the MRI, the mother is placed either supine or in the left lateral position. A true midline sagittal view is important for viewing the facial structures of the fetus. The midsagittal and parasagittal views show the nasal cavity, soft palate, tongue, maxilla and mandible. A coronal MR is useful for observing the lips, nasal cavity and orbits, while an axial view better demonstrates the maxilla and mandible. [9]

MRI helps to perform various measurements from the upper lip to the chin. The two measurements that can be taken according to the RSNA are the inferior facial angle and the jaw index. The inferior facial angle is assessed by having a line drawn between the superior portion of the nasal bones to the tip of the mentum or tip of chin. The jaw index is calculated by finding the quotient of the anteroposterior diameter of the mandible and the biparietal diameter.[10] Acquiring these measurements helps with the diagnosis and the future reconstructive surgeries.

High resolution MRI or CT is helpful when evaluating hearing loss for postnatal patients. One of the physical characteristics of TCS is the deformity of the medial and external ear structures (Fig. 7). The MRI is used to show the size, shape, and position of the auricle. It also shows the malformation of the auditory ossicles or the complete absence.[9]

X-ray

Diagnosis is primarily made by clinical and radiographic findings. Craniofacial radiographs have been extremely useful when proving if a patient has zygomatic hypoplasia. The postnatal radiographs help to differentiate between TCS and other facial deformity diseases. Postnatal diagnosis takes place shortly after birth due to obvious facial deformities. When individuals have very mild TCS, it can be difficult to diagnose. Because this is hereditary, when a child is born with this syndrome, the parents are evaluated to see if they also have a less severe form of TCS that has not been officially diagnosed.[1] The individuals that have mild TCS are usually diagnosed after giving birth to a child that is severely affected.

Typically, the skull is the main anatomical area needed to be radiographed. Skull x-rays can be used to demonstrate the facial bones, nasal bones, sinuses, and orbits. The anatomy found in these specific images are measured and studied by a radiologist. Plain radiographs of the skull and face can show deformities; however, Computed Tomography (CT) provides clear details that give additional information to the surgeons for later reconstruction.[10]

TCS can be complicated to diagnose due to other syndromes that have similar characteristics. For example, Nager Syndrome is similar to TCS because both result in the downward slanting of the eyes. However, TCS patients have different mandibular anomalies than Nager patients. Miller Syndrome can also be confused with TCS. Miller Syndrome results in more cases of cleft palate and cleft lip. TCS patients are only affected by facial defects, but Nager and Miller syndrome patients can have defects of all four limbs, such as the shortening of the radius and ulna.[1]

Ultrasonography, MRI, and diagnostic x-ray are very important in the diagnosis of Treacher Collins Syndrome. Using these modalities is very beneficial for visualizing the external and internal bone and soft tissue structures. With the advances in technology, xray and MRI can be used to map out surgical reconstruction.

Options for Managing TCS

Treatment revolves around the specific needs of the individual and the severity of the syndrome. Managing these needs is usually determined by the treatment team. This team consist of geneticists, plastic surgeons, head/ neck surgeons, otolaryngologist, oral surgeons, orthodontists, audiologist, speech pathologist, and a psychologist.[4] The most common and well-known treatment is reconstructive surgery. Patients that suffer from severe TCS undergo many surgeries throughout their lives. Most of these operations are not 100% successful.[1]

Managing the issues of TCS occur in different sections. These sections are broken down into age groups. The first group is from birth to age two. The areas of interest for this group are the airway and feeding difficulties. The delivery team will be aware and prepared for the potential life-threatening neonatal airway compromise. If needed, there will be a surgical intervention of the airway to improve respiratory functions. This could include restoring the nostrils and reconstruction of the mandible. Once completed, the team will assess the feeding ability to determine if a gastrostomy is needed. Other assessments would later include ophthalmologic and hearing evaluations.[4]

The second age group for management is ages three-twelve years. The major issues at this stage are speech therapy and craniofacial reconstruction, if appropriate. Soft tissue corrections generally take place before reconstruction. Some bony reconstruction can include zygomatic and orbital surgeries, which usually occurs between the ages of five and seven years. After the age of six years, external ear repair will take place as well as dental repairs. The last management group is ages 13-18 years. Nasal reconstruction and maxillomandibular repair should follow orthognathic surgeries. Periodic assessment of growth and development is recommended after these repairs.[4]

Managing TCS requires planning many operations to reconstruct soft tissue as well as orbitomalar and maxillomandibular bony abnormalities. The goal for these patients is to, in the end, achieve normalcy. The initial stage of surgical reconstruction involves the mandible if there is any obstruction of the airway. Reconstruction of the eyes is the next stage. This will usually

take place after five years of age. Lastly, reconstruction of the oral cavity and any other improvements are performed.[4]

The most common and well-known treatment is reconstructive surgery. Patients that suffer from severe TCS undergo many surgeries throughout their lives and most of these surgeries do not turn out to be completely successful. These operations are used to improve function as well as appearance. Treatment ranges from a variety of different operations that include a tracheostomy for a mandibular hypoplasia, cleft palate, reconstruction of airways soft palate and hard tissue as well as remodeling of the cheek bones, orbits and mandible. Virtual surgical planning, or VSP, gives surgeons the ability to accurately provide and create a 3D model for reconstruction surgeries (Fig. 8). This makes it easier to find the correct shape and implant for the desired facial bone.[11]

Some surgical options may include reconstruction of the eyelids, closure of a cleft palate if present, repairing of the maxillofacial bones and repositioning, lengthening of the lower jaw, and ear reconstruction. Ear surgery is performed to restore hearing for patients. External ear or microtia repair is done for cosmetic reasons and middle ear repair is done to regain hearing. These adjustments are made between the ages of five and seven years. Eye surgery is usually performed during the infants' early years. However, facial reassembly is one of the last surgeries that should be performed.[12]

Treacher Collins Syndrome is not a progressive disease, but bimaxillary surgery should be performed as late as possible to avoid any shift in anatomy. It is hard to determine skeletal maturity due to unpredictable growth. After surgical changes have been made, it is difficult to maintain them. Often repeat surgeries are necessary. Tessier has documented that "the midfacial segment combined with mandibular lengthening have a strong tendency to relapse due to the backward pull of the soft tissues, as compared to the stability of orbital movements. . ." Because of the patients' poor bone stock and soft tissue deficiencies, it can be challenging to accomplish certain surgeries.[13]

The long-term goal for stopping TCS is to formulate a natural compound to administer before and during pregnancy that will provide protection to the embryo from apoptosis without

harming the fetus or causing more severe side effects. Many different avenues of treatment options are being explored.[1]

One particular option that is still controversial is the blocking off of the p53 protein that causes the apoptosis of the neuroepithelial cells needed for the formation of cartilage and tissue growth of the face. Chemical and genetic obstruction of p53 has been tested on mice. The mice that underwent the inhibition of p53 showed a large reduction of neuroepithelial apoptosis compared to those who were not treated. However, mice who were completely blocked from the p53 developed large masses, which eventually lead to death. This concludes that the type of treatment would heavily rely on dose. Without the p53, tumorigenesis will occur and other problems could arise.[2]

Neuroepithelial apoptosis occurs when increased stress levels of the tumor protein called p53 takes place. This protein helps in the regulation of the cell cycle and in tumor suppression. To suppress tumors, p53 creates a balance between activities that help the cells survive and help destroy cells that are proliferating too fast. This correlates with the apoptosis of neuroepithelial cells in TCS patients.[2]

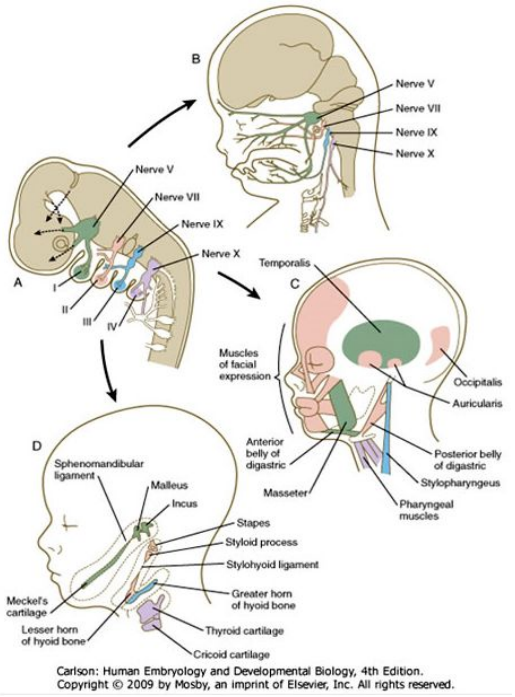
The most common technique used to restore facial anomalies is bone grafting. However, bone grafting is preferred at an older age because growth of facial structures would no longer have to be considered. Bone grafting is the process of using tissue from other places, such as the hip or the leg, to rebuild or restore damaged bone. Bone grafting is also known as bone flaps. Bone flaps can be used to recreate and normalize the zygoma and orbits. Local flaps can be used to perfect the slanting of the eyelids.[12]

Two types of bone grafts are autograft and allograft. Autograft is when the healthy bone is taken directly from the patient's own body. Allograft uses the tissue from a donor. When undergoing allograft, there is always a risk of the body rejecting the foreign tissue. This rejection is uncommon; however, because the transplanted bone does not include living cells, there is no need for matching blood types. [11]

Conclusion

Treacher Collins Syndrome is a rare craniofacial development disorder that only affects 1 out 50,000 live births. It can be caused by genetics or random mutations. Common physical characteristics of this disease include a foreshortened mandible, downslanting of the eyes, and rotation of the external ear. Ultrasound, x-ray, CT and MRI, can be used to further diagnose and verify the location of the abnormal underlying structures. Although TCS is incurable, there are many treatment options to manage the disease. Reconstructive surgery and bone grafting are common treatment options. However, research has helped determine another solution. Blocking off of the p53 protein is still controversial, but is leading a path to many other treatment options.

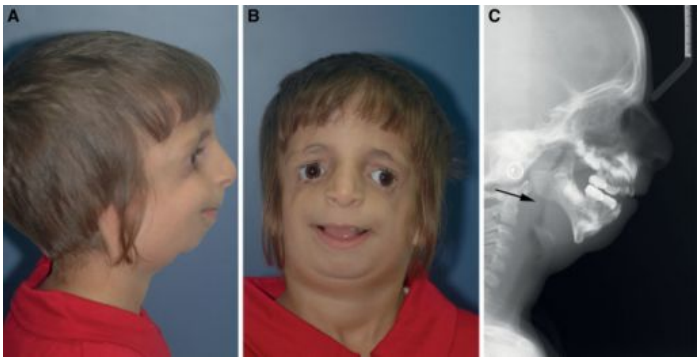
Fig. 1 Demonstration of the pharyngeal arches



Henrik. Craniofacial and Pharyngeal Arch Development. SlideServe.https://www.slideserve.com/henrik/craniofacial-and-pharyngeal-arch-development. Published July 22, 2014. Accessed December 19, 2019.

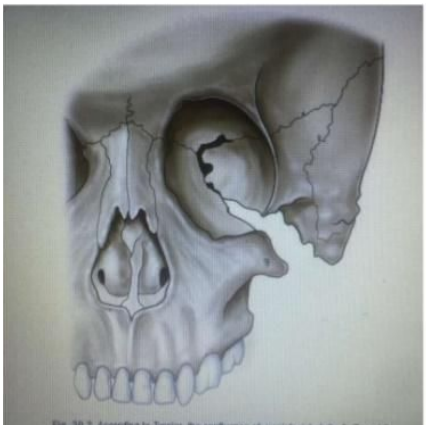
Fig. 2 Small mandible, down slanting eyes

Patient before treatment with external distraction device. A and B, Five-year-old boy with Treacher Collins syndrome associated with mandibular hypoplasia and obstructive sleep apnea. C, Preoperative lateral cephalometric x-ray demonstrating mandibular micrognathia and airway constriction (arrow).



External versus Internal Distraction Devices in Treatment ... https://www.researchgate.net/publication/268875917_External_versus_Internal_Distraction_Devices_in_Treatment_of_Obstructive_Sleep_Apnea_in_Craniofacial_Anomalies. Accessed December 19, 2019.

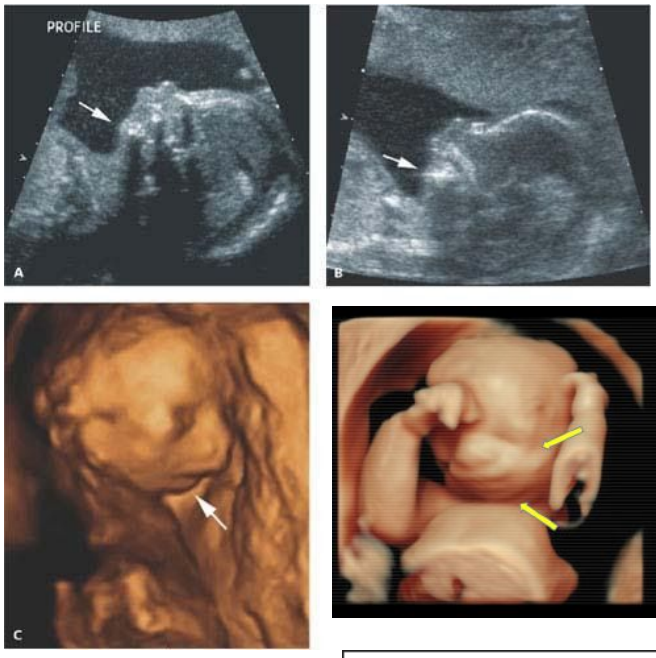
Fig. 3 Hypoplasia of the Zygoma and Orbit



According to Tessier, the confluence of craniofacial clefts 6, 7, and 8 produces the hypoplasia or absence of bony structures, including the zygoma, orbit, maxilla, and ascending ramus of the mandible

Suiyibangbe. Treacher colllins syndrome. LinkedIn SlideShare.https://www.slideshare.net/100000579483512/treacher-colllins-syndrome. Published July 24, 2018. Accessed December 19, 2019.

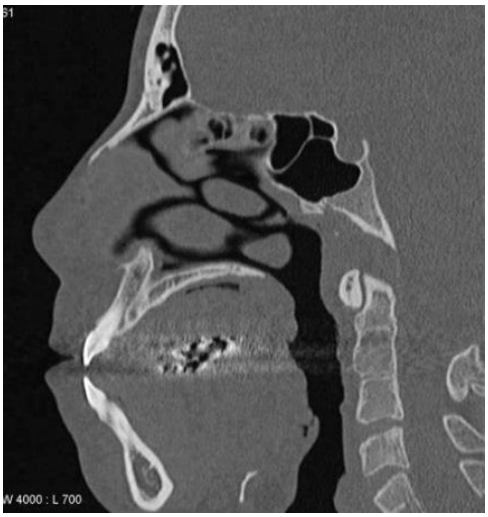
Fig. 6 In utero ultrasounds of foreshortened mandible



Fetal face demonstrated by the rendering mode of 3D ultrasonography at 29 weeks' gestation showing micrognathia (left), symmetrical downslanting palpebral fissures (left and right) and macrostomia (right) (yellow arrows).

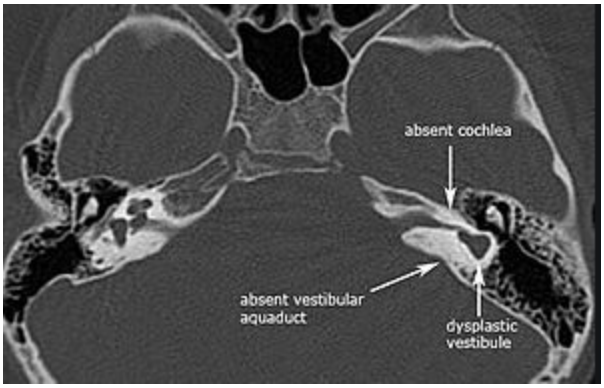
Kubo S, Horinouchi T, Kinoshita M, et al. Visual diagnosis in utero: Prenatal diagnosis of Treacher-Collins syndrome using a 3D/4D ultrasonography. *Taiwanese Journal of Obstetrics and Gynecology*. 2019;58(4):566-569. doi:10.1016/j.tjog.2019.05.024.

Fig. 7 Sagittal cut showing foreshortened mandible



Singh G. Treacher Collins syndrome: Radiology Reference Article. Radiopaedia Blog RSS. https://radiopaedia.org/articles/treacher-collins-syndrome. Accessed December 19, 2019.

Fig. 8 Axial cut showing absence of the cochlea



Cochlear aplasia in a 4-year-old girl with profound left SNHL. Axial CT image shows absence of the left cochlea and vestibular aqueduct. The left vestibule and lateral semicircular canal are dysplastic.

Fig 9. Before vs. after surgical reconstruction

Preoperative photos with three-dimensional computed tomography. Patient has malar hypoplasia with complete absence of zygomatic arch and malar prominence, hypoplastic lateral orbital wall, and inferior orbital rim. Patient also has retromicrognathia with anterior open bite.

Guo Y, Lopez J, Yang R, Macmillan A, Dorafshar A. The Use of Virtual Surgical Planning in Total Facial Skeletal Reconstruction of Treacher Collins Syndrome: A Case Report. *Craniomaxillofacial Trauma & Reconstruction*. 2017;11(03):230-237. doi:10.1055/s-0037-1604424.

References

1. Trainor, Paul A, Dixon, Jill & Dixon Michael J. Treacher Collins Syndrome: Etiology, Pathogenesis and Prevention. European Journal of Human Genetics. 2008; 3: 275-283
2. Richard Van Gijn, Daniel, Tucker, Abigail S, Cobourne, Martyn T. Craniofacial Development: Current Concepts in the Molecular Basis of Treacher Collins Syndrome. British Journal of Oral and Maxillofacial Surgery. October 2012; 384-38
3. Ma, Xiaoyang (MD), Xie, Fang (MD), Zhang, Chao (MD), Xu, Jiajie (MD), Lu, Jianjian (MD), Teng, Li (MD). Correlation Between Mandible and External Ear in Patients with Treacher Collins Syndrome. Mutaz B. Habal. 2019; 30: 975-979
4. Huston Katsanis, Sara (MS), Wang Jabs, Ethylin (MD). Treacher Collins Syndrome. Gene Reviews. September 27, 2018
5. Anderson, Peter J, David J, David, Thompson, James T. Treacher Collins Syndrome: Protocol Management From Birth to Maturity. The Journal of Craniofacial Surgery. November 2009; 2028-2035
6. Luquetti, Daniela V. (MD, PhD), Brajcich, Michelle R. (BS), Stock, Nicola M. (MSC, PhD), Heike, Carne L. (MD, MS), Johns, Alexo L. (PhD, ABPP). Healthcare and Psychosocial Experiences of Individuals with Craniofacial Microsomia: Patient and caregivers Perspective. HHS Public Access. April 2018; 10: 164-175
7. Kubo, Sayo, Horinouchi, Takashi, Kinoshita, Masahiro, Yoshizato, Toshyaki, Kozumam Yutaka, Shinaguwa, Takaaki, Ushijima, Kimio. Visual Diagnosis in Utero: Prenatal Diagnosis of Treacher Collins Syndrome using a 3D/4D Ultrasonography. Taiwanese Journal of Obstetrics and Gynecology. July 2019; 58: 566-569
8. Krakow, Debra. Acrofacila Dystosis. Elsevier Clinical Key. 2019; 58:288-291
9. Joshi, Varsha M, Kishore, G. Ravi, Kumar, E.C. Vinay, Navelkar, Shantanu K, Reddy, K. Jitender. CT and MR Imaging of the Inner Ear and Brain in Children with Congenital Sensorineural Hearing Loss. RadioGraphics. May 5, 2012; 32: 685-697
10. Bhabad, Sudeep, Byrd, Sharon, Sharbidre, Kedar, Nagarajan, Murali. MR Imaging of the Fetal Face: Comprehensive Review. RSNA Radiographs. April 13. 2018: 38(3); 962-978
11. Guo, Yifan, Lopez, Joseph, Yang, Robin, Macmillan, Alexandra, Dorafshar, Amir H. The Use of VirtualSurgical Planning in Total Facial Skeletal Reconstruction of Treacher Collins Syndrome: A Case Report. Craniomaxillofacial Trauma Reconstruction. July 21, 2017; 11 (3): 230-237
12. Department of Health & Human Services. Treacher Collins syndrome. Better Health Channel. https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/treacher-collins-syndrome. Published August 30, 2013. Accessed November 25, 2019.
13. Nguyen, P.D, Caro, M.C, Smith, DM, Tompson B, Forrest, C.R, Philips, J.H. Long-Term Orthognathic Surgical Outcomes in Treacher Collins Patient. Journal of Plastic, Reconstruction, and Aesthetic Surgery. June 2015; 69: 402-408