Doctor should I be worried? Recognizing common and uncommon birthmarks

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Conflicts of interest:

- None

Learning objectives

- Recognize common and less common congenital skin lesions in the outpatient setting
  - RED Vascular lesions: capillary malformations, hemangiomas, vascular tumors
  - BROWN Pigmented lesions: congenital nevi
  - BLUE dermal melanoyctosis
  - YELLOW/TAN Benign hamartomas: nevus sebaceous, connective tissue nevi
  - Developmental anomalies: aplasia cutis, hair collar sign

- Identify those congenital skin lesions that require urgent referral and additional investigations

Red birthmarks

Classification of vascular anomalies

- Incorrect nomenclature→ *misunderstanding* between colleagues and with patients
- Incorrect nomenclature→ *misdiagnosis*
- Accurate diagnosis is crucial for appropriate evaluation and management
- Classification serves as a guide for clinicians

Archaic terms

- “Strawberry hemangioma”
- “Cavernous hemangioma”
- “Capillary hemangioma”
- Historically speaking “hemangioma” has been used for vascular tumors and malformations

ISSVA classification of vascular tumors ©

Benign vascular tumors
Infantile hemangioma / Hemangioma of infancy — see details
Congenital hemangioma
Rapidly involuting (RICH) *
Non-involuting (NICH)
Partially involuting (PICH)
Tufted angioma * °
Spindle-cell hemangioma
Epithelioid hemangioma
Pyogenic granuloma (aka lobular capillary hemangioma)
Others
Locally aggressive or borderline vascular tumors
Kaposiform hemangioendothelioma * °
Retiform hemangioendothelioma
Papillary intralymphatic angioendothelioma (PILA), Dabska tumor
Composite hemangioendothelioma
Kaposi sarcoma
Others
Malignant vascular tumors
Angiosarcoma
Epithelioid hemangioendothelioma
Others

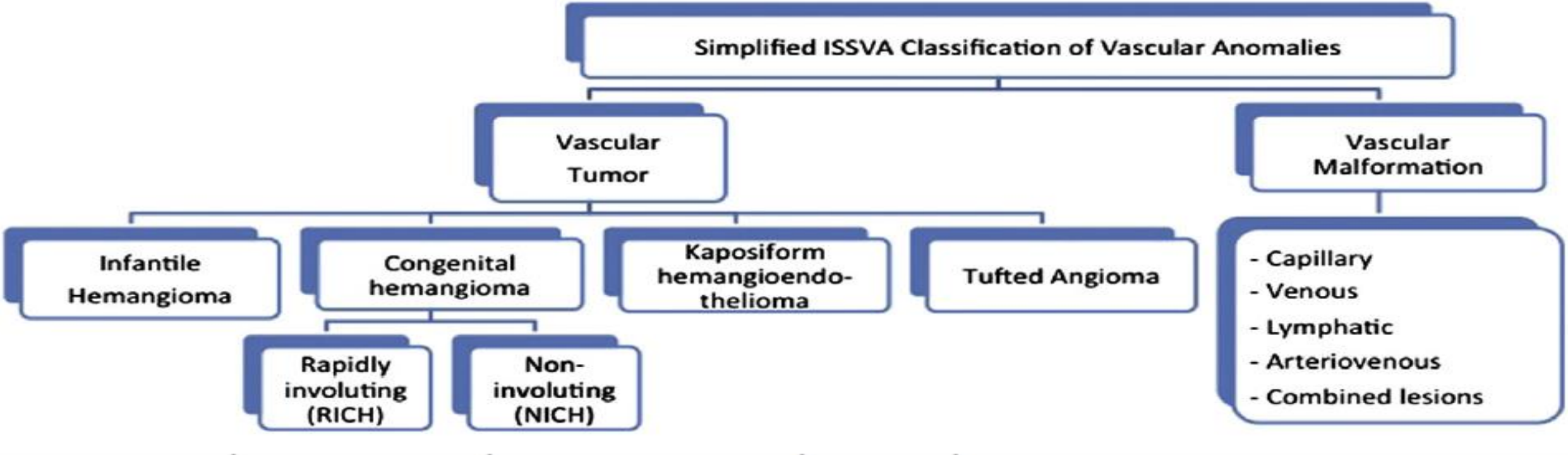
* some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

° many experts believe that these are part of a spectrum rather than distinct entities

N.B. reactive proliferative vascular lesions are listed with benign tumors

Wassef M et al. Pediatr 2015

A simpler version



Puttgen KB. Pediatr Clin N Am. 2014

Infantile hemangiomas (IH): classic vascular “tumor”

- 4-10% of infants, head and neck
- Most common soft tissue tumor of infancy
- Present first few weeks of life
- Proliferation of benign endothelial cells
- Initial rapid growth followed by slow involution

Infantile hemangiomas: risk factors

- **Low birth weight infants (exclusive of GA)**
- Females (~2:1)
- White (non-Hispanic) race
- Pre-term infants
- Multiple gestation pregnancy
- Other: advanced maternal age, placenta previa, preeclampsia, CVS, antenatal vaginal bleeding

Anatomy of IH: depth

- Superficial: bright red, thin, firm or spongy
- Deep: firm, compressible, blue nodules
- Mixed: 25-30% (most)

Depth can help predict concern for deformity and residua!

Anatomy of IH: distribution/outline

- Focal=single focal point, solitary nodule
- Segmental=occupy subunit or broad segment
- Multifocal=small, monomorphic, multiple
- Indeterminate (more “geographic”)

This provides valuable prognostic information about associated complications/conditions and need for treatment.

Natural history of an IH

- Nascent phase: pallor, ecchymotic macules, & telangiectatic patch
- Start proliferative phase: 2-4 wks of life
- Most rapid growth occurs between *5.5-7.5 wks*
  - 80% of max size between 3-5 months of age
  - Max size by 9 months and up to 12 months
- Deeper hemangiomas start later and grow later

Tollefson M and Frieden IJ. Pediatr 2012
Chang LC et al. Pediatr 2008
Brandling-Bennett HA et al. Arch Dermatol 2008

Natural history of an IH

- Proliferation period→ plateau→ involution
- Involution occurs over several years (1-4 yrs)
- RED->PURPLE->GREYISH with involution
- Loses turgor, becomes soft, smaller, lighter
- Alters shape with fibrofatty residuum

Hemangioma complications

- Most: benign course, anticipatory guidance
- ~10%-12% are complex and require a referral
  - Ulceration
  - Obstruction (eye, airway, auditory canal)
  - Cardiac compromise
  - Liver compromise
  - Disfigurement

Haggstrom AN et al. Pediatr. 2006

IH: when to refer

1. Risk of ulceration or currently ulcerated
   - Lip, perioral, diaper area, other folds, ear

2. Risk of functional impairment
   - Eye occlusion, difficulty feeding, airway, auditory

3. Risk of association of other syndromes/ comorbidities
   - PHACE, LUMBAR, hepatic hemangiomas

4. Risk of permanent disfigurement/scarring
   - Large facial IH, lip, nasal tip, ear, ulceration

Table 3
Anatomic locations of IH associated with increased morbidity

High-Risk IH Presentations	
Large, facial segmental	PHACE
Segment 3 (mandibular or beard area)	Airway IH, PHACE, risk of coarctation of the aorta
Segment 1 and 4 (frontotemporal and frontonasal)	Risk of cerebrovascular anomalies, structural brain abnormalities
Nasal tip, ear, large facial	Disfigurement, destruction of anatomic landmarks, scarring
Lip, perioral	Ulceration, disfigurement, feeding difficulties
Periorbital or retrobulbar	Ocular axis occlusion, astigmatism, amblyopia, tear duct obstruction
Lumbosacral	LUMBAR syndrome, tethered cord, genitourinary anomalies
Perineal, axilla, neck, perioral	Ulceration
Multifocal	Visceral involvement (liver, gastrointestinal tract)
Hepatic	Congestive heart failure, consumptive hypothyroidism

Puttgen KB. Pediatr Clin N Am. 2014

IH and ulceration

- Most frequent complication (up to 25% referrals)
- 1st 4 months highest risk period
- Graying or white coloration
- Risk in areas exposed to friction/moisture
- Lip, diaper area, neck, axillae
- Causes significant pain
- Results in scarring, rare bleeding

IH and disfigurement

- Critical sites: nasal tip, lip, ear, large facial

- Concept of “slope”*
  - Consider height (“step-off”) and volume
  - Minimal slope =less risk of residuum
  - Steep slope=higher risk of abnormal tissue

- Residuum- scarring, wrinkling, fibrofatty tissue, coloration/telangiectasias

*Holland KE and Drolet BA. Dermatol Clin 2013

IH and functional impairment

- Periocular-cause visual axis occlusion, astigmatism, amblyopia, tear duct obstruction
- Mandibular location or “beard area”—
  - Risk of airway compromise due to subglottic IH
- Ear-risk of obstruction of auditory canal
- Lip-feeding difficulties, poor weight gain

IH & risk of systemic complications: *diffuse neonatal hemangiomatosis*

- Multiple, often small, monomorphic IHs
  - ≥ 5-100's
  - Refer and screen with 5 or more
- Liver involvement most common
  - Screening abdominal ultrasound
- Association with multifocal and diffuse IH of liver

IH & risk of systemic complications: *diffuse neonatal hemangiomatosis*

- Mutifocal IH of liver—often asymptomatic
  - Follow same life cycle as cutaneous IH
  - Can cause high-output cardiac failure, hypothyroidism

- Diffuse IH of liver-significant morbidity
  - Abdominal compartment syndrome
  - Respiratory/cardiac compromise
  - Profound hypothyroidism (MR and cardiac risk)

PHACE(S): complications of segmental IH

- **P**osterior fossa malformations
- **H**emangioma (segmental)
- **A**rterial anomalies
- **C**ardiac anomalies and aortic **C**oarctation
- **E**ye abnormalities
- **S**ternal clefting and **S**upraumbilical raphe

Metry D et al Pediatr 2009

TABLE 2 Diagnostic Criteria: PHACE Syndrome

PHACE Syndrome		
Facial Hemangioma >5 cm in diameter PLUS 1 Major Criteria OR 2 Minor Criteria		
Possible PHACE Syndrome		
Facial Hemangioma >5 cm in diameter PLUS 1 Minor Criteria	Hemangioma of the Neck or Upper Torso PLUS 1 Major Criteria OR 2 Minor Criteria	No Hemangioma PLUS 2 Major Criteria
Organ System	**Major Criteria**	**Minor Criteria**
Cerebrovascular	Anomaly of major cerebral arteries Dysplasia[a] of the large cerebral arteries[b] Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate to severe hypoplasia of the large cerebral arteries Aberrant origin or course of the large cerebral arteries[b] Persistent trigeminal artery Saccular aneurysms of any cerebral arteries	Persistent embryonic artery other than trigeminal artery Proatlantal intersegmental artery (types 1 and 2) Primitive hypoglossal artery Primitive otic artery[c]
Structural brain	Posterior fossa anomaly Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia	Enhancing extra-axial lesion with features consistent with intracranial hemangioma[c] Midline anomaly[d] Neuronal migration disorder[e]
Cardiovascular	Aortic arch anomaly Coarctation of aorta Dysplasia[a] Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch (double aortic arch)
Ocular	Posterior segment abnormality Persistent fetal vasculature (persistent hyperplastic primary vitreous) Retinal vascular anomalies Morning Glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma Coloboma	Anterior segment abnormality Sclerocornea Cataract Coloboma Microphthalmia
Ventral or midline	Sternal Defect Sternal cleft Supraumbilical raphe Sternal defects	Hypopituitarism Ectopic thyroid

[a] Includes kinking, looping, tortuosity, and/or dolichoectasia.
[b] Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
[c] See Structural Brain Anomalies section for discussion.
[d] Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.
[e] Polymicrogyria, cortical dysplasia, or gray matter heterotopia.

Characteristic segmental facial IH (>5cm) + at least 1 major or 2 minor criteria

Metry D et al Pediatr 2009

PHACE(S) syndrome

- Neurocutaneous syndrome
- Female 90% > Male, 8-9:1 ratio
- Singleton birth, term, normal weight
- Cerebrovascular and cardiovascular anomalies most common-IMAGING
- Few cases of endocrinopathies
- Almost 1/3 of large, segmental IH*

Metry DW et al. Am J Med Genet A 2006

Screening for PHACE(S)

- Echocardiogram
- MRI/MRA brain and neck (great vessels)
- Eye examination

(often done in hospital to expedite testing and start therapy under observation if needed)

Lumbosacral/pelvic IH & systemic associations

- LUMBAR/PELVIS/SACRAL syndrome
- Look for other skin findings (lipomas, skin tags)
- Spinal dysraphism association
- Various GU anomalies (renal, bladder, anus)
- IH often flat & telangiectatic, large/segmental, extensive—BE SUSPICIOUS
- Can be neurologically asymptomatic at birth

PELVIS Syndrome*

- **P**erineal hemangioma, **E**xternal genitalia malformations, **L**ipomyelomeningocele, **V**esicorenal abnormalities, **I**mperforate anus, **S**kin tags

- Look for anogenital, spine, renal, urinary tract abnormalities with imaging

*Girard C et al. Arch Dermatol. 2006

SACRAL Syndrome*

- **S**pinal dysraphism, **A**nogenital anomalies, **C**utaneous anomalies, **R**enal and urologic anomalies, **A**ngioma of **L**umbosacral area
- Hemangiomas in perineal area
- Superficial hemangiomas likely complicated by ulceration and developmental anomalies

*Stockman A et al. Dermatol 2007

LUMBAR syndrome*

- Greatest # of cases
- Lower body IH + regional congenital anomalies
- Lipoma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial & renal anomalies

*Iacobas I et al. J Pediatr. 2010

Screening for segmental lower body IH

- Infants < 3 months
  - Screening US of spine, abdomen, pelvis
- Infants > 3 months
  - MRI of spine, US/MRI screening of other affected areas based on exam/ROS

Historical Treatments for IH

- Oral corticosteroids—gold standard (3mg/kg)
- Topical corticosteroids for localized lesions
- Intralesional triamcinolone (Kenalog)
- Treatment resistant:
  - Vincristine
  - Alpha-interferons (spastic diplegia)
  - Cyclophosphamide
  - Surgical excision

Newer treatments for IHs

- Oral beta-blockers-propranolol→ new standard
- Topical beta-blockers-timolol

Propranolol-how does it work?

- Proposed mechanism of action:
  - Rapid vasoconstriction (color change in 1-2 days)
  - Inhibition of angiogenesis
  - Hastening induction of apoptosis (earlier regression)

Propranolol-safety and efficacy

- Multi-center, double blinded, randomized, placebo controlled phase II-III trial*
- Pediatric-specific oral solution
- Infants 1-5 m with growing IH, needing tx
- 456 infants received treatment
  - Best efficacy: 3 mg/kg/day dosing X 6 months
  - 60% vs. placebo 4% (P<0.001)
  - 88% showed improvement at 5 wks
  - Infrequent AEs in propranolol group

*Leaute-Labreze C et al. N Eng J Med. 2015

Topical timolol and IH

- Alternative for smaller, cosmetically sensitive IH
- Can be used as adjunct to systemic therapy or after tapering off systemic therapy
- 1-2 drops of gel-forming solution BID or TID
- Reportedly safe in small case series
- Local side effects: irritation, allergy

Wound care for ulceration

- Barriers: zinc oxide, petrolatum frequently
- Hydrocolloid dressings or vaseline gauze
- Topical or oral antibiotics for infection

Congenital hemangiomas

- Present in full form at birth-no growth phase

- *Noninvoluting (NICH)*
  - Round to ovoid, pink to purple, prominent telangiectasias and rim of pallor
  - Grow proportionately
  - Glut-1 negative

- *Rapidly involuting (RICH)*
  - May appear like RICH or typical IH
  - Most resolve over 1st 12 months
  - Glut-1 negative

Kaposiform hemangioendothelioma- aggressive vascular tumor

Vascular malformations

ISSVA classification for vascular anomalies ©

(Approved at the 20th ISSVA Workshop, Melbourne, April 2014)

Overview table

Vascular anomalies				
Vascular tumors	Vascular malformations			
	Simple	Combined °	of major named vessels	associated with other anomalies
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

° defined as two or more vascular malformations found in one lesion

* high-flow lesions

N.B. The classification tables do not list exhaustively all known vascular anomalies. Some rare "dermatologic" vascular anomalies will be found in dermatology textbooks.

The tumor or malformation nature or precise classification of some lesions is still unclear. These lesions appear in a separate provisional list.

Wassef M et al. Pediatr 2015

Vascular malformations

- Congenital anomalies, usually visible at birth
- Dysplastic vessels withOUT cellular proliferation
- Grow with child, often accelerated in puberty
- May expand with hormones, trauma, surgical intervention
- NO spontaneous regression
- Mainly classified by vessel type, combination

Capillary malformations (PWS)

Can thicken and darken with time

Soft tissue and/or bony overgrowth

Sturge-Weber Syndrome (SWS)

- Somatic activating mutation in **GNAQ^**
- Facial PWS-*no longer trigeminal patterns*
  - Hemifacial, midline, temporal, nasal area*
  - Reflects mosaic distribution
- Leptomeningeal angiomatosis (CT/MRI)
  - Seizures usually by age 2, often severe
  - Developmental/cognitive delay
  - Headaches, emotional/behavioral issues
- Ocular involvement (60% glaucoma)

^Nakashima M et al. J Hum Genet 2014

*Dutkiewicz AS et al. J Am Acad Dermatol. 2015

Screening for SWS*

- No evidence that MRI screening in presymptomatic phase results in better neurodevelopmental outcomes
- Utility of EEG screening is also not established
- Neurodevelopmental outcomes depend on urgent recognition of neurologic red flags and control of seizures
- Know higher risk PWS areas—forehead and frontonasal

*Zallman M et al. Pediatr Dermatol 2017

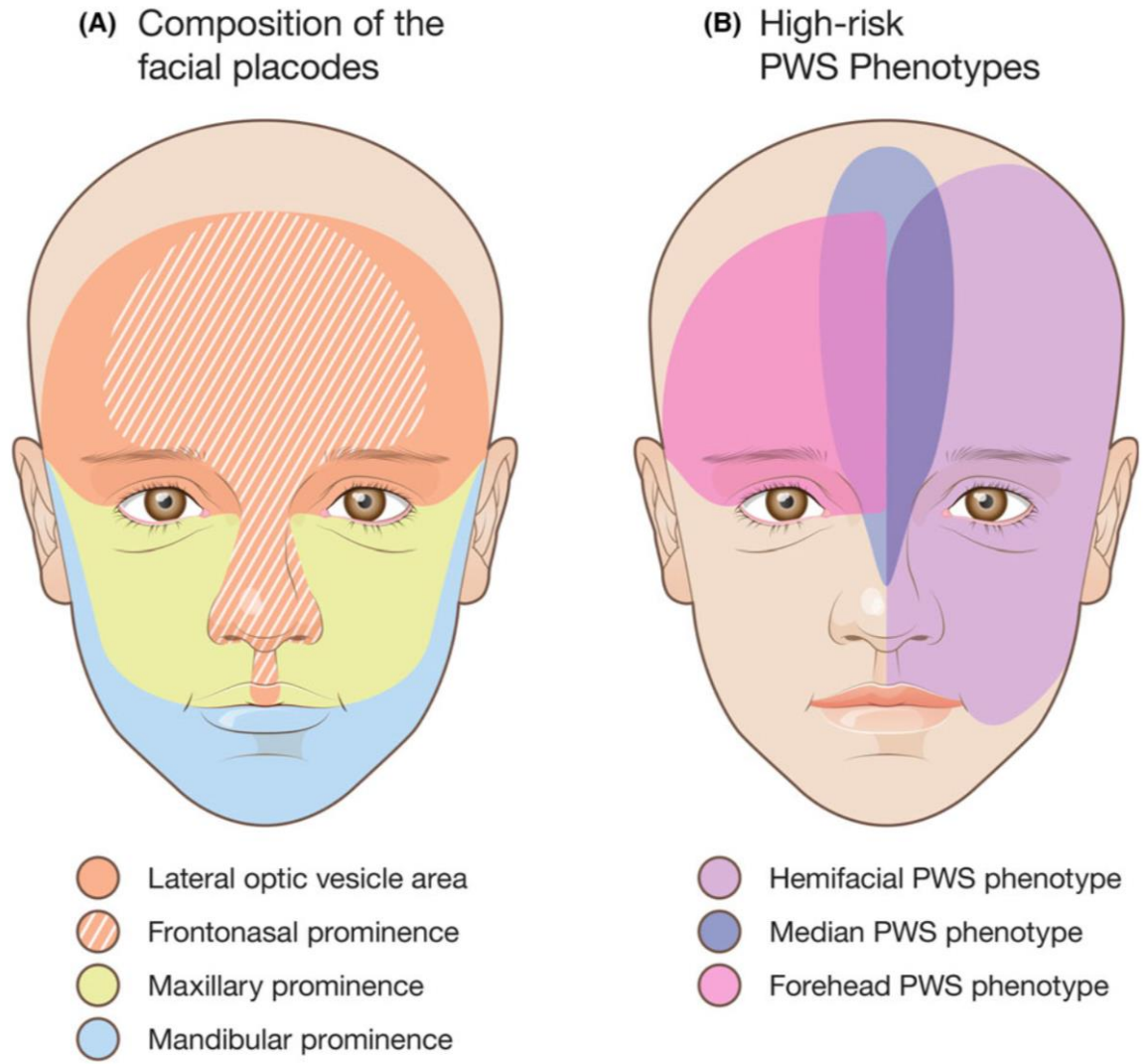


FIGURE 1 (A and B) Port-wine stain phenotypes conferring the highest risk of Sturge-Weber syndrome and their relationship to embryonic prominences

*Zallman M et al. Pediatr Dermatol 2017

Port wine stains-treatment

- Pulsed dye laser is gold standard
  - Consider timing of treatment and risk of GA
- Adjuvant therapy with topical sirolimus

Port wine stains-when to refer

- Early in life to evaluate risk of systemic complications/associated syndromes
  - Refer to ophthalmology
  - Refer patients with forehead, hemifacial (higher risk areas-FRONTONASAL) involvment to neurology
  - Refer patients with neurologic symptoms or concerns to neurology

- Early in life (before 6 months) so that treatment of facial PWS can be discussed
  - Treatment with pulsed dye laser is gold standard
  - Risks of general anesthesia must be discussed (smart tots)

Resources for vascular birthmarks

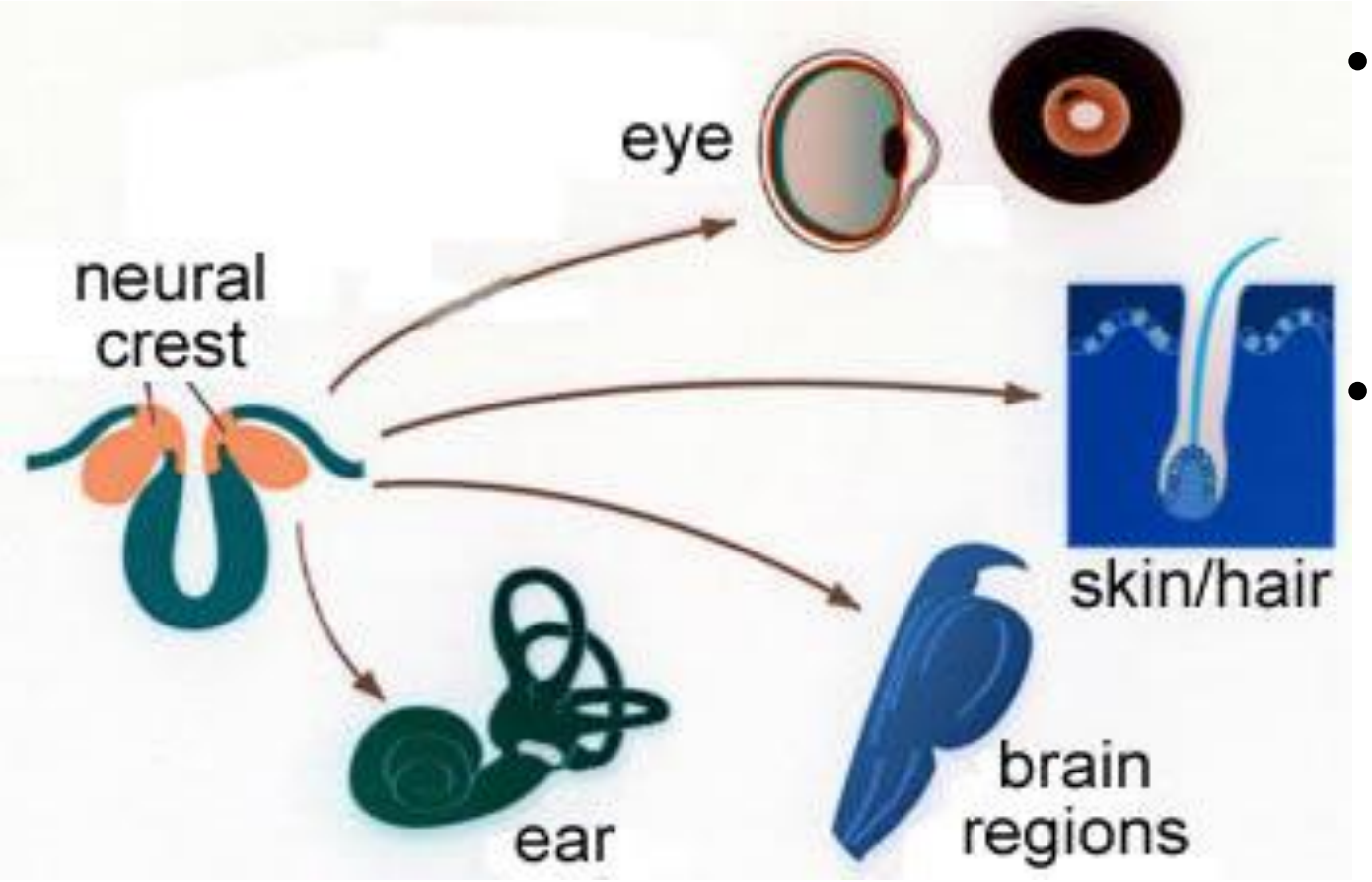
- sturge-weber.org
- phacesyndromecommunity.org
- ISSVA issva.org
- pedsderm.net
- birthmark.org

Brown birthmarks

Congenital melanocytic nevi (CMN): definition

- Hamartomatous proliferations of neuroectoderm
- Melanocytes, nevus cells and neural elements
- Apparent at birth, or first few days/weeks of life
- Determined *in utero*
- Mosaic, post-zygotic mutations in *NRAS/BRAF*

Neural crest and melanocytes



- Melanocytes that arrest their development can become clusters/nevi along the path
- NCM may be marker for abnormal neuronal migration

http://www.madsci.org/posts/archives/2004-01/1073579182.Me.r.html

Prevalence of CMN

- Overall 1-6% of live births

- Large/giant CMN 1:20,000-1:500,000 births

Are all CMN created equal?
Are the risks the same?

CMN historical classification by size

Small

<1.5 cm final size

Medium

1.5-20 cm final size

Large

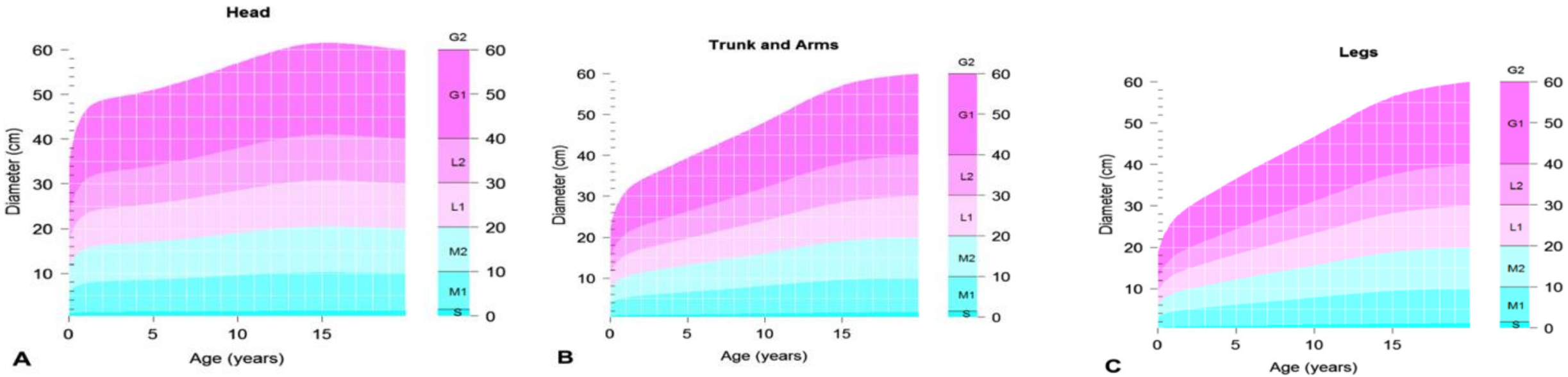
>20 cm final adult size
≥12 cm on the face/scalp of newborn
≥7 cm on the trunk/arms of newborn
≥6 cm on the legs of newborn

Head enlarges by X 2.8
Trunk and arms by X 8
Legs by X 12

Size	Color	Rugousity	Nodules	Hypertrichosis
Based on estimated adult size (PAS)	**Heterogeneity**	**Surface texture**	**Dermal and sub Q**	**“Hairiness”**
Small - <1.5 cm **Medium (M1)** **1.5-10 cm** **Medium (M2)** **10-20 cm** **Large (L1)** **20-30 cm** **Large (L2)** **30-40 cm** **Giant (G1)** **40-60 cm** **Giant (G2)** **60 cm** **Multiple (MCMN)** **3 or more**	None (C0) moderate (C1) Marked (C2)	none (R0) moderate (R1) Marked (R2)	None (N0) scattered (N1) Extensive (N2)	None (H0) notable (H1) marked (H2)
Satellites	**CMN Localization**			
S0 (none) S1 (<20) S2 (20-50) S3 (>50)	CMN of head: face, scalp CMN of trunk: neck, shoulder, upper back, middle back, lower back, breast/chest, abdomen, flank, gluteal region, genital region CMN of extremities: upper arm, forearm, hand, thigh, lower leg, foot			

Expert consensus was used to develop a comprehensive classification scheme (Krengel S. et al. JAAD 2012)

Size estimation in adulthood



Krengel S. et al. JAAD 2012

CMN patient approach

- Size of nevus-> calculate PAS
- Categorize based on size, age and location
  - Small, medium, multiple-medium, large, giant
- Note location(s), patterns
- Satellite number (if present)
- Neurologic status, head circumference
  - For multiple CMN or large/giant CMN

Is patient higher risk for NCM, melanoma?

Small and medium CMN

- Common
- Proportional growth during childhood
- Evolve over time-most changes are acceptable!
  - Hypertrichotic
  - Papules/nodules
  - Multiple colors
  - Lighten/darken

Small & medium CMN and melanoma

- Lifetime risk overall ~ < 1%*
- Rare before puberty
- Likely tend to arise superficially (SS type), at leading edge
- Previous studies overestimated risk
  - Pathology based studies (“congenital features”)
  - Many times no congenital history
  - Retrospective, referral bias

*Kinsler 2009, Sahin 1998, Swerdlow; Fernandes 2009

Monitoring of small & medium CMN in childhood

- Baseline skin examination
  - Clinical photographs
  - Dermoscopic patterns noted and photographed
- If stable, proportional growth, return at puberty
- Expect regular follow-up with PCP
- Counsel for concerning changes

Monitoring of small & medium CMN in childhood-when to worry?

- Rapid growth, not proportional
- Abnormal dermoscopic/gross features (especially at the leading edge)
- SXS: pain, itching, ulceration, bleeding
- Any changes concerning for melanoma
- Difficulty monitoring due to location, topography

Prophylactic removal of benign appearing/behaving small and medium CMN to prevent cancer *is no longer warranted.*

Large/giant CMN

Large/giant CMN patient approach

- Size of nevus-> calculate PAS, categorize
- Note location(s) and prominent topographic features
- Number of accompanying CMN
- Palpation of lymph nodes, nevus
- ***Ask about neurologic status, note head circumference, development, behavioral issues***

Accompanying CMN or “Satellite Nevi”

- Present at birth with large/giant CMN
- Multiple congenital nevi
- May continue to increase in number & then stabilize
- Important risk factor for development of complications
- Benign, no real melanoma risk

Variation in L/GCMN

- Dermal/subcutaneous nodules
  - Often in CMN >40 cm PAS
  - Back, buttocks, genitalia
- Multiple or single colors
- Lipomatous, neurotized, fat atrophy
- Hypertrichosis
- Cutis verticis gyrata (scalp)
- Verrucous or rugous appearance
- Lightening and halo phenomenon

Complications in the neonate/infant that may make you worry

Transient erosions

- Due to skin fragility in neonatal period
- Evident at birth-first few days of life
- Heal spontaneously over days to weeks
- Wound care

Giam et al Pediatr Derm 1999
Gonzalez et al JAAD 2003

CMN and proliferative nodules (PN)

- At birth or arise in 1st years of life
- May mimic melanoma, but benign course
  - Rapid growth, atypical histologic features
- Often lead to biopsy, aggressive surgery
- CGH/FISH supports benign behavior*

*Bastian et al Am J Pathol 2002
*Murphy et al JAAD 2008

PNs versus melanoma in CMN*

- PNs more common than melanoma (22 vs 2)
- Multiple lesions seen
- Infrequent ulceration
- Several distinct histologic/molecular patterns
  - Lower mitotic counts than melanomas
  - Whole chromosome copy number aberrations

*Yelamos et al Am J Surg Pathol 2015

When to worry about NCM, melanoma?

Neurocutaneous melanosis (NCM)

- Melanocytic proliferations in leptomeninges and brain parenchyma
- Benign or malignant
- Diffuse or localized
- Associated with CMN
- “Symptomatic” or “asymptomatic”

NCM-how common is it?

- 100++ cases in literature
- Symptomatic patients often present by age 5 y
  - 72% within first 2 years*
- Second peak 2nd/3rd decade
- Overall incidence: 7%** in L/GCMN patients
  - Range 2.5%-18% based on literature

*Kinsler VA. Br J Dermatol 2008.
**Ramaswamy V et al. 2012.

NCM symptoms

- *Seizures*
- Cranial nerve palsies
- Sensorimotor deficits
- Bowel and bladder dysfunction

- *Increased intracranial pressure*
  - Headache
  - Recurrent vomiting
  - Lethargy
  - Photophobia
  - Hydrocephalus

Symptoms may range from mild to severe.

NCM continued

- Symptomatic: 2/3 of high risk patients
- Asymptomatic: 1/3 of high-risk patients
  - Rate of progression to symptoms was 7% over 5 yr^
- Presence of *NRAS* mutations in NCM tissue*

^Foster RD et al. Plast Reconstr Surg 2001
*Salgade CM et al. Pediatr Devel Path. 2015
*Kinsler VA J Invest Dermatol. 2013

Other “neurological involvement”

- Developmental delay & learning disabilities
- Abnormal tone
- Dandy-Walker or Arnold-Chiari malformation
- Lissencephaly
- Corpus callosum agenesis
- CNS tumors: astrocytoma, choroid plexus papilloma, ependymoma, pineal germinoma

NCM risk factors

- *Number of accompanying nevi*
  - Risk 5X higher with >20 satellites*

- Larger SIZE: > 20, 40 cm or more (PAS)

- Posterior midline is confounder, not risk

*Marghoob et al. Arch Dermatol 2004
*Kadonaga and Frieden. JAAD 1991

Evaluation of NCM

- MRI with contrast is best choice

- Who to screen?
  - *Anyone with neurological symptoms*
  - Higher risk patients without symptoms (?)
    - >20 satellite lesions at birth
    - Larger size CMN (>40 cm PAS)
    - *Multiple medium CMN*
- *Recommended by 4-6 months of life*

NCM prognosis

- Symptoms *can* portend a poor prognosis
  - 50% mortality within first 3 years of dx
  - Usually due to melanoma or complication of hydrocephalus, mass effect
- Malignant transformation ~2.3% patients*
- Asymptomatic patients may do better

Significant group of symptomatic NCM patients doing well!

*Hale 2005

Neurological/NCM treatment

- VP shunt for hydrocephalus
- Anti-seizure medications (+mood stabilizers)
- Neurosurgical interventions
  - Removal of tumors and cysts
- Chemotherapy often minimally effective
- Role of NRAS pathway inhibitors evolving*

*Basu D et al. Neuro-Oncol

*Kusters-Vandevelde H et al. Acta Neuropath Com 2014

Spinal complications and L/GCMN

- Midline lumbosacral area
- Can be a sign of spinal dysraphism
- Tethered cord, arachnoid cysts, syringomelia
- Screening ultrasound <3 months age
- Order MRI of spine with brain
- Little information exists on incidence

Symptoms and treatment

- Delayed motor milestones, lower extremity weakness, or toe walking (myelopathy)
- Delay in toilet training
- Back pain
- Treatment of tethered cord: surgical release
- Treatment cord compression (symptomatic): steroids, surgical decompression

Melanoma risk and Large/giant CMN

- *Best estimate is <=5% lifetime risk (2.5%)*
  - Compare to 2% risk in USA (SEER)
  - Older data is biased, retrospective, small sample size, limited follow-up, limited pathology review
- *Associated with larger size (>40, >60 cm PAS)*
- *Association with truncal location controversial (?)*
  - Less likely isolated head/scalp/limbs
  - Not in satellites (physician verified)
  - Most L/GCMN have truncal location

Melanoma and L/GCMN

- ~50% tend to arise in first 5 years of life
- Can develop in older patients
- Cutaneous/extracutaneous sites
  - 25% cases origin unknown
  - 50% cases non-cutaneous
- Many arise deeper in tissues of CMN (2/3)
- Impact of early surgical removal unknown

What to look for/ask?

- Rapidly growing lumps/bumps
  - Can be deep, firm and non-mobile->PALPATE!
- Ulceration (post neonatal period)
- Painful areas
- Rapidly changing areas
- Lymphadenopathy/+ROS

Treatment for melanoma

- Primarily a surgical disease if localized
- Staging work-up by oncologist
- Disseminated disease
  - Chemotherapy (decarbazine, interferon)
    - Little to no benefit
  - Role for targeted therapies:
    - Vermurafenib *(Braf inhibitor)*
    - Ipilimimab *(immune treatment)*
    - MEK-inhibitors *(NRAS mutations)****

Does excision of larger CMN affect the risk of cutaneous melanoma?

- *No clear-cut answer in the literature*
  - Trend toward lower incidence of melanoma in patients whose nevi were excised
  - However, the largest nevi (which have a higher melanoma risk) are more likely to be ‘inoperable’

- *It is usually impossible to remove every nevus cell*
  - Location
  - Extensive size
  - Involvement of deeper structures (muscle, fascia)

Monitoring for L/GCMN

- No guidelines in literature
- Consider parental anxiety, need for support
- Consider complexity/ongoing complications
- My strategy (in stable patient):
  - Frequent visits early in life (Q month-3 months)
  - Every 6 months as toddlers, yearly at school age

Behavioral/psychological impact of larger CMN

- Considerable burden family/child
- Social problems (~30% patients)
- Behavioral (up to 26%) & emotional problems
- Impaired self-image
- Anxiety (risks, procedures)

Refer families to support groups!

Moss AL. Br J Plast Surg 1987
Koot et al. Clin Exp Dermatol 2000
Berg, Lindelof. Pediatr Dermatol 2002

Yellow/tan birthmarks

Nevus sebaceous: about

- Congenital or early lesion, 0.3% infants
- Often solitary, on face or scalp
- Hairless plaque, well-circumscribed
- Waxy orange-yellow color, oval-linear
- Sporadic, post-somatic mutation (KRAS, HRAS)

Nevus sebaceous-natural history

- Growth is proportional over time
- Birth-few months: appears velvety, verrucous, can be thin/flat
- Less prominent after infancy
- Puberty: thicker, verrucous, oily/scaly

Nevus sebaceous: complications

- Large, extensive, multiple-> syndromic form
  - Mutations in HRAS, KRAS, NRAS
- Secondary malignant neoplasms—look for growing nodules, papules or ulceration
- Secondary nonmalignant neoplasms
  - SCAP and trichoblastoma
  - Can look like warty outgrowths

Nevus sebaceous & secondary neoplasms

- 13 year period, 706 patients
- Non-malignant growths were majority
- Malignant tumors 2.5%
  - Basal cell carcinoma 1.1% (8 patients)
  - No cases in childhood, first onset adolescence
- *Refer patients with NS with new growths, symptoms or unexpected changes!*

Idriss and Elston. J Am Acad Dermatol 2014.

Nevus sebaceous-treatment

- Complete surgical excision optional in childhood
  - Timing controversial
  - Consider location, size, cosmetic significance
  - Local versus general anesthesia risk
- Refer to pediatric dermatology to discuss surgery and timing as well as *observation (active nonintervention)*

Aplasia cutis congenita: about

- Congenital defect of skin
  - Localized absence of 1-3 layers
  - Possible extension to bone, underlying dura or meninges
- Commonly on scalp
  - Can involve skin of face, trunk, extremities
- Solitary (70%) > multiple (8-20%)
- Sporadic most common
- Several associations

Aplasia cutis congenita: clinical diagnosis

- Sharply demarcated
- Weeping, granulating
- Oval to circular, ulceration/erosion
- When healed appear as a scar/depression
  - Smooth, hairless scar
- Look for associated ‘hair collar sign’
  - *Form fruste* of a neural tube defect

Aplasia cutis congenita: associations

- Adams-Oliver syndrome, trisomy 13, 4p-syndrome, oculocerebrocutaneous syndrome, EB (any type)
- Teratogens: Methimazole; HSV, VZV
- Cleft lip/palate, eye defects, limb reduction defects, cardiac anomalies, GI tract malformations, OSD, hydrocephalus, seizures, vascular anomalies, fetus papyraceous

Classification of Aplasia Cutis Congenita

Group	Associations
I	Scalp ACC without multiple abnormalities
II	Scalp ACC with limb abnormalities: hypoplastic or absent distal phalanges, syndactyly, club foot, others
III	Scalp ACC with epidermal and sebaceous nevi
IV	ACC overlying embryologic malformations such as gastroschisis, omphalocele, meningomyelocele, and others
V	ACC with fetus papyraceus or placental infarct
VI	ACC associated with epidermolysis bullosa
VII	ACC limited to extremities without epidermolysis bullosa
VIII	ACC due to teratogens such as HSV, VZV, or medications
IX	ACC associated with syndromes of malformation such as Goltz syndrome, trisomy 13, ectodermal dysplasia, and others

Table I. Proposed classification for aplasia cutis congenita

Category	Body area affected	Associated abnormalities	Inheritance
Group 1: scalp ACC without multiple anomalies	Scalp, usually vertex	Cleft lip and palate; tracheoesophageal fistula; double cervix and uterus; patent ductus arteriosus; omphalocele; polycystic kidney; mental retardation; cutis marmorata telangiectatica congenita	Autosomal dominant or sporadic
Group 2: scalp ACC with associated limb abnormalities	Midline scalp	Limb reduction abnormalities; 2-3 syndactyly; clubfoot; nail absence or dystrophy; skin tags on toes; persistent cutis marmorata; encephalocele; woolly hair; hemangioma; heart disease; cryptorchidism; postaxial polydactyly (1 family)	Autosomal dominant
Group 3: Scalp ACC with associated epidermal and organoid nevi	Scalp, may be asymmetric	Corneal opacities; scleral dermoids; eyelid colobomas; psychomotor retardation; seizures	Sporadic
Group 4: ACC overlying embryologic malformations	Abdomen, lumbar skin, scalp; any site	Meningomyeloceles; spinal dysraphia; cranial stenosis; congenital midline porencephaly; leptomeningeal angiomatosis; ectopia of ear; omphalocele; gastroschisis	Depends on underlying condition
Group 5: ACC with associated fetus papyraceus or placental infarcts	Multiple, symmetric areas, often stellate or linear, on scalp, chest, flanks, axillae, and extremities	Single umbilical artery; developmental delay; spastic paralysis; nail dystrophy; clubbed hands and feet; amniotic bands	Sporadic

ACC: Aplasia cutis congenita; EB: epidermolysis bullosa.

TABLE I. *Cont'd*

Category	Body area affected	Associated abnormalities	Inheritance
Group 6: ACC associated with epidermolysis bullosa (EB): Blistering, usually localized, without multiple congenital anomalies	Extremities	Blistering of skin and/or mucous membranes; absent or deformed nails; metatarsus varus; congenital absence of kidney (seen in cases of recessive, dystrophic EB; dominant, dystrophic EB; and EB simplex)	Depends on EB type: may be autosomal dominant or recessive
Widespread skin fragility with congenital anomalies	Large areas on extremities and torso	Pyloric or duodenal atresia; abnormal ears and nose; ureteral stenosis; renal abnormalities; arthrogryposis; amniotic bands; nail dystrophy	Autosomal recessive
Group 7: ACC localized to extremities without blistering	Pretibial areas; dorsal aspects of hands and feet; extensor areas of wrists	None	Autosomal dominant or recessive
Group 8: ACC caused by specific teratogens	Scalp (with methimazole); any area (with varicella and herpes simplex infections)	Imperforate anus (methimazole); signs of intrauterine infection with varicella and herpes simplex infections	Not inherited
Group 9: ACC associated with malformation syndromes	Scalp; any location	Trisomy 13; 4p− syndrome; many ectodermal dysplasias; Johanson-Blizzard syndrome; focal dermal hypoplasia; amniotic band disruption complex; XY gonadal dysgenesis	Varies, depending on specific syndrome

Frieden IJ. J Am Acad Dermatol 1986
Kelly BJ. et al. Pediatr Dermatol 2002

Aplasia cutis congenita: management

- Scalp ACC + congenital anomalies = chromosomal evaluation
- Small isolated superficial lesions heal in with scar
  - General wound care recommended
- Differentiate from other birth injury
- Larger/deeper lesions may need surgery with grafting (prevent thrombosis, meningitis)→plastic surgery

ACC-when & how to investigate

- More than 2 findings--→ REFER
- + Hair collar sign and/or underlying nodule
  - Encephaloceles, meningoceles, heterotopic brain tissue
- MRI is gold standard, CT can identify bony defects
- Other anomalies--consider genetic syndrome

‘Hair collar sign’

- Sign of cranial dysraphism
- Congenital ring of hypertrichosis
- Hair is often denser, darker, coarser
- Encephalocele, meningocele, heterotopic brain tissue may be present
- Hair collar sign + capillary stain + **scalp nodule** is highly suspicious

‘Hair collar sign’ work-up

- Ultrasound as screening test, not definitive (low sensitivity)
- MRI is gold standard
- Subsequent neurosurgery is definitive
- Always image before biopsy/surgery
  - Ensure imaging is performed/read by experienced staff

Blue birthmarks

- Mongolian spot
- Nevus of Ota/Ito
- Blue nevi (congenital/acquired)

Mongolian spots (dermal melanocytosis)

- Flat blue-grey macules/patches
- Lumbosacral, buttocks
- Can be on extremities
- African, Native American, Asian, Hispanic populations
- Present at birth, fade over 1-3 years
- Other locations, multiple, large lesions may persist
- Rare genetic association possibility→REFER
  - Lysosomal storage disease, gangliosidosis, Hunter/Hurler, phakomatoses

Nevus of Ota

- Unilateral, brown/blue/grey patch on face
  - Periorbital, temple, forehead, cheek, nose
  - Scleral involvement (2/3)
  - Rare on palate or bilateral
- Asian/African decent
- Persists, speckled appearance
- Eye exam
- Refer for treatment consideration (laser)