Birthmarks—Concerning or not concerning?
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Objectives
• Describe the morphology of congenital birthmarks
• Differentiate a benign birthmark from one that requires additional management
• Identify how to differentiate birthmarks with similar presentations in order to be able to manage these appropriately

Speaker Introduction
• Dr. Judith O’Haver is currently a practicing nurse practitioner and research scientist in pediatric dermatology at Phoenix Children’s Hospital. She is also an adjunct instructor at University of Arizona and adjunct faculty at Arizona State University in the DNP program. She has been a consulting nursing scientist at Rady Children’s Hospital in San Diego for the past six years. She holds appointments as assistant professor of pediatrics, Mayo Clinic College of Medicine, clinical assistant professor, Department of Child Health, University of Arizona, College of Medicine, Phoenix and assistant clinical professor in the department of pediatrics, Creighton University School of Medicine, Phoenix Regional Campus. She is a retired lieutenant colonel in the United States Air Force Reserves. Dr. O’Haver’s research interests include Intervention research with underserved pediatric populations and their families to promote healthy lifestyle choices with a special focus on children and adolescents with dermatologic conditions and chronic disease.

Disclosures
• I have no conflicts of interest related to this presentation

Thank you
• To Dr. Price for her contributions to this presentation

Case one
• Toddler presents to clinic to establish care
• Hx of congenital melanocytic birthmark
• Over time it has become darker and thicker with more hair
• Does not have eczema except for over the birthmark itself
• Is otherwise healthy but mom is concerned and wonders if it should be removed
Congenital melanocytic nevi (CMN)

- Benign proliferation of melanocytes
- Neural crest in origin

Neural crest and melanocytes

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

Size of nevus calculated bases on age of presentation and diameter to determine projected adult size (PAS)

Update on classification of CMN and implications for practice

- Size (diameter) of the congenital melanocytic nevi (CMN) determines risk for adverse outcomes
  - Small < 1.5 cm
  - Medium 1-1.5-10 cm
  - Medium 2-10-20 cm
  - Large 1-20-30 cm
  - Large 2-30-40 cm
  - Giant 1-40-60 cm
  - Giant 2-60 cm

Additional characteristics

- Number of Satellites
  - Grouped 0, 1-20, >20-50, >50
- Location
- Color heterogeneity
- Surface rugosity
- Hypertrichosis (none, moderate, marked)
- Nodules (none, scattered, extensive)

Genetic mutations

- NRAS mutations Q61 (n=51, 77.3%)
  - giant CMN and NCM patients
  - Higher incidence of hypertrichosis
- BRAF mutations V600E (n=5, 6.9%)
  - Associated with L/G CMN and NCM
  - Dermal and subq nodules
- Small sample size limits generalizability
- No mutations found in these genes (n=10, 15.2%)
- Race may play a role in this
- Nodules in all patients with BRAF and only 16 patients with NRAS
- Increase in satellites corresponded to neurocutaneous melanosis
- Neurocutaneous melanosis (NCM)
  - Risk of NCM is increased with more satellites (more than 20)
  - Leptomeningeal deposits in brain parenchyma
  - Multiple medium CMN without a single lesion is more at risk for NCM
  - Neurologic manifestations generally occur within the first 2 years of life, often related to increased intracranial pressure.
  - Associated structural anomalies of the CNS have been reported in NCM, such as the Dandy-Walker complex.
- CNS melanoma
- Spinal arachnoid cysts (LS region)

- Current discussion continues on value of surgery for these affected areas

Small & medium CMN and melanoma risk
- Yagerman and Marghoob. JAAD 2013
  - Lifetime risk overall < 1%
  - Rare before puberty
  - Likely tend to arise superficially, at leading edge
  - Previous studies overestimated risk
    - Pathology based studies
    - Many times no congenital history
    - Retrospective

Large/giant CMN and complications: melanoma risk
- 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) and numerous CMN
  - Can develop early in life (50% in first 5 years)
  - Melanoma can be cutaneous or extracutaneous

Screening for cutaneous melanoma
- H. Price
  - Rapidly growing lumps/bumps
    - Can be deep, firm and non-mobile—PALPATE!
  - Ulceration (post neonatal period)
  - Painful areas
  - Rapidly changing areas
  - Lymphadenopathy/+ROS

NCM
- Seizures
  - Cralia nerve palsies
  - Sensorimotor deficits
  - Bowel and bladder dysfunction
- Increased intracranial pressure
  - Headache
  - Recurrent vomiting
  - Lethargy
  - Photophobia
  - Hydrocephalus
- Who to do we generally screen?
  - Presents with neurological symptoms
  - Higher risk patients without symptoms: larger sizes, numerous lesions
  - Recommended by 4-6 months of life—THUS NEED TO REFER EARLY

Implications for Care
- Continued surveillance
  - Importance of inspection and photos
  - Importance of estimating adult size correctly as may affect risk
  - Number of satellites or lack of central lesion affects risk
  - MR imaging for symptoms
    - Referral to dermatology and possibly neurology, neurosurgery, ophthalmology, psychology, plastic surgery
  - Unclear as to whether the lesions should be removed
  - More research to come
  - The CMN is often more likely to have AD over the lesion-treat as AD

Symptoms may range from mild to severe.
Case 2

- 3 month old female infant has been sent for consultation for a growing vascular plaque
- Occasionally bleeds and results in ulceration
- Child was born 1 month prematurely

Differential Dx

- Hemangioma
- Port wine stain
- AVM, lymphatic malformation, venous malformation
- Kaposiform hemangioendothelioma
- Pyogenic granuloma
- Soft tissue malignancy

Infantile Hemangiomas (Harter and Mancini, 2019)

- Affects 4-5% of all infants
- More common in females, Caucasians
- Increased incidence
  - Prematurity
  - Low Birth weight
  - Multiple gestation pregnancy
  - Invasive antepartum procedures such as Chorionic villus sampling
  - Advance maternal age
  - Pre-eclampsia
  - Placental abnormities
  - Assistive reproductive technology
What are infantile hemangiomas?

- Most common benign tumor of infancy (~5%)
- Endothelial cell proliferation
- GLUT1 positive
- Typical onset by < 4 weeks of age
- 3 phases
  - Proliferation
  - Plateau
  - Involution

Classification of IH

IH have been classified as one of the benign vascular tumors

- Unique immunohistochemical markers which help to identify them (glucose transporter 1 [Glut-1], Lewis Y antigen, Fcg II receptor [FcgRII], and merosin),
- Classified as superficial, deep and mixed (Combined)
  - sub-classified as focal, multifocal, segmental, and indeterminate

IH TYPES (Anatomy)

- Superficial: bright red, thin, firm or spongy
- Deep: firm, compressible, blue nodules
- Mixed: 25-30% (SUPERFICIAL + DEEP)
- Reticular/abortive/minimal growth

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

Besides infantile hemangiomas also consider these congenital Hemangiomas

- RICH-rapidly involuting congenital hemangioma
- NICH non-involuting congenital hemangioma
- Less common

Problem Patterns and sites of involvement

- Large facial hemangiomas
  - PHACE syndrome
- Beard distribution
  - Mandibular distribution, subglottic lesions
- Lumbosacral
  - Tethered cord
- LUMBAR syndrome
- Periocular
  - Vision threatening
- Multiple-numerous
  - Diffuse neonatal hemangiomatosis, multifocal lymphangiendotheliomatosis (MLT)
Ulceraions

- Barrier products
- Dressings
- Topical antimicrobials
- Pain control
- Laser therapy
- Excision
- Treat the lesion

PHACE Syndrome

- Type of segmental IH
  - Posterior fossa anomaly
  - Hemangiomas
  - Arterial anomalies
  - Cardiovascular anomalies
  - Eye anomalies
  - Omental clefting and/or suprarenal lamellae

LUMBAR (SACRAL, PELVIS) association/syndrome

- Lower body hemangioma
- Urogenital anomalies
- Ulceration
- Myelopathy
- Bony deformities
- Anorectal malformations
- Arterial anomalies
- Renal anomalies

Multifocal IH

- Usually appears at 1-3 weeks of age
- Usually resolves at 1-5 years of age
- Responds to usual systemic therapies
- No associated thrombocytopenia
- In addition to skin, the liver is most commonly affected (52%)
- Rarely GI, spleen, lung
- Segmental IH more commonly have GI bleeding

Impact of Screening on outcomes for Hepatic Hemangiomas

- 3 different type focal, multifocal and diffuse
- Registry study n=213
  - If patients had been screened they were less likely to develop CHF (p<0.001), less likely to develop thyroid disease (p<0.01), less likely to develop abdominal compartment syndrome (27% vs 0).
  - 28% of those that were not screened died and none of the 43 patients screened died
- Multivariable logistic regression analysis confirmed that independent of CHF and disease pattern, screening was a significant predictor of reduced mortality (p=.04)

Indications for imaging

- Hemangiomas on the face > 5 cm to r/o PHACES
- Hemangiomas >5 cm on the back if midline or in the perineal area or if segmental
- MRI of spine if concern for spinal dysraphism
- 5 or more cutaneous hemangiomas-US liver
- Atypical lesions that occur after 6 months
Involution

- Involution occurs beginning at about 1 year of age
- Involution may not result in resolution with normal skin
- Increase risk for scars on glabella, nose, lips and ears and may be indication for earlier intervention

Treatment considerations

- Important to be sure you have the right diagnosis
- Guidelines published in Jan 2019
- Consider potential complications (Harter and Mancini, 2019)
  - Visual or feeding impairment if periocular or perioral
  - Deformity if large or in a sensitive area such as the nasal tip
  - Airway obstruction (beard distribution)
  - CHF multiple hemangiomas or hepatic IH
  - Transient hypothyroidism (hepatic or parotid, PHACES)
  - Bleeding (rare)
  - Psychosocial implications
  - Ulceration

Treatment modalities Menapace et al (2016)

- Watchful waiting
- Systemic beta-blockers (propranolol, topical timolol)
- Systemic corticosteroids, intralesional corticosteroids
- Excisional surgery
- Laser treatment
- Interventional radiology

Changing the playing field

- A case series of 11 pediatric patients (2-6 mos) was published by Léauté-Labrèze as a letter to the editor which described the use of propranolol HCL (non-selective β adrenergic blocking agent) in hemangioma patients (initially to treat heart failure)
- Previous therapies had a higher risk for adverse effects so this letter started a significant change in therapy and propranolol to treat infantile hemangiomas is the standard of care.

Considerations and oral propranolol

- Non-selective beta adrenergic receptor blocker
- Exact mechanism of effect not known
- Approved by the FDA as standard of care treatment
- Side effects
  - lowers heart rate and B/P, rare AV block
  - bronchospasm
  - hypoglycemia
  - sleep issues
  - cool hands and feet
  - GI disturbance

For superficial lesions may consider the use of timolol gel forming soln topically
**Table 3 Anatomic locations of IH associated with increased morbidity**

| High-Risk IH Presentations | Large, facial segmental | PHACE | Segment 4 (mandibular or head area) | Airway IH, PHACE, risk of coarctation of the aorta, Segment 1 and 4 (frontotemporal and occipital) | Risk of cerebrovascular anomalies, structural brain abnormalities | Nasal tip, ear, large facial | Disfigurement, destruction of anatomical landmarks, scarring | Lip, perioral | Ulceration, disfigurement, feeding difficulties | Periorbital or retrobulbar | Ocular axis deviation, astigmatism, amblyopia, tear duct obstruction | Lumboosacral | LUMBAR syndrome, tethered cord, genitourinary anomalies | Perineal, axilla, neck, perioral | Ulceration | Multifocal | Vascular involvement (e.g., gastrointestinal tract) | Hepatitis | Congenital heart failure, consumptive coagulopathy |

**IH: when to refer AND refer EARLY**

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

2. **Risk of functional impairment (or life threatening)**
   - 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

**Vascular malformations (George, Mori & Noufal, 2014)**

- Fast or high flow
  - Arterial malformations
  - Arteriovenous malformations
  - Arteriovenous fistulas

- Slow or low flow
  - Capillary malformations
  - Venous malformations
  - Lymphatic malformations

**Differences between IH and VM**

<table>
<thead>
<tr>
<th>Hemangiomas</th>
<th>Vascular Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>Presursor mark Develops over time</td>
</tr>
<tr>
<td>gender</td>
<td>Female (5:1)</td>
</tr>
<tr>
<td>course</td>
<td>Grows over the first year and then involutes over many years</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>GLUT 1 positive (and other stains)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Watchful waiting Other (will discuss)</td>
</tr>
</tbody>
</table>

**Portwine stain**

- Also called nevus flammeus
- Capillary malformation that may be an isolated birthmark or associated with other syndromes
- Darken and thicken over years but generally in young children are flat
- Generally do not improve over time
- If involve forehead concern for Sturge-Weber syndrome and will need to see ophthalmology and neurology
Epidermal nevus

- Benign Hamartomas
- Usually asymptomatic
- May be noted at birth or early childhood.
- Maybe unilateral or bilateral and more darkly pigmented, may appear warty.


Forms

- Linear following Blaschko’s lines.
- May also appear like acanthosis nigricans as a velvety thickening but as isolated lesion.
- Inflammatory form (inflammatory linear verrucous epidermal nevus) (ILVEN) present as more chronically pruritic and scaling.

When to be concerned

- Lesions should be biopsied to check histologically for epidermolytic hyperkeratosis (EHK) which implies a change to keratin genes which can be transmitted to progeny.
  - 5 types of epidermal nevus syndromes and may include defects in the CNS, eye and musculoskeletal systems.

Treatment

- Challenge to treat.
  - May include destruction therapies, laser ablation, retinoids, topical steroids, surgery as well as others all with varying success.
  - If suspect epidermal nevus syndrome will need biopsy and referral to appropriate specialty to include dermatology, neurology, ophthalmology, plastic surgery.

Case 3

- Newborn female presents to clinic with vesicles on an erythematous base to limbs in a linear distribution.
- Vesicles also appear on trunk but distribution is more of a whorled pattern.
- The child is well appearing.
Differential Diagnosis

- Incontinentia Pigmenti
- Erythema toxicum
- Miliaria crystallina
- Scabies (rare in the first month of life)
- Neonatal herpes (which in this case would be the biggest concern)
  - The vesicles from this are usually clustered, occur in areas of trauma and the child is ill
- Bullous impetigo
- Infantile acropustulosis
- Eosinophilic pustular folliculitis
- Epidermolytic bullous
- Congenital syphilis
- Epidermolytic hyperkeratosis

Incontinentia Pigmenti (Bloch-Sulzberger syndrome)

Spitz, 2005

- This is an X linked dominant disorder that is usually lethal to males
  - Male survivors may also have Klinefelter syndrome
- Presents in a Blashko line distribution which distinguishes it from other newborn rashes
- NEMO gene on Xq28

4 stages

- I-Vesicular
  - May present at birth
  - Appears as blisters or pustules on an erythematous base or erythematous macules and papules in the Blashko line distribution
- II-Verrucous
  - Usually seen about 2-6 weeks of age and consists of warty lesions that are usually red brown and scaly
  - Resolves by 4-6 months

III-Hyperpigmentation

- Usually 3-6 months
  - Linear and whorls and swirls hyperpigmentation that may persist for years along Blaschko lines

IV-Hypopigmentation

- Hypopigmented atrophic streaks (adulthood) may be associated with or without follicular atrophy

Associated features

- May be overlap of stages
- Alopecia, dystrophic nails, pegged/missing teeth
- Multiple ocular issues
- CNS anomalies
- Orthopedic

Diagnosis and Treatment

- Biopsy confirms the diagnosis
- CBC—peripheral eosinophilia during infancy
- Consult ophthalmology and genetics and eventually dental
- Additional evals pending symptoms (neurology, orthopedics)
- Symptomatic treatment as needed for the lesions
  - Topical antibiotics in vesicular stage to open areas to prevent infection
  - Emollients to warty areas
- Prognosis is a normal life span
References


Web references

- issva.org/classification
- https://www.nfed.org/learn/types/incontinentia-pigmenti

Thank you!!

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