Early Diagnosis and Intervention of Vascular Anomalies (Infantile Hemangiomas and Malformations)

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Disclaimer

- Presenter Bernard A. Cohen, MD, FAAP
  - I have no financial disclosures.
  - I am a member of the International Society for the Study of Vascular Anomalies (ISSVA).
  - There is finally a US Food and Drug Administration (FDA)-approved treatment for infantile hemangiomas.
  - I will discuss off-label use of medications for infantile hemangiomas.

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What’s new (and old but relevant) on Infantile Hemangiomas (and other assorted vascular lesions)
Webinar Outline

- Definitions...vascular tumors of infancy
- Pathogenesis, morphology, course
- Management of uncomplicated infantile hemangioma (IH)
- High risk lesions...segmental, PHACES
- New variants you should know
- Rx options for complicated lesions
First a little quiz...

Hemangioma (A) or malformation (B)?
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A Capillary
B Venous
C Lymphatic
D Arteriovenous
E Combined
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Vascular Tumor vs Vascular Malformation

- Vascular anomalies
  - Vascular tumor
    - Infantile hemangioma
    - Kaposiform hemangioendothelioma
    - Tufted angioma and other tumors
  - Vascular malformation
    - Venous, arterial, AVM, capillary, lymphatic

Definitions: Distinguish from Vascular Malformations

**Infantile Hemangioma**
- Usually not present at birth
- Dynamic
- Regressing
- Proliferative

**Vascular Malformation**
- Present at birth
- Static
- Persistent
- Non-proliferative
Infantile Hemangiomas

- **Incidence**: 8–10% at 2 months (<1% of newborns)
- **Family history**: 8–10%
- **Location**
  - Head, neck: 50%
  - Trunk: 30%
  - Extremities: 20%

(Data from multiple observational studies over last 5 decades.)
Newer Epidemiologic Data

- Female predominance: 2.4:1
  - Previously published: 1.4–4:1
- White, non-Hispanic
- Twins – usually only 1 affected
- Mothers – increased age, placental abnormalities
- Prematurity
- **Low birth weight**
  - #1 risk factor for IH
  - For every 500-g decrease in birth weight, risk of IH increases 25%
  - Hemangiomas in 1 in 4 infants <1,000 g

Pathogenesis

- Dysregulation of angiogenesis
- Imbalance of pro- and anti-angiogenic factors
- Dysregulation of endothelial cell proliferation

VEGF & bFGF ↑ in serum during proliferative phase and ↓ in involuting phase
Infantile Hemangiomas: Morphology

- Superficial
- Deep (not to be confused with venous malformation)
- Most both
Superficial
Subcutaneous
Combined superficial/deep
Hemangioma Patterns

- Focal (localized)
- Multifocal (multiple localized)
- Segmental
Infantile Hemangioma

- **Size**  1 mm–20 cm

- **Number**  85% 1 lesion
  Rare >100
**Infantile Hemangioma: Early Course**

- Early, pale macule, central telangiectasia
- Growth phase (510 patients [Lampe, 1965])
  - 50% until 6 months
  - 50% until 12 months
  - 80–90% < X 2
  - 5% X 3
  - 2% X 4
- 85% peak by 3 months (most rapid growth 2–7 weeks)
- Certain lesions with prolonged growth phase

Uncomplicated Infantile Hemangioma: Prognosis

- (Generally) independent of
  - Size
  - Number
  - Sex
  - Location
  - Growth
  - Prematurity
  - Presence of deep component

- But focal vs multifocal vs segmental is important
Uncomplicated Infantile Hemangioma: Management

- Complete physical examination
- Close observation
- Photodocumentation (website)
- Avoidance of aggressive therapy
- Parent counseling
Infantile Hemangiomas: Complications

- Involvement of vital structures
  - Airway
  - Eye
  - Urethra, anus
  - Gastrointestinal (GI) tract
- Infection/ulceration (local, sepsis)
- Pain
- Cardiac failure (liver lesions, and large lesions anywhere)
- Body image
- Special patterns (eg, segmental)
Risk of Complications

- Data from 1,058 cohort

- Increased risk with large size, facial location, segmental morphology for short term outcome = complication (24%) and treatment (38%)

- Rx for ulcer (23%), eye (6.9%), airway (1.8%), auditory canal (1.1%), cardiac (0.4%)
Labial hemangioma
Buttock hemangioma
Disfiguring

Eye/airway involvement
## High Risk Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Associated Conditions/Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large, facial segmental</td>
<td>PHACES</td>
</tr>
<tr>
<td>Nasal tip, ear, large facial</td>
<td>Disfigurement, scarring</td>
</tr>
<tr>
<td>Periorbital or retrobulbar</td>
<td>Ocular axis occlusion, astigmatism, amblyopia, tear duct obstruction</td>
</tr>
<tr>
<td>Segmental “beard area” (S3)</td>
<td>Airway IH</td>
</tr>
<tr>
<td>Perioral</td>
<td>Ulceration, disfigurement, feeding difficulties</td>
</tr>
<tr>
<td>Segmental over lumbosacral spine</td>
<td>Tethered cord, genitourinary anomalies, PELVIS</td>
</tr>
<tr>
<td>Perineal, axilla, neck, perioral</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Anogenital area</td>
<td>Caudal regression syndromes (PELVIS, SACRAL, LUMBAR)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>Visceral involvement (liver, GI)</td>
</tr>
</tbody>
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Lumbosacral Hemangiomas

- Spinal dysraphism
- Anomalies of bony and soft tissue cord
- Consider ultrasound before 6 months
- Magnetic resonance study after 6 months—requires sedation
- Many subsets of segmental hemangiomas
Complicated Presentations Cervicofacial (Beard IH)

- 63% association with upper airway hemangiomas
- 33% of airway hemangiomas with cutaneous hemangioma
- Stridor, cough, cyanosis, hoarseness
- ~40% with airway hemangioma will require tracheostomy

Segmental/field/non-localized hemangioma
PHACES

- Posterior fossa vascular malformations
- Hemangiomas
- Arterial anomalies
- Coarctation of aorta, cardiac defects
- Eye abnormalities (microphthalmia, optic nerve hypoplasia, cataracts, increased retinal vascularity)
- Sternal clefting +/- supraumbilical raphe

Complicated Presentations

Facial Segmental

- Higher correlation with structural cerebral and cerebrovascular anomalies
- Higher correlation with ventral and cardiac defects, including coarctation

PHACE(S)

- Female-to-male ratio: 9:1
- >20% infants with facial IH: segmental hemangioma
  - 2% of all hemangiomas
  - ? More common than Sturge-Weber
- Diagnosis with hemangioma and 1 extracutaneous finding

Another Segmental Hemangioma
Segmental Hemangiomas

- Complications
- Greater need for treatment
- Worse outcome
- Associated structural anomalies
- Segmental lesions: risk for visceral hemangiomas
  - Liver > GI, brain, mediastinum
  - 25% mortality

Infantile Hemangiomas: Risk of Slow Regression or Scarring

- Parotid
- Lip
- Tip of nose
Infantile Hemangioma Variants

- RICH (rapidly involuting)
- NICH (non-involuting)
- PICH (partially involuting)
- Features of IH, vascular malformations
- Glut-1 negative
Rapidly Involuting Congenital Hemangioma
RICH

- Develop in utero
- No postnatal growth
- 50% gone by 7 months
- Glut-1 negative – not = IH
- Some histologic features of IH
Non-involuting Congenital Hemangioma
NICU

- Develop in utero
- May grow somewhat
- Glut-1 negative – not = IH
- High flow = IH
- Persistent
- Surgical excision – not recurrence
Another Variant

Minimal Growth Infantile Hemangioma

Hemangiomas: Rx

- **Systemic corticosteroids**
  - Edgerton (1967)
  - Esterly (1968)
  - Brown (1972)
  - Feingold (1978)

- **Intralesional steroids**
  - Central retinal artery occlusion
  - Eyelid necrosis
  - Atrophy, hematoma
  - Eyelid depigmentation
  - Growth delay
Systemic Steroids: Other Considerations

- Hypertension
  - Particularly with high doses
  - Monitoring?
  - Long-term risk

- Growth
  - Dose, length of Rx
  - Catch up growth

- Behavioral changes/central nervous system development

- Adrenal suppression

- Fungal infection

- Other risks...
Newly approved stuff...
TO THE EDITOR: Despite their self-limited course, infantile capillary hemangiomas can impair vital or sensory functions or cause disfigurement. Corticosteroids are the first line of treatment for problematic infantile capillary hemangiomas; other options include interferon alfa and vincristine. We have observed that propranolol can inhibit the growth of these hemangiomas. Our conal orbital involvement, as well as an intracervical mass causing compression and tracheal and esophageal deviation (see the Supplementary Appendix). Ultrasonography showed increased cardiac output, and treatment with propranolol, at a dose of 2 mg per kilogram of body weight per day, was initiated. Seven days later, the child was able to open his eye sponta-

Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action

C.H. Storch*† and P.H. Hoeger‡

- Vasoconstriction of supplying capillaries
  - Visible color change in first 48 hours
  - From decreased release of nitric oxide
- Inhibition of angiogenesis
  - Effects on pro-angiogenic growth factors, VEGF & bFGF, MMP-2 & MMP-9
  - Arrest of growth
- Induction of apoptosis
  - Regression of IH

August 13, 2008 (before Rx)
August 14, 2008 (day 1)
August 15, 2008 (day 2)
August 28, 2008
2 weeks later
September 22, 2008
1 month later
Our Experience: Methods

- Retrospective analysis in 70 patients with function-threatening or disfiguring cutaneous hemangiomas treated with propranolol
  - Response to therapy
  - Complications (hypoglycemia, hypotension, cool hands and feet, etc.)
  - No serious adverse effects
  - Drop in blood pressure with first dose but not clinically important
Ongoing experience...

- Over 1,000 babies
- No serious complications
- Our current dosing: 2 mg/kg/d (We are off-label!)
New stuff...

- First drug ever approved for treating IH
- Great safety and efficacy data
- Most exciting drug discovery and implementation in my career
- Easy to access
Hemangeol (propranolol hydrochloride 4.28 mg/mL)

- Phase II/III clinical trial
- 60.4% complete or nearly complete resolution compared to 3.6% placebo
- 88% improved at week 5
- Most common adverse drug reactions: ~10% sleep disorders, aggravated upper respiratory infections, diarrhea, vomiting
- <2% stopped medication for safety
Topical timolol for superficial IH, PG, etc.
More Cool Stuff...

- Topical beta-blockers
- Collaboration with pedsplastics on rebounding IH
- Scalp, periocular, nasal tip lesions
- Identification of IH requiring early intervention
- Other segmental IH
- Risk factors for hemangiomas
- Hemangiomatosis and visceral lesions
- Vascular malformations (oral sirolimus, topical sirolimus, etc.)
Impact of Vascular Anomalies on the Family System
Linda Rozell-Shannon (April 2017)

- For new parents, having an infant is stressful, but when that infant is diagnosed with a potential disfiguring vascular anomaly, parents will experience additional stress.

- Wandering from doctor to doctor to find an accurate diagnosis and appropriate treatment plan can result in symptoms of acute stress, disruption to normal family routines, and feelings of helplessness and hopelessness by the entire family, primarily the parents.

- Additionally, the stress from the uncertainty over how large or disfiguring these lesions can become can interfere with maternal bonding as the mother becomes fixated on treatment, missing significant milestones in the infant’s normal development.

- To further complicate the matter, insurance companies routinely deny the treatment of benign vascular anomalies leaving the families feeling helpless and hopeless.
Studies conducted to assess the impact of having an infant with a facial vascular anomaly concluded that there was an interference with normal maternal bonding, the fear of the unknown negatively impacted the family system, and inconsistent information from physicians and potential denial of treatment by insurance providers resulted in symptoms of acute stress.

Due to the lack of consistent information regarding the diagnosis and treatment of these lesions, families often seek outside sources, such as not for profits, that provide accurate information and support to the affected families.

Outdated medical information that promotes a “benign neglect” philosophy further complicates the fact finding of parents who learn about early treatment options on the internet through organizations such as the Vascular Birthmarks Foundation.

Online medical advice provided by vascular anomalies experts provides hope to the families but is often impeded by insurance companies who deny out of network treatment. As a result, families experience cyclical highs and lows as they wander from doctor to doctor and internet resources to internet resources trying to find appropriate treatment options.
What can be done????

Affected families need to know they are not alone. Support groups, such as the Vascular Birthmarks Foundation, exist, which can connect families newly diagnosed with families who have successfully navigated the diagnosis and treatment process.

Affected families need to know there are treatment options available, and these options should be presented and discussed, weighing pros and cons.

Outdated benign neglect protocol needs to be abandoned for a more appropriate approach to early intervention.

Babies need to be referred early for treatment, following the 4-week well baby check up.

If needed, practitioners need to provide documentation for the medical necessity for treatment.

Last, but not least, physicians need to be cognizant and sensitive to the fact that having an infant with a potentially problematic and disfiguring vascular anomaly can interfere with maternal bonding, as well as the entire family system. In some instances, families may need to be referred to a social worker or appropriate mental health expert to resolve any psychosocial issues.
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