Infantile Hemangiomas: Past, Present, Future

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Objectives

• To recognize changing concepts about infantile hemangiomas (IH)
• Be familiar with new emerging therapeutic options for IH
• To know when to perform a more extensive evaluation of a newborn with an IH
When is treatment necessary for Infantile Hemangioma

- Large
- Ulcerate
- Lesions that impair vision, hearing, breathing or feeding
- Fail to resolve by school age
Hemangiomas are more common in low birth weight infants

- Female
- White skin
- Premature
- Multiple births
- Advanced maternal age
- Familial history of infantile hemangiomas
<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck</td>
<td>60%</td>
</tr>
<tr>
<td>Trunk</td>
<td>25%</td>
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<tr>
<td>Extremities</td>
<td>15%</td>
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</tbody>
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Tests

- Ultrasonography
- Magnetic Resonance Imaging (MRI)
- Biopsy
Types of Infantile Hemangiomas

- Superficial: 50-60%
- Subcutaneous or Deep: 15%
- Mixed: 25%
Morphology of Infantile Hemangiomas

- Focal (localized)
  Located on bony prominences
  60% head and neck
- Multifocal
- Segmental
  Covers one or more segments of face and/or body
Most Recent FDA Approved Therapy
HEMANGEOL

• Propanolol hydrochloride oral solution
  4.2 mg/ml
• Dosing Calculator on website
PHACES SYNDROME

- Posterior fossa brain malformations
- Hemangioma large, facial
- Arterial abnormalities
- Cardiac abnormalities and aortic coarctation
- Eye abnormalities
- Sternal clefting and/or supraumbilical raphe

Increased prevalence in females (9:1), Hispanics, and whites
Atenolol Versus Propanolol for the Treatment of infantile Hemangioma: a Randomized Controlled Study

23 patients: 13 - atenolol
10 - propanolol

Complete response after 6 months:

53.8% - atenolol
60.0% - propanolol  NS

JAAD 2014,1045-1049
Atenolol

- Acts on $\beta_1$ receptor
- Does not cross blood-brain barrier
- Less $\beta_2$ receptor effect
  - Less bronchial adverse effects
  - Avoid risk of hypoglycemia
Most infantile hemangiomas do not improve significantly after 3.5 years of age. Reconstructive procedures should be considered at this age. Tumor has been allowed to regress and the deformity is improved before the development of long-term memory and psychosocial morbidity.

Future Needs

- Better understanding of pathogenesis
- Improve triage to stratify risk to let parents know when IH must be treated
- New treatments
Pretreatment Evaluation for Propranolol

- Heart rate
- Blood pressure
- Cardiac and pulmonary assessment
- EKG?
Initiation of Propranolol

- In hospital setting
  - < 8 weeks of gestationally corrected age
  - Co-morbid conditions

- Out Patient
  - > 8 weeks of gestationally corrected age
  - Adequate social support
Myth: Infantile Hemangioma Goes Away Completely

Some hemangiomas leave a permanent fibrofatty tissue.

Although IH disappears, normal skin is not necessarily the result.

Conflicting studies:

Worse outcomes

- Superficial and deep hemangiomas
- Larger size
- Steep border
- Very thick superficial hemangiomas
- IH on central face
Myth: IH growth occurs in first 3-6 months of life

- 80% of growth occurs by 3 months of age
- 80% completing growth by 5 months

Deep IH tend to grow longer than superficial IH.

Segmental IH tend to exhibit more continued growth after 3 months.
Myth: The rate of involution is 10% per year

- 92% of IH have complete involution by age of 4 years
Main Risk of Propranolol Use for IH

- Cold hands and feet
- Sleep disturbances
- Hypoglycemia
- Gastrointestinal disturbances

Pediatrics 2013; 131:128-140.
Contraindications to Propranolol Therapy

- Cardiogenic shock
- Sinus bradycardia
- Hypotension
- Greater than first-degree heart block
- Heart failure
- Bronchial asthma
- Hypersensitivity to propranolol hydrochloride

Pediatrics 2013; 131:128-140.
IH: a vasculogenesis disorder, resulting from a hypoxic stress?

**PROLIFERATIVE PHASE**
- Birth
- 3-12 months

**INVOLUTIVE PHASE**
- 12-36 months
- 3-7 years

- Hypoxic stress
- CD133 stem cell
- Immature endothelial cell (GLUT1 positive)
- Pericyte
- Adipocyte
- Mast cell
- VEGF, bFGF
- Caspases+, ICAM1+

Leaute-Labreze, AAD 2014 Summer Meeting
Fig. 2. Proposed segment map (reproduced with permission from Hagstrom et al., in press). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

IH with Structural Anomalies
(e.g. PHACE syndrome)
Cellular and *In Vitro* Characteristics

- Unlike other vascular tumors or malformations: Glut1 positive
- Progenitor cell phenotype suggest neural crest or pericyte origin
- Plasticity: IH cells → adipocytes

Evolution of a hemangioma from 4 mos to 2 years
Natural History of Infantile Hemangiomas (IH)

• Spontaneous involution is the rule
• Normal skin is not necessarily result after involution
• What are best predictors of residual skin changes?
High-Risk for Disfigurement: Location

- Nasal tip
- Perioral
- Glabella
- Eyebrow
- Central face

Early Growth

• 80% of infantile hemangioma (IH) growth occurs by age 3 mos
• 80% of IHs have *completed growth* by age 5 months
• Growth characteristics before 3 months hard to study because most infants present later than 3 months

Chang et al. Pediatrics 2008;122:360-7
Myth # 5
Rate of involution is 10% per year
(e.g. 50% age 5,
90% by age 9)
Initiation and Use of Propranolol for Infantile Hemangioma: Report of a Consensus Conference
Pediatrics 2013;131:128; originally published online December 24, 2012; DOI: 10.1542/peds.2012-1691
The Reality

• Propranolol has become 1\textsuperscript{st} line treatment for hemangiomas requiring systemic therapy

• Topical β-blockers may be sufficient for early and superficial IH

Guo et al. Arch Ophthalmology Feb 2010
Conclusions

• Pulsed dye laser is clinically used for
  ▪ Superficial lesions at sites of functional impairment and/or face
  ▪ Ulcerated hemangiomas
  ▪ Residual erythema and telangiectasia of involuted hemangioma

• Early laser treatment does not prevent proliferating growth of deep component
POST HEMANGIOMA REMOVAL
UPPER LIP
10-22-08
7-27-09
RESOLVING HEMANGIOMA
RT UPPER LIP