Infantile Hemangiomas:
Not Just Strawberries

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Conflict of Interests:
Consultant: Pierre Fabre

Off-label discussion:
I do intend to discuss unapproved/ investigative use of commercial products/devices in my presentation (there are NO FDA-approved medications for hemangioma therapy)

Overview

- Hemangiomas:
  - Glut-1 and unique vascular phenotype
  - Hemangiomas: Congenital and Infantile
- Infantile hemangiomas:
  - Recognizing which hemangiomas pose greatest risk
  - Who needs referral and when
  - Propranolol as novel new therapy
Congenital Hemangiomas

- What about hemangiomas that are fully-formed tumors at birth
- These are almost never infantile hemangiomas.
Infantile Hemangiomas

- Absent or barely evident at birth
- Rapid growth phase followed by gradual involution
- Key clinical feature: tremendous heterogeneity

Unique Vascular Phenotype: What it Means

- Infantile hemangiomas NOT neoplasm of “normal” cutaneous capillaries
- Share genomic molecular fingerprint with placental blood vessels
- Not just a disease of “regular angiogenesis”

Management for Pediatricians

- Common problem
- Mostly innocuous
- Significant minority are troublesome
- What features are most predictive of complications and/or need for treatment?
- Is there an optimal time to refer?
Not all “red dots” have the same destiny

Hemangioma Patterns
Localized and Segmental

- **Segmental**: Broad anatomic region or recognized developmental unit (such as the entire ear)
- **Localized**: Confined spatially, often appear to arise from central focal point

Importance of Segmentals

- Segmental hemangiomas were 11 times more likely to experience complications and 8 times more likely to receive treatment than localized hemangiomas, even when controlled for size.
- Facial segmental hemangiomas 43x more likely to receive systemic treatment compared to non-facial, non-segmental IH.
- Main indication for treatment is risk of disfigurement not “medical” morbidity

Hemangioma Patterns
Localized and Segmental

PHACE SYNDROME
Occurs in 30% of large facial IH
- P: Posterior fossa and other brain anomalies
- H: Large facial hemangiomas
- A: Arterial anomalies especially CNS anterior circulation
- C: Cardiac defects esp. aortic coarctation
- E: Eye defects especially “morning glory anomaly” retinal vascular anomalies,

What about Growth: *When* to Refer?

Growth is the 4th Dimension

<table>
<thead>
<tr>
<th>Birth</th>
<th>10 days</th>
<th>5 weeks</th>
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<tbody>
<tr>
<td>7 weeks</td>
<td>8 weeks</td>
<td>3 months</td>
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Day 5, Day 12, Day 30, Day 49, Day 75
Growth during Infancy

- Study of over 1000 patients followed minimum 8 to maximum 22 months
- Hemangiomas reach 80% of maximum size at a mean age of 3 months
- Growth over by 5 months of age in 80%
- Segmental hemangiomas and deep hemangiomas grow longer
- Average age of first visit to dermatology was 5 months

Chang et al. Pediatrics 2008;122:360-7

Precursor lesion and proliferation:
Territory “marked out” in utero

![Territory marked out in utero](image)

Courtesy of Eulalia Baselga M.D.

10 mos  18 mos

![Hemangiomas over time](image)
Implications of Growth Characteristics: Hemangioma Crisis Period

- Recognition of high-risk hemangiomas (segmental, large, central face) key
- Critical growth period is first few weeks to months
- Worry more early and much less later
- Specialists need to see high-risk patients promptly

Management

Do Hemangioma “Go Away”?  

5 months  18 months
3 months 4 years

Dermal Involvement: Impact on Residual Skin Changes

**Poorer Prognosis**
- Pedunculated
- Sharp drop-off or steep slope

**Better Prognosis**
- Thin plaques
- Gradual slope to normal skin

**Rx of hemangiomas: Yes BUT…**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>LIMITATIONS</th>
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<tr>
<td>Systemic steroids</td>
<td>Many side effects, need high doses for months</td>
</tr>
<tr>
<td>Intralesional steroids</td>
<td>Smaller lesions, intra-arterial injection; benzyl alcohol</td>
</tr>
<tr>
<td>Topical steroids</td>
<td>Effect is very superficial</td>
</tr>
<tr>
<td>Pulsed dye laser</td>
<td>Effect superficial; NOT an eraser; Risk ulceration</td>
</tr>
<tr>
<td>Interferon</td>
<td>Risk spastic diplegia ~20%</td>
</tr>
</tbody>
</table>
Propranolol as Rx

Léauté-Labrèze C et al
June 12, 2008
358:2649-2651

FIGURE 1 Patient 3, with palpebral occlusion


Taban et al. Ophthalmology; 2010;117:e196
Questions you should be asking yourself (and others)

- Does it work?
- Is it safe?
- Dose and duration?
- Does rebound growth occur?
- Oldest age where it might (still) work?
- Rx for other vascular tumors (e.g. KHE etc)?
Answers to Questions: I

- Does it work? Preliminary results very impressive – not just stabilize but shrinkage
- Is it safe? Some reports of hypoglycemia and other AEs - well tolerated in most…
- Dose range: 1-3 mg/kg/day divided BID or TID
- Duration of Rx? Not certain - ? 6 mos

Answers to Questions: II

- Can rebound occur? Yes, but not in all patients and can be partial
- Age range – can shrink fully grown lesions
- Site-specific effects? Not certain but would not be surprising
- What about for other vascular tumors… (Doubtful…)
- Could it prolong involution phase?

Two preliminary reports re: Topical β-blockers

3mo  
s/p Clobetasol

5mo  
s/p Timolol

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Is propranolol 1st line Rx of IH?

- New doesn’t necessarily mean better (interferon experience)
- Anecdotes and small case series not enough to declare a therapy first-line especially re: safety concerns
- Even larger studies are not adequately powered to detect low-risk (but potentially serious) AEs
- "Old" medication but arguably will be largest use of propranolol in infancy to date

Currently at UCSF (as of 6/3/10)

- >6 months of age usually first line
- <3 months of age try steroids first and switch if not effective or well-tolerated
- 3 to 6 mos…depends on situation
- Using BID w/o late evening dose
So before you write out the Rx…

- Generally considered benign drug BUT no consensus on monitoring in young infants
- Hypoglycemia, bradycardia, hypotension, hypothermia, exacerbation asthma potential side effects
- ? Issue with PHACE arteriopathy
- Still need to know which hemangiomas need Rx


From Strawberries to Glut-1 to ????

- 21st century has been an exciting time to study infantile hemangiomas
- More on pathogenesis
- New therapies
- Stay tuned for more to come