Management of Pediatric Hemangiomas

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Case

- 21 day old infant presented to the ER
  - biphasic stridor and retractions
- At birth
  - telangiectasias of upper chest, ears and mandibular areas
Case

- Cutaneous lesions proliferated over first three weeks of life
- ‘beard’ distribution
- lower lip
- tongue, gingiva
- anterior chest
Case

- Flexible fiberoptic laryngoscopy
  - Erythema and edema of supraglottis
  - Subglottis was difficult to visualize
- Patient admitted
- Direct laryngoscopy and bronchoscopy performed on HD #2
How would you manage?

a) Tracheotomy
b) Oral steroids
c) Laser
d) Submucosal resection
e) Propranolol

You are considering using propranolol:
Which of the following is true?

a) There are no serious risks to using propranolol and it should be first-line treatment.

b) A risk of propranolol is complete heartblock and it should be used with caution.

c) A risk of propranolol is hypoglycemia and infants should be fed every 3 hours to prevent this problem.

d) Severe airway hemangiomas should almost always be managed with tracheotomy and propranolol should not be considered.
Case

- Started on prednisolone at 3mg/kg/day and propranolol at 2mg/kg/day
- Within 24 hours, he had dramatic improvement in stridor and retractions
- PHACES workup revealed ‘morning-glory’ disc anomaly
- Echo was unremarkable
- MRI/MRA planned to rule out other possible PHACES associations
- Patient kept in NICU for 7 days
- Repeat bronchoscopy 7 days later
Case

- Weaned off of prednisolone at 3 months.
- Currently 10 months old with no stridor.
Objectives

- Epidemiology of infant hemangioma
- Presentation and evaluation
- Management
  - Medical
  - Surgical

Epidemiology

- Most common pediatric head and neck tumor
- Incidence (Bruckner & Frieden, 2003)
  - Neonatal: 1.1–2.6%
  - 12 months: 10–12% of white children
- Subglottic hemangioma rare
  - 1.5% of congenital airway lesions (Holinger & Brown, 1967)
  - Beard distribution
  - PHACES syndrome
Subglottic Hemangioma

Presentation

- Asymptomatic at birth
- Proliferative phase
  - Begins 1 to 2 months
- Inspiratory → biphasic stridor
- Respiratory distress
- Feeding problems
- Misdiagnosis as croup
- Proliferation for one year
- Involution over 5+ years

Presentation

- Subglottic hemangioma
  - 50% have cutaneous beard distribution
- Cutaneous
  - 9-63% have SGH

Frieden, et al., 2005
Presentation

PHACES syndrome
(Frieden, et al., 1996)
- Posterior fossa malformations
- Segmental facial Hemangiomas
- Arterial anomalies
- Cardiac defects
- Eye abnormalities
- Sternal defects

Management

<table>
<thead>
<tr>
<th>Modality</th>
<th>Year</th>
<th>Authors</th>
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<tbody>
<tr>
<td>External radiation</td>
<td>1919</td>
<td>New &amp; Clark</td>
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<td>Tracheotomy</td>
<td>1940</td>
<td>Suehs &amp; Herbut</td>
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<td>Surgical excision</td>
<td>1949</td>
<td>Sharp</td>
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<td>Sclerotherapy</td>
<td>1962</td>
<td>Pierce</td>
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<td>Systemic corticosteroids</td>
<td>1969</td>
<td>Cohen</td>
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<td>Observation</td>
<td>1971</td>
<td>Fearon &amp; Ellis</td>
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<td>Cryotherapy</td>
<td>1972</td>
<td>Schecter &amp; Biller</td>
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<td>Implantation (radium)</td>
<td>1973</td>
<td>Holborow &amp; Mott</td>
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<td>Electrocautery</td>
<td>1976</td>
<td>Kim &amp; Hendren</td>
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<td>Carbon dioxide laser</td>
<td>1979</td>
<td>Simpson et al</td>
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<td>Gold implants</td>
<td>1983</td>
<td>Benjamin &amp; Carter</td>
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<td>Argon</td>
<td>1985</td>
<td>Parkin &amp; Dixon</td>
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<tr>
<td>Intralesional steroids</td>
<td>1986</td>
<td>Shikhani et al</td>
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<tr>
<td>Nd: YAG laser</td>
<td>1986</td>
<td>McCaffrey &amp; Cortese</td>
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<tr>
<td>Interferon</td>
<td>1997</td>
<td>Sherrington et al</td>
</tr>
<tr>
<td>KTP laser</td>
<td>2001</td>
<td>Madgy et al</td>
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</tbody>
</table>
Management

- **Tracheotomy**
  - Historical standard of care
  - Rahbar, et al., 2004:
    - 28% trached
    - 9% observed
    - no complications
    - complications 12-20% for other treatments
  - Significant morbidity for a self-limiting disease
    - Complications: 18-51%
    - Mortality: 1-2%
    - (Ozmen, et al., 2009; Mahadevan, et al., 2007)

Systemic Steroids

- First effect incidentally noted in treating thrombocytopenia
- Mainstay of more severe non-airway hemangiomas
  - Segmental, orbital, large or aggressive
- Most often stop further growth
  - Dermatology literature: response 30 to 60%
  - ~20-25% symptomatic control of airway lesions
  - Likelihood of readmission higher than other treatments
- Complications:
  - Behavior change, cushingoid, growth delay, lipoid pneumonia, peptic ulcer disease

Intralesional steroids

- Early study: 56% resolution (Hoeve, 1997)
  - Mean 6 procedures
  - Mean 37 days intubation
- 20% monotherapy success (Chatrath, et al. 2001)
- Systemic steroids and intralesional (Saetti, 2008)
  - 11 patients
  - 73% success
  - One procedure
  - Mean intubation 8.3 days
  - 3 required trach

Interferon-alpha

- Inhibits angiogenesis
  - Numerous derm studies:
    - 40-50% complete response (Frieden, et al., 2005)
- Toxicity:
  - Fever, myalgia, transaminase elevation, neutropenia, anemia, weight loss, anorexia
  - Spastic diplegia and developmental delay up to 10 to 30% (Frieden, et al., 2005)
Vincristine

- Induces apoptosis
- Less toxicity than IFN-alpha
- Efficacy close to 100% with weekly infusion
- Replaced IFN-alpha
- Complications: peripheral neuropathy, GI upset, jaw pain, constipation, fever, headache, hematologic toxicity, SIADH, PICC line complications (Frieden, et al., 2005; Enjolras, et al., 2004)

CO2 Laser Resection

- Highly popular modality
  - Success 88.9 % Mean: 2 procedures (range 1-5)
- Complications:
  - Web formation
  - Pneumothorax
  - Interarytenoid scarring
  - Subglottic stenosis: 5.5-25%
- Not ideal for bilateral or circumferential
- May require temporary trach

Cotton & Tewfik, 1985; Bitar, et al., 2005
Saett, et al., 2008
KTP Laser Resection

- Laser resection: KTP
  - Preferential absorption by hemoglobin
  - Potentially less destructive
  - Deep penetration
  - Low complication rate in limited studies (Pransky, et al., 2004; Kacker, et al., 2001)

Other lasers: Nd:YAG, pulse dye

Submucosal resection

- First described by Sharp, 1949
- Requires open excision
- Careful submucosal dissection
- Post-operative intubation
  - 3-7 days
- Excellent for circumferential or bilateral
- Success over 94%
- Decreased number of surgeries for large lesions
- Risks: laryngotracheal stenosis, granulation

Bajaj, et al., 2006; Bitar, et al. 2005; Rahbar, et al., 2004; Vijayasekaran, et al., 2006; Wiatrak, et al., 1996; Vijayasekaran, et al., 2006; O-Lee, et al., 2007; images.google
Propranolol

- NEJM, June 2008 (Leaute-Lebreze, et al.)
  - Letter to the editor
  - Hemangioma with cardiac disease
    - Treated with propranolol
    - Incidental regression
  - Treatment of additional 11 children
    - All with change observed in 24 hours
    - U/S showed objective regression in 5/5

- Not randomized or controlled
- No discussion of risks

9 weeks old
Post-4 weeks of systemic corticosteroids
10 weeks old
post-7 days propranolol

6 months age
steroids discontinued at 2 mos
9 mos age
propranolol discontinued

Mechanisms

- Hemangioma proliferation
  - Two proangiogenic factors
    - Basic fibroblast growth factor (bFGF)
    - Vascular endothelial growth factor (VEGF)

- Possible mechanisms
  - Vasoconstriction
  - Decreased VEGF and bFGF expression
  - Triggered apoptosis of capillary endothelial cells
  - Mesenchymal stem cell differentiation inhibition

Propranolol

- Theletsane, et al., 2009
  - Single case: airway, good response
  - No risks discussed
- Denoyelle, et al., 2009
  - 2 patients with airway lesions
  - Treated concomitant with vincristine and/or steroids
  - Spectacular regression
  - Developed safety protocol
  - Advocate as first line treatment for SGH

Propranolol

- Sans, et al., 2009:
  - Only published larger study: Observational
  - Complicated hemangioma
  - 32 children, mean age 4.2 mos; 13 with previous steroids
  - Dose 2-3 mg/kg/day divided in 2 or 3 doses
  - Monitored 6 hours: EKG, echo, BP, HR
  - Results:
    - Immediate effect color and growth in all
    - Clinical and US regression at 2 mos
    - Steroids stopped in few weeks
    - Mean duration treatment 6.1 mos
    - Relapses mild and responded to re-initiation
  - Limited side effects: one discontinuation for wheeze
Propranolol

- Since initial article in June 2008
  - 24 articles in the literature
  - 2 accepted publications from our group
  - 46 patients total
  - 13 subglottic cases
  - 100% response
  - First-line therapy?

Risks

- Follow-up letter to NEJM (Siegfried, et al., 2008)
  - Bradycardia
  - Hypotension
  - Bronchospasm
  - Blunted hypoglycemia signs
    - Risk of long-term neurologic sequelae
  - Masked high-output heart failure
  - Easy to monitor inpatient, most patients are outpatient
Limitations

- No RCTs of efficacy and toxicity
- Many variables:
  - Location, size, reason for intervention, prior or concomitant tx, age at initiation
  - No standardized criteria for measuring response or monitoring toxicity
- Evaluation/Monitoring
  - EKG, echo, admission, home nursing, CBC, BP, HR, lytes, LFTs, glucose, TFTs, urine glucose, abdominal US
- Starting dosage, max dosage
- Length of treatment
- Combined vs. isolated treatment

Proposed Protocol (Siegfried, et al., 2008)

- Baseline echocardiography
- 48-hour hospitalization or home nursing visits
- Monitor vital signs, blood glucose
- q8h delivery
- Initial dose 0.16mg/kg to max 2 mg/kg/day
- Gradual taper over 2 weeks
UCSF Protocol

- Developed with dermatology, cardiology, OHNS
- Symptomatic airway disease or less than 3 months old
  - inpatient observation
  - Initial dose: 1 mg/kg/day as initial dose and increase to 2 mg/kg/day a few days later
  - q8h dosing
- Older than 3 months of age, no airway disease
  - Heart rate monitored at home or by PCP every few days
  - Slowly increasing doses: start 0.3 mg/kg/day increases every 3 days at 0.3 mg/kg increments to a target dose of 2 mg/kg/day.
- Patients less than 6 months of age must be fed every 3 to 4 hours to avoid drug-induced hypoglycemia

UCSF experience

- Treated 18 patients to date.
- One unexplained bradycardia and hypoglycemia requiring brief hospitalization with rapid recovery.
- Dose reduction for mild decrease in BP.
- Dose reduction for excessive sleepiness.
- A few parents have reported sleep disturbances.
Case

At admission 6 days post-propranolol

Recommendations

- Treat in collaboration with derm and cards
- Refer to centers participating in randomized trials
- Current trials: clinicaltrial.gov
  - NCT00744185; NCT01056341, University Hospital, Bordeaux
    - DB-RCT: Propranolol and hemangiomas
  - NCT01010308, Toronto Hospital for Sick Children
    - Non-randomized, historical control: nadolol and H&N hemangiomas
  - NCT00967226, Children National Medical Center
    - Randomized, propranolol vs prednisolone
- Subglottic hemangioma so rare: multi-institutional RCTs needed to fully evaluate
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Thank you!
**articles**

- Buckmiller, et al., 2009
  - One patient
  - Tracheal lesions, persistent stridor near 2 y/o
  - Late tx with propranolol
  - Developed protocol with cardiology
- Maturo & Hartnick, 2010
  - 2 patients treated with propranol only
  - Initial dose of 0.5–1 mg/kg is started and if well tolerated increased to a dose of 2–3 mg/kg divided bid to tid over 24–48 h
- Jephson, et al., 2009: one case airway, no SE, says 30 cutaneous treated but no data presented
- Truong, et al., 2009: propranolol and steroids single case report
- Marsciani, et al., 2010: one case hepatic
- Taban, et al., 2010: orbital
- Mousa, et al. 2009: one case thorax
  - Hypotension and hyperkalemia

**Denoyelle protocol**

- Baseline cardiac u/s
- BP, HR
- Monitoring of blood glucose first 48h
- 0.16 mg/kg/8h to max 2mg/kg/day