Infantile Hemangiomas: An Update for the Pediatrician

Cynthia Baker, MD
Department of Pediatrics, LAMC

Valentina Sosa, MD
Department of Dermatology, LAMC

Stacey Francis, MD
Department of Plastic Surgery, Fontana/Ontario

Kp.org web version

- We have deleted the facial photos of our VBMC patients from this website version or have covered their eyes for privacy.
- The facial photos you see are not of our patients.

Disclosures

- None of the three speakers have any disclosures.
- Some of our photos are of our VBMC patients. All of their families have given informed written consent for photographs for teaching.
- We will discuss an off label use for topical timolol.

Educational Objectives

- Synthesize a plan to evaluate and manage uncomplicated hemangiomas
- Recognize several “red flags” and syndromes associated with hemangiomas
- Refer appropriate patients to the Vascular Birthmark Clinic (VBMC) at LAMC

Outline

- VBMC Multidisciplinary Team
- Classification of Vascular Anomalies
- Definitions, Epidemiology and Patterns
- Pathophysiology
- Clinical Presentation
- Indications for Referral
- Management
- Resources for Pediatrician
The Vascular Birthmark Clinic at LAMC

- Founded in 1994 to help patients with hemangiomas in a multidisciplinary format. Dermatology, Plastic Surgery and Pediatrics met at lunchtime once a month to see these patients with hemangiomas.
- Now has developed into a multidisciplinary team that meets one full day a month (second Thursday)
- Serves KP patients from all over Southern California
- We take referrals through the Dermatology dept at LAMC, Doctor’s advice and encourage good histories, descriptions and measurements of lesions as well as photos if possible.

The VBMC Team

- Valentina Sosa - Pediatric Dermatology and Laser (Director)
- Marvin Klapman - Dermatology and Laser
- Cynthia Baker - Pediatrics
- Stacey Francis and Melissa Poh - Plastic Surgery
- Roman Sydorak - Pediatric Surgery
- Carolyn Nguyen and David Tieu - Pediatric Head and Neck Surgery
- Naomi Ellenhorn - Pediatric Ophthalmology
- Dennis Der, Tina Hardley, Lei Feng, Elan Rosenthal - Interventional Radiology
- Bernadette Maloles - Case Manager
- Dermatology Residents, LAMC

Our Vascular Birthmark Team

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Vascular Anomalies

- 1/3 of children have a vascular birthmark or anomaly
- 1% will be significant and require evaluation and treatment
- 1/1000 (0.1%) will be complex and require multidisciplinary treatment
ISSVA Vascular Anomalies Classification

- Revised April 2014
- ISSVA.org
- Nomenclature—often terms used incorrectly leading to incorrect diagnosis.
- Important that we’re all talking about the same thing, describing it and photographing for documentation and follow up.

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Infantile Hemangiomas (IH) - Definition

- Benign vascular tumors
- Marked by the proliferation of the endothelial cell
- Clinical course: early proliferation followed by spontaneous involution
- Either absent or present at birth as precursor lesions
- Rapid proliferation phase: within the first few weeks of a child’s life

Infantile Hemangiomas - Epidemiology

- Most common benign tumor of infancy
- Affects 4-5% of all infants
- Occurs in up to 30% of premature babies
- More common in females (3:1), Caucasians (10-12X black and Asian), multiple gestation, prematurity and low birth weight infants.
- 12% develop complications: ulceration, impaired vision/functional impairment or permanent disfigurement.

Pearl: The pediatrician needs to determine which lesions require early intervention, what intervention is most appropriate and when consultation with a specialist is advisable.
Other Types of Hemangiomas - Congenital

RICH-rapidly involuting NICH-noninvoluting

Congenital Hemangioma vs Infantile Hemangioma

Congenital (RICH and NICH)
- Present at birth and potentially diagnosable during fetal development via ultrasound.
- Growth is complete at birth, or it may grow proportionately as your child grows.
- Occurs equally in males and females.
- Less common than infantile hemangiomas, but not rare.
- Rapid or no involution (shrinking).

Infantile
- Visible between 2 weeks and 4 months of age.
- Grows rapidly for about 6 to 12 months (average is around 8 months).
- Occurs in five females for every male.
- Common (4-5 percent incidence in newborns).
- Slow shrinking that takes months or years.

Infantile Hemangiomas Types

- **Superficial** – bright red, “strawberry” marks. 50-60% of infantile hemangiomas.
- **Deep** - subcutaneous masses, present as protruding tumors that appear under normal or bluish skin. 15% of IH.
- **Mixed** - combined hemangiomas, both superficial and deep characteristics. 25-35% of IH.
- **Reticular/abortive/minimal growth** - less common

Infantile Hemangiomas-Patterns

- **Focal (solitary)**
  - Multifocal (multiple in 15-20%) >5, recommend abdominal ultrasound (liver)
- **Segmental**
  - Higher risk of complications-check thyroid
  - Association with visceral hemangiomas
  - Association with syndromes: PHACE, SACRAL, PELVIS, LUMBAR

Infantile Hemangiomas-Patterns Focal

Infantile Hemangiomas-Patterns Multifocal
Infantile Hemangiomas-Patterns
Segmental

Infantile Hemangiomas-Patterns
Segmental in Sacral Region

Case Presentation-
What’s your diagnosis?
• 6 week old male with enlarging facial lesions noted shortly after birth
• 36 weeks gestation, NSVD, no complications
• Normal growth and development
• PE-large, bright red, nonconfluent macules and plaques in a temporal distribution extending medially to the eyelid and laterally to the scalp.
• What could this be?

PHACE Syndrome
• P-posterior fossa brain malformations
• H-hemangiomas
• A-arterial cerebrovascular anomalies
• C-cardiovascular anomalies
• E-eye abnormalities (rarely endocrine)
• S-ternal defects
• S-upraumbilical raphe

PHACE Syndrome
• Neurocutaneous syndrome characterized by a spectrum of abnormalities
• Syndrome has a 9:1 female-to-male predominance.
• 98% percent of patients with PHACE syndrome have a large segmental IH present on the face or head
• Should be considered in children with large facial hemangiomas (> 5 cm)
• Can be telangiectatic or reticular in newborns and confused with PSW/SWS
• Segmental infantile hemangiomas more likely to ulcerate, persist, poorer outcome

Segmental Hemangioma-r/o PHACE - Workup
• Recommend referral to multidisciplinary team
• Workup-MRI/MRA of brain/head and neck
• ECG and Echocardiogram
• Ophthalmologic examination
• May need additional evaluation by Neurology and Cardiology
• Treatment with propranolol but if cerebrovascular anomaly, need caution (risk of ischemic stroke)
**PHACE Syndrome Findings**

**Association with Other Lesions-Syndromes**

**LUMBAR (SACRAL, PELVIS)**

- Lower body hemangioma,
- Urogenital anomalies,
- Ureteration,
- Myelopathy,
- Bone deformities,
- Anorectal malformations,
- Arterial anomalies
- Renal anomalies

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**Pathogenesis: Unique properties**

- Benign vascular tumors
- Proliferation of benign plump endothelial like cells
- Cells are in disarray but go on to form vascular spaces and channels
- Possess unique histochemical markers: GLUT-1, Lewis Y antigen, FcyRII and Merosin
- Same markers are found on placental blood vessels

**Infantile Hemangiomas – Pathogenesis:**

Vasculogenesis/Angiogenesis
Pathogenesis: **Vasculogenesis/Angiogenesis**

- **Environmental factors**: hypoxia, local growth factors, cytokines, estrogens
- **Placental embolization**: cells are "embolized" by the placenta
- **Somatic mutations** in gene mediating cell proliferation
- **Endothelial progenitor cell (EPC)** as source of origin of the tumors
- **Hypoxia**: placental insufficiency vs "metastatic niche theory"
- **Angiogenic peptides**: B-fibroblast GF, VEGF2, Proliferating cell nuclear antigen, Insulin-like GF

Pathogenesis: **Hypoxia**

- Driving factor for the pathogenesis of vascular proliferation ➔ HYPOXIA
- IH proliferation maybe a homeostatic **attempt to normalize hypoxic tissue**
- **Stimulates release of EPCs** ➔ EPCs hone to hypoxic sites
- **Hypoxia associated factors**: low birth weight, advanced maternal age, maternal placenta previa or preeclampsia
- **GLUT-1** is a sensor for hypoxia and present in IH

Pathogenesis: **Endothelial Progenitor Cells (EPC)**

- EPCs are **vascular stem cells**
- Play **role in the development of IH**
- Stain positive for **GLUT-1, CD32 and merosin**
- **Mediators of EPC trafficking**: VEGF-A
  - **Hypoxia inducible factor -1 alpha**

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Clinical Presentation

- Blanching of the involved skin
- Occasionally a shallow ulceration
- Fine telangiectasias ➔ red or crimson macule or papule, often surrounded by a faint halo of vascular blanching
- Range from the size of a pinhead to greater than 20cm in diameter; usual size is 0.5cm -5cm
Clinical Presentation

Seen shortly after birth
  • Within a few weeks

- **Proliferation phase**: first 9-12 months
  • Most rapid growth: first 4-8 weeks
  • 80% by 5 months

- **Progression phase**: growth slows between 6-12 months

- **Location**
  • Head and neck (60-70%)
  • Trunk (25%)
  • Extremities (15%)

Clinical Presentation

Becomes more dome shaped, elevated, lobulated, plaque like, tumoral, or combo

Clinical Presentation

- **Involution Phase**: over first decade of life
  • 50% at 5 years
  • 70% at 7 years
  • 90% at 9 years old

- Often when involute still leave bad cosmesis

Photos of Clinical Progression over the First Year

Photos Of Clinical Progression Over Early Years
Photos of Clinical Progression Over First Year

Photos Of Clinical Progression over early years

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Indications for Referral
- Diagnosis help
- Complication
- Multiple hemangiomas (> 5)
- Segmental
- High level of suspicion
- Location: beard, large facial, periorbital, periauricular, lumbosacral, midline over spine

Indications for referral: Complications
- Obstruction
- Ulceration/Pain
- Bleeding
- Cosmetic/Psychosocial Burden

Visual Obstruction
- Risk for amblyopia and astigmatism
- Refer to VBMC and Pediatric Ophthalmology
- Begin by patching unaffected eye daily
Airway Obstruction

- Beard location: 60% with airway obstruction
- Stridor, recurrent croup, and work of breathing
- Endoscopy can diagnose and treat

Indications for Referral: Cosmetic Concerns

Complications: Bleeding

Indications for Referral: Multifocal and Segmental

Indications for Referral: Syndromes: PHACES, LUMBAR

11/5/2014
Indications for Referral: High Level of Suspicion

- Kasabach-Merritt Syndrome = consumptive coagulopathy DIC picture
- Tufted angioma or kaposiform hemangioendothelioma
- This is a malformation- NOT a hemangioma!

Location
Beard
Large Facial
Nose
Lips
Periorbital
Lumbosacral
Midline Spine
Vulva

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Management of Hemangiomas Overview
- Reassure
- Non-Invasive
  - Laser
  - Topical
- Systemic
- Invasive:
  - Intraleisional injection
  - Surgical

Management: Reassure
- Nothing you did
- Will resolve, but will take 5-10 years
- Will grow for first year
- Not a cancer
- Won’t bleed to death
Local Treatments - Laser Indications
- Bleeding
- Ulceration
- Pain
- Thin lesions, no longer in growth and tail end of final involution stage, “mop up” telangiectasias

Local Treatments - Laser

Local Treatments - Laser Indications
Contraindicated in proliferation phase
significantly more scarring in the infants treated with PDL vs observation; superior outcomes in observational group.

Batta, K. et al. Randomized controlled study of early pulsed dye laser (PDL) treatment of uncomplicated childhood hemangiomas: results of a one year analysis. Lancet 2002; 360:521-527 Birmingham, UK study. (N = 121 randomized observation vs PDL (<3 months of age))

Local Treatments - Topical Timolol
4 distinct mechanisms:
- local vasoconstriction → leads to reduced blood flow in the IH → early color change and softening of the lesion within the first hours or days after starting a beta blocker med
- trigger apoptosis of capillary endothelial cells
- inhibition of angiogenesis or vasculogenesis (caused by decreased release of VEGF limiting proliferation of vasculature and possibly arresting growth)
- recruitment of endothelial progenitor cells (EPCs) to the site of the hemangioma

Local Treatments - Topical Timolol
- Mechanism of action of beta blockers on hemangiomas: unknown
- Beta andrenergic receptors are expressed on endothelial cells of IH (and found in abundance in the proliferative phase of IH)
Local Treatments - Topical Timolol
- Best practice: superficial and small IH
- 0.5% timolol gelfoam suspension BID
- Caution with use: increased potency of between 4 and 10 times greater than propranolol and topical absorption would bypass first-pass metabolism in the liver.

Management of Hemangiomas
Overview
- Reassure
- Non-Invasive
  - Laser
  - Topical
  - Systemic
- Invasive:
  - Intralungal injection
  - Surgical

Management: Systemic Treatments
- In the past, options were limited.
- Mainstay was intralesional and oral steroid.
- Systemic steroid was effective but significant side effects and rebound.
- Interferon and Vincristine with side effects.

Pics Of Clinical Progression Over First Year

Management: Propanolol
- In 2008, Leaute-Labreze et al first fortuitously described the efficacy of beta-blockers the the treatment of IH.
- Propranolol is a systemic nonselective beta-blocker used for decades for CV disease.
- Theories of mechanism of action for IH: capillary vasoconstrictive effect, suppression of growth factors, induction of apoptosis of endothelial cells and blockade of GLUT1 receptors
- Efficacious but potential side effects - hypotension, bradycardia, hypoglycemia and bronchospasm.
**Propranolol**
- Careful monitoring is required, particularly medically fragile infants
- Initiation as inpatient vs outpatient.
- Collaborative care is optimal.
- Risk-benefit issues.
- Consensus statement in Pediatrics 2013—helpful re optimal dosing, age of initiation and duration of therapy, avoiding rebound.
- General dose recommended is 2-3 mg/kg/day divided tid for young infants. Can later give as bid.
- May require treatment until 14-15 months (rebound)

**A.H. -3 months of propranolol**

**A.W. -5 months of propranolol**

**A.S. - 5 months of propranolol**

**Propranolol Started After One Year**

**Management of Hemangiomas**
- Overview
- Reassure
- Non-Invasive
  - Laser
  - Topical
- Systemic
- Invasive:
  - Intrallesional injection
  - Surgical
Management:
E.B.- Intralesional Steroid

Management:
K.F.- Early Surgical Excision

Delayed Surgical Excision

Involutert Hemangiomas

Management:
Delayed Surgical Excision- School Age

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What can you do?
• Provide accurate education to parents
  • “HemangiomaEducation” Smart Phrase
  • Websites for families
• Know when to refer/use doctor advise
• Upload pictures to the chart
  • Visible Light or isite, parent photos via kp.org
• Help with local follow ups
  • “VBMC remote Champions”
Hemangioma Websites

- [http://www.childrenshospital.org/health-topics/conditions/hemangioma](http://www.childrenshospital.org/health-topics/conditions/hemangioma)

Websites for Parents

- [www.childrenshospital.org/health-topics](http://www.childrenshospital.org/health-topics)
- [http://www.hemangiomaeducation.org/info_faq.html](http://www.hemangiomaeducation.org/info_faq.html)
- [http://www.novanews.org/information/hemangioma](http://www.novanews.org/information/hemangioma)
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Questions