Pedicatric Vascular Disorders

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Introduction: History & Classification

• 1982-- Proposed classification for vascular birthmarks based on clinical appearance, biologic behavior and histopathologic features
  1. Hemangiomas
  2. Vascular malformations

• 1996-- International Society for the Study of Vascular Anomalies (ISSVA)
  • Classification was modified to reflect the awareness that other vascular tumors (ex: tufted angiomas, pyogenic granuloma) could arise in infancy
  1. Vascular Tumors
  2. Vascular Malformations
Introduction: Vascular Tumor & Vascular Malformation

- Vascular tumor
  - Primarily due to excess angiogenesis
- Vascular malformation
  - Result from errors in vascular development and remodeling
  - Classified according to distorted vessel type
  - Can cause significant morbidity as a result of hemorrhage, mass effect, induction of connective tissue hypertrophy, and limb asymmetry and pain
## 1996 ISSVA Classification: Vascular Tumors vs. Malformations

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<th>Vascular Tumors</th>
<th>Vascular Malformations</th>
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<td>Infantile Hemangioma</td>
<td>Capillary Malformation: (Slow flow): ex: Port-Wine stains, Telangiectasias</td>
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<td>Congenital Hemangioma, Rapidly Involuting Congenital Hemangioma (RICH), or Noninvoluting Congenital Hemangioma (NICH)</td>
<td>Venous Malformation: (Slow flow): ex: Cavernous hemangioma, Phlebectasia</td>
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<td>Congenital hemangiopericytoma</td>
<td>Lymphatic malformation (slow flow): Macrocytic or Microcystic</td>
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<td>Spindle cell Hemangioma</td>
<td>Glomuvenous malformation</td>
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<td>Pyogenic Granuloma</td>
<td>Arteriovenous malformation (fast flow)</td>
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<td>Kaposiform Hemangioendothelioma</td>
<td>Combined malformation (slow or fast flow): ex: angiokeratoma, cutis marmorata telangiectatic congenita</td>
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<td>Tufted Angioma</td>
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Infantile Hemangiomas
Introduction:

- Various other names have been used in the literature including:
  - *Nevus maternus*
  - *Angioma simplex*
  - *Angioma cavernosum*
  - *Angiodysplasia*
  - *Strawberry nevus*
  - *Capillary hemangioma*
Introduction:

- Hemangioma is the most common soft tissue tumor of infancy
- Neoplasm of benign endothelial cells
- Typical growth pattern characterized by early proliferation → gradual, spontaneous involution
Epidemiology

- 4-5% of infants
- Female: Male ratio of 2–5 : 1
- More frequent in premature infants
- Threefold increased incidence in infants born following chorionic villus sampling
Pathogenesis

Not fully elucidated

Theories include:

- Mutations involving vascular endothelial growth factor (VEGF) signaling
- Placental hypothesis (shared immunohistochemical phenotype)
  - Glucose transporter protein-1 (GLUT-1) expression
  - Other placenta-associated vascular antigens, including merosin, FcγRII and Lewis Y antigen, are present in hemangioma specimens and placental chorionic villi
- Association with hypoxia
  - Upregulates expression of GLUT-1 and VEGF
Presentation

• Become evident during the first few weeks of life
• Precursor lesions
  1. Telangiectasias surrounded by a vasoconstricted halo
  2. Pink macules or patches
  3. Blue bruise-like patches

Presentation: Common Types

- **Superficial hemangiomas**
  - Most common type

- **Larger plaque-type or segmental pattern**
  - Less common and more worrisome
  - More likely to be associated with regional extracutaneous anomalies, including PHACE(S) and LUMBAR syndromes

- **Deep hemangiomas**
  - Warm, ill-defined, light blue–purple masses with minimal or no overlying skin changes
  - A thrill may be felt or a bruit auscultated
Presentation: Superficial and Segmental

Superficial Hemangioma

Segmental Hemangioma

Presentation: Deep Hemangiomas
Natural History

1. **Early proliferation**
   - Rapid increase in size
   - 80% reach their final size by the end of 3 months

2. **Late proliferation**
   - Continued growth at a slower rate

3. **Plateau**
   - Existence as a distinct phase debated

4. **Involution**
   - May begin during first year of life
   - Earliest signs: color change from bright red to gray–purple and flattening of the surface
     - 30% of lesions involute fully by 3 years of age
     - 50% by 5 years
     - 70% by 7 years
     - 90% by 9 years
   - Some involute completely, while others leave atrophic, fibrofatty or telangiectatic residua
Residua of Hemangiomas

Fig. 103.7 Residua of hemangiomas.
A, B Minimal hypopigmentation (arrows) and a circular scar at site of ulceration in the same patient 20 years later; C telangiectasias; and D atrophy and fibrofatty changes.
A, B, D, Courtesy of Ronald P Rapini MD.
Complications

- Include:
  - Ulceration
    - Most common complication
    - Those on the lip and in the anogenital region or other skin folds (e.g. the neck) have the greatest tendency to ulcerate
  - Disfigurement
    - Vulnerable locations: Periocular, Nasal Tip, Lip, Ear, Breast, Anogenital
  - Functional impairment
    - Periocular: Most commonly cause astigmatism
      - Should be evaluated by an ophthalmologist
  - Systemic Involvement
Systemic Involvement - Large facial hemangiomas

- **PHACES syndrome**:  
  - Posterior fossa and other structural brain malformations  
  - Hemangioma  
  - Arterial anomalies of cervical and cerebral vessels  
  - Cardiac defects (especially coarctation of the aorta)  
  - Eye anomalies  
  - Sternal defects and supraumbilical raphe
Systemic Involvement - “beard” hemangiomas

- Lower facial or beard hemangiomas associated with airway involvement
  - Typically subglottic
  - Noisy breathing or subglottic stridor
- Onset of symptoms ranges from a few weeks to several months of age
- Refer to ENT
Systemic Involvement- Large hemangiomas on the lower body

- **LUMBAR syndrome**:  
- Lower body/lumbosacral hemangioma and lipomas or other cutaneous anomalies  
- Urogenital anomalies and ulceration  
- Myelopathy (spinal dysraphism)  
- Bony deformities  
- Anorectal and arterial anomalies  
- Renal anomalies
Multiple Hemangiomas

- Evaluation for visceral involvement is recommended when ≥5
- Most infants with both internal and skin involvement have many small, superficial cutaneous hemangiomas
- Liver is the most common site of visceral hemangiomas
  - Screening test: Ultrasound
  - Complications:
    - High-output CHF due to AV or arterioportal shunts
    - Abdominal compartment syndrome related to massive hepatomegaly
    - Hypothyroidism

Hypothyroidism

• ↑ levels of type 3 iodothyronine deiodinase have been identified in tissue from proliferating hemangiomas ➔ hypothyroidism
  • enzyme that deactivates thyroid hormone
• Screening for hypothyroidism in the immediate neonatal period is inadequate
Differential Diagnosis

- Capillary Malformation
- Kaposiform hemangioendothelioma
- Pyogenic granulomas
- Tufted angioma
- Infantile hemangiopericytoma
- Spindle cell hemangioma
- Eccrine angiomatous hamartoma
- Congenital fibrosarcoma

- Infantile myofibromatosis
- Lipoblastoma
- Nasal glioma
- Neuroblastoma
- Primitive neuroectodermal tumor
- Lymphoblastic lymphoma
- Dermatofibrosarcoma protuberans
- Rhabdomyosarcoma
Treatment: Infantile Hemangiomas

- Goals of management:
  1. Preventing or reversing life-or function threatening complications
  2. Treating ulcerations
  3. Preventing permanent disfigurement
  4. Minimizing psychosocial distress to patients and their families
  5. Avoiding overly aggressive potentially scarring procedures
Treatment

- Small hemangiomas with an excellent prognosis for spontaneous resolution with a good cosmetic outcome
  - No intervention required
- Ulceration
  - Local wound care +/- treatment of infection +/- additional therapies
Treatment: Local Therapies

• Local therapies
  • Intrallesional corticosteroids
    • Localized lesions such as small lip hemangiomas
    • Do not exceed 3-5 mg/kg per treatment session
    • Dosages vary from 5-40 mg/ml of triamcinolone acetonide
  • Topical corticosteroids
    • Class 1 topical steroid
    • Further studies needed, but likely thinner lesions will respond better
  • Topical β-Blockers
    • Timolol 0.5% gel or solution
    • Anecdotal reports of improvement
Treatment: Systemic Therapies

- Systemic Corticosteroids (Prednisone or prednisolone)
  - Treatment of life-or function threatening hemangiomas, disfiguring, or persistently ulcerated lesions
  - Suppresses VEGF production
- Adverse reactions include:
  - Immunosuppression
    - Pneumocystis jiroveci (carinii) pneumonia has been described
    - live-virus vaccines should be avoided while an infant is receiving corticosteroids and until they have been discontinued for at least 1 month
- Prednisone 2-3 mg/kg/day most commonly used
  - Maintain dosage until cessation of growth or shrinkage occurs
  - Then taper gradually
Treatment: Systemic Therapy

- β-Blockers (Propranolol)
  - 2-3 mg/kg/day divided BID or TID
    - Usually 2 mg/kg/day
  - 6 months average of treatment
  - ADR
    - Hypotension, bradycardia, hypoglycemia (can lead to seizures), bronchospasm, sleep disturbances
    - May increase the risk of stroke in children with PHACE syndrome
    - Drops BP and may attenuate flow through absent, occluded, narrowed or stenotic vessels
    - Do MRI/MRA of head, neck and cardiac vessels
Treatment: Systemic Therapy

- β-Blockers
  - Pretreatment
    - Consider EKG
    - Inpatient hospitalization for initiation of treatment if infants ≤ 8 weeks or comorbid conditions
    - Outpatient initiation if >8 weeks with adequate social support and no significant comorbid conditions
  - CV monitoring
    - Check BP and HR 1 & 2 hours after first dose and after significant dose increase
  - Blood glucose
    - Routine screening not indicated
    - Administer during daytime hours with a feeding shortly after administration
Treatment: Laser Therapy

• PDL (585-600 nm)
  • Greater efficacy for superficial lesions

• Nd: YAG
  • May have greater efficacy for deeper lesions
  • Higher risk of scarring
Vascular Malformations
Vascular Malformations

• Localized defects in embryonic vascular morphogenesis
• Persistent and tend to worsen over time if not treated
• Majority sporadic
• 1. Slow-flow malformations
  • Capillaries, veins, lymphatics
  • Most apparent at birth or become evident within 1st few months or yrs of life
• 2. Fast-flow malformations
  • AV shunting
  • Some present at birth but majority become evident in childhood or adulthood
Vascular Malformations

- Capillary malformations (CMs)
- Venous malformations (VMs)
- Lymphatic malformations (LMs)
- Arteriovenous malformations (AVMs)
- Complex-Combined malformations (CCMs)
Capillary Malformations

- Slow-flow
- Most common vascular malformation
- Major types
  - 1. Nevus flammeus “stork bites”
  - 2. Port-wine stain
    • Often develop deeper red hue, especially those in V1-V2 areas
    • Pinkish-red (birth) to purplish-red (adulthood)
    • Skin may thicken and become nodular
  - 3. Telangiectasias
    • Punctate, stellate, or linear red lesions
    • Localized, segmental, or generalized
Port-Wine Stain (PWS)
Syndromic Capillary Malformations

- Sturge-Weber syndrome
- Klippel-Trenaunay syndrome
- Proteus syndrome
- CLOVES syndrome
- CLAPO syndrome
- Macrocephaly-capillary malformation
Sturge-Weber Syndrome (SWS)

- Sporadic
- Facial PWS (typically V1) + ipsilateral ocular and leptomeningeal/brain anomalies
- Ocular involvement:
  - Glaucoma (especially PWS in both V1 and V2)
- Neurologic involvement:
  - Cerebral hemiatrophy and gyriform calcifications later in childhood (tram track)
  - MRI with gadolinium
- Complications
  - Seizures (partial motor)
  - Contralateral hemiparesis or hemiplagia
  - Developmental delays (attention deficits)
Sturge-Weber Syndrome (SWS)

Klippel-Trenaunay Syndrome (KTS)

• Limb CVM or CLVM with progressive overgrowth of affected extremity
• Sharply demarcated geographic appearance along lateral aspect of thigh, knee, and leg
• Associations:
  • Chronic coagulopathy
  • Hand/foot malformations
  • GI or GU tract bleeding if involved
  • Lymphedema
• Doppler U/S for vascular anomalies
• MRI for extent of soft tissue and bone involvement
• Colonoscopy or capsule endoscopy for GI bleeding
Klippel-Trenaunay Syndrome

Capillary Malformations: Telangiectasias Associations

- Cutis marmorata telangiectatic congenita
- Hereditary hemorrhagic telangiectasia
- Ataxia-telangiectasia
- Angiokeratomas
- Cerebral capillary malformation and hyperkeratotic cutaneous capillary-venous malformation
Cutis Marmorata Telangiectatica Congenita (CMTC)

- Dark red-purple, broad reticulated lesions intermingled with telangiectasias
- Persists upon warming
- Often lightens after 1st year
- Up to 50% have associated:
  - Hypoplasia (girth > length) of affected limb
  - Glaucoma (facial CMTC)
  - Neurologic defects (> generalized CMTC)
Cutis Marmorata Telangiectatica Congenita (CMTC)

Hereditary Hemorrhagic Telangiectasia (HHT)

- Osler-Weber-Rendu disease
- Autosomal dominant
- Mutations in endothelial transforming growth factor-β (TGF-β) receptors
  1. HHT1 – *endoglin (ENG)* gene
     - Higher risk of pulmonary/cerebral AVMs
  2. HHT2 – *activin receptor-like kinase 1 (ACVRL1)* gene
     - Higher risk liver AVMs
- Presents with epistaxis in childhood
- Telangiectasias of skin and oral mucosa after puberty
Hereditary Hemorrhagic Telangiectasia (HHT)

Vascular Malformations

- Capillary malformations (CMs)
- Venous malformations (VMs)
- Lymphatic malformations (LMs)
- Arteriovenous malformations (AVMs)
- Complex-Combined malformations (CCMs)
Venous Malformations (VMs)

- “cavernous hemangioma” – misnomer
- Recognized by their blue hue, softness, compressibility, and tendency to fill with dependency
- Syndromic Associations
  - Maffucci syndrome
  - Blue rubber bleb nevus syndrome
  - Glomuvenous malformation
  - Familial cutaneous and mucosal venous malformation
Venous Malformations (VMs)
Blue Rubber Bleb Nevus Syndrome (BRBNS)

- Sporadic disease
- Widely distributed dark blue papules and nodules with skin-colored compressible protuberances “rubber blebs”
- GI VMs
  - Melena, iron deficiency anemia
  - Check hemoccult
- Less commonly, CNS, lungs, and heart lesions
Blue Rubber Bleb Nevus Syndrome (BRBNS)
Maffucci Syndrome

- Sporadic disorder
- Blue to skin-colored nodules (VMs) + enchondromas
- Most commonly on extremities, leading to orthopedic and cosmetic defects
Maffucci Syndrome: Venous Malformations and Enchondromas
Vascular Malformations

- Capillary malformations (CMs)
- Venous malformations (VMs)
- Lymphatic malformations (LMs)
- Arteriovenous malformations (AVMs)
- Complex-Combined malformations (CCMs)
Arteriovenous Malformations (AVMs)

- Fast-flow vascular malformations with direct communications (AV shunts) between arteries/veins
- Least common but most dangerous vascular anomaly!
- Visible at birth (40%)
- Most common location is cephalic (~70%)
- Puberty (75%), pregnancy (25%), and trauma worsen AVMs
- Ultrasound and MRI to diagnosis and determine extent of lesion
- Syndromic Associations:
  - Cobb syndrome
  - Parkes Weber syndrome
  - PTEN hamartoma tumor syndrome
  - Stewart–Bluefarb syndrome
Arteriovenous Malformations (AVMs)
Cobb syndrome

- Sporadic
- Cutaneous, vertebral, and intraspinal AVMs
- Spinal AVMs
  - 20% have congenital red or red-brown vascular stains mimic PWS (stage 1 AVM) or throbbing masses with dilated veins (stage 2 AVM)
  - Neurologic deficits usually present in young adulthood due to mass effect on spinal cord and subarachnoid hemorrhage
    - Back pain, radiculopathy, rectal or bladder dysfunction, paraparesis, paraplegia
  - Diagnose by MRI and angiography
Cobb Syndrome

Treatment: Vascular Malformations

- Unlike hemangiomas, medical treatment is **not as effective** in vascular malformations
  - In general surgical resections, embolization, sclerotherapy, may provide benefit for selected lesions
  - Many vascular malformations remain unresectable or too extensive for destructive modalities
- Low-molecular weight heparin or ASA if coagulopathy present
Treatment: Vascular Malformations

- **Capillary malformations** (Port-wine stains & telangiectasias)
  - PDL is treatment of choice
  - Treat early in life to avoid lesional thickening

- **Venous malformations (VM)**
  - Goals of therapy is to prevent distortion of facial features, limit bony deformation, preserve function and minimize painful swelling
  - Must obtain coagulation profile FIRST to rule out underlying coagulopathy
  - Can treat with surgery, sclerotherapy or a combination of both
  - Elastic compression garments
Treatment: Vascular Malformations

- Arteriovenous malformations (AVMs)

  - Partial treatment results in recurrences that may be more difficult treat
    - If not disfiguring or impairing function **follow closely** and avoid premature partial treatment
  - Extreme pain, ulceration, bleeding and extensive enlargement are indications for treatment
    - pre-operative embolization + surgical resection to prevent excessive bleeding
Conclusions

- Majority of vascular anomalies of infancy and childhood can be classified as hemangioma or vascular malformation
  - Hemangiomas proliferate rapidly in infancy only to involute in early childhood
  - Vascular malformations are vessel abnormalities due to errors of vascular morphogenesis
    - They derive from embryonal capillary, venous, arterial, or lymphatic channels, or combinations thereof
    - They persist and often require a thorough work-up
## Summary

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<th>Clinical</th>
<th>Epidemiology</th>
<th>Immunohistochemistry</th>
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<tr>
<td>Infantile Hemangioma</td>
<td>■ Absent at birth</td>
<td>■ More common in girls premature/low birth weight infants</td>
<td>GLUT-1+, Lewis Y antigen +, Merosin +, FcγRII+</td>
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<td>■ Rapid proliferation for several months</td>
<td>■ Infants whose mothers underwent CVS sampling</td>
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<td>■ Spontaneous involution over years</td>
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<tr>
<td>Vascular Malformation</td>
<td>■ Evident at birth</td>
<td>■ No gender or gestation predilection</td>
<td>GLUT-1-, Lewis Y antigen -, Merosin-, FcγRII-</td>
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<td></td>
<td>■ Slow expansion</td>
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<td></td>
<td>■ Grow proportionately with child</td>
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<td></td>
<td>■ Persists into childhood</td>
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Thank you!
References


