Skin Lesions & Cerebrovascular Disease in Children: A Neurointerventionalist’s Perspective

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No financial disclosures

No neuroendovascular devices are manufactured or tested in children, so all treatment mentioned are off-label

CNS Vascular Anomalies/Syndromes: A History of “Splendid Isolation”

CLASSIFICATION SYSTEM FOR SPINAL ARTERIOVENOUS LESIONS:

Type I: Dural AVF
Type II: Intramedullary (glomus) AVM
Type III: Juvenile or combined AVM
Type IV: Intradural perimedullary AVF

Age 12
Age 17

3yo girl with new murmur on auscultation
RAPID POSTNATAL GROWTH AND SLOW INVOLUTION

Female:male, 5:1

INVOLUTING PHASE

Grow commensurately with child

Capillary
Venous
Arterial
Lymphatic
Fibrofatty

NORMAL ENDOTHELIAL CELL CYCLE

GROWTH RATES

FEMALE:MIS. 5:1

FEMALE:MIS. 3:1

Hemangiomas and Vascular Malformations in Infants and Children: A Classification Based on Endothelial Characteristics

John B. Mulhern, M.D., and Jula Glauser, Ph.D.

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MATERIALS AND METHODS:
The neuroradiology and neurosurgery literature is replete with reports of true infantile hemangiomas insinuated within the neuraxis. Two board-certified neuroradiologists reviewed the available imaging of these patients, and important associated CNS findings. Histopathologic confirmation was available for 2 patients and was reviewed by our pathologist.

BACKGROUND AND PURPOSE:

The neuroradiology and neurosurgery literature is replete with reports of true infantile hemangiomas insinuated within the neuraxis. Two board-certified neuroradiologists reviewed the available imaging of these patients, and important associated CNS findings. Histopathologic confirmation was available for 2 patients and was reviewed by our pathologist.

CLASSIFICATION OF VASCULAR ANOMALIES

Fig 1. Classification of vascular anomalies in children.

“VERTEBRAL BODY HEMANGIOMA”

Cobb Syndrome
Cutaneomeningospinal Angiomatosis

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SUGIES OF THE SPINAL CORD

Intracranial and Intraspinal Angiography

Revised Classification System

The revised classification system now has two main categories: vascular tumors and vascular malformations. In 1996, this classification system was modified to include kaposiform hemangioendothelioma (KHE), tufted angioma (TA), and a unique natural history, which should not be confused with hemangiomas and anemia (patient 3) and is illustrated in Fig 1.
2008 – age 4 months

2012 – age 4 years

INFANTILE INTRASPINAL AND EXTENSIVE CUTANEOUS HEMANGIOMAS

Excellent response to propranolol

A 6-week-old girl presented with multiple cutaneous hemangiomas (figure 1). She had brisk lower extremity reflexes without other deficits. Imaging revealed extensive hemangiomas in liver and extrapleural and oropharyngeal areas. Spine MRI showed a C5-T9 intraspinal-extradural hemangioma producing cord compression (figure 2A). There was minimal response of the hemangiomas to steroids but improvement with propranolol (figure 2, B and C). Intraspinal hemangioma is rarely associated with extensive cutaneous hemangiomas.1

Corticosteroids are first-line treatment for extensive infantile hemangiomas. Propranolol’s mechanism of vessel regression involves vasoconstriction, apoptosis of capillary endothelial cells, and decreased expression of vascular-endothelial and basic-fibroblast growth-factor genes.2

Partha S. Ghosh, MD, Debabrata Ghosh, MD, Cleveland, OH

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Figure 1 Multiple cutaneous hemangiomas on head, face, neck, back, and leg

Figure 2 Cervical and thoracic spine MRI showing hemangioma (A) T2-weighted prior to steroid treatment; (B) slight reduction in size after steroid treatment; and (C) marked reduction of the hemangioma 8 weeks after starting propranolol.

PHACES

Posterior fossa abnormalities (Dandy-Walker cyst, cerebellar dysgenesis)

Hemangioma (large H&N regional infantile hemangioma)

Arterial anomalies (agenesis, persistent fetal vessels, aneurysms, ectasias)

Cardiac anomalies (coarctations, VSD, aortic arch anomalies)

Eye anomalies (coloboma, glaucoma)

Sternal anomalies (clefing)

"Arterial"

Agenesis of arteries

Dysplasias of arteries

Persistent fetal arteries

Aneurysms

Stenoses of arteries

Stroke in Children With Posterior Fossa Brain Malformations, Hemangiomas, Arterial Anomalies, Coarctation of the Aorta and Cardiac Defects, and Eye Anomalies (PHACES) Syndrome: A Systematic Review of the Literature

Categories of Pediatric AIS

Neonatal/perinatal (≥14 mo/ive birth)

Moyamoya

Dissection – isolated, post-traumatic, syndromic

Emboli/thrombotic – cardiac, hematologic, infectious procedure-related (cardiac interventions)

Focal cerebral arteriopathy

Other – SCD, vasculitic, etc.
Moyamoya

Progressive stenosis of the terminal ICA/M1/A1 + lenticulostriate proliferation

Moyamoya usually presents in isolation, but has a higher than baseline incidence with other conditions (NF1, Tr18, SCD, PHACE)

MMD accounts for 6% of childhood stroke in western countries

In Japan, MMD is the most common pediatric cerebrovascular disease. In the US, Asians have the highest incidence (OR 4.6 compared with Caucasians, with Hispanics having an OR of 0.5)

Familial incidence in first-degree relatives is ~10% in Japan (5% at BCH)

MMD has 80% concordance in monozygotic twins

Bimodal distribution of presentation, with AIS in the first decade of life, and hemorrhagic stroke at 30-40 years

Moyamoya

Severe and progressive headache is a common early symptom

Ischemic symptoms follow crying, hyperventilation, coughing, straining, fever, dehydration

Stroke is multiple and recurrent, usually in the ICA territory

Beyond AIS, 50-66% of untreated MMD patients have progressive neurological dysfunction and decline, declining to 2.6% in revascularized patients

How to revascularize? Direct STA-to-MCA bypass is difficult and usually unsuccessful in small children

BCH post-synangiosis results – 67% had stroke preoperatively, and 7.7% perioperatively (patients are kept well hydrated). For those with over 5 year follow-up, stroke prevalence postoperatively is 4.3%

ASA for life (3-5 mg/kg/day)

Attempted angioplasty/stenting for MMD has been universally unsuccessful

No IH – Possible PHACE?
LUMBAR

Associated intraspinal arterial anomalies?

CLOVES

NewlyDefined Syndrome of Congenital Lipomatosis-Overgrowth, Vascular Malformations, and Epidermal Nevus (CLOVES) Syndrome in Seven Patients
John C. Yapp, MD, John R. Cipo, MD, Ashish K. Rana, MBBS, and Frederick A. Regnier, MD

Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and spinal anomalies: a descriptive study of 10 cases of CLOVES syndrome
Abstract: Acral, truncal, and intraspinal vascular malformations were first described by Happle et al (1996) as a distinct syndrome to explain the anomalies seen in a patient who had a familial association of cutaneous vascular malformations and lipomatico-overgrowth. In 1999, Basdevant et al (2000) reported three patients with cutaneous vascular malformations, truncal lipomatosus overgrowth, and associated intraspinal arterial anomalies. The patients in this study present with acral, truncal, and intraspinal vascular malformations. There is a high degree of association between acral, truncal, and intraspinal vascular malformations in this group of patients. The combination of truncal lipomatico-overgrowth, acral vascular malformations, and spinal intraspinal arterial anomalies is distinct from other congenital malformation syndromes and is characterized by complex truncal overgrowth, vascular anomalies, and spinal intraspinal arterial anomalies. These findings suggest a new entity, CLOVES syndrome.

Fatty truncal mass: can extend from the back to the abdomen and into gluteal or groin region; and its deep extension can be intraspinal. Overlying skin typically has a capillary malformation
Vascular anomalies: the fatty mass is associated with venous, lymphatic, and arteriovenous anomalies
Abnormal extremities & scoliosis: macrodactyly, wide sandal gap
Other abnormalities: small or absent kidney, abnormal patella and/or hip joints, neurologic abnormalities (tethered cord, neural tube defect, seizures)

2004 – age 2 years

3/13/2006 – L arm weakness
3/13/2006 – incontinence
12/4/2006 – worsening L arm weakness
Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome.

**Figure 1.** PCR amplification products generated by using primers specific for PIK3CA exons 16 and 20 from genomic DNA (top) and RNA (bottom) of CLOVES-affected individuals CL1, CL2, CL3, CL4, and CL5. PCR products were analyzed by gel electrophoresis. The products are shown in the middle, and the DNA is shown in the left and right columns.

**Figure 2.** Somatic activating mutations in PIK3CA exons 16 and 20 identified by massively parallel sequencing of DNA. a. Massively parallel sequencing reads identified a somatic activating mutation in participant CL4. The right column is lipomatous tissue from CLOVES-affected participant CL5 (the blank lane represents the sequencing read). b. Massively parallel sequencing reads identified a somatic activating mutation in participant CL6. The right column is lipomatous tissue from CLOVES-affected participant CL5 (the blank lane represents the sequencing read).

**Figure S1.** Experimental design of the study. a. Fresh or frozen tissue samples from CLOVES-affected individuals were used for DNA and RNA sequencing. b. DNA sequencing libraries were prepared from fresh or frozen tissue samples by using the Select human exome kit (Agilent Technologies, Santa Clara, CA). c. RNA sequencing libraries were prepared from fresh or frozen tissue samples by using the TruSeq Stranded Total RNA kit (Illumina, San Diego, CA). d. DNA and RNA sequencing libraries were sequenced on an Illumina HiSeq 2000 system. e. Somatic mosaic mutations were identified by using massively parallel sequencing.

**Figure S2.** Overview of the study design. a. Fresh or frozen tissue samples from CLOVES-affected individuals were used for DNA and RNA sequencing. b. DNA sequencing libraries were prepared from fresh or frozen tissue samples by using the Select human exome kit (Agilent Technologies, Santa Clara, CA). c. RNA sequencing libraries were prepared from fresh or frozen tissue samples by using the TruSeq Stranded Total RNA kit (Illumina, San Diego, CA). d. DNA and RNA sequencing libraries were sequenced on an Illumina HiSeq 2000 system. e. Somatic mosaic mutations were identified by using massively parallel sequencing.

**Table 1.** Summary of somatic activating mutations identified in PIK3CA exons 16 and 20.

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**Figure 3.** Flowchart of the experimental design. a. Fresh or frozen tissue samples from CLOVES-affected individuals were used for DNA and RNA sequencing. b. DNA sequencing libraries were prepared from fresh or frozen tissue samples by using the Select human exome kit (Agilent Technologies, Santa Clara, CA). c. RNA sequencing libraries were prepared from fresh or frozen tissue samples by using the TruSeq Stranded Total RNA kit (Illumina, San Diego, CA). d. DNA and RNA sequencing libraries were sequenced on an Illumina HiSeq 2000 system. e. Somatic mosaic mutations were identified by using massively parallel sequencing.
Lumbar malformations (LMs) are a common cause of low back pain. They can affect the spinal cord, cauda equina, nerve roots, or sacrum. Lumbar malformations can be associated with congenital anomalies, such as sacral agenesis, spina bifida, and tethered cord syndrome. These malformations can lead to neurologic symptoms, including pain, weakness, and motor dysfunction. Surgical treatment options include decompression, nerve root stripping, and dural takedown. The choice of treatment depends on the patient's symptoms and the underlying cause of the malformation. Overall, lumbar malformations can be challenging to diagnose and treat, and early recognition and intervention are critical for optimal outcomes.
Sinus Pericranii

3 months

5.5 years

28 weeks fetal MRI

8 months

4 weeks

4 months
The extradural-intradural A VMs corresponded with metameric lesions, which involved the soft tissue, spinal canal, and nerve root along an interface of the spinal canal, spinal cord, and paravertebral column. Superselective angiography and endovascular embolization. The extradural-intradural A VMs corresponded with metameric lesions, which involved the soft tissue, spinal canal, and nerve root along an interface of the spinal canal, spinal cord, and paravertebral column. Superselective angiography and endovascular embolization.

Fig. 2. Systemic heparinization was performed via the femoral route and the right TCT route (Fig. 2). Systemic heparinization was performed via the femoral route and the right TCT route (Fig. 2). Systemic heparinization was performed via the femoral route and the right TCT route (Fig. 2). Systemic heparinization was performed via the femoral route and the right TCT route (Fig. 2).

Fig. 1

Metameric spinal vascular anomaly: a lesion that extends beyond the cord surface and that can involve any other tissue in the same segmental dermatome (skin, muscle, paraspinal tissue, dura).

Spinal endothelial cells share a mesodermal origin with skin and muscle. Cobb is nonhereditary and likely results from a somatic mutation during angiogenesis, with affected cells migrating throughout the metamere.

Cobb Syndrome
Cutaneomeningospinal Angiomatosis
SAMS: Spinal Arteriovenous Metameric Syndromes

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Cobb Syndrome
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• The study of vascular anomalies within the "neuro" specialties has focused largely on anatomic localization, prognosis, and treatment – e.g., intramedullary, perimedullary, epidural

• However, contextualizing CNS vascular lesions within the broader world of vascular anomalies is essential for progress, and begins with accurate classification – infantile hemangioma, venous malformation, lymphatic malformation, AVM, AVF

• Although many vascular lesions have been mislabeled “hemangioma”, true IH can involve the CNS

• Regional infantile hemangiomas involving the H&N should evoke PHACES, and lower trunk regional IH should trigger a search for associated anomalies – anorectal, renal, spinal (LUMBAR)

• Think of a capillary malformation on the back or H&N as a red flag
  ▶ Look for associated findings: lipomatous mass, AVM involving all tissues in a metamere, unusual spinal AV-fistulae, paraspinal lymphatic malformations
  ▶ Think syndromes: Cobb, CLOVES, RASA1
  ▶ Capillary stain on the back with severe back pain or neurological symptoms: keep looking until you find a lesion

• Sinus pericranii does not necessarily need treatment. Treatment should be considered for cosmesis or in rare cases of a large skull defect. Cases with obligate brain venous drainage via the SP cannot be safely treated

• We are likely at the threshold of a new era of deeper understanding of genetics, pathophysiology, and treatment targets of CNS vascular malformations

Thank You