Approach to Neonatal Dermatology
Diagnosis and Management of Select Birthmarks

Symposium S006

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No Relevant Conflicts of Interest
- Advisory Board: Leo Pharma
Learning Objectives

Identify select “birthmarks” of medical importance

Determine lesions which warrant additional evaluation and imaging
Outline

- Select vascular birthmarks and associated features
- Lumbosacral birthmarks
- Congenital melanocytic nevi
Capillary Malformations (CMs)

- Port wine stains or nevus flammeus
- 0.3% live births
- Congenital
- Often sporadic
- Ectatic dermal capillary malformations
- Differentiate from nevus simplex

- Lesions may be confluent or reticulated
- Localized or widespread
Capillary Malformations

- **Natural history**
  - Enlarge with growth
  - Darken with time
    - Lightening age 3-6 months
  - Skin thickening
  - Soft tissue hypertrophy, bony overgrowth

- **Treatment**
  - Pulsed Dye Laser
  - Subspecialty evaluation
Sturge-Weber Syndrome (SWS)

- V1 capillary malformation (+/- V2, V3)
- Cerebral vascular malformation
- Glaucoma, vascular malformation
- 8-20% patients
- Epilepsy
- Cognitive impairment
- Behavior abnormalities
- Spastic hemiparesis
- Visual abnormalities
SWS: Upper Facial Port Wine Stain

- 66 patients over 7 years
  - 11 SWS, 4 suspected SWS
- SWS defined as upper facial port wine stain and cerebral MRI changes
  - Ophthalmologic changes optional
- 16.1% positive
- Midline crossing, temporal area and nose area higher risk

Six facial patterns identified

At risk topography includes extension to midline, scalp, nose, temporal area

Corresponds to somatic mosaicism
  - Specific patterns at risk for Sturge-Weber syndrome

Suggest ophthalmic division of trigeminal nerve distribution should be abandoned

★ Image
★ more information needed

Somatic activating mutation in guanine nucleotide-binding protein alpha-Q (GNAQ)

- Upregulates expression of mutant Gαq protein
- Activating mutation in GNAQ (c.548G>A mutation, R183Q)
  - 88% of pathologic tissue samples in SWS (brain and skin)
  - 92% (skin) from nonsyndromic PWS
- Confirmatory reports
    - c.548G>A, p.Arg183Gln in GNAQ
    - SMARCA4, EPHA3, MYB, PDGFR-β, and PIK3CA mutations
Sturge-Weber Syndrome (SWS): Imaging and Evaluation

- MRI is typical imaging modality
- Neurologic findings
  - Parieto-occipital most common
  - Not static lesions
- Seizures most common
  - Often present age < 1 year
  - Early recognition/treatment of seizures
- Progressive cortical atrophy
- Early referral to ophthalmology with ongoing monitoring

Capillary Malformation (Port Wine Stain)

- **CMs and Limb lesions**
  - Klippel Trenaunay Syndrome (KTS)
    - Capillary Malformation
    - Venous varicosity
    - Overgrowth soft tissue and bone
  - Capillary Malformation with Overgrowth (CMO)
  - Parkes Weber Syndrome (PWS)
    - Association with high flow AVM

- **CMs and Overgrowth Syndromes**
  - Epidermal nevus
  - Lipoma
  - Limb asymmetry/overgrowth/undergrowth
  - Digital anomalies
  - Macrocephaly
- Similar clinical appearance
- Different diagnoses
- Difficult to differentiate early in life
- Different prognosis
- Need to reassess

- Imaging and genetics can help to distinguish
- Ongoing subspecialty monitoring

Klippel Trenaunay (KTS) - Slow flow anomalies (CM+VM+/LM+hypertrophy)
Parkes Weber (PWS) - Capillary malformation
Fast flow AVM - Overgrown limb (CMO)

Overgrowth Syndromes

- Clinically heterogeneous disorders
- Share similar features
  - Hemihypertrophy or partial overgrowth
  - Soft tissue growths
  - Vascular anomalies
  - Skeletal anomalies
  - Epidermal nevi
  - Variable neurodevelopmental deficits
  - Variable malignancy risk
- Many caused by mutations in genes in PIK3CA-AKT-mTOR pathway
  - PI3K Related Overgrowth Spectrum (PROS)
    - Mutations in PIK3CA causing different clinical entities
      - Additional mutations?
      - Timing of mutational event?
      - Tissues impacted?
- Mosaicism
  - Challenges associated with genetic testing
Segmental Overgrowth Syndromes

- Spectrum of involved organs, including the soft tissue, muscles, lymphatics, and vasculature

## Vascular Malformations Overgrowth

<table>
<thead>
<tr>
<th>Syndrome/Gene</th>
<th>Malformation</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocephaly-CM</td>
<td>Facial persistent “nevus simplex’ and CM(reticulated or confluent PWS) trunk/extremities</td>
<td>Macrocephaly, hydrocephalus, cerebral and cerebellar anomalies, Skin/joint laxity, macrosomia, syndactyly</td>
</tr>
<tr>
<td>Megalencephaly-CM</td>
<td>CM, LM, CLVM</td>
<td>Hemihypertrophy, lipoma, Epidermal nevi, brain malformations, MR</td>
</tr>
<tr>
<td>(PIK3CA and AKT-1)</td>
<td>Truncal combined malformation</td>
<td>Congenital Lipomatous overgrowth, Bony abnormalities, epidermal nevus, “neural tube defects”</td>
</tr>
<tr>
<td>Proteus</td>
<td>CM, Combined</td>
<td>Macrocephaly, penile macules, lipoma</td>
</tr>
<tr>
<td>(AKT-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOVES</td>
<td>CM AVM</td>
<td>Variable phenotype, CNS and soft tissue AVMs, Not all patients with Parkes Weber have RASA1 mutations</td>
</tr>
<tr>
<td>(PIK3CA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bannayan, SOLAMEN, “PTEN Associated”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PTEN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM-AVM (some Parkes Weber patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RASA1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beckwith- Wiedemann</td>
<td>CM (central facial persistent “nevus simplex”)</td>
<td>Macroglossia, macrosomia, tumors, ear creases/pits, hypoglycemia</td>
</tr>
<tr>
<td>Dysregulation of the expression of imprinted genes 11p15.5 region</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multiple cutaneous CM
  - Small congenital or often acquired pale halo
  - Increase in number

Cutaneous, subcutaneous, intraosseous and/or cerebral AVM
  - AVM may underlie the CM

Autosomal dominant, mutations in RASA1

Variable phenotype within families

Nevus Simplex

- Most common neonatal vascular lesion
- Incidence 19-82%
- Pink to red, blanchable
- Indistinct borders
- Variable intensity
  - Prominent with crying, temperature changes, activity
- Fade over months to years
  - Nape of neck > glabella may persist
Nevus simplex: A reconsideration of nomenclature, sites of involvement, and disease associations

Anna M. Juern, MD, a Zoey R. Glick, MD, b Beth A. Drolet, MD, a and Ilona J. Frieden, MD c

Milwaukee, Wisconsin; Washington, DC; and San Francisco, California

Nevus Simplex: Less Common Sites

- Nose
- Cutaneous lip
- Occipital scalp
- Parietal scalp
- Upper/lower back
# ISSVA Classification of Vascular Birthmarks

## Vascular tumors
- Proliferate, “out of proportion”
- Infantile hemangioma
- Congenital hemangiomas
- Others

## Vascular malformations
- Errors in vascular morphogenesis
- Often at birth, slower expansion/proliferation
- Characterized by vessel type and flow characteristics
  - Capillary (CM)

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Hemangiomas: When to Worry?
Beard Hemangioma

- Lower lip
- Chin
- Neck
- Mandible

63% airway involvement\(^1\)

\(^1\) J Pediatr 1997131:643-646
Large Facial Hemangioma

PHACE Syndrome

- Facial hemangioma 5cm or greater in diameter
Embryonic Segments: Unifying Pattern


PHACE Syndrome

- Posterior fossa abnormalities
- Hemangioma
- Arterial (head and neck)
- Cardiac
- Eye abnormalities
  (Sternal, Supraumbilical raphe)

PHACE Imaging:
- MRI, MRA head
- MRA neck, aortic arch
- Echocardiogram
- Ophthalmologic examination

FIGURE 2
Diagram of the proposed facial segments.
MRI often requires sedation, general anesthesia

- Increased risk of cardiac arrest children less than 1 year old

- General anesthesia may affect neurologic, cognitive, social development
  - Anesthetic agents during brain development result in neuronal apoptosis, *cognitive defects* in animal models¹
  - *Developmental or behavior disorder* diagnosis increased with anesthesia before age 3²
  - Increased risk *learning disabilities* with 2 or more anesthetics and cumulative exposure³
    - Language and abstract reasoning deficits
    - ADHD

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² J Neurosurg Anesthesiol 2009;21:286-91
³ Anesthesiology 2009;110:796-804
“It is not yet possible to know whether anesthetic drugs are safe for children in a single short-duration procedure. Similarly, it is not yet possible to know whether use of these drugs poses a risk, and if so, whether the risk is large enough to outweigh the benefit of needed surgery, tests, or other procedures. Until further research clarifies the significance of these findings, parents and caregivers should discuss the timing of planned procedures with their child’s healthcare providers. Concerns regarding the unknown risk of anesthetic exposure to the child’s brain development must be weighed against the potential harm associated with cancelling or delaying a needed procedure. Each child must be evaluated individually based on age, the type of procedure, level of urgency, and other health factors.”

http://smarttots.org/consensus-statement-supplement/
Imaging and Sedation: Considerations in Children

- Long term studies ongoing
  - PANDAS (Pediatric Anesthesia NeuroDevelopment Assessment Study)\(^1\)
    - Single gas anesthesia prior to 36 months without significant decrease in IQ at age
  - MASK (Mayo Safety in Kids) Study\(^2\)
  - GAS (General Anaesthesia and Awake–Regional Anaesthesia) study\(^3\)
    - Cognitive, language, and motor functions at age 2 years were comparable between children exposed to general sevoflurane anesthesia and regional anesthesia
    - Pending: primary outcome of global cognitive function at age 5 years

\(^1\) JAMA. 2016 Jun 7;315(21):2312-20
\(^2\) Contemp Clin Trials. 2015 Mar;41:45-54
\(^3\) Lancet. 2016 Jan 16;387(10015):239-50
Feed and Wrap MRI

- aka “feed and sleep,” “feed and swaddle,” or “feed and bundle”
- 75% success in age 3 month and younger
- 100% diagnostic in cardiac MRI in infants less than 6 months
- Review of internal data, 99% provided clinically useful information, 75% complete information obtained
  - Less successful scans premature infants, spinal studies

1 Clin Radiol. 2005;60:731-741
2 Pediatr Cardiol. 2015 Apr;36(4):809-12
3 Antonov NK et al. Retrospective review of feed and wrap MRI technique in infants. PAS Annual Meeting, April 2015
LUMBAR Syndrome

- **L**ower body hemangioma and other cutaneous defects
- **U**rogenital anomalies, Ulceration
- **M**yelopathy
- **B**ony deformities
- **A**norectal malformations, Arterial anomalies
- **R**enal anomalies

aka PELVIS and SACRAL Syndrome

Figure 5. Algorithm for comprehensive diagnostic imaging guidelines of LUMBAR association.
LUMBAR: Diagnostic Approach

large (≥2.5 cm) midline or segmental IH in lumbosacral and/or perineal region

→ physical examination

before age 3 months

ultrasonography
spine, abdomen and pelvis

→ no abnormalities

→ MRI
spine

age 3-6 months

no abnormalities

→ no evidence for LUMBAR syndrome

→ consider LUMBAR syndrome

abnormalities of urinary tract, kidneys and/or intraspinal anomalies

→ urodynamic assessment

Multiple Hemangiomas: When to Screen

Liver Hemangioma Risk Factors

- **Multiple**
  - 5 or more hemangiomas
    - 16% incidence of hepatic hemangiomas
- **Segmental**
  - Larger
    - Involve region or territory of skin
- **Ultrasound liver with doppler**

Additional Screening

- **CBC**
- **Stool for occult blood**

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Lumbosacral Birthmarks
76% of patients (range, 43%-95%) have overlying midline lumbosacral cutaneous lesions\(^1\)

**Occult spinal dysraphism (OSD)**
- Incomplete fusion midline bony elements spine
- Skin-covered without exposed neural tissue

**Findings include**
- Tethered cord
- Lipoma
- Sinus tract

\(^1\) Guggisberg et al. Arch Dermatol Vol 140 2004
Potential Consequences of a Tethered Spinal Cord

- Low back pain
- Pain and weakness of the legs
- Difficulty ambulating
- Loss of bladder and bowel control
Sacral Dimples

- Lumbosacral dimples are common
- Usually small shallow within crease
- Atypical dimples higher risk of dysraphism
  - Deep dimples (sinus tracts to CNS)
  - Associated skin lesions (2+cutaneous features)
  - Above the crease
- Do not probe deep dimples

Deviated Gluteal Fold

- Symmetric: low risk
- Asymmetric Deviated Gluteal Fold
  - Underlying mass

## Spinal Dysraphism

<table>
<thead>
<tr>
<th>Low Index of Suspicion</th>
<th>High Index of Suspicion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small / shallow dimples</td>
<td>2+ “low risk”</td>
</tr>
<tr>
<td>Deviated gluteal cleft</td>
<td>Hypertrichosis</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>Atypical Dimples</td>
</tr>
<tr>
<td>Nevus simplex</td>
<td>Large</td>
</tr>
<tr>
<td>Capillary malformation</td>
<td>&gt;2.5 cm from anal verge</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Tags, tails</td>
</tr>
<tr>
<td>Melanocytic nevi</td>
<td>Hemangioma</td>
</tr>
<tr>
<td></td>
<td>Lipoma</td>
</tr>
<tr>
<td></td>
<td>Aplasia cutis/scar</td>
</tr>
<tr>
<td></td>
<td>Dermoid cyst/sinus</td>
</tr>
</tbody>
</table>
Prospective study 254 infants with lumbosacral lesions

All infants underwent ultrasounds and neurosurgical evaluation

- 157 simple sacral dimple or deviated gluteal fold
  - 96% high quality
  - No abnormalities

- High concordance between ultrasound and MRI
  - 96% sensitivity, 96% specificity, PPV 96%
  - Low sensitivity for dermal sinus (46%)

Ultrasound good screening tool for low risk lesions, MRI for high risk lesions
Association with underlying spinal dysraphism
- 1/3 patients
- Tethered cord
- Intraspinal hemangioma
- Intraspinal lipoma

2.5 cm or greater diameter

Ultrasound poor screening tool
- Sensitivity 50%, specificity 77%

Conclusion: Screening MRI is recommended for children with these lesions

## Lumbosacral Cutaneous Stigmata and Imaging in Neonate

- **Low risk**
  - Ultrasound
- **High risk**
  - MRI
- **Intermediate risk**
  - Gray zone

### Table 3. Assessment of Congenital, Medial Lumbosacral Cutaneous Lesions in the Absence of Neurologic or Orthopedic Manifestations*

<table>
<thead>
<tr>
<th>Risk of OSD</th>
<th>Congenital Lumbosacral Midline Skin Lesion</th>
<th>Age &lt;6 mo</th>
<th>Age ≥6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;2 Lesions of any kind</td>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>One lesion and spinal cord dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipoma†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tail†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermal sinus†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Group 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atypical dimple†</td>
<td>USD</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Unclassified hamartoma†</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td></td>
<td>Aplasia cutis congenita†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deviation of gluteal furrow†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemangioma *</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PWS *</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertrichosis *</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pigmentary nevus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple dimple†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mongolian spot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; OSD, occult spinal dysraphism; PWS, port-wine stain; USD, ultrasound.

*Neurologic and morphologic evaluations are required in the presence of clinical symptoms.
†Considered as isolated lesion.
‡High risk of cerebrospinal fluid infection leading to rapid spinal MRI and neurosurgical evaluation.
§All authors do not agree with this opinion for isolated PWS.
| Simple dimple is defined as an isolated small lesion (≤5 mm in diameter) 2.5 cm or closer to the anus.

*Arch Dermatol. 2004 Sep;140(9):1109-15

Congenital Melanocytic Nevi
**Congenital Melanocytic Nevus**

- Birth or early infancy
- 1-2% infants
- May resemble café-au-lait macule early in life

- **Size matters**
  - Small < 1.5cm
  - Medium, everything in between
  - Large > 20 cm (adult), 6cm body (infant), 9cm scalp (infant)
  - Giant >40 cm

- **N-Ras mutation mosaicism**

Large lesions are uncommon (0.02%)
- Uniformly present at birth
- Location matters
  - Limb lesions
    - Hypoplasia
  - Axial (head, neck, back)
    - Neurocutaneous Melanosis
    - Satellite nevi
- Melanoma risk variably reported (4-10%)
  - First decade of life
  - Giant (>40cm)
  - Trunk
  - Satellite
# Neurocutaneous Melanosis (NCM)

- Leptomeningeal melanocytic hyperplasia in association with congenital nevus
  - Proliferation of nevus cells in the CNS

- **Congenital Melanocytic Nevus (CMN) Syndrome**\(^1\)
  - Neurological abnormalities of the central nervous system
  - Accounts for non-melanotic lesions

- **Risk factors**
  - Large nevi
  - Multiple small/satellite nevi\(^2\)

- **Symptoms**
  - Hydrocephalus
  - Increased ICP
  - Developmental delay
  - Seizures
  - Nerve palsies, sensory/motor deficits, bowel/bladder dysfunction

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\(^1\) Waelchli R et al. BJD 2015 May 12.Epub
\(^2\) BJD 2015 173, pp1522–1524
NCM/CMN Syndrome: Evaluation

- Neurodevelopmental monitoring, head circumference

- MRI imaging of choice
  - Typically prior to age 4-6 months
    - Brain myelination obscures melanin deposits
  - Best predictor of neurodevelopmental outcomes

- Symptoms by age 2
- Asymptomatic involvement may also occur

- Poor prognosis especially if symptomatic
  - Melanoma, mechanical obstruction

CMN Syndrome: Imaging

- MRI abnormalities in 20%
  - Most common: isolated intraparenchymal melanosis
    - foci of melanin-containing cells in the brain parenchyma
  - Less common:
    - syringomyelia, nonmalignancy-related hydrocephalus, tumors and malformations

- MRI guided practice
  - Placement of VPS, resection of problematic tumors, biopsy of growing lesions, neurodevelopmental monitoring

- Reimaging
  - Follow significant abnormalities
  - With new neurologic symptoms

Waelchli R et al. BJD 2015 May 12.Epub
Proposed Management of CMN


Figure 4

CMN

Single CMN
- Normal neurology and development
  - Access to Paediatric Dermatology services if change in lesion
- Abnormal neurology or development

Multiple CMN (≥ 2 CMN)
- Age < 2 years
  - Abnormal neurology or development
  - Gadolinium-enhanced MRI whole CNS (ideally in first 6 months) with paediatric neuroradiology review
  - Other pathology
    - Individually assessed multi-disciplinary care with paediatric dermatology, neurology, neurosurgery, neuroradiology
  - Intraparenchymal melanosis only
    - No routine repeat MRI
    - Neurodevelopmental assessment yearly by paediatric neurologist in pre-school years
- Age > 2 years
  - Normal neurology and development
  - Normal
    - No routine repeat MRI

3-6 monthly follow up for first 2 years, then 6-12 monthly, with neurodevelopmental assessment by paediatrician in pre-school years
Large/Giant Congenital Melanocytic Nevus: Treatment

- **Staged/serial excisions**
  - Decrease burden of nevus cells
    - Decrease risk malignancy
  - Incomplete removal, recurrence
    - Difficulty detecting melanoma

- **Timing**
  - Individualized
  - 6 months to 2 years

- **Partial thickness**
  - Dermabrasion
  - Peels
  - Laser

**Diagram:**

- Malignancy reduction a concern?
  - No
    - Cosmetically concerning?
      - Yes
        - Excision likely to cause significant disfigurement or impair function?
          - No
            - Under 3 Years old?
              - Yes
                - Excision
              - No
                - Patient education and surveillance as appropriate
          - Yes
            - Excision
        - No
          - Consider partial thickness removal or combination procedures
    - Yes
      - Excision likely to cause significant disfigurement or impair function?
        - Yes
          - Consider partial thickness removal or combination procedures
        - No
          - Excision

Various vascular lesions present in the newborn period and warrant proper identification.

Vascular birthmarks may be cutaneous manifestations of underlying disease.

Vascular precursors may mimic one other and warrant close follow-up.

Cutaneous features may be the sole manifestation of spinal dysraphism; MRI is warranted in high risk lesions.

Giant congenital melanocytic nevi and multiple satellite nevi place the neonate at risk for neurocutaneous melanosis/congenital melanocytic nevus syndrome.