Congenital Melanocytic Nevi, Cafe au lait Macules and Everything in Between

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Disclosure of Relationships with Industry

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S062: Managing Birthmarks and Neonatal Skin Diseases

Disclosures

I have no relevant relationships with industry
Objectives

Patterned Pigmentations/Somatic Mosaicisms-

Checklist for when to evaluate for associated systemic findings and what to evaluate for

- Congenital Melanocytic Nevi
- Becker’s Nevi
- Segmental Pigmentation Disorder
- Linear and Whorled Nevoid Hyper/Hypo-melanosis
- Broad blaschko-linear patterned pigmentation as a marker for McCune Albright Syndrome
- Pigmentation of the genitals
- Dermal Melanocytosis and when to worry
LCMN is a mosaic mutation of NRAS
Initial Visit Checklist

• Does this child have neurocutaneous melanosis?
• Is there a melanoma?
• What are these weird lumps?
Neurocutaneous melanosis?

• **50% who develop symptoms do so prior to 1 year**
  – most by 2 years of age
  – another small peak at time of puberty
  – Seizures, hydrocephalus, cranial nerve deficits, mass effects

• **Number of satellites most predictive**
  – >20 satellites 5 fold increase in risk of NCM
  – 3 or more small or medium congenital nevi with no “mother ship”

• **Size**
  – > 20cm increases risk
  – Infant → about 6 cm on head and 9 cm on body

• **Location of LCMN**
  – Posterior midline
Large mothership with multiple satellites

Multiple small/medium congenital nevus phenotype
Imaging for NCM

- **Image if:**
  - LCMN with (10 or more?) satellites
  - 3 or more small or medium congenital nevi
  - LCMN with posterior midline (+ spine)

- **MRI of the brain**
  - Ideally before 6 months of age (3-6 months old)
  - Try feed and swaddle or sedate to avoid general anesthesia
  - Non contrast, heavily T1 and T2, volumetric sequences
  - Spine if possible, particularly if lumbosacral involvement

- **If positive**
  - Close follow up with Pediatric Neurology
  - Increases risk for melanoma

- **Follow up Imaging**
  - only if develop symptoms
Is there a melanoma?

- **Risk is around 5% lifetime for LCMN**
  - Half occur before 5 years old and almost all before puberty
  - Larger size → higher risk (75% assoc w > 40 cm)
  - Truncal location and multiple satellites → increase risk
  - Risk much higher for melanomas including cutaneous and extra-cutaneous if NCM

- Cutaneous MM present as **deep, fast growing or ulcerated nodules in the mothership**
  - Palpate
  - Pictures

- **CNS melanoma** actually may be more common
  - Especially if there is NCM with a LCMN
What are these weird lumps?

- **Proliferative nodules**
  - Don’t increase risk of melanoma
  - Ulcerate less often and less extensively than melanoma
  - Atypical histologic feature common on biopsy
    - Cytologic atypia, architectural disorder, pagetoid spread, high mitotic index
    - IH, FISH seem to have limited value
    - Some evidence for reduced methylation in melanomas
  - Get expert and second opinions
First Follow up Checklist

• Will it fade?
• Should we go straight to the surgeon?
• Support groups
Will it fade?
Should we go to the surgeon?

- Get to know your family
- Join the support group before discuss
- Complex discussion - experienced surgeon
  - Has not shown to decrease melanoma risk
  - Early surgery carries increased anesthesia risk and may not be advantageous
  - Surgical intervention adverse effects?
    • Darkening, peripheral lesions, new lesions
  - Scars vs nevi - function and form
  - Wait 1 year with photos to assess lightening


Support Groups-

*parents immediately, child before school age*

**Nevus Outreach** - www.nevus.org

**Nevus Network** - www.nevusnetwork.org

**The Congenital Nevus Support Group**

2018 - Our 35th Year!
Follow up Checklist LCMN

• Serial exam with palpation every 3 months first 2 years then q6 months until age 5 then annually
  – Total body photography to assess for lightening and new lesions

• Counsel regarding xerotic skin, pruritus, and hypohidrosis
  – Ondansetron

• Counsel not to limit activity due to fear

• Low threshold for neurodevelopmental assessment

• The hope:
  – RAF and MEK inhibitors for tx of LCMN and NCM
Small and Medium CMN
MM in small/intermediate CMN

- Most were superficial
- Age range 18 to 79 years.

Illig L, et al. Congenital nevi less than or equal to 10 cm as precursors to melanoma. 52 cases a review, and a new conception. Arch Dermatol. 1985;121:1274-81.
Checklist Small and Medium CMN

• Risk of Melanoma low
  – <1% over a lifetime
  – Occur after puberty

• Periodic evaluation after puberty with photos

• Discussion of removal
  – Functional concerns
  – Psychosocial/Cosmetic concerns
  – Usually wait till after 3 yo
The exception to the rule

- 8 year-old Report of MM arising in CMN
- Change over months
- No regular medical monitoring done prior to visit for nodule
- PET scan and sentinel node neg
- NED 12 months later

Favorite References


Becker’s Nevus
(post zygotic beta-actin mutation)
Becker’s Nevus Checklist

• Is it in a **female over the breast?**
  – Watch breast development
  – Consider **spironolactone 50-100 qd** during thelarche

• **If extensive rare skeletal or muscular abnormalities** (like epidermal nevus syndrome)
  – Scoliosis most common

• **Increased sebum production**
  – Tinea versicolor, acne, pityrosporum folliculitis
    • Selenium sulfide wash
A funny café au lait spot: Could this be NF1?
Checklist for patterned pigmentation

• **What is the pattern here?**
  – Checkerboard, blaschkonian, round
  – Jagged coast or smooth
  – Café au lait or just café
  – Midline cutoff?

• **Detailed physical exam**
  – Are there other birth marks, CALM, skin findings, macrocephaly, or stigmata of NF1 or other diseases
  – JXG and nevus anemicus- NF1

• **Detailed History**
  – Developmental milestones
  – Issues with vision, musculoskeletal
  – Endocrine or precocious puberty

- **Double hit of Lynch Syndrome genes**- Can have multiple CALM, axillary freckling and hyperpigmented “mini macules” and other features of NF1
- **CMMRD** - more hematologic (NHL), colorectal cancer, hi grade gliomas, medulloblastomas
- Any patient with diagnosis of “sporadic NF1” who develops a malignancy other than malignant peripheral nerve sheath tumor, JMML or optic glioma at an early age should be evaluated for CMMRD
Segmental Pigmentation Disorder

- Blocky, segmental, hyper/hypo-pigmented, patches with midline cutoffs
- Smooth borders
- Café au lait, not just café

- Generally good prognosis
  
  (Hogeling M, Frieden IJ. Br J Dermatolog 2010)
  - Ask about developmental milestones
  - Talk about CNS and eyes but no routine referrals
  - Sun protection, self tanners
If the pigmentary mosaicism is more blaschkonian
“Linear and Whorled”
Nevoid Hyper/Hypo-melanosis

• Useful term for pigmentary change in more swirly whorly, blaschkonian pattern

• **Perhaps more systemic findings** then segmental pigmentation disorder (30% in this study) - >if hypo+hyper
    • 54 patients with nevoid hyper and hypo pigmentation
    • 15/54 had neurologic abnormalities, usually developmental delay and seizures
    • 3/54 hemihypertrophy
    • 2/54 cardiac: PDA, VSD
    • 1 with conical teeth, 1 with scoliosis

• **Detailed exam and history**
Is this McCune Albright?

- CALM is most common presenting sign
  - Usually present at birth
  - Unilateral with sharp midline cutoff
  - “Broad blaschko-linear pattern”
  - Usually darker- just café, with no milk
  - Jagged “coast of Maine” border

- Look for oral pigmentation
  - Vermillion and mucosal pigmentation

Table. Differential Diagnosis of Syndromes With Oral Lentigines

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance/ Gene</th>
<th>Cutaneous Pigmentation</th>
<th>Testicular Tumors</th>
<th>Gastrointestinal Involvement</th>
<th>Malignancy</th>
<th>Thyroid Abnormalities</th>
<th>Other Endocrinopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCune-Albright syndrome</td>
<td>Somatic/ GNAS</td>
<td>Coast of Maine café au lait patches; oral mucosal lentigines</td>
<td>Leydig cell hyperplasia; Sertoli cell hyperplasia</td>
<td>Possible hamartomatous polyps; IPMN</td>
<td>Small increase in risk of malignancies in affected tissues (thyroid, bone, pancreas)</td>
<td>Patchy heterogeneity and cystic changes; hyperthyroid</td>
<td>Precocious puberty; GH excess; neonatal Cushing syndrome</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>AD/ STRK1 (LKB1)</td>
<td>Mucosal and cutaneous lentigines</td>
<td>Large-cell calcifying Sertoli cell tumor</td>
<td>Hamartomatous polyps</td>
<td>Ovarian; breast; pancreatic; thyroid; cervix; cholangiocarcinoma</td>
<td>Malignancy</td>
<td>None</td>
</tr>
<tr>
<td>Carney complex</td>
<td>AD/ PRKAR1a</td>
<td>Cutaneous and mucosal lentigines; blue nevi; melanocytic nevi; CALM; hypopigmented lesions</td>
<td>Large-cell calcifying Sertoli cell tumor; Leydig cell tumor</td>
<td>Psammomatous melanocytic schwannoma; pancreatic lesions including IPMN</td>
<td>Adrenal; hepatocellular; pancreatic; osteochondromyxomas</td>
<td>Hyperplasia; cystic changes; malignancy</td>
<td>PPNAD; GH excess; prolactin excess; pituitary adenomas; Cushing syndrome</td>
</tr>
<tr>
<td>Laugier-Hunziker syndrome</td>
<td>Acquired</td>
<td>Melanonychia striata; genital pigmentation; palmoplantar pigmentation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; CALM, café au lait macule; cAMP, cyclic adenosine monophosphate; GH, growth hormone; GNAS, complex locus, guanine nucleotide α-stimulating; IPMN, intraductal papillary mucinous neoplasms of the pancreas; PPNAD, primary pigmented nodular adrenocortical disease; PRKAR1a, protein kinase cAMP-dependent regulatory, type 1, α; STK11, serine/threonine kinase 11.

*In 50% to 70% of reported Carney complex cases.

*Majority due to mutation of PRKAR1a; second locus on chromosome 2p16 identified, but gene unknown.*
If worry for McCune Albright:

- Bone survey for **polyostotic fibrous dysplasia** (not always near pigment)
  - Craniofacial 90% by 3.5 yrs old
    - Painless lump
  - Extremities 90% by 14 yrs old
    - Limp, pain, pathologic fracture

- **Endocrine abnormalities** (hyperfunctioning)
  - Hyperparathyroid, pituitary adenomas (GH), adrenal adenomas (Cushing, aldosteronism), thyroid cysts, testicular Leydig/Sertoli cell hyperplasia

- **Precocious puberty**
  - Menstrual spotting
  - Scrotal thickening and enlargement

- Gene requires affected tissue- mosaic
CALM looking macule of the genitals
PTEN Hamartoma Syndrome
(Bannayan Riley Ruvalcaba)
If lentigines of penis or vulva:

• Look for
  – Macrocephaly
  – Lipomas
  – Vascular malformations
  – Oral papillomas, acral keratoses, acanthosis nigricans
  – Joint hyperextensibility, scoliosis

• Ask about
  – Hypotonia, developmental delay, autism
  – Hamartomatous intestinal polyps (PHx, FHx)
Favorite References


Checklist Dermal Melanocytosis

• Location
  – Periocular location is more concerning for associated malignancy or glaucoma

• Associated birthmarks
  – Capillary malformations might think of phakomatoses
  – Café au laits, might think about constitutional mismatch repair deficiency

• Progressive rather than regressive
  – More appear and after birth, get darker, get more extensive, more defined borders or ragged borders
  – Might think about metabolic disorder
• Whether you see conjunctival involvement or not- **Eye exam if periocular**
• Glaucoma
• **Uveal melanoma**
  – Reported with Nevus of Ota (1/400)
  – Reported with phakomatosis pigmentovascularis
    – Usually associated with other mutations in concert with GNAQ- like BAP1
• **Yearly ocular exam before puberty, bi-annual after puberty**
Nevus of Ito and other locations

- Risk of melanoma in this and other (non-periocular) locations vanishingly low

- No real worrisome associations unless extensive all over the body
Dermal Melanocytosis with Capillary Malformation

Phakomatosis Pigmentovascularis
Phakomatosis Pigmentovascularis and Extensive Dermal Melanocytosis

- Used to think PPV was due to non-allelic twin spotting
- Post-zygotic mosaic activating mutations in GNA11 and GNAQ
  - Same genes as Sturge Weber
  - G-protein alpha subunit gene mosaic condition, like McCune Albright
- Identical mutation in both capillary malformation areas and dermal melanocytosis areas to pluripotent progenitor cell
- Other factors such as location and background ethnic skin color factors control expression
Sturge Weber?

• If High risk
  – Argument MRI is not 100% sensitive
    • Requires contrast
    • Requires GA
    • Perhaps just refer to Pediatric Neuro to be educated
  – Evidence for ASA preventing Sz is not clear

Screening for Sturge-Weber syndrome: A state-of-the-art review

Phakomatosis Pigmentovascularis (and extensive dermal melanocytosis)

• About 50% have extracutaneous involvement in some series
  – Neurologic conditions include
    • psychomotor retardation, seizures, and cerebral atrophy;
    • symptoms typically present within the first months of life
  – Ophthalmologic associations include
    • conjunctival melanocytosis, episcleral vascular malformations, and glaucoma
    • Melanoma choroid and conjunctiva
  – Overgrowth of soft tissues or limbs

• Referral to ophthalmology, neurology, and close neurodevelopmental monitoring recommended.


Dermal melanocytosis as a clue to constitutional mismatch repair deficiency repair syndrome

Dermal melanocytosis, hyperpigmentation and hypopigmentation in a 23-month-old female with constitutional mismatch repair deficiency syndrome (a). Blue-grey macules of dermal melanocytosis were seen with irregular, ragged edges (b, c). Widespread hyperpigmented macules, again with ragged edges, were present with one large clearly defined café au lait macule (d).


Checklists for Birthmarks

- Large congenital melanocytic nevi are different from small and medium
- Becker’s and breast hypoplasia
- Constitutional mismatch repair deficiency can look like NF1
- Which patterned pigmentations to not worry about
  - Segmental pigmentary disorder not so much
- Which patterned pigmentary pigmentations to worry about
  - Swirly whorly nevoid hyper or hypopigmentation if extensive
  - McCune Albright can take till puberty to fully manifest
- Macrocephaly and genital melanotic macule ➔ think PTEN
- Dermal melanocytosis- annual eye exams for periocular. Should we evaluate forehead involvement like you would a PWS?
- Phakomatosis pigmentovascularis- check eyes and neurodevelopmental