Dermatology Grand Rounds:  
Pediatric Case-Based Dilemmas  

Julie V. Schaffer, M.D.  

Associate Professor of Pediatrics & Dermatology  
Hackensack Meridian School of Medicine at Seton Hall University
Case 1: Multiple café-au-lait macules

• Healthy 6-year-old girl
  – Multiple hyperpigmented macules/patches in a widespread distribution, increasing in number since infancy
  – Normal growth & development, no neurologic issues
  – No family history of similar lesions

• Previous evaluation
  – Genetic testing for neurofibromatosis type 1 (NF1) and Legius syndrome negative
  – Skin biopsy showed mildly increased epidermal melanin
Which of the following would you do next to help determine the diagnosis?

A. Ask about exposure to photosensitizing agents
B. Assess Darier sign and serum tryptase level
C. Evaluate for vascular component of lesions
D. Ophthalmologic examination for Lisch nodules
E. Skin biopsy for fibroblast culture and chromosomal analysis
F. Whole exome sequencing
Café-au-lait macules? Or are they vascular lesions?

- **Red-brown** color
  - Red component blanches with diascopy
  - No obvious warmth or thrill
Capillary malformation-AVM (CM-AVM) syndrome

- **Autosomal dominant > mosaic**
  - Loss-of-function in **RASA1** RAS-GTPase activating protein (CM-AVM1) or partner **EPH receptor B4** (CM-AVM2) in *endothelial cells*
  - Suppress RAS-MAPK signaling, as in NF1

- **Small, multifocal capillary malformations**
  - Onset infancy-childhood, progressive
  - Pink to red-brown, thumbprint-like
  - Often blanched halo, hypotrichosis
  - Pulsed Doppler may show decreased peripheral vascular resistance

*References:
Sibley & Ramien JAMA Derm 2019; Gandon et al Ped Derm 2016; Martin-Santiago et al Br J Derm 2015, Larralde et al Int J Derm 2014*
Dermoscopy in CM-AVM syndrome

Linear, branched vascular pattern

With diascopy: light brown fine network or homogeneous with perifollicular hypopigmentation

Gandon et al Ped Derm 2016
Edwards et al Ped Derm 2018
Which of the following studies is most appropriate?

A. CBC with platelet count and D dimer level
B. Gastrointestinal endoscopy
C. Liver ultrasound
D. MRI of brain and spine
E. Ophthalmologic examination
F. Transthoracic contrast echocardiography
Capillary malformation-AVM syndrome

- AVMs in 20% (CM-AVM2) to 35% (CM-AVM1)
  - 5-10% of patients have Parkes Weber
  - Brain/spine AVM in ~10%, which can lead to headaches, seizures, neurologic deficits - *screen with MRI/MRA*

Capillary malformation-AVM (CM-AVM) syndrome

- Punctate telangiectatic macules
  - May be primarily on extremities
  - Pale halo, early onset, and larger # of lesions differ from hereditary hemorrhagic telangiectasia (HHT)

CM-AVM2: 
**EPHB4** mutations

- Lesions may have *central* blanching
- 15% with punctate telangiectasias favoring lips and upper trunk
- Bier spots more frequent

- Occasionally recurrent epistaxis, contributing to concern for HHT
- Less frequent CNS AVMs (<5%)
  - Vein of Galen aneurysmal malformations described

Cellular proliferation

SHP2

SOS1

RAS GDP

RAS GTP

RAF

RASA1

CM-AVM

NF1

(= RAS GTPase-activating proteins)

NEUROFIBRIN

EPH B4
Nevus anemicus: clue to diagnosis of NF1

- >50% of pediatric NF1 patients in recent prospective series ($n_{\text{total}}=219$)
- Favor the mid chest
  - More evident after stroking
- Assoc. with macrocephaly

Hernandez-Martin et al Ped Derm 2015
Marque et al JAAD 2013
Case 2: Multiple café-au-lait macules

- Healthy 3-year-old boy
  - Referred by pediatrician for suspicion of neurofibromatosis type 1
  - Multiple hyperpigmented macules/patches, increasing in number since infancy
    - >10 are >0.5 cm in size
  - Normal growth & development, no neurologic issues
  - No family history of similar lesions
Which of the following is the most likely to develop in this patient?

A. Learning difficulties
B. Pigmentary findings only
C. Plexiform neurofibroma
D. Renal artery stenosis
E. Scoliosis
F. Segmental cutaneous neurofibromas
G. Unilateral Lisch nodules
Mosaic neurofibromatosis type 1

- 5 case series ($n_{\text{total}} = 271$)
  - Mean age 16 years
  - 75% had pigmentary findings only, with freckling + CALM in >50%

- Extracutaneous findings uncommon
  - Lisch nodules in 2%
  - Skeletal in 5% (e.g., scoliosis, sphenoid wing dysplasia due to regional plexiform NF)
  - Learning difficulties in 5%; optic glioma, seizures in <1%

- Possible NF1 in offspring
  - 6% of patients in largest series ($n = 124$)
  - Affected skin does not need to overlie gonads

Neurofibromatosis 1: pigmentary findings

- ≥6 CALMs typically develop by age 1-2 y
- Intertriginous “freckling” in ~80%, usually by age 6-8 y
- Lisch nodules usually by late childhood
- JXGs by age 2-3 in 15-30%
  - Consider NF1 if JXGs + CALMs
Neurofibromatosis 1: neurofibromas

- Plexiform in >25%, superficial lesions usually apparent by age 3-5 y
- Cutaneous neurofibromas around puberty
Multiple CALM in children presenting to NF1 referral clinic (n=110)

**NF1**
- Mean age = 1 y
- Distinct, regular borders
- Uniform pigmentation

**Not NF1**
- Mean age = 6 y
- Irregular, smudgy borders
- Less homogeneous pigmentation
‘Typical’ CALM
• 1-5: None dx with NF1
• ≥6: ~75% dx with NF1

‘Atypical’ CALM
• 1-5: None dx with NF1
• ≥6: ~10% dx with NF1
Legius (NF1-like) syndrome

- Recognized in 2007
- Common cause of familial CALMs
- Patients can meet NF1 criteria
  - >5 café-au-lait spots
  - Flexural freckling
  - ± Macrocephaly, developmental delay, ADHD
- No neurofibromas, optic gliomas, Lisch nodules
- ± Lipomas, hypopigmented macules, hemangiomas/vascular malformations

Stowe et al Genes Devel 2012
Mosaic Legius syndrome
Another NF1 mimic: constitutional mismatch repair deficiency syndrome

- **Homozygous/biallelic** mutations in mismatch repair genes (eg MLH1, MSH2, MSH6, PMS2)
  - ? also **somatic NF1** mutations
  - HNPCC ± Muir-Torre in *heterozygotes*

- **Skin features**
  - NF1-like: multiple CALMs > axillary freckling, neurofibromas
  - ± hypopigmented macules, atypical dermal melanocytosis, pilomatricomas

- **Extracutaneous features**
  - CNS gliomas, leukemia/lymphoma, colorectal cancer

Wimmer et al Clin Genet 2017
Genetic testing for NF1 and related conditions

- ~97% of individuals with non-mosaic NF1 meet classical clinical criteria by age 8 y
  -but-
- Analysis of the NF1 and SPRED1 genes is available
  - Comprehensive, cost-effective panels (eg at U of Alabama)
  - ≥98% sensitive for non-mosaic NF1
  - Biopsy of affected skin for culture (eg of melanocytes or Schwann cells) often needed for mosaic NF1