Coffee break: Café-au-lait Macules in Genodermatoses

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Objectives

- Diagnose Neurofibromatosis Type I (NFI) more accurately
- Formulate a management plan for patients with NF1 or related conditions
- Distinguish conditions that closely mimic NFI

Café-au-Lait Macules

- Well-circumscribed, homogenous pigment
- 1 mm to > 20 cm
- Darker on dark skin
- Increased pigment in melanocytes and keratinocytes

Epidermal-Melanin Unit (Normal)

Macromelanosomes in NF1


DISCLOSURES

I do not have any relevant relationships with industry.
Generally, NF1 Café-au-lait macules resemble “coast of California”

What’s normal?

Prevalence

- More common in African-Americans newborns compared to Caucasians
  - 0.3% Caucasian
  - 12% African-American
- > 3 CALM in 2% of African-Americans
- School-age: 1 CALM in 26% to 33%

Café-au-Lait Macules

- Melanoma association unlikely: only two case reports
- In children with > 6 café-au-lait macules, 75% were diagnosed with NF1 by age 6; almost all by age 10

Neurofibromatosis I

- Common: 1 in 3,000; >90% of NF patients
- Autosomal dominant
- 50% de novo mutation
  - 80-90% paternally derived
- 100% penetrance
- Variable expressivity

Neurofibromin mutation on chromosome 17q11.2

Neurofibromin is GTPase-activating cytoplasmic protein that negatively regulates Ras activation; Neurofibromin is an inactivator of Ras proto oncogene
NF1 Evaluation

• Eye exam by ophthalmologist, pediatric if possible for children
• Physical exam with attention to features of NF1
  ➢ X-rays not recommended for screening
• Blood pressure assessment

Criteria for Diagnosis of NF1

• ≥ 6 CAL macules
  ➢ > 5 mm prepubertal
  ➢ > 15 mm postpubertal
• Axillary or Inguinal freckling
• Plexiform neurofibroma
• ≥ 2 neurofibromas
• ≥ 2 Lisch nodules
• Optic nerve glioma
• Skeletal dysplasia
• Tibial dysplasia
• Orbital dysplasia
• Affected 1st degree relative

Two or more (usually CAL + another feature) to make the diagnosis

Common Features of NF1
Adapted from Bologna Text

• Hypertelorism
• Glaucoma
• Macrocephaly
• Local bony overgrowth
• Absent patellae
• Pheochromocytoma (1%)
• Juv. Myelomonocytic Leukemia
• CNS tumors
• Rhabdomyosarcoma
• Duodenal carcinoid
• Somatostatinoma
• Parathyroid adenoma
• Unidentified bright objects (UBO) on MRI
• Learning difficulties, Seizures
• Aqueductal stenosis, hydrocephalus
• Hypertension
• Pulmonic stenosis
• Renal Artery Stenosis

Café-au-lait Spots

• Often present at birth or 1st months
• Increase in number, size, pigmentation, esp. in first 5 years
• ≥ 6 suggestive of NF1
• Usually first skin feature to appear, usually < age 2

Café-au-lait Macules represent a “second hit” in melanocytes

• Melanocyte-specific mutation in normal allele
  DeSchepper. JID 2008;128:1050
• Darker spots with haploinsufficiency mutations
  Boyd et al. JAAD 2010;63(3):440-447

Wood’s lamp

Café-au-lait Spots

Café-au-lait Spots

- Darker spots correlate with (more) severe haploinsufficiency mutations
  Boyd et al. JAAD 2010;63(3):440-447
- Not useful clinically due to varied skin types

Dermal Neurofibromas

- Unusual in childhood
- 84% of adults
- Increase in number during pregnancy, puberty
- Common on trunk
- Blueish or violaceous depressions

Tumors of Neurofibromatosis

Plexiform Neurofibromas

- Often hyperpigmented, with borders of increased pigmentation concordant with borders of the neurofibroma

MRI to visualize

Plexiform Neurofibromas

- Congenital, perhaps not apparent for months to years
- Progressive enlargement
- Often on face, shoulders, paraspinal areas, so palpate carefully
- Difficult to eradicate

Tumors of Neurofibromatosis

Plexiform Neurofibromas

- Often hyperpigmented, with borders of increased pigmentation concordant with borders of the neurofibroma

• MRI to visualize
**Neurofibromas**
- Plexiform Neurofibroma
  - Congenital
  - Grow slowly
  - Usually not > 3 cm
  - Remain benign

**Lisch Nodules**
- Pigment hamartomas, harmless
- Usually bilateral, large numbers
- Increases with age; none at birth; 50% have by 5 years; 75% at 15 years; 95-100% >30 years

**Optic Glioma**
- MRI from Dr. A. Paller

**Optic Glioma**
- Affect 15-20% of NF1 patients
- Most present from infancy
- More indolent in NF-1 than optic gliomas without NF-1
- 2/3 are asymptomatic, not progressive
- Progression will present by 10 years in 90%; may regress spontaneously


**Optic Glioma**
- Only 33% develop symptoms or signs
  - Decreased visual acuity, visual field; proptosis; strabismus
  - Yearly eye exams until 10 years, every other year to age 18
  - MRI to evaluate; baseline MRI not recommended

**Optic Glioma**
- Precocious puberty associated with optic pathway tumors (in up to 40% of patients with posterior chiasm and hypothalamic areas)
- Presentation of Optic Glioma
- Early growth spurt may be first sign

Juvenile Xanthogranuloma (JXG)

a Warning of Leukemia in NF1?

• Juvenile Chronic Myelomonocytic Leukemia (JCMMML) more common in NF1
• Controversy: 20-30X higher risk with JXG in some studies; No association in others
• JXG not uncommon with CALM’s, rarely associated with leukemia
• Periodic complete blood counts for NF1 patients with JXG


Nevus anemicus

Juvenile Xanthogranuloma and Nevus Anemicus may aid diagnosis under age 2

• Diagnostic criteria less useful
• JXG
  • 10% of NF1 patients; 30% of those less than age 2
• Nevus anemicus
  • 25% of NF1; 35% under 2

Ferrari et al. Juvenile Xanthogranuloma and Nevus Anemicus in the Diagnosis of Neurofibromatosis Type 1 JAMA Derm January 2014.

NF1 Genetic Testing

• Diagnosis is considered clinical
• Mutation identifiable in 95% of individuals who meet clinical criteria
• Mild variant identified: 3 base pair, in frame, deletion of exon 17 with few neurofibromas and multiple café-au-lait spots
• Severe variant in 5% with deletion of entire NF1 gene

Ferrari et al. Juvenile Xanthogranuloma and Nevus Anemicus in the Diagnosis of Neurofibromatosis Type 1 JAMA Derm January 2014.
Reproductive Technology

- Due to high prevalence, NF1 is increasingly common referral to clinics that use reproductive technology
- In 77 couples, 156 PGD cycles: 33 cycles (21%) → live birth

Merker et al. Outcomes of preimplantation genetic diagnosis NF1; Fertil Steril. Vol 103(3)2015

Reproductive Technology

- Early referral recommended for interested couples

Merker et al. Outcomes of preimplantation genetic diagnosis NF1; Fertil Steril. Vol 103(3)2015

“Segmental” neurofibromatosis

“Mosaic-localized” NF-1 usually presents with café-au-lait macules/ freckling
- Can present without café-au-lait macules or freckling (eg isolated tibial pseudoarthrosis or plexiform neurofibroma of eyelid + sphenoid wing dysplasia + Lisch nodules)
- Can present as neurofibromas

Reprinted by permission from Macmillan Publishers Ltd: Nature Genetics, Biesecker LG et al. 2013

“Segmental” neurofibromatosis

- 1:10 frequency of “generalized” NF-1
- “Mosaic-generalized” NF-1 cannot be distinguished clinically from classic patients with inherited germ-line mutations
- Risk of transmission through germ-line cells (eggs, sperm)


“Segmental” neurofibromatosis

- If segmental NF1 is suspected and genetic testing of blood is negative, consider tissue DNA diagnosis
- University of Alabama (UAB) performs testing: complex-special media, biopsy of three separate macules, buccal swab and blood

“Crowe Sign”
Autosomal Dominant Inheritance

- Multiple family members and multiple generations.

Germline Mosaicism

- Unaffected parents have increased risk of future affected child.

Skeletal Changes

- Macrocephaly
- Short stature
- Kyphoscoliosis, often thoracic

“Pseudoarthrosis” of the tibia

- “Anterolateral tibial bowing” is more correct term for clinical sign
- Usually visible in first year
- Fracture at site of dysplasia leads to pseudoarthrosis

Ongoing Monitoring

Learning Disabilities and Speech

- In 50% of affected children, Verbal
- Nonverbal
- Attention deficit
- Severe in 5% of patients (total gene deletion)

Vasculopathy

- Regular Blood Pressure Check
- Manageable with medication

Disrupted RAS-MAPK Pathway

- Alters synaptic plasticity
- Cognitive impairment in 80%
- Social function impairment “shy”, “awkward”, bullied, autism spectrum
**Plexiform Neurofibroma**
- Slow growing; can become too heavy, irritating
- Develop along peripheral nerve
- Cause disfigurement, airway constriction, hearing loss, intestinal blockage, spinal cord compression, chronic pain
- In 50% of affected people
- Photography to help monitor size

**Neurofibrosarcoma**
- Most severe complication is malignant peripheral nerve sheath tumors: rare before age 10 years
- “Second hit” mutations; Lifetime risk: 10%
- Heralded by
  - unexplained pain or sudden growth in a pre-existing plexiform neurofibroma
  - New onset neurologic symptom (pain, numbness, tingling, loss of function)

**Monitor Growth**
- Early Growth spurt may be first sign of precocious puberty
- Precocious puberty with tumors of Optic Chiasm that affect pituitary (Optic glioma)
- Scoliosis becomes more obvious at the time of growth spurt

**Neurofibromatosis I Laser**
- Some case reports of treatment e.g. Q-switched 755-nm alexandrite laser
- No large studies
- Literature describes tendency for post-inflammatory hyperpigmentation, recurrence and lack of response

**Neurofibromatosis I Laser**
- Post-inflammatory Hyperpigmentation after use of Q-switched Nd:YAG
Multiple Café-au-lait Macules: Differential Diagnosis
Adapted from Bolognia Text (1)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Features</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson syndrome</td>
<td>Short stature; pulmonic stenosis; MR; Lisch nodules, freckling, neurofibromas</td>
<td>allelic with NF1</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>short stature; webbed neck; cardiac, skeletal defects; ker pilaris; lymphedema</td>
<td></td>
</tr>
<tr>
<td>Cardio-facial-cutaneous syndrome</td>
<td>Short stature; low-set ears; cardiac defects; MR; sparse curly hair; dry skin</td>
<td>BRAF, KRAS MEK1, MEK2</td>
</tr>
<tr>
<td>Jaffe–Campanacci syndrome</td>
<td>Non-ossifying fibromas of long bones, jaws; hypoplasia; MR; giant cell granulomas</td>
<td></td>
</tr>
<tr>
<td>McCune–Albright syndrome</td>
<td>Polystatic fibrous dysplasia, hyperfunction of endocrine glands, (sexual precocity); CALMs may overlie bony changes; May follow Blaschko lines</td>
<td>GNAS1 gene that encodes Gsα</td>
</tr>
</tbody>
</table>

MR= Mental Retardation

Multiple Café-au-lait Macules: Differential Diagnosis
Adapted from Bolognia Text (2)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Features</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberous Sclerosis</td>
<td>MR, seizures, hypopigmented macules, fibrous plaques</td>
<td>TSC1, TSC2</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>Congenital hypopigmented macules, MR, growth retardation</td>
<td></td>
</tr>
<tr>
<td>Pielabaldism</td>
<td>CALMs in involved and uninvolved skin</td>
<td>KIT proto-oncogene</td>
</tr>
<tr>
<td>Mukamel syndrome</td>
<td>Premature graying, lentigenes; depigmented macules, MR, spastic paraparesis, microcephaly, scoliosis</td>
<td></td>
</tr>
<tr>
<td>LEOPARD syndrome</td>
<td>Cal's noir macules</td>
<td>PTEN</td>
</tr>
<tr>
<td>Bannayan-Riley-Ruvalcaba syndrome</td>
<td>Penile lentigenes, vascular malformations, lipomas, hamartomas, macrocephaly</td>
<td></td>
</tr>
</tbody>
</table>

Most likely mimics

- Ras-MAPK related disorders
- LEOPARD syndrome
- Legius syndrome

Summary

- Acquired
- Develops during adolescence
- More common in males
- Usually on shoulder, upper chest or upper back
- Associated hypertrichosis

Becker Nevus

- Acquired
- Develops during adolescence
- More common in males
- Usually on shoulder, upper chest or upper back
- Associated hypertrichosis

This file is licensed under the Creative Commons Attribution 3.0 Unported license. Photo by Siller.
Becker nevus: an Epidermal nevus
- Hamartomatous proliferation within ectoderm layer, NOT melanocytes
  - keratinocytes, hair follicles, eccrine, apocrine, sebaceous glands
- Associations:
  - adrenal hyperplasia
  - bone, muscle, breast and fat hypoplasia (mostly ipsilateral)
  - hemivertebrae, spina bifida, pectus, scoliosis,
  - localized lipodystrophy, accessory nipple,
  - facial asymmetry, accessory scrotum

Urticaria Pigmentosa
- Clonal somatic KIT mutation in many cases
- Increased melanin and melanocytes overlying mast cell proliferations
- Cause of hyperpigmentation unknown
  - Possible that histamine triggers a type of post-inflammatory hyperpigmentation
- Appears under age 2

Café-au-lait Macules
- Having 3-4 typical CAL macules is not uncommon in darker-skinned patients
- Irregular, often subtle “CAL” spots are seen in red-heads, children with parents of different skin coloration and is not suggestive of NF-1

Multiple Café-au-Lait Spots in a Group of Fair-Skinned Children
**McCune-Albright syndrome**

- Cardinal features: (1) polyostotic fibrous dysplasia (2) precocious puberty or other endocrinopathy (3) café-au-lait macules
  - 2 of 3 required for diagnosis
- Presenting feature of polyostotic fibrous dysplasia may be pain, fracture, skeletal asymmetry
- GNAS1 mutation is post zygotic

**Lines of Blaschko**

Lines of embryologic development

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**McCune-Albright syndrome**

- mosaic condition
- Café-au-lait macules tend to be segmental, follow Blaschko’s lines
- Associated with precocious puberty and fibrous dysplasia

**Lines of Blaschko**

Lines of embryologic development
PTEN Hamartoma Syndromes

Cowden
Banayan-Riley-Ruvalcaba
Proteus-like

- All require PTEN mutation for diagnosis
- Autosomal Dominant

PTEN Hamartoma Syndrome Criteria

**Pathognomonic**
- Adult Lhermitte-Duclos disease
- Mucocutaneous
  - Facial trichilemmomas
  - Acral keratoses
  - Papillomas

**Major**
- Breast cancer
- Thyroid cancer
- Macrocephaly
- Endometrial cancer

**Minor**
Thyroid lesions, low IQ, intestine polyps, fibrocystic breasts, lipomas, fibromas, genitourinary tumors

PTEN Hamartoma Syndrome

Cowden syndrome

- Oral papillomas
- Acral papules
- Oral papillomas

PTEN Hamartoma

Facial Trichilemmomas

Ras-MAPK Pathway
Legius Syndrome: an NF1-like syndrome

- Overlaps with NF1: Pigment changes without tumors
- 1 to 2% of patients seen in NF Clinic
- Due to SPRED1 (Sprouty-related, EVH1 domain containing 1) mutation
- Second allele mutation in CALMs
- A Ras-MAPK signaling pathway disorder
- Testing strategy: consider if NF1 is negative

Legius Syndrome Overlapping features with NF1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NF1</th>
<th>Legius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocephaly</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lipomas</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Noonan-like face</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Development delay</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tumor growth</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lisch nodules</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

SPRED1 gene encodes Spred-1 protein, which suppresses the Ras/MAPK signaling pathway.

Ras/MAPK pathway

GDP → Ras → GTP

Activated

Neurofibromin

cell proliferation

PIEBAILDISM

- Caused by KIT proto-oncogene mutation or SLUG (SNA12)
- Overlapping NF1 and piebaldism in the past, no NF1 mutation detected
- KIT activates SPRED1 at its KIT binding domain

Chiu et al. Association of Piebaldism and SPRED1; Ped Derm. Vol 30(3)2013

KIT1 activates Spred1, which normally suppresses the Ras/MAPK pathway.

- Down slanting Palpebral Fissures
- Low-set, Posteriorly Rotated Ears
- Ptosis
LEOPARD Syndrome
Noonan syndrome with Multiple Lentigines

- Lentigines
- Echocardiographic abnormalities
- Ocular findings (hypertelorism, epicanthal folds, ptosis)
- Pulmonic stenosis
- Abnormal genitalia
- Retardation of growth
- Deafness

LEOPARD syndrome

- Not all features in each patient
- Large diameter dark spots "café-noir" spots may develop on the trunk-usually few
- No relationship with sun exposure

Lynch Syndrome: Muir-Torre Variant

I. Age, 50
   Stomach Cancer

II. Endometrial

III. Colon
    Endometrial

= Skin Sebaceous Neoplasm or Keratoacanthoma

Lynch Syndrome

Testing recommended in stepwise fashion

- Mismatch Repair Genes
  - MLH1, MSH2, MSH6, PMS2
- Microsatellites: repetitive DNA sequences
  - e.g. AAAAAAA
- Microsatellite instability (MSI) creates mutations, tumors

Constitutional Mismatch Repair Syndrome

- Homozygous Lynch syndrome mutations
  - MLH1, MSH2, MSH6, PMS2
- Café-au-lait macules most common feature; in 97% from early childhood patients
- CALM with more diffuse borders, hypopigmentation
- Parents likely consanguineous


Constitutional Mismatch Repair Syndrome


Used with permission. Modern Pathology (2006) 19, S93–S126
**Constitutional Mismatch Repair Syndrome (CMMR)**

- Associated cancers:
  - high-grade glioma, acute myeloid leukemia
  - childhood hematologic malignancies
  - medulloblastoma
- Possible that rare cancers associated with NF1 occurred in misdiagnosed children that had CMMR

**In Summary....**

Multiple café au lait macules

- Becker nevus
- Urticaria pigmentosum
- Red hair (normal)
- Pigmentary mosaicism
- McCune-Albright syndrome
- PTEN hamartoma syndrome

RAS/MAPK pathway

- Legius syndrome
- Piebaldism
- Noonan syndrome with multiple lentigines

CMMR (Mismatch Repair)

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Thank You!