Neurofibromatosis type 1 and RASopathies

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Neurofibromatosis Type 1
NF1- diagnostic criteria

Two or more of the following:

- 6 or more café-au-lait macules
  - >5 mm in greatest diameter in prepubertal individuals
  - >15 mm in greatest diameter after puberty

- Two or more neurofibromas or one or more plexiform neurofibromas

- Freckling in the axilla and inguinal region (Crowe’s sign)
- Tumor of the optic nerve pathway
- Two or more lisch nodules (iris hamartomas)
- Distinctive osseous lesions, sphenoid wing dysplasia or long-bone bowing (with or without pseudoarthrosis)
- A first degree relative with NF1
NF1 genetics

- Autosomal dominant
- Caused by mutations in neurofibromin
- Whole gene deletion associated with:
  - Large numbers and early appearance of cutaneous neurofibromas
  - More frequent
  - More severe cognitive abnormalities
  - Dysmorphic facial features
Café-au-lait macules

- Hallmark lesion, present in ~100%
- Can occur anywhere on body
- Often appear in first few months
- Increase in number over first couple years of life
Axillary or inguinal freckling

- Multiple freckles 2-3 mm in diameter
- Presents later in childhood
- Not generally present in infancy
Neurofibromas

- Begin to appear in childhood or later, not usually present in infancy

- Increase in number in puberty and pregnancy

- They are covered by normal skin
Lisch Nodules

• 2 or more iris Lisch nodules

• Melanocytic hamartomas

• Slit-lamp examination

• Present in ~ 75% with NF-1
  – prevalence increases with age
Quiz

A patient with multiple café au macules and axillary freckling presents with increased growth velocity and mild proptosis. What is the most likely diagnosis?

• A. Optic glioma
• B. Tubers
• C. Meningiomas
• D. Subependymal nodules
Quiz

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Optic Glioma

• Incidence ~15%
  – Most asymptomatic
  – May have low of visual acuity
  – Precocious puberty
  – Proptosis
Treatment of plexiform neurofibroma

- Plexiform neurofibromas generally cannot be completely removed because they run deep along the nerves.

- In some cases, plexiform neurofibromas can be debulked or partially removed, but tend to regrow.
Pigmented plexiform neurofibroma: Distinction from a large congenital melanocytic nevus
A patient with known NF1 presents with an enlarging mass within a plexiform neurofibroma. What is the most likely diagnosis?

- A. Rhabdomyosarcoma
- B. Lymphoma
- C. Schwannoma
- D. Malignant peripheral nerve sheath tumor
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MPNST

• Often occur in late childhood/adolescence
• May present with enlarging mass, pain or weakness
• Surgical excision recommended
• Respond poorly to chemotherapy
• Clinical trials ongoing
Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype

**SPRED1**: Negative regulator of RAS->RAF interaction and MAPK signaling

Clinical features:
- Multiple café-au-lait spots
- Axillary freckling
- Macrocephaly
- No neurofibromas

Mosaicism for a SPRED1 deletion revealed in a patient with clinically suspected mosaic neurofibromatosis.

Noonan with multiple lentigenes syndrome: Formerly known as LEOPARD

• Autosomal Dominant
  – PTPN11, BRAF, RAF1, MAP2K1

• LEOPARD
  – Lentigines
  – Electrocardiographic conduction defects
  – Ocular hypertelorism
  – Pulmonic stenosis
  – Abnormal genitalia
  – Retardation of growth
  – Deafness
Cardio-facio-cutaneous syndrome: Clinical features

- Autosomal dominant
  - *BRAF* (~75%), *MAP2K1* and *MAP2K2* (~25%), and *KRAS* (<2%)
- Craniofacial:
  - Bitemporal constriction
  - Hypoplasia of the supraorbital ridge
  - Downslanting palpebral fissures
  - Decreased nasal bridge with anteverted nostrils
  - Ear helix abnormalities
  - High arched palate

CFC skin findings

• Melanocytic nevi:
  – Greater than 50 nevi: 23 % (14/61)
  – Greater than 100 nevi: 8% (5/61)

• Keratosis pilaris: 80% (49/61)
• Ulerythema ophryogenes: 90% (55/61)
• Infantile hemangiomas: 26% (16/61)

Which syndrome is this?
Germline mutations in HRAS proto-oncogene cause Costello syndrome

Dermatologic phenotype in Costello syndrome: consequences of Ras dysregulation in development.

Siegel DH(1), Mann JA, Krol AL, Rauen KA.
Acquired acanthosis nigricans with tripe palms in a patient with interstitial lung disease
Costello syndrome and Cancer

• Patients with Costello have an increased risk of cancer
  – Rhabdomyosarcoma
  – Ganglioneuroblastoma
  – Bladder carcinoma

• Abdominal ultrasounds every 3 months for the first 8 years are recommended
Rhabdomyosarcoma and nevus spilus with agminated Spitz nevi

• Rhabdomyosarcoma and spitz nevi positive for HRAS G13R mutation
Activating *HRAS* Mutation in Agminated Spitz Nevi Arising in a Nevus Spilus

- Clonal activating point mutation in *HRAS* in the Spitz nevi and underlying nevus spilus

- Copy number increase in *HRAS* on chromosome 11p in the Spitz nevi (the second hit)

Phacomatosis pigmentokeratotica and precocious puberty associated with HRAS mutation

- Precocious puberty at age 2 years with enlarged genitalia, pubic hair, accelerated growth, extensive epidermal nevi and multiple melanocytic nevi
- Adult levels of LH and testosterone.

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