Neurofibromatosis type 1 and RASopathies

Dawn Siegel, MD
Medical College of Wisconsin
American Academy of Dermatology
San Diego, CA
February 19th, 2018

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

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

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

Journal of the American Academy of Dermatology
Volume 56, Issue 5, May 2007, Pages 862-868

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

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

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

Brems et al, Nat Genet. 2007 Sep;39(9):1120-6. Epub 2007 Aug 19.

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

Jobling et al , Br J Dermatol. 2016 Jul 16. doi: 10.1111/bjd.14873.

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

Kavamura MI, CFC index for the diagnosis of cardiofaciocutaneous syndrome. Am J Med Genet. 2002 Sep 15;112(1):12-6. Review.

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)

Br J Dermatol. 2011 Mar;164(3):521-9. doi: 10.1111/j.1365-2133.2010.10122.x. Epub 2011 Jan 28. Dermatological findings in 61 mutation-positive individuals with cardiofaciocutaneous syndrome. *Siegel* DH(1), McKenzie J, Frieden IJ, Rauen KA

Which syndrome is this?

Germline mutations in HRAS proto-oncogene cause Costello syndrome

Aoki et al, Nat Genet. 2005 Oct;37(10):1038-40. Epub 2005 Sep 18.

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

Br J Dermatol. 2012 Mar;166(3):601-7. doi: 10.1111/j.1365-2133.2011.10744.x.
Dermatological 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

JAAD Case Rep. 2016 Feb 3;2(1):59-62. doi: 10.1016/j.jdcr.2015.11.008. 2016

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)

Sarin et al, JAMA Dermatol. 2013:149(9):1077-1080. doi:10.1001/jamadermatol.2013.4745.

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.

Martin et al, *Phacomatosis pigmentokeratotica and precocious puberty associated with HRAS mutation*. Br J Dermatol. 2018 Jan;178(1):289-291. doi: 10.1111/bjd.15643. Epub 2017 Nov 27.

PeDRA gives me a platform for collaborating with investigators on pediatric dermatology research.

Helping Children with Skin Diseases through Collaborative Research

www.pedraresearch.org