Neurofibromatosis 1

Introduction

- ***Multisystem*** disorder primarily involving the skin and NS
- some features may be present at **birth** and others are ***age-related*** manifestations
- prevalence is 1 in 2500-3500 individuals
- usually recognized in early childhood when cutaneous manifestations are apparent
- associated with ***marked variability***, but children generally do well with growth and development
- one of the most common autosomal dominant conditions
- caused by a germline inactivating mutation in the NF1 gene on chromosome 17
- about ½ of the cases of familial and ½ are de novo mutations
- severity does not differ in familial vs. de novo

Diagnosis

- Criteria established in 1987 by National Institutes of Health Consensus Development Conference.

- **<u>Diagnosis is made in an individual with any 2 of the following</u>**

  - café-au-lait spots
  - intertriginous freckling
  - Lisch nodules (iris hamartomas)
  - Neurofibromas
  - Optic pathway gliomas (OPGs)
  - Distinctive bony lesions
  - First-degree family relative with NF1

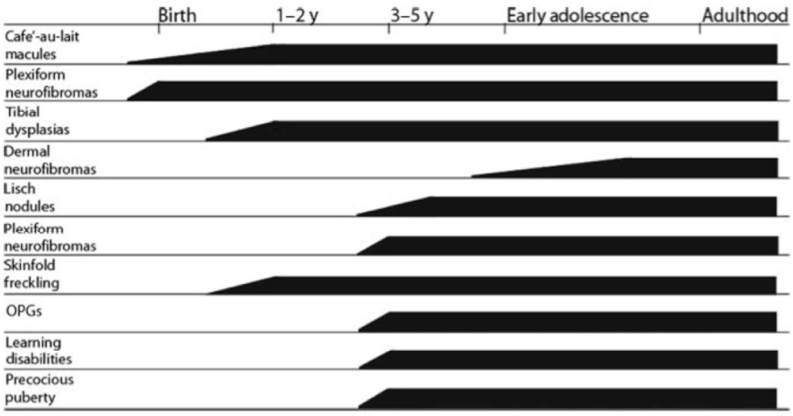
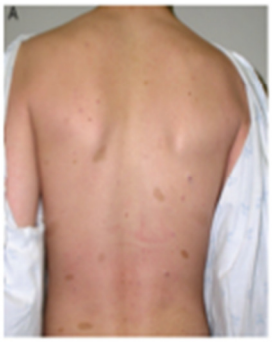
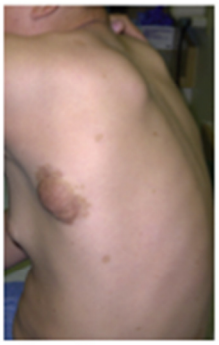


Image from *Pediatrics* 2009;123;124

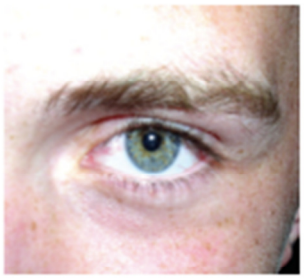
Café-au-lait spots:
Café-au-lait spots are generally the initial clinical manifestation, sometimes present at birth, and develop between early months of life and 2 years. For diagnosis you need ≥ 6 café-au-lait spots > 0.5 cm before puberty or > 1 cm after puberty. No tendency toward malignant transformation.

Intertriginous freckling (Crowe's sign):
Usually detected between 3-5 years of age. Typically small (<93mm). Axillary and inguinal location, in some individuals spreads further.

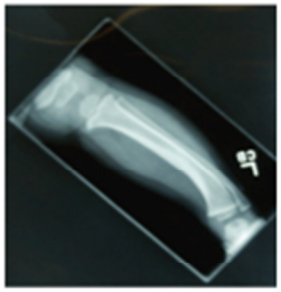




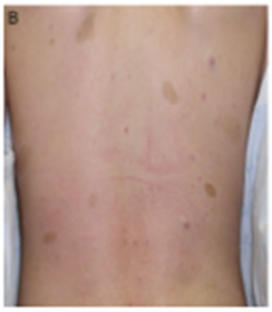
Neurofibromas



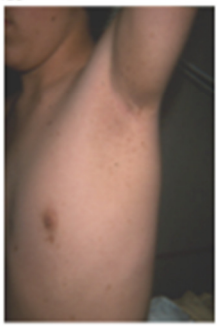
Lisch nodules (iris harmatomas)



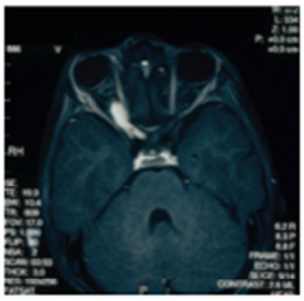
Distinctive bony lesions



Café-au-lait spots



Axillary Freckling



Optic Pathway Gliomas

Pediatrics 2008;121;633

Lisch Nodules:
Pathognomonic of NF1, melanocytic iris hamartomas, which do not affect vision. Present between 5-10 years. Most reliably identified by slit-lamp exam.

Neurofibromas:
Benign Schwann cell tumors arise from fibrous tissue surrounding peripheral nerve sheaths. Composed of Schwann cells, fibroblasts, perineural cells, and mast cells. Plexiform neurofibromas are found in 25% of individuals with NF1

The four types of neurofibromas are

- **Cutaneous**: Benign, most common, soft fleshy arising from peripheral nerve sheath. Increase in size and number with age. Can increase with pregnancy.
- **Subcutaneous**: Usually apparent at start of adolescence, firm, tender, nodules along peripheral nerves.
- **Nodular plexiform**: Complex clusters, decreases in size after the patient treated with high dose carboplatin.
- **Diffuse plexiform**: Overlie an area where a lesion will develop and enlarge steadily with age.

Distinctive bony lesions:
Include psuedoarthrosis and bone dysplasia as well as short stature, scoliosis and osteoporosis.

Optic pathway gliomas (OPGs):
Occur in 15% of children <6 years old. Appear on MRI as enlargement of the optic nerve and chiasm. Generally have normal vision, however, a few may have decreased visual acuity or color vision, abnormal pupillary function, proptosis and optic nerve atrophy.

Complications

- **Seizures:** not frequent, however increased in NF1 patients vs. normal (RR 2). If seizures present, MRI performed to assess risk CNS tumor.

- **Macrocephaly:** absolute in 25-50% NF1 children, increased brain volume secondary to inherent skeletal features. Acute growth evaluated for hydrocephalus secondary to stenosis.

- **Peripheral neuropathy:** nerve compression (4% NF1 patients), spinal root compression (3% NF1). Increased morbidity secondary to spinal complications and malignant peripheral new sheath tumors.

- **Hypertension:** associated with increased mortality in NF1 population.

- **Short stature:** 1/3 of NF1 patients. No increased mortality with short stature.

- **Neuroimaging abnormalities:**

    - **NF-associated bright spots:** areas of increased signal intensity on MRI. Found in 60-70% of NF1 patients. Not malignant and decrease with age. Occur most frequently in the basal ganglia, cerebellum, brainstem, and subcortical white matter secondary to increased fluid in the myelin associated with glial proliferation. There is controversy regarding the association between cognitive function and the bright spots.

    - **Increased brain volume**

- **Bleeding and/or anemia:** can develop from neurofibromas in the gastrointestinal tract. Can also have signs of mechanical obstruction.

- **Behavioural abnormalities:** increased incidence of ADHD, autism spectrum disorders, and psychosocial issues. Increased incidence of mental retardation (4%-8%). Intellectual abilities are average to low average. Lower levels of visual-spatial and perceptual skills.

- **Congenital Heart Disease and Coronary Hear Disease:** increased frequency relative to general population. Pulmonary artery stenosis i= 25% of these malformations.

- **Vasculopathy:** increased stenosis, aneurysms, and arteriovenous malformations. 1% of patients with NF1. 2nd leading cause of death in this population. Frequently diagnosed in children with weakness, involuntary movements, headaches, or seizures.

- **Renal artery stenosis:** most common cause death in pediatric NF1 population

- **Coarctation of the aorta**

- **Pheochromocytoma:** occurs at a frequency of 0.1%-5.7%.

Treatment

- Carefully **check skin** for new peripheral neurofibromas, new plexiform neurofibromas, and/or progression of current skin findings.
- Check **BP** for possible developing HTN (can be secondary to renal artery stenosis, aortic stenosis, and pheochromocytoma)
- Evaluate growth (height, weight, head circumference)
- **Skeletal changes** (scoliosis, vertebral changes, limb abnormalities, assess for tibial dysplasia)
- **Ophthalmologic exam** + vision screen yearly
- Tanner staging for precocious puberty and/or abnormal growth acceleration (optic glioma can compress chiasm)
- **Check development**: neurodevelopmental progress, assess for ADD, monitor school performance
- If patient has plexiform neurofibromas- evaluate for progression to malignancy
- **Echo** considered to screen for MVP (increased incidence with NF1 microdeletions)
- Children with NF1 may need to be followed by a **special needs** coordinator (in addition to treatment with teachers, educational psychologists, occupational therapists, and pediatricians.
- **Psychosocial counseling** should be offered to all patients and families.
- **Genetic counselling** may be a consideration as well in a NF1 patient who is planning on having a family.

Neurofibromatosis Type 2

- Predisposes individuals to tumors of the nervous system.
- Less relevant in pediatrics because patients usually present with symptoms around age 20. However, children diagnosed with NF2 often have an atypical but more severe presentation.
- Dominant inheritance caused by mutations in the NF2 gene (a tumor suppressor) located on chromosome 22
- Development of schwannomas requires inactivation of both NF2 alleles

- **Clinical features**
    - bilateral vestibular **schwannomas** present in 90-95% patients
    - schwannomas of other cranial nerves
    - intracranial **meningiomas**
    - spinal tumors
    - peripheral neuropathy
    - **cataracts**
    - **retainal hamartomas**
    - cutaneous tumors
    - skin plaques
    - subcutaneous tumors

- **Screening** for NF2 should be done in the following cases and may identify pediatric patients:

    - individuals with 1st degree relative
    - patients with multiple spinal tumors
    - patients with cutaneous schwannomas

- **If a child is NF2 positive after screening f/u with**: annual hearing examination, ophthalmologic exam, cutaneous exam, and craniospinal MRI starting @ 10-12 then every 2y until 20, every 5y after 20.

- NF2 vs. NF1: NF1 has lisch nodules, NF2 rarely undergoes malignant change, NF2 does not lead to same cognitive deficiets as NF1.

References

1. "Health Supervision for Children with Neurofibromatosis" *Pediatrics* 2008;121;633
2. "Neurofibromatosis Type 1 Revisited" *Pediatrics* 2009;123;124
3. Up to Date: "Neurofibromatosis Type 1 (von Recklinghausen's disease)"
4. "Neurofibromatosis type 2 (NF2): a clinical and molecular review," *Orphanet J Rare Dis* 2009; 4:16
5. "Pediatric presenation of type 2 neurofibromatosis," Arch Dis Child 1999; 81:496