Neurofibromatosis Type 1 (Von Recklinghausen's Disease)

Background
1. Definition
   o Autosomal dominant neurocutaneous disorder that affects multi-organ systems
   o Can produce tumors along nerve pathways, as well as soft tissue and bony deformities
   o Signs and symptoms are variable and evolve over a patient's lifetime
   o Neurofibromatosis Type 1 (NF1)
     ▪ More common type
     ▪ Accounts for almost 90% cases
     ▪ Neurologic, cutaneous, and musculoskeletal manifestations include:
       • Neurofibromas
       • Multiple café-au-lait spots
       • Lisch nodules of the iris
       • Learning disabilities
       • Skeletal dysplasia
       • Scoliosis
   o Neurofibromatosis Type 2 (NF2)
     ▪ Major features are:
       • Congenital bilateral acoustic neuromas
       • Meningiomas
       • Schwannomas
       • Mutation on chromosome 22
2. Characteristics of NF1
   o Café-au-lait spots
     ▪ Flat, uniformly hyperpigmented, medium brown macules
   o Lisch nodules
     ▪ Yellow or brown dome-shaped elevations on iris
   o Peripheral neurofibromas
     ▪ Benign tumors that are made of Schwann cells, fibroblasts and mast cells
       ▪ Four types
         o Cutaneous
         o Subcutaneous
         o Nodular plexiform
         o Diffuse plexiform
       ▪ Arise along peripheral nerve roots, along course of nerve or at nerve endings
   o Tumors
     ▪ A prospective study showed overall risk of cancer was incr by a factor of 2.7 in pts with NF1 (SOR:B)
     ▪ Soft tissue sarcomas
       • Plexiform neurofibromas can transform into malignant peripheral nerve sheath tumors (MPNSTs) with lifetime risk as high as 10% (SOR:B)
• Initial signs/symptoms: severe pain, rapid growth of nodule
  o CNS neoplasms
    ▪ **Optic pathway gliomas (OPG)**
    o Most children with OPG have normal vision
    o Small percentage will present decr visual acuity or color vision, abnormal papillary function, or optic nerve atrophy
    o If involves optic chiasm, presents with either premature or delayed puberty due to hypothalamic involvement
    ▪ Astrocytomas and brainstem gliomas

**Pathophysiology**
1. Pathology of disease
   o Autosomal dominant disorder
   o Mutation or deletion of NF1 gene located on chromosome 17
   o NF1 gene encodes the protein, neurofibromin
     ▪ Hypothesized to act as a tumor suppressor
     ▪ Found in a variety of tissues such as brain, kidney, spleen and thymus
   o Highest rate of new mutation of any known single-gene disorder
   o About 50% of cases represent new mutations rather than inherited mutations
2. Incidence/prevalence
   o Incidence: 1/3,000-4,000
3. Risk factors
   o Family Hx
4. Morbidity/mortality
   o Information on mortality is limited
   o Appears that life expectancy is decr in pts with NF1, most likely due to malignant tumors and vascular complications

**Diagnostics**
1. NF1 is a clinical diagnosis based on history and physical exam (SOR:A)
2. History
   o Patients are often identified at a young age when parents notice café-au-lait macules
     ▪ Some are asymptomatic and identified during routine exam, or when a positive family Hx is known
   o Symptoms
     ▪ Visual complaints
     ▪ Weakness or neurologic deficits
     ▪ Headaches
     ▪ Seizures
   o Social hx
     ▪ Review developmental Hx and school progress
     ▪ Learning disabilities are common in pts with NF1
     ▪ Detailed family Hx
     ▪ Possibly identify symptoms of NF1 in 1st degree relatives
3. Physical exam
   o BP (elevated)
   o Height for age (short stature)
   o HEENT
- Macrocephaly
- Lisch nodules
  - Skin
    - Café-au-lait spots
    - Freckling
      - Groin, axillary areas
    - Peripheral neurofibromas
  - Musculoskeletal
    - Pseudoarthrosis
    - Bone dysplasia
    - Scoliosis

4. Diagnostic testing
   - Laboratory evaluation
     - Genetic testing available but does not predict disease severity or specific complications
     - May be beneficial to individuals meeting only one of diagnostic criteria, or when diagnosis is unclear (SOR:C)
     - Prenatal testing available via amniocentesis or chorionic villus sampling
   - Diagnostic imaging
     - Consensus panel convened by Children's Tumor Foundation did not recommend neuroimaging for screening in asymptomatic children with NF1 (SOR:C)

5. Diagnostic "Criteria" (if indicated):
   - Listed below are NIH Consensus Conference Diagnostic Criteria (SOR:A)
   - At least 2 of following clinical features must be present to make diagnosis of NF1
     - 6 or more café-au-lait macules >5 mm before puberty or >15 mm after puberty
     - Skin fold freckling
     - 2 or more neurofibromas or 1 plexiform neurofibroma
     - 2 or more Lisch nodules
     - Optic pathway glioma
     - Characteristic skeletal dysplasia (tibial or orbital dysplasia)
     - Affected 1st degree relative
   - Diagnosis of NF1 often not yet possible in children <8 yrs old using NIH Diagnostic Criteria (SOR:B)

**Differential Diagnosis**
1. Neurological findings
   - Neurofibromatosis Type 2
   - Brainstem gliomas
   - Low-grade astrocytoma
   - Meningioma
   - Spinal cord hemorrhage
   - Spinal cord infarction
   - Spinal epidural Abscess
   - Seizure disorder
2. Dermatological findings
Familial multiple café-au-lait spots
McCune-Albright syndrome
Multiple endocrine neoplasia type IIB
Tuberous sclerosis
Bannayan-Riley-Ruvalcaba syndrome

Therapeutics
1. Acute treatment
   - Children suspected of having NF1 should be evaluated by a multidisciplinary team
     - Pediatric neurology
     - Genetics
     - Ophthalmology
2. Long-term care
   - American Academy of Pediatrics Committee on Genetics recommends monitoring children with NF-1 by: 9
     - Annual physical exam and development assessments
     - Annual ophthalmologic evaluation until age 8 (SOR:B) then every 2 yrs until 18 yrs of age (SOR:C)
     - Audiologic exam prior to school age
     - Annual BP eval
     - Continuous monitor for growth, change or pain in neurofibromas because could be a sign of malignant transformation
     - Genetic counseling for pt and families

Follow-Up
1. Return to office
   - Annually unless new symptoms or complications arise 8
2. Refer to specialist
   - Genetic counselor
     - Since autosomal dominant inheritance pattern all pts and their families should be referred (SOR:C); prenatal testing available6
   - Orthopedic surgery: if pt has tibial dysplasia or scoliosis
   - General surgery
     - Enlarging plexiform neurofibroma or suspected malignancy
   - Ophthalmology
     - See long-term care
3. Admit to hospital
   - Not normally indicated unless surgery is needed for removal of neurofibroma or malignancy

Prognosis
1. Varies due to wide variety of phenotypes

Prevention
1. Genetic counseling

Patient Education
1. Childhood Tumor Foundation and referral to local chapter for family support.
   <www.ctf.org>

References


3. Listernick, R, Ferner, RE, Liu, GT, Gutmann, DH. Optic pathway gliomas in neurofibromatosis-1: Controversies and recommendations. Ann Neurol 2007; 61:189. <http://www3.interscience.wiley.com/journal/114200114/abstract>; Note: This is only the abstract I was able to get the full-text through my medical school's access.


Authors: Elizabeth Rosato, MD, & Jane Weida, MD, Penn State Hershey Medical Center, PA

Editor: Robert Marshall, MD, MPH, Capt MC USN, Puget Sound Family Medicine Residence, Naval Hospital, Bremerton, WA