Neurofibromatosis 1 and 2 - What you need to know for primary care

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Disclosures
- I have no financial disclosures
- Because I live in the world of pediatrics, I will briefly discuss off-label and investigational uses of drugs and devices

Learning Objectives
- Describe diagnostic criteria for NF-1 and NF-2
- Identify common co-morbidities and complications specific to each disease process
- Discuss disease management guidelines and treatment strategies

Neurofibromatoses
- NF1 and NF2 are autosomal dominant inherited multi-system disorders
  - Inheritance pattern for schwannomatosis less clear. Seems to be autosomal dominant with incomplete penetrance
- 3 distinct diseases, each associated with a different genetic mutation
- Diagnosis based on clinical findings

Fast facts - NF1
- Affects ~1 in 3,000 people
- Previously known as von Recklinghausen disease
  - NOT "Elephant Man" syndrome
- Café au lait macules are seen in most individuals
- Axillary/inguinal freckling is seen 90% of the time
- Cutaneous neurofibromas are common
  - Many plexiform neurofibromas are internal and asymptomatic
- 10% risk of developing a cancerous tumor
- ~2/3 of patients will never experience significant health problems
- Life expectancy is slightly reduced (most likely due to malignant tumors and vascular manifestations)
NF1 Diagnostic Criteria *(must exhibit 2)*
- 6 or more café au lait macules (CALs) >5 mm in prepubertal patients and 15 mm in longest diameter in postpubertal patients
- 2 or more neurofibromas or 1 plexiform neurofibroma
- Inguinal or axillary freckling
- Optic pathway glioma
- 2 or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion
- A first-degree relative with NF-1 according to these criteria

Pathophysiology
- NF1 gene located on chromosome 17 at band q11.2
  - This gene encodes neurofibromin, which suppresses tumors by downregulating Ras proteins
  - When the NF1 gene does not work, the Ras cell signaling pathway goes into overdrive
  - Genetic mutation leads to nonfunctional version of neurofibromin, resulting in tumors along nerves throughout the body

NF1 Genetics
- 50% inherited; the other 50% are de novo mutations
  - Other family members may have NF1 and not know it
  - Extremely variable gene expression
  - Genetic testing is available to confirm a clinical diagnosis (90-95% detection rate) or to make a diagnosis when only one of the criteria is met
    - False negatives or results of ‘unknown significance’

Mosaicism
- Bloodwork may be negative for NF mutation, or show positive mutation in only a percentage of the lymphocyte sample
- Can skin biopsy 2 or more CAL macules (different sites) and look for gene mutation in skin cells
- Can also consider testing urine sedimentation (due to shedding of epithelial cells) to look for mutation
- Proportions of gonadal tissue may also contain the mutation

Segmental NF
- Occurs as a result of mosaicism
- Clinical features limited to one area of the body
  - Example: Skin lesions do not cross the midline

NF1 disease surveillance
  - Yearly clinical evaluation
    - Skin exam for new findings
    - Growth parameters
    - Neurologic exam
    - Skeletal changes
    - Blood pressure
    - Developmental assessment
    - Review of school progress
  - Ophthalmologic exam
  - MRI of brain and orbits (yearly from age 18 months until ~age 7)
  - MRI of total spinal canal
    - Done if symptomatic for back pain, numbness, weakness
    - May be done to determine presence of 2nd diagnostic criteria
Skin findings
• Remember: “All that spots is not NF” and not all NF patients have café au lait spots...

Skin findings
Cutaneous neurofibromas
Subcutaneous Neurofibromas

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Skin findings
Plexiform neurofibroma

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Malignant peripheral nerve sheath tumors (MPNSTs)
• MPNSTs are the primary cause of early mortality in NF1 patients
  ▫ Mean age of presentation is 27.6 years
  ▫ 10% lifetime risk of developing a MPNST
  ▫ Can develop from any benign plexiform tumor
• Fast-growing cancers
  ▫ Often associated with severe pain
  ▫ Can be difficult to treat
  ▫ Can adapt biologically and become resistant to treatment
  ▫ 5 year survival rate ~46% (females>males)

Management of skin lesions
• Surgical resection
  ▫ Done when there is cosmetic disfigurement, pain, or alteration in function
• Neurofibromas do grow back
• Radiation therapy is avoided
  ▫ Can stimulate the growth of plexiform neurofibromas
• Alternative techniques for dermal tumor removal
  ▫ CO2 laser ablation and electrosurgery
  ▫ Er:YAG laser treatment

Ophthalmologic findings
• Lisch nodules
• Optic nerve tortuosity
• Congenital ptosis
• Sphenoid bone dysplasia
  ▫ May cause asymmetry and proptosis
Optic glioma

- ~20% risk of developing an optic pathway glioma
  - Most common type of central nervous system tumor in NF1
  - See in children as young as 18 months of age
    - At risk until typically between ages 6-7
  - Typically benign, but can ultimately impact vision

- Symptoms
  - Involuntary eye movement
  - Proptosis
  - Squinting
  - Vision loss in one or both eyes
    - Starts with the loss of peripheral vision
    - May eventually lead to blindness
  - Growth issues or precocious puberty

Management of optic gliomas

- Monitored closely
  - Treated only when and if they interfere with vision
- May be unresponsive to chemotherapy
  - Urgent need for effective drug treatments!
- When tumors are present along optic pathway, brainstem and cerebellum, surgery can cause loss of vision or other function

NF1 and CNS tumors

- Pilocytic astrocytomas
  - Many tumors are low grade, asymptomatic and require no treatment
  - Grade III and IV astrocytomas require aggressive treatment
    - Complete surgical resection + chemotherapy effective

Distinctive osseous lesions

- ~1/3 of patients with NF1 will develop some type of bone abnormality
  - Long-bone dysplasia
  - Bone structural weaknesses
  - Scoliosis
  - Osteopenia or osteoporosis
  - Short stature
  - Relative macrocephaly

Scoliosis

- Most common bone abnormality in NF1
  - Seen in about 30% of patients.
  - A rapidly-progressing form of kyphoscoliosis, called dystrophic scoliosis, may develop between ages 3 and 5 years of age
    - Requires surgical correction.
  - Milder forms of scoliosis typically develop during adolescence.
MRI findings

- T2 hyperintensities (UBOs) found in up to 80% of children with NF1
  - Tend to disappear with age
  - Predominantly show up in two regions of the brain: the globus pallidus (regulates voluntary movement), and the cerebellum (regulates balance)
  - ?? correlation with learning disabilities

Vascular abnormalities in NF1

- A variety of vascular abnormalities can occur in NF1, including aneurysms and stenosis
  - Renal artery stenosis responsible for HTN
  - Routine blood pressure measurement is essential
  - Most persons with NF1 are not routinely screened for vascular abnormalities
  - Often progress silently without detection

“Spinal NF1”

- Form of NF1
- Develop multiple spinal tumors on both sides of the spinal cord & on the nerve roots of the spine
- Tumors may affect all nerve roots.
- Typically later onset
- May otherwise exhibit only minimal features of NF1

Hormonal influences

- Pubertal development typically normal
  - Precocious puberty associated with optic chiasm tumors
- During puberty, dermal neurofibromas have been reported to increase in number
  - May also see increase in axillary/inguinal freckling and CALs
- Plexiform and dermal neurofibromas tend to grow in pregnant NF1 patients
  - Pregnancy may also trigger onset of hypertension and proteinuria
**NF1 and the GI tract**
- Oral tumors, such as neurofibromas on the tongue
  - Impact on speech and oromotor movement
- Gastrointestinal stromal tumors (GIST) affect up to 1/3 of persons with NF1
  - 20% of NF1-related GISTs may become cancerous
  - Must be carefully monitored and appropriately managed

**Other co-morbidities**
- Below average height
- Above average head circumference
- High blood pressure (due to renal artery stenosis)
- Headaches (20% of patients)
- Seizures (~7% of patients; ~3x > general population)
- Small number of pheochromocytomas (adrenal tumors) reported
- Peripheral neuropathy

**NF1 and learning disabilities**
- Estimated that up to two-thirds of patients with NF1 will develop some form of learning disability
- Deficits in attention, visual-spatial memory and executive function
- Language problems
- Academic underachievement
- Majority of patients show average to low-average IQ scores
- Neuropsychological testing often indicated
  - Recommend retesting during big transition periods (school/work)

**NF1 and ADHD**
- Up to a half of children with NF1-related learning disabilities will also develop attention deficit disorder (ADHD), with or without hyperactivity
- Treatment principles the same as with general population with ADHD
  - Behavioral modification therapy
  - Medication management
  - Accommodations in school and home setting

**Link to autism?**
- 2013 UK study in Pediatrics
  - NF1 population prevalence estimate
    - 24.9% ASD (95% C.I. 13.1%–42.1%)
    - 20.8% ‘broad’ ASD with partial features (95% C.I. 10.0%–38.1%)
    - A total of 45.7% showing some ASD phenotype

**Management of school issues**
- Determination of relative strengths and weaknesses
- Educational testing and appropriate IEP services
- School-based counseling for social concerns
- Section 504 accommodation plans
  - Learning and behavioral accommodations for ADHD symptoms
  - Accommodations for orthopedic concerns

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Social challenges

- Concerns for body image
- Isolation
- Lower self-esteem
- Difficulty with social cues and speech pragmatics
- Concern for the future
- Family planning
- Transition from pediatric to adult care

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Legius Syndrome

- Legius Syndrome, or NF1-like syndrome, occurs due to mutations in the SPRED1 gene
- Characterized by the presence of café-au-lait spots and learning disabilities
  - Does not lead to the development of tumors
- Approximately one to four percent of persons who have café-au-lait spots will ultimately be diagnosed with Legius Syndrome rather than NF1

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Neurofibromatosis-2 (NF2)

- AKA: “bilateral acoustic neurofibromatosis”
  - NF2 mostly affects the CNS, causing brain and spinal cord tumors
- Birth prevalence is 1:25,000
- In the past, largely diagnosed in the teens or twenties
  - There are an increasing number of diagnoses in young children as well as older adults

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NF2 Diagnostic Criteria

<table>
<thead>
<tr>
<th>Either</th>
<th>OR</th>
<th>Family history of NF2 (first degree family relative)</th>
</tr>
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<tbody>
<tr>
<td>• Presence of bilateral vestibular schwannomas</td>
<td>• Either a unilateral vestibular schwannoma before age 30</td>
<td>• Any 2 of the following:</td>
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<tr>
<td></td>
<td></td>
<td>• Glioma</td>
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<td>• Meningioma</td>
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<td>• Schwannoma</td>
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<td></td>
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<td>• Juvenile posterior subcapsular lenticular opacity (juvenile cortical cataract)</td>
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NF-2 Pathophysiology

- NF-2 gene on chromosome 22q 12.2
  - Codes a protein called Merlin
  - Studies suggest that Merlin helps to organize cells in the developing brain and contributes to effective myelination
  - When Merlin is reduced or absent, these cells may be disorganized
  - Leads to neuropathic pain and tumor formation

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NF-2

- Vestibular schwannomas (acoustic neuroma)
  - Lead to gradual hearing loss
- Meningiomas are seen in over half of persons with NF2
  - Though largely benign, they can continue to grow and can eventually become malignant
- Ependymomas
- Risk of developing schwannoma tumors along the spine, in peripheral nerves, and on skin
  - Studies show that more than 90% of patients also suffer eye lesions.
    - Most common: Juvenile subcapsular cataracts in young people
    - Lead to vision loss
- Other complications
  - Tinnitus
  - Headaches
  - Facial pain/numbness
  - Balance issues
  - General muscle wasting
Vestibular schwannoma

Images courtesy of Google Images

NF2 disease surveillance

- Eye exam for presence of cataracts
- MRI imaging
  - brain
  - spine
- Evaluation of hearing
  - audiometry
  - electronystagmography
  - ABRs

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Treatment options

- Removing a vestibular schwannoma when it is still small (in order to preserve cochlear nerve function), then placing a cochlear implant on the same side either during the same surgery or later (to facilitate hearing)
- Auditory brainstem implant v. cochlear implant
- Stereotactic radiosurgery
  - Radiation therapy remains controversial in its use in NF2 tumor management
- Targeted biological therapies

Schwannomatosis

- Rarest, least-well-understood form of NF
- Affects ~1:40,000 persons
  - Rarely seen in people before ages 20s-30s
- May be associated with mutation of the SMARCB1 gene on Ch. 22 at locus proximal to NF2 gene
- Multiple schwannomas on cranial, spinal and peripheral nerves
  - The possibility of NF2 has to be excluded before a diagnosis of schwannomatosis is made

Emerging therapies

- Molecular-targeted drugs that stabilize signaling molecules involved in cell division and growth
- Epidermal growth factor receptor (EGFR) inhibitors
  - Erlotinib (Tarceva)
- Vascular endothelial growth factor (VEGF) inhibitors
  - Ranibizumab
  - Bevacizumab (Avastin)

Where to find help?

Clinics that are part of the NF Clinics Network (part of the Children’s Tumor Foundation)
References

- www.ctf.org
- www.nfnetwork.org
- www.uptodate.com

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Questions?

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