A Compact Guide to the Diagnosis and Management of Neurofibromatosis Type 1

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BRIEF INTRODUCTION

Neurofibromatosis type 1 (NF-1) is a multisystem neurocutaneous disorder resulting from mutations in the **NF-1** gene on chromosome 17 (q11.2). Mutations in NF-1 result in deficient activity of the tumor suppressor protein **neurofibromin**, allowing for uncontrolled constitutive activity of the proliferative **Ras-pathway** in several neural cell types, including neurons, oligodendrocytes, astrocytes and Schwann cells.[1] Half of NF-1 cases are inherited in autosomal dominant fashion, while half develop sporadically. The syndrome has 100% penetrance but highly variable expressivity. The prevalence of this syndrome is 1/3,000, making it common enough to warrant **YOU**, the physician, taking a moment to learn how to recognize and manage it.

DIAGNOSTIC CRITERIA

The diagnostic criteria for neurofibromatosis type 1 developed by the NIH in 1987 remain the most widely accepted and utilized in clinical practice today. They are able to diagnose most patients within the first year of life and essentially all patients by the age of four.[2]

A patient is diagnosed with NF-1 if they meet **two or more** of the following criteria:

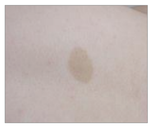
1) ≥ 6 café au lait macules
2) ≥ 2 neurofibromas of any type or ≥ 1 plexiform neurofibromas
3) ≥ 2 Lisch nodules
4) ≥ 1 first-degree relative with NF-1
5) Freckling in the axillary or inguinal regions
6) Optic glioma
7) Characteristic osseous lesion (e.g. sphenoid or tibial dysplasia)

HISTORY AND PHYSICAL EXAM

Many of the diagnostic criteria for NF-1 can be identified by the primary care physician through careful history and physical examination alone.[3]

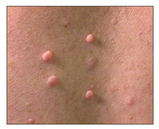
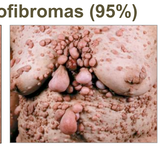
Diagnostic Criterion Evident on Physical Exam

Café au lait macules (99%)



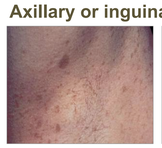
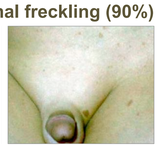

- Pigmented lesions darker than one's own complexion
- Contain large granules of pigment ("macromelanosomes")
- Asymptomatic and entirely benign
- Present from birth or childhood and fade considerably with age
- Most common reason for referral for evaluation of NF-1

Cutaneous neurofibromas (95%)

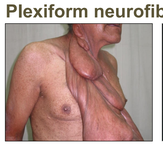
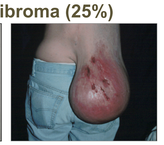
- Dome shaped, soft pedunculated skin masses
- Range from skin color to bluish purple
- Axons, fibroblasts, mast, Schwann, perineural, endothelial cells
- NO risk of malignant transformation
- First appear just before puberty, increase in number with age

Axillary or inguinal freckling (90%)

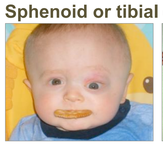
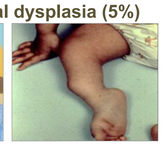
- Similar to café au lait spots in color but smaller
- Asymptomatic and entirely benign
- Appear during early childhood

Plexiform neurofibroma (25%)

- Often visible on physical exam, but may require imaging to see
- May cause disfigurement, functional impairment or threaten life
- Have a characteristic feeling similar to a "bag of worms"
- Similar histology to other types of neurofibromas
- 5% undergo malignant transformation to MPNSTs

Sphenoid or tibial dysplasia (5%)

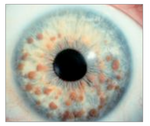
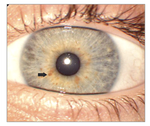
- Sphenoid dysplasia has classic radiographic "empty orbit sign"
- Tibial dysplasia predisposes to fracture and pseudoarthrosis
- Both are associated with low bone mineral density [4]
- Scoliosis is another common finding, but is non-specific
- Almost always present from birth

DIAGNOSTIC IMAGING

Most diagnoses of NF-1 can be made by physical exam and history alone. However, in cases where history and physical raise significant clinical suspicion but are not diagnostic, opthalmologic evaluation and diagnostic imaging are indicated. More importantly, many of the major causes of morbidity and mortality in NF-1 lurk internally, making diagnostic imaging universally indicated and crucially important during the evaluation of newly-diagnosed neurofibromatosis patients.

Slit Lamp Opthalmologic Findings

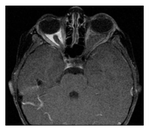
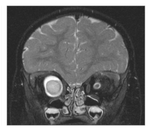
Lisch nodules (100%)

- Small yellow-brown lesions on iris ("iris hamartomas")
- Composed of pigmented cells, fibroblast-like cells and mast cells
- Do NOT cause any visual dysfunction or symptoms
- Not visible to the naked eye (require slit lamp evaluation)
- Not present at birth, but typically develop during childhood

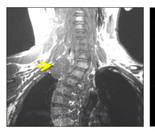
Diagnostic Imaging Findings

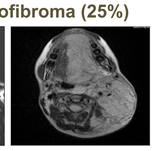
Optic nerve glioma (15%)

- Most common CNS tumor in NF-1
- May involve the optic nerve, optic chiasm or both
- Usually asymptomatic
- May cause loss of vision, proptosis or optic disc atrophy
- Usually presents in early childhood

Plexiform neurofibroma (25%)


Neck


Scalp and neck

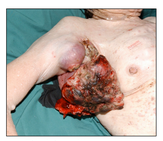
- Often visible on physical exam, but may require imaging to see
- May cause disfigurement, functional impairment or threaten life
- Have a characteristic feeling similar to a "bag of worms"
- Similar histology to other types of neurofibromas
- 5% undergo malignant transformation to MPNSTs

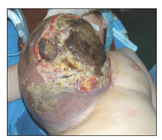
ADDITIONAL COMMON FINDINGS IN NF-1

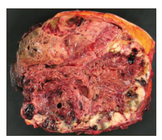
- Learning disability or ADD (50%)
- Short stature (40% are below the 10th percentile)
- Macrocephaly (35%)
- Scoliosis (20%)

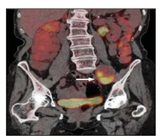
MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MPNST)

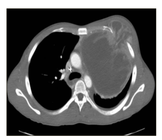
Malignant peripheral nerve sheath tumors (MPNSTs) are the deadliest complication of NF-1. In the majority of cases, these malignancies result from malignant sarcomatous transformation in pre-existing plexiform neurofibromas.[5] Patients typically present with the primary complaint of sudden onset of pain or rapid increase in size of a pre-existing diffuse plexiform neurofibroma. Approximately 5% of larger plexiform neurofibromas undergo malignant transformation and about 8% of NF-1 patients will have an MPNST during their lifetime. This malignancy is extremely aggressive, with dismal 5-year survival rates of around 20%. The average age of onset of MPNSTs in NF-1 patients is around 26 years.


Right axillary area


Right breast


Right breast


Left iliopsoas


Left chest

References

[1] Gottfried O, Viskochil D. Neurofibromatosis Type 1 and tumorigenesis: molecular mechanisms and therapeutic implications. *Neurosurg Focus*. 2010, 28:E8
[2] NIH Concensus Development Panel. Neurofibromatosis: NIH Consensus Statement. 1987, 13-15;6:1-19
[3] Radtke H, Sebold C, Schneider G. Neurofibromatosis Type 1 in Genetic Counseling Practice: Recommendations of the NSGC. *J Genet Counsel*. 2007, 16:387–407
[4] Stevenson D, Moyer-Mileur L, Murray M, Viskochil D. Bone Mineral Density in Children and Adolescents with Neurofibromatosis Type 1. *J Pediatr*. 2007, 150:83–88
[5] Tucker T, Wolkenstein P, Revuz J, Friedman J, Zeller J. Association between benign and malignant peripheral nerve sheath tumors in NF1. *Neurology*. 2005, 65:205-11
[6] Hersh J, Committee on Genetics. Health Supervision for Children With Neurofibromatosis. *Pediatrics*. 2008, 121;633-642
[7] Hottinger A, Khakoo Y. Neuro-oncology of Neurofibromatosis Type 1. *Curr Treat Options Neurol. 2009*, 11:306-14
[8] Yohay K. Neurofibromatosis type 1 and associated malignancies. *Curr Neurol Neurosci Rep*. 2009, 9:247-53

MANAGEMENT

The diversity of medical professionals involved in the management of patients with NF-1 mirrors the diversity of its pathological manifestations. Caring for the neurofibromatosis patient is truly a multidisciplinary endeavor and commonly includes the participation of at least the following clinicians: **geneticist** (diagnosis and coordination of care), **PCP** (coordination of care and yearly blood pressure monitoring), **dermatologist** (recognition of cutaneous manifestations of NF-1), **orthopedic surgeon** (management of bone dysplasia), **ophthalmologist** (evaluation for Lisch nodules and yearly vision exam), **psychiatrist** (management of learning disorders, ADHD and appearance-related social issues) and **radiologist** (detection and assessment of internal tumors).[6, 7]

Management guidelines for each of the manifestations of NF-1 vary across institutions and individual clinicians, but some of the more generally accepted recommendations include:

Routine: annual blood pressure + annual eye exam + evaluation of all 1st-degree relatives
Cutaneous neurofibromas: no intervention unless causing significant discomfort
Plexiform neurofibromas: varies widely by site and structure involved
Optic nerve gliomas: chemotherapy only if causing significant symptoms [8]
Tibial dysplasia: orthopedic consult for management and prevention of fractures
Sphenoid dysplasia: usually no treatment, although cosmetic surgery may be indicated
MPNST: surgical resection with as wide of margins as possible ± radiation

AN ILLUSTRATIVE CASE OF THE MANAGEMENT OF NF-1

A 72 year old female presents with a neck mass…

CHIEF COMPLAINT AND HISTORY OF PRESENT ILLNESS

- Right neck mass that has been enlarging over the past two months
- Progressive dysphagia to solids
- 35 pound weight loss

PAST MEDICAL HISTORY

- Neurofibromatosis type 1
- Type 2 diabetes mellitus
- Hypertension

PHYSICAL EXAM

- Large, hard, mobile mass extending from the posterior to the right lateral neck
- Numerous cutaneous neurofibromas

CT

- Right posterior-lateral bilobed neck mass, arising from C1-C2, C2-C3 neuroforamina
- Extends from the oropharynx to the hypopharynx and encroaches on the airway
- Encases the right vertebral artery and displaces the right carotid arteries anteriorly

SURGICAL DEBULKING AND BIOPSY

- Limited surgical debulking is carried out to reduce the mass effect of the tumor
- It is not possible to remove the entire mass
- A sample is sent off for permanent section and pathological evaluation

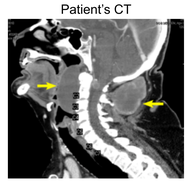
PATHOLOGY REPORT

- Histology shows spindle and epithelial cells with marked atypia any many mitoses
- No benign neurofibroma component can be identified
- Immunohistochemical staining is negative for neurofilament and S-100 (not uncommon)
- Diagnosis is recorded as malignant peripheral nerve sheath tumor (MPNST)

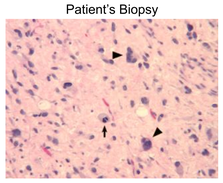
FOLLOW-UP FDG PET/CT

- Large MPNST with central necrosis and hypermetabolic activity (maximum SUV = 6.9)

Patient's CT



Patient's Biopsy



Benign neurofibroma (control)