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 proline-rich, 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 history and physical examination alone.

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, ophthalmologic evaluation is indicated. More importantly, the majority of the 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.

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 Liisch 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 bilateral 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.²

Diagnostic Criteria 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

- Axillary or inguinal freckling (99%)
  - Similar to café au lait spots in color but smaller
  - Asymptomatic and entirely benign
  - Appearing during early childhood

- Sphenoid or bilateral dysplasia (9%)
  - Classic radiographic appearance of "empty orbit sign" in NF-1
  - Bilateral dysplasia predisposes to fracture and pseudoarthrosis
  - Both associated with low bone mineral density
  - Scoliosis is another common finding, but is non-specific
  - Almost always present from birth

- 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

- Scoliosis (20%)
  - Asymptomatic and entirely benign
  - Usually asymptomatic
  - May cause loss of vision, proptosis or optic disc atrophy
  - Usually presents in early childhood

- Macrocephaly (35%)
  - Increased head circumference at birth
  - Usually asymptomatic

- Short stature (40% are below the 10th percentile)

- Freckling in the axillary or inguinal regions

- Optic glioma

- Plexiform neurofibromas

- Café au lait macules

DIAGNOSTIC IMAGING

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%)
  - 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)
- Macroadenophy (30%)
- Scoliosis (20%)
- Hypertension

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 transformation in pre-existing plexiform neurofibromas.³ 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 large 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.

DIAGNOSTIC CRITERIA

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).⁴ ⁵ ⁶

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 1° 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

- Tuberous dysplasia: orthopedic consult for management and prevention of fractures

- Plexiform neurofibromas: surgical resection with as wide of margins as possible + radiation

- 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

MANAGEMENT

CT

- Right posterior-lateral bilobed neck mass, arising from C1-C2, C2-C3 neurofibroma

- Extends from the oropharynx to the hypopharynx and on the airway

- Encroaches the right vertebral artery and displaces the right carotid artery anteriorly

SURGICAL DEBUKING AND BIOPSY

- Limited surgical debuking 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, many mitoses
- No benign neurofibroma component can be identified

- Neuroectodermal stromal cell neoplasm is negative for neurofibromatosis and S-100 (uncommon)

- Diagnosis is confirmed as a malignant peripheral nerve sheath tumor (MPNST)

FOLLOW-UP FDG PET/CT

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

REFERENCES


