no patient handout*

Neurofibromatosis

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Synopsis

□□ Type 1 General ManifestationsNeurofibromatosis type 1 (von Recklinghausen disease or NF1) is a multisystem genetic disorder with hallmark cutaneous findings, including café-au-lait macules, neurofibromas, and axillary freckling. NF1 may affect the skin, nervous system, eyes, bone, and soft tissue. It is the most common autosomal dominant genetic disorder, affecting approximately 1 in 3,000 human beings and occurring as either an inherited defect or, frequently, as a spontaneous (ie, *de novo*) mutation.

NF1 occurs equally in all ethnicities and among both sexes and is often identified in childhood with the appearance of café-au-lait macules. The genetic defect is in a tumor suppressor gene on chromosome 17, which codes for neurofibromin, a RAS GTPase activating protein. Patients are at increased risk of developing benign and malignant neoplasms. Benign neoplasms include neurofibromas – complex tumors of admixed Schwann cells, fibroblasts, myelinated and unmyelinated nerve axons, endothelial cells, and mast cells – that occur in 1 of 4 forms: cutaneous, subcutaneous, nodular, and deep. **Plexiform neurofibromas** (present in 25% of patients) are a variant of neurofibroma that are typically deeper, more anatomically complex, and more likely to be symptomatic. Deep plexiform neurofibromas may degenerate into **malignant peripheral nerve sheath tumors**. Other malignancies and tumors associated with neurofibromatosis include gliomas (especially optic pathway gliomas in 10%-15% of patients), pheochromocytomas, meningiomas, sarcomas, gastrointestinal tumors of neuroendocrine origin such as duodenal carcinoid tumors, and juvenile myelomonocytic leukemia. In addition to tumors and skin findings, patients may also have learning disabilities (30%-50%), skeletal anomalies, vasculopathies, and endocrinologic abnormalities.

The diagnosis of NF1 is made on clinical grounds, based on 2 or more of the following features:

- Six or more café-au-lait macules greater than 5 mm in prepubertal individuals and greater than 15 mm in diameter in postpubertal patients
- Two or more Lisch nodules (iris hamartomas) in older patients
- Sphenoid dysplasia or thinning of a long bone's cortex, with or without pseudoarthrosis
- Two or more neurofibromas of any type or a single plexiform neurofibroma

- Freckling in the axillary or inguinal region
- Optic glioma (in early childhood)
- First degree relative with NF1 (although new mutations are frequent)

Patients with neurofibromatosis type 2 (NF2) present primarily with acoustic neuromas (schwannomas of the eighth cranial nerve). NF2, which is 10 times less common than NF1, is associated with mutation of a different tumor suppressor gene that is located on chromosome 22 and codes for a protein called merlin. Patients have fewer café-au-lait macules than those with NF1, and they do not form Lisch nodules in the iris.

Many individuals with NF lead long and healthy lives. Overall life expectancy may be decreased by as much as 15 years secondary to complications, however.

For more information on Neurofibromatosis Type I, see **OMIM**.

For more information on Neurofibromatosis Type II, see **OMIM**.

Codes

ICD10CM:
Q85.01 – Neurofibromatosis, type 1
Q85.02 – Neurofibromatosis, type 2

SNOMEDCT:
19133005 – Neurofibromatosis syndrome

Look For

Multiple (6 or more) café-au-lait macules (flat, uniformly darker patches with sharp borders) in postpubertal patients. The macules are typically larger than 15 mm in diameter.

Also look for axillary freckling or freckling in other intertriginous areas.

Neurofibromas will increase with age and appear as pink, brown, or skin-colored soft tumors and nodules. Cutaneous neurofibromas are soft and will descend into the underlying dermis with direct pressure (the "button hole" sign). Subcutaneous neurofibromas are tender (often painful) and can be up to several centimeters in size. Plexiform neurofibromas are deep, sometimes involving all layers of the skin to the fascia. They are thick and irregular and may infiltrate or disfigure nearby structures. Plexiform neurofibromas may also cause hyperpigmentation and/or hypertrichosis of overlying skin.

Iris hamartomas (Lisch nodules) are also associated with the disease and are ultimately identifiable in 90% of patients.

Diagnostic Pearls

Café-au-lait macules may appear lighter than the surrounding skin in heavily pigmented individuals.

When applying diagnostic criteria or evaluating a patient, it is important to remember the age-related penetrance of manifestations of NF1:

- Sphenoid wing dysplasia – birth
- Long-bone bowing – birth to early childhood
- Optic pathway tumors – birth to early childhood
- Café-au-lait macules – birth to childhood
- Plexiform neurofibromas – birth to adulthood
- Hypertension – lifelong
- Intertriginous freckling – childhood
- Scoliosis – childhood
- Neurofibromas – late childhood to adolescence
- Nerve sheath tumors – adolescence to adulthood

Differential Diagnosis & Pitfalls

The differential diagnosis of NF1 includes the following.

Other forms of neurofibromatosis:

- **Segmental** / mosaic NF1
- Watson syndrome (a subset of neurofibromatosis associated with pulmonic stenosis)
- Autosomal dominant multiple **café-au-lait macules** alone (some allelic with NF1)
- Neurofibromatosis type 2
- Schwannomatosis (disorder associated with mutation in the gene *INI1*)

Other conditions with café-au-lait macules:

- **McCune-Albright syndrome** – premature puberty, bony abnormalities, and a few large café-au-lait macules with an irregular outline. In NF1, the outline of the café-au-lait macule is smooth.

- Genetic disorders of DNA repair or chromosomal instability
- Homozygosity for one of the genes causing hereditary nonpolyposis
- **Cancer of the colon**
- **Noonan syndrome**

Conditions with pigmented macules confused with NF1:

- **LEOPARD syndrome**
- Neurocutaneous melanosis
- **Peutz-Jeghers syndrome**
- **Piebaldism**

Localized overgrowth syndromes:

- **Klippel-Trenaunay-Weber syndrome**
- **Proteus syndrome**

Conditions causing tumors confused with those seen in NF1:

- Lipomatosis (see **lipoma**)
- **Bannayan-Riley-Ruvalcaba syndrome**
- Fibromatosis
- Multiple endocrine neoplasia type 1 (**MEN1**) and 2B (**MEN2B**)

Note: One or two café-au-lait macules may commonly be seen in patients unaffected by NF1.

Isolated **neurofibromas** without neurofibromatosis are also common.

Best Tests

See Synopsis section for the clinical diagnostic criteria. It may be helpful to examine family members.

Check for Lisch nodules with a slit-lamp examination.

If the patient is having neurologic symptoms, obtain an MRI of the brain, orbits, and/or spinal

cord. It may also be useful to perform an MRI of any particularly deep or changing plexiform neurofibromas.

Genetic testing is possible in equivocal cases.

Plain radiographs may be obtained if bony involvement is suspected.

Excise or biopsy any lesion suspected of undergoing malignant transformation. Skin biopsy of neurofibromas is not needed but may be performed on symptomatic or atypical lesions.

Neurofibroma Histopathology Findings:

- Dermal or subcutaneous nodule with randomly arranged spindle cells with small wavy or boomerang-shaped nuclei
- Stroma is "bubble-gum pink," mucinous or myxoid
- Increased mast cells common

Management Pearls

A multidisciplinary approach is essential to the management of NF1.

Genetic counseling is an important aspect of proper care because children have a 50% chance of inheriting this disorder. It is noteworthy that parents with segmental neurofibromatosis may have children with neurofibromatosis I.

Neurofibromas are sex hormone sensitive and can be expected to develop and grow during adolescent years and pregnancy.

Children should have comprehensive vision exams performed by an ophthalmologist annually to age 8 and then every other year to age 18 to look for signs of optic glioma. Adults should have only routine vision screening. Routine MRIs to look for optic gliomas in asymptomatic patients are controversial and generally not indicated.

Orthopedic surgeons may be consulted in the management of bony abnormalities such as scoliosis or tibial bowing.

Psychological or psychiatric assessment may be necessary for those with learning disabilities.

Plastic surgery may be indicated to correct deformities.

Screening for pheochromocytoma with urine catecholamine measurement is indicated for any NF1 patient who will undergo general anesthesia.

Blood pressure should be measured annually in all patients, including children, to screen for

pheochromocytoma or renovascular hypertension.

Excise or biopsy any lesion suspected of undergoing malignant transformation. Five to ten percent of patients will develop malignant peripheral nerve sheath tumors, which can be highly aggressive.

Therapy

Excision of tumors is palliative and should be reserved for symptomatic or grossly disfiguring lesions. Surgery is not practical for patients with a large burden of disease. Simple excision is often performed when there are few or symptomatic neurofibromas. Many small lesions can be treated at once using monopolar diathermy with a wire loop. Healing is by secondary intention.

Vaporization with the carbon dioxide laser has also been used to treat neurofibromas.

Methods for treating plexiform neurofibromas and malignant peripheral nerve sheath tumors with angiogenesis inhibitors and anti-inflammatory agents are largely experimental. Thalidomide and 3-D conformal radiotherapy have also been used.

Symptomatic or growing optic gliomas in children are treated with a combination of carboplatin and vincristine.

Ketotifen has been used with success to treat pain and pruritus: 2-4 mg p.o. daily. Common antihistamines typically do not work for pruritus in NF1.

Café-au-lait macules can be treated cosmetically with the Nd:YAG, ruby, or pulsed dye laser.