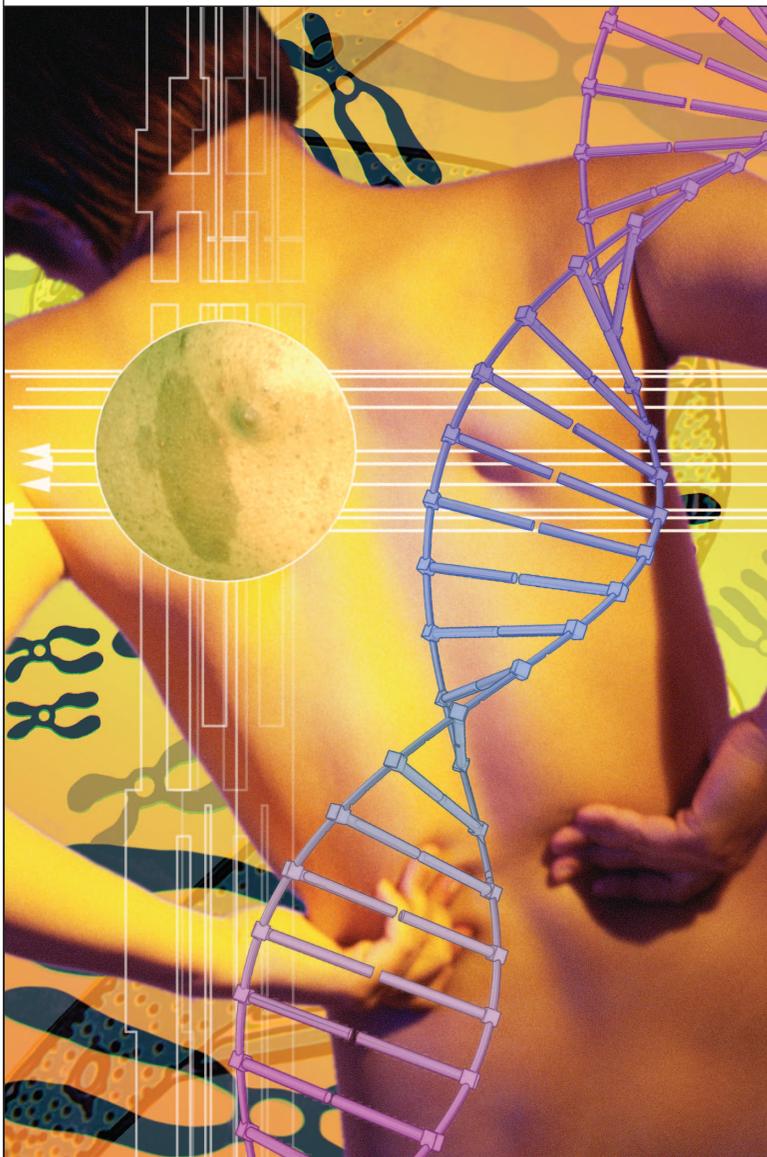


Primary Care for Patients with Neurofibromatosis 1

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Many practitioners are surprised to discover that neurofibromatosis type 1 (NF1) is one of the most common genetic syndromes, affecting approximately 1 in every 3,000 to 4,000 live births.^{1,2} The incidence of NF1 is comparable to that of cystic fibrosis.³ Neurofibromatosis 1 and 2 were once collectively known as von Recklinghausen's disease. It is now understood that these are two distinct genetic disorders affecting two separate chromosomes.³ Neurofibromatosis type 1, the more common of the two, is an autosomal dominant disorder of chromosome 17. Over 50% of all new cases of NF1 are the result of a spontaneous genetic mutation.⁴ Spontaneous mutations occur more often in the NF1 gene than any other human gene.²

The affected gene is a tumor suppressor gene that produces the protein neurofibromin. Neurofibromin is similar to another protein, guanosine triphosphatase-activating protein (GAP) that has been indicated as a factor in tumor suppression in some types of cancers and possibly as a regulator of chemical interactions and cell growth. The similarities between these two proteins indicate that neurofibromin may play a similar role in cell growth regulation and a lack of this protein may be responsible for the abnormal cell growth and tumor development that occurs in NF1.⁵

Neurofibromatosis type 1 is a progressive systemic disorder with a variety of manifestations, the most common being pigmentation disorders, tumor growth, and skeletal abnormalities. There are other manifestations

Illustration by Lisa A. Witter

of the disorder including, but not limited to, learning disabilities, short stature, endocrine disorders, epilepsy, and headaches.^{4,6} Patients with NF1 may develop only a few of these expressions or be severely affected to the point of disability and death. This variability can occur even between affected individuals in the same family.^{4,7}

Primary care providers (PCPs) require a basic knowledge of NF1 in order to identify the disorder, especially in cases without a family history of NF1. Early identification of the disorder allows for prompt referral to a specialist. The specialist then screens for potential rare but severe complications of NF1, many of which occur during childhood. Although annual examinations by the NF1 specialist are desirable, most patients without severe complications can receive routine healthcare from their PCP. The PCP should monitor the patient for indicators of complications between examinations by the NF1 specialist. Optimal healthcare for these patients depends on a collaborative effort between a knowledgeable PCP and regional specialists in genetics, plastics, orthopedics, neurology, dermatology, and psychology.

■ Diagnosis

Because NF1 is progressive in nature, affected individuals may not show manifestations of the disorder at birth. Signs and symptoms may begin to appear gradually in the first few years of life. Although most NF1 patients show evidence of these criteria by 8 years of age, the PCP should consider that in many cases, NF1 may not be evident in the first year of life.⁸ Later discovery of NF1 is a greater possibility when the case is a spontaneous mutation and therefore not anticipated by family history (see Table: “Clinical Diagnosis of Neurofibromatosis”).

■ Hyperpigmentation

Café au lait spots are brown macules that are frequently the first manifestation of NF1 to become evident. Most patients with NF1 will develop more than five café au lait macules within the first year of life, and may continue to develop these macules until 4 years of age.⁸ Removal with bleaching agents has not been successful however, laser or surgical removal may be considered for cosmetic purposes.⁹ Parents and patients should be informed that the number of café au lait spots do not correlate to the number or locations of future NF1 tumors.¹⁰ These macules are benign and they do not cause any functional disability in the NF1 patient (see Figure: “Café au Lait Spots on an NF1 Patient”).

Axillary and inguinal freckling are another hyperpigmentation sign of NF1. This characteristic freckling develops by 7 years of age and is often the second sign of NF1 to be discovered.⁸ Café au lait macules or this characteristic freckling indicates the need to do a thorough screening for

Clinical Diagnosis of Neurofibromatosis

Two or more of the below criteria indicate NF1

Café au-lait macules

Note: must have six or more that are more than 5 mm in greatest diameter before puberty, or 15 mm after puberty

Neurofibromas

Note: two of any type or 1 plexiform

Axillary or inguinal area freckling

Optic glioma

Lisch nodules

Note: two or more

Enlarged or deformed bone

Note: not including the spine

Severe scoliosis

First degree relative with NF1

Source: National Institute of Neurological Disorders and Stroke—National Institutes of Health

Café au Lait Spots on an NF1 Patient



other diagnostic manifestations of NF1, including referral to ophthalmology to examine for Lisch nodules (iris hamartomas) or optic gliomas.

Lisch nodules are specific to NF1 and useful in the diagnosis of the disorder.¹⁰ These are areas of hyperpigmentation on the iris that can be identified by slit lamp examination by 6 years of age.¹⁰ It is important to inform patients and

parents that these nodules do not affect vision and they may or may not be present in NF1.

■ Tumors

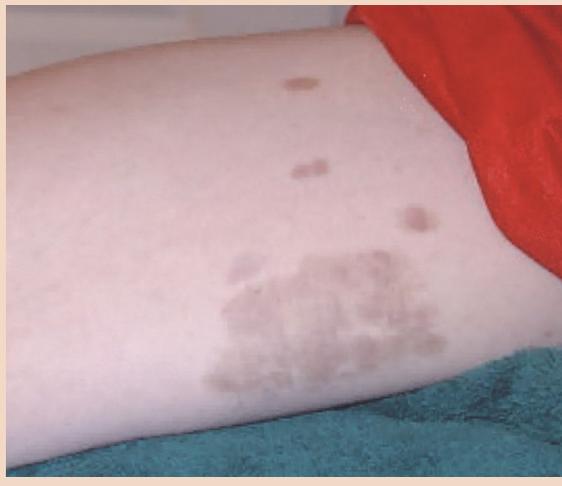
Patients with NF1 develop peripheral and plexiform neurofibromas that consist primarily of Schwann cells, fibroblasts, and axons. Peripheral neurofibromas are well-defined cutaneous and subcutaneous tumors that can develop along any nerve sheath in the body. These tumors usually begin to appear in later childhood and seem to proliferate during periods of accelerated growth and during pregnancy.¹⁰ These tumors can increase in size and number throughout the lifespan and in some cases can become numerous.

Neurofibromas can be removed if they are disfiguring or in a bothersome location. Patients need to understand that the underlying problem, a lack of neurofibromin, still exists so new tumors may replace the ones removed. In one study, researchers found it easier to remove large tumors using traditional surgical techniques while smaller tumors healed more effectively if they were removed using carbon dioxide laser.¹¹

Plexiform tumors are invasive subcutaneous tumors. They can be self-limiting or grow to be very large, disfiguring tumors that can cause organ dysfunction, interfere with bone and soft tissue growth, or undergo malignant transformation.¹² Although they may not be readily identified at birth or during early childhood, plexiform tumors can be congenital.¹² These tumors may initially be missed because they can look like raised areas of hyperpigmentation. Plexiform tumors can also be nodular with satellite lesions (see Figure: “Plexiform Tumor”).

When these benign tumors become malignant, they are called malignant peripheral nerve sheath tumors (MPNST) or neurofibrosarcomas. Plexiform and nodular plexiforms

Plexiform Tumor



form tumor. Malignant peripheral nerve sheath tumors are metastatic, so it is important to immediately refer the patient for evaluation of any area or lump that begins to grow rapidly, itches, bleeds, or becomes painful.^{12,13} Plexiform tumors, due to their potential to cause disfigurement and disability are one of the most difficult physiological and psychological manifestations of NF1. Current research is hopeful that a future drug therapy to prevent the development of these tumors will be discovered.¹⁴ Surgical removal may be attempted in some cases but can be very difficult, resulting in residual pain and tumor regrowth. Neurofibromatosis type 1 patients should be aware of the risk of malignancy and report any pain, change in sensation, or bleeding from tumors.

Optic gliomas are the primary central nervous system tumors associated with NF1. These tumors can lead to vision loss and have demonstrated an association with secondary CNS tumors.^{1,8} There is evidence that NF1 associated optic gliomas are less aggressive and have a better survival rate than sporadic optic gliomas.¹ At one time, annual magnetic resonance imaging exams (MRIs) were performed on NF1 patients to screen for CNS tumors.

Since these optic gliomas are less aggressive, a baseline MRI of the CNS followed by close monitoring of the patient for symptoms such as neurological deficits, unexplained severe headaches, or visual disturbances may be sufficient. Patients with NF1 who present with symptoms such as proptosis, developmental delays, signs of increased intracranial pressure or endocrine disturbances should be evaluated for optic gliomas.¹ Headaches are common with NF1 but a change in pattern or new onset of unexplained headache should be



Plexiform tumors may initially be missed because they can look like raised areas of hyperpigmentation.

are more likely to become malignant than other NF1 tumors. Although individuals without NF1 can develop MPNST, they are more prominent in NF1 patients than the general population. Evans discovered that the lifetime risk for developing MPNST may be as high as 8% to 13% in patients with NF.¹³ Prior to this study, the lifetime estimated risk for this malignant transformation was lower.¹³ Malignant peripheral nerve sheath tumors are often associated with plexiform neurofibromas, but can also occur in areas where there is no plexi-

evaluated.¹² Children under the age of 6 years may have difficulty articulating changes in vision and they should have routine annual vision evaluations to screen for optic gliomas.¹ Due to the severe morbidity associated with these tumors, early identification and referral of NF1 patients with optic gliomas is essential.

A very common finding on the brain MRIs of children with NF1 are areas termed “unidentified bright objects” (UBO). These areas are not tumors and have not shown a correlation to CNS tumors. A possible link between the pathophysiology of UBOs and learning disabilities in NF1 is being investigated.¹⁵

Additional tumors that have been associated with NF1 on a less frequent scale include pheochromocytomas, juvenile chronic myeloid leukemia, and rhabdomyosarcomas. These disorders are rare and do not warrant specialized screening.¹² Routine annual exams should be sufficient in monitoring for these disorders. However, patients should be instructed to report symptoms such as elevated blood pressure or new onset of pain or fatigue. Although infrequent, it is also important to remember during patient evaluations that nonvisible tumors may result in the dysfunction of organs such as the gastrointestinal tract, kidney, and spine.

■ Skeletal Abnormalities

Skeletal growth abnormalities that are associated with NF1 include short stature, kyphoscoliosis, macrocephaly, macrodactyly, pectus excavatum, and osseous lesions such as sphenoid dysplasia, pseudarthrosis, and thinning of the long bones.^{1,6,10,16} Hypotonia and poor coordination have also been associated with NF1.¹⁰ The presence of precocious puberty or short stature in NF1 patients warrants an endocrine evaluation.⁶ Height, weight, head circumference, muscle strength, and coordination should be assessed during the annual physical exam. Although the macrocephaly and macrodactyly generally do not lead to additional complications, the other skeletal anomalies mentioned can have additional consequences and should be followed by orthopedics.

Scoliosis is one of the more common skeletal manifestations of NF1. Treatment of scoliosis may necessitate bracing for curves < 40 degrees to help prevent the curve from progressing. Surgery may be required for curves > 40 degrees or if the patient is experiencing respiratory problems or limited movement.¹⁷ Scoliosis may or may not be associated with spinal tumors (termed dumbbell tumors) or dysplastic thoracic vertebra, both of which can result in spinal cord damage.¹⁰ Scoliosis should be monitored during the annual exam, particularly during times of rapid growth. Stable curves that suddenly worsen or become associated with neurologic dysfunction should be immediately referred (see Figure: “Lumbar Spinal Curve and Café au Lait Spots”).

Common Indicators for Referral in NF1 Patients

Tumors	<ul style="list-style-type: none"> • Any area that develops unexplained pain, itching, tingling, or bleeding • Neuropathy • A change in mobility or coordination • Vision changes • Precocious puberty • A new onset or change in headache pattern • Elevation in blood pressure
Renal artery stenosis	<ul style="list-style-type: none"> • Blood pressure elevation
Scoliosis	<ul style="list-style-type: none"> • Pain in the spine • Rapid curve progression • Progression of curve in adult years • New onset neurological deficit • Change in mobility
Endocrine	<ul style="list-style-type: none"> • Precocious puberty • Sudden elevation in blood pressure • Severe short stature
Learning disabilities	<ul style="list-style-type: none"> • Difficulty with schoolwork • Behavior problems (associated with attention deficit disorder)

■ Learning Disabilities

Although most individuals with NF have normal intelligence, learning disabilities affect as many as one-half of patients with NF1.^{2,10} These disabilities can range from attention deficit hyperactivity disorder (ADHD) to mental retardation.¹⁰ As mentioned before, there may be a possible link between UBOs and learning disabilities, however, a correlation has not been established.² There is also no demonstrated association between macrocephaly and learning disabilities. Screening for learning disabilities in the early school years can allow for rapid intervention. Medications to control ADHD may be considered.

■ Primary Care and Follow-up

Some individuals may have only a few signs of NF1 while others may develop severe manifestations. If NF1 is suspected, a detailed family history and family tree may provide useful information. All patients suspected of having NF1 should have an initial evaluation by an NF1 specialist, usually a genetics specialist. Although patients will continue to be followed by these specialists on an annual and as-needed basis, routine medical care is provided by the PCP.

Routine primary care for patients with NF1 includes check-ups every 6 to 12 months for children and annually for adults. During the routine physical exam for a NF1 patient, special attention should be paid to skin evaluation, neurologic func-

tion, blood pressure, and vision and hearing function. A thorough musculoskeletal exam, including scoliosis screening, is also essential. Hypertension in NF1 is usually present and can be managed by traditional means. However, when NF1 patients develop hypertension, renal artery stenosis and pheochromocytoma must be considered as a possible etiology (see Table: "Common Indicators for Referral in NF1 Patients").

Neurofibromatosis type 1 patients should be examined for masses. Documenting the size and location of plexiform neurofibromas can identify rapid growth of these potentially harmful tumors, which would indicate the need for referral. Cutaneous tumors may not begin to appear until adolescence, but as they continue to grow they can become very difficult to count and document. This is not a great concern because of their benign nature. Teaching patients and/or parents about important signs that indicate the need for evaluation can help identify problems that require early intervention.

Family Counseling

Because NF1 is progressive, and the extent of associated manifestations varies, there is a great deal of uncertainty regarding how this diagnosis will ultimately affect the life of the individual. This diagnosis can be emotionally difficult for parents and children. One study examined parents' responses to the diagnosis and found that they reported feelings of shock, upset, and even depression. Suggestions for breaking this news to parents include: disclosing the information when there is time for the parents to ask questions; providing accurate and hopeful information; clarifying that this is not the Elephant man's disease; and scheduling a follow-up appointment to discuss additional questions that will come after the initial news.¹⁸ Presenting parents or young adult patients with a possible diagnosis of NF1 should be carefully planned to allow time for this counseling.

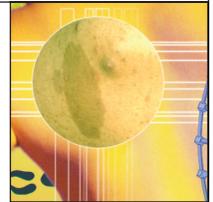
Conclusion

NF1 is a complicated disorder with many of the life threatening complications occurring in childhood and the young adult years. In young adulthood, these patients face difficult decisions on issues such as disclosing their diagnosis to new relationships and the risk of passing the genetic condition to a child. In later adult years, many patients with NF1 continue to struggle with an increased risk for morbidities such as cancer, while also battling disfiguring tumors and bone anomalies. Patients with more severe expressions of the disorder have decreased life expectancy of approximately 15 years.²

The National Neurofibromatosis Foundation ([http://](http://www.nf.org)

www.nf.org) provides information on current research, treatments, and NF medical specialists. This organization also provides an online bulletin board where families and individuals with NF1 can network and share information and concerns. There is also information on youth camps and lo-

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cal NF organizations. The PCP can guide a collaborative plan of care for the NF1 patient that includes both medical and psychological resources. ^{MP}

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