



Neurofibromatosis Type 1

By Tricia Z. Page, MS, CGC and Judith Franklin, RN, MSN, APNG

Amy didn't want to admit to herself what she had felt when she touched her favorite student, Caroline, on the shoulder. Although she had been the nurse at Greenfield Middle School for only a year, she had known Caroline, a friend's daughter, since infancy. She knew school had not been easy for the girl, who struggled in reading and was often teased by other children for being short. As if middle school wasn't hard enough, Amy thought, she didn't want to think about the small, soft mass hidden beneath Caroline's T-shirt.

After dinner that night, Amy mustered up the courage to call Becky, Caroline's mother, and asked if they could meet at a local coffeehouse. Her friend, alarmed at Amy's anxious tone, readily agreed. It took Amy thirty minutes of small talk to reveal her discovery at last. Concerned as well, Becky resolved to call Caroline's pediatrician the next morning.

A week later, Caroline was evaluated by a pediatric geneticist, who noted that she also had freckling in her arm pits, and seven darkened areas of skin on her trunk, arms and legs. He explained to Caroline and her mother that the tumor felt by Amy was caused by a condition called Neurofibromatosis type 1.

What is Neurofibromatosis type 1?

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's neurofibromatosis, is an inherited disorder characterized by benign tumors of the nerve sheath, called neurofibromas. The condition is one of the most common genetic disorders, occurring with an incidence of approximately 1/4,500 individuals, regardless of racial group or ethnicity. NF1 affects both males and females with equal frequency.

One of the unusual features of Neurofibromatosis type 1 is its high degree of variability. Fortunately, two-thirds of people with NF1 are mildly affected — similarly to Caroline. These individuals represent an important, potentially undiagnosed group of patients who need to be identified. In contrast, children who are severely affected often have devastating complications, such as neurological deficits, overgrowth of a body part, premature onset of puberty, bony abnormalities, and even blindness. Because many of these symptoms arise early in life, most children with serious complications are diagnosed in early childhood.

How is a diagnosis of NF1 made?

In 1987, a National Institutes of Health consensus conference established diagnostic criteria for NF1. For a person to be diagnosed with the condition, he or she must have two or more of the following features:

1. Six or more café-au-lait spots (flat, hyperpigmented areas on the skin)
 - a. 1.5 cm or larger in individuals after puberty
 - b. 0.5 cm or larger in individuals before puberty
2. Two or more neurofibromas of any type (usually occurring at either the end of a nerve or at a discrete location along a nerve's length), or one or more plexiform neurofibromas (benign tumors that extend along the length of a nerve, often infiltrating surrounding tissues)
3. Freckling in the armpits or groin
4. Optic glioma (tumor of the optic pathway)
5. Two or more Lisch nodules (benign iris hamartomas, identifiable by an ophthalmologist using a slit lamp)
6. A distinctive bony lesion, such as dysplasia of the sphenoid bone or tibia
7. A first-degree relative, such as a parent, with NF1

In attempting to establish a diagnosis of NF1, it is important to understand that the various features of the condition arise at different times in the life of an affected person. For example, café-au-lait spots often become evident in the first two years of life, increasing in both size and number as a child grows. (It is important to realize, however, that 10–15% of the general population will have one to three café-au-lait spots. This finding alone is *not* sufficient to warrant a diagnosis.) Optic gliomas, plexiform neurofibromas, and bone dysplasias also present themselves during early childhood. In contrast, skin neurofibromas are rarely seen before the onset of puberty. Severe complications in early childhood do not necessarily correlate with a more serious course in later life. Therefore, it is important for anyone suspected of having NF1 to be evaluated by a physician, such as a pediatric geneticist or neurologist, who is familiar with the condition's natural history.

What other features can occur?

Although not specific to NF1, there are other problems that occur more commonly than in the general population. Approximately half of people with NF1 have a learning disability. In addition, affected individuals are at increased risk for macrocephaly, short stature, epilepsy, and scoliosis. People with NF1 have a 5% increased lifetime risk for malignancy, specifically for peripheral nerve sheath tumors, pheochromocytomas, and myeloid leukemias.

What causes NF1?

NF1 is caused by a mutation in the gene *NF1*, which is located on chromosome 17. This gene codes for a protein, called neurofibromin, which under normal circumstances works to suppress tumor development by helping to regulate cell growth. The *NF1* gene is very large, with many different mutations causing the disease.

A laboratory test has recently become available to help with diagnosing parents. However, the diagnosis can rarely be established by the clinical criteria alone.

How is NF1 inherited?

Neurofibromatosis type 1 is inherited in an autosomal dominant fashion, with the presence of one gene mutation being sufficient to cause the condition. The disease is fully penetrant; if there is a mutation in the *NF1* gene, there will be symptoms. If no symptoms have presented themselves by age 5, a child who is at risk because of a family history is unlikely to have the condition.

Affected individuals have a 50% risk for passing *NF1* on to each of their children, regardless of whether they are male or female. Approximately half of affected individuals have a parent with the disease. In the other half of cases, there is no family history of neurofibromatosis: the child represents a new mutation, where the changed *NF1* gene was present in either the egg or the sperm. It is not known why these mutations occur. There is nothing that a parent can do to either cause or prevent these errors from happening.

How is NF1 treated?

At present, treatment focuses on the patient's specific problems. For example, surgery or chemotherapy may be required in a child with a plexiform neurofibroma. A pediatric ophthalmologist is needed to monitor an infant with an optic glioma for loss of vision. An adult with a painful dermal neurofibroma can see a plastic surgeon to have the tumor removed.

Because of the wide range of problems facing patients with NF1, most are followed annually in a neurofibromatosis clinic, where a physician familiar with the condition coordinates their care with other specialists who may be needed. A multi-disciplinary care approach for individuals with NF1 may include referrals to a long list of specialists, including orthopedists, pediatric oncologists, ophthalmologists, dermatologists, radiologists, and plastic surgeons. A physician specializing in pain management may also be important, as neurofibromas sometimes are painful.

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Are there other types of Neurofibromatosis?

Several other forms of neurofibromatosis exist. Neurofibromatosis type 2, or NF2, is a distinctly separate condition from NF1, although they are sometimes confused. NF2 is most commonly characterized by bilateral vestibular schwannomas, or benign tumors of the nerve that connects the ear to the brain. Although the majority of patients with NF2 develop symptoms in their late teens or twenties, approximately 10 percent will present in childhood, usually with tinnitus, hearing loss, or problems with balance. Other features possible include cataracts, peripheral schwannomas, and café-au-lait spots (although few people with NF2 will have 6 or more spots as seen in NF1). NF2 occurs more rarely than NF1 and is caused by a change in a gene on chromosome 22.

Additionally, segmental, or localized, forms of both NF1 and NF2 exist, where one or more body segments are affected with the remainder spared. This results from a gene mutation occurring at some point after conception during the development of the affected region(s).

NF1 affects both males and females with equal frequency

What is the role of the school nurse?

A school nurse can play an important role in identifying undiagnosed cases of neurofibromatosis type I. Attention should be paid to children with six or more café-au-lait spots or freckling in areas not exposed to the sun (such as in the armpits, or under the neck). Dermal neurofibromas tend to appear as puberty begins, or shortly before, increasing in number as the child grows. In addition, any tumors that begin growing rapidly or become consistently painful should be brought to a physician's attention. Blood pressure should be monitored regularly, since hypertension is associated with both pheochromocytoma and renal artery stenosis, both (rare) complications of NF1.

Some children may need counseling and extra support to deal with the psychosocial and emotional implications of their unusual appearance. The cosmetic burden of café-au-lait spots, dermal neurofibromas (which can number from a few to hundreds), or a large plexiform neurofibroma is significant, and sensitivity to this issue is important. Affected children should be monitored for learning disabilities so that problems can be detected and addressed as early as possible. The school nurse can be a resource for teachers, other educational staff and families. Because there is currently no way to predict the severity or course of the disease, it is important that support systems be in place for the child and his or her family.

Neurofibromatosis type 2: Same name, different disease

Tommy had just turned nine when his teacher sent the note home to his mother. He was worried he had done something wrong, although he didn't know what. After reading it, a wrinkle creasing her forehead, his mother asked whether he had been falling down and having trouble hearing the teacher. Relieved that he wasn't in trouble,

Tommy admitted that this was true. He also told his mother that he had been having headaches that wouldn't seem to go away. After a trip to his pediatrician, Tommy was referred to a pediatric neurologist. An MRI revealed that he had tumors growing along the main nerves connecting his ears to his brain. He was given a diagnosis of Neurofibromatosis type 2 (NF2).

While NF2 is a distinctly separate disease from NF1, the two conditions are sometimes confused, both causing tumors that surround nerves. In NF2, however, the tumors arise from Schwann cells, instead of the myelin sheath cells as seen in NF1. Neurofibromatosis type 2 occurs more rarely than NF1, and is caused by a change in a separate gene on chromosome 22. The two disorders do share the same inheritance pattern giving an affected person a fifty-percent risk for passing on the condition to each of their offspring.

NF2 is most commonly characterized by bilateral vestibular schwannomas, or benign tumors of the eighth cranial nerve, which functions to transmit signals from the ear to the brain. These tumors often lead to partial or complete hearing loss. Other features can include peripheral schwannomas and café-au-lait spots (although few people with NF2 will have 6 or more spots as seen in NF1). Some children with NF2 will also develop tumors along their optic nerves (optic nerve sheath meningioma) or cataracts that can compromise their vision.

Although the majority of patients with NF2 develop symptoms in their late teens or twenties, approximately ten percent will present in childhood, usually with tinnitus (ringing in the ears), hearing loss, or problems with balance. To date, treatment focuses on surgery and radiation therapy, although clinical trials and research are ongoing in hopes of improving the health and quality of life for affected people and their families.

If a diagnosis of neurofibromatosis is suspected, the child should be referred to a neurofibromatosis clinic for evaluation. A local clinic can be identified by contacting the National Neurofibromatosis Foundation. This organization is also an important source of information and support for both families and medical professionals dealing with this disorder. For more information, they can be contacted at: The National Neurofibromatosis Foundation, Inc., 95 Pine Street, 16th Floor, New York, NY 10005; 1-800-323-7938; www.nf.org. 🍷

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