Health Supervision for Children With Neurofibromatosis

Committee on Genetics

This set of guidelines is designed to assist the pediatrician in caring for the child in whom the diagnosis of neurofibromatosis has been made. Although the pediatrician's first contact with the child is usually during infancy, occasionally the pregnant woman who has been given the prenatal diagnosis of neurofibromatosis will be referred for advice. Therefore, these guidelines offer advice for this situation as well.

At least two distinct types are recognized—neurofibromatosis 1, or NF-1 (previously known as von Recklinghausen disease or generalized neurofibromatosis), and neurofibromatosis 2, or NF-2 (previously known as bilateral acoustic neurofibromatosis). This discussion addresses only issues concerning the diagnosis and management of NF-1.1-8

Neurofibromatosis 1 is a progressive, multisystem disorder affecting about 1 in 3,000 individuals.9 A National Institutes of Health (NIH) Consensus Development Conference10 regarding NF-1 demarcated seven features, of which two or more are required to establish firmly the diagnosis of NF-1:

1. Six or more cafe-au-lait spots (CLS) or macules, greater than or equal to 5 mm in diameter in prepubertal patients and 15 mm in diameter in postpubertal patients;
2. Two or more neurofibromata of any type, or one plexiform neurofibroma;
3. Freckling in the axillary or inguinal region;
4. Optic glioma;
5. Two or more Lisch nodules (iris hamartomas);
6. A distinctive osseous lesion such as sphenoid dysplasia or cortical thinning of long bones, with or without pseudarthrosis; or
7. A first-degree relative (parent, sibling, or child) with NF-1 according to the preceding criteria.

Diagnosis in nonfamilial pediatric cases may be difficult because certain clinical features are age-dependent. For the same reason, the severity of NF-1 in later life may be underestimated in an affected child.

Congenital lesions include CLS and, less commonly, axillary freckling and neurofibromata. Some affected children have no characteristic lesions at birth. CLS tend to increase in size and number throughout early childhood. Later in childhood, neurofibromata become evident as skin nodules or tags located in cutaneous or subcutaneous tissues, or as subcutaneous masses involving deep tissues (plexiform neurofibromas). Skin overlying plexiform neurofibromas sometimes shows hyperpigmentation and hypertrichosis. Neurofibromata can be found in all organ systems, giving rise to specific symptoms depending on size, location, and degree of encroachment on surrounding tissues. Marked growth of these lesions can occur anytime in childhood but particularly in adolescence and pregnancy.

COMPLICATIONS

The complications of NF-1 result from direct involvement of multiple systems by neurofibromata, an increased risk for malignancy (mostly fibrosarcomas but also other malignancies, including leukemia),11 and poorly understood associations such as mental retardation, short stature, and neurologic and vascular changes unassociated with neurofibromatosis. Sarcomatous changes may occur in neurofibromata, characteristically in deep lesions. Pain, rapid growth, and new localizing neurologic findings sometimes suggest malignant changes, which are otherwise difficult to detect.

Among the unusual but more serious complications of which the family should be aware are optic gliomas (leading to blindness) and other brain and nerve tumors, hypertension, kyphosis and/or scoliosis (leading to diminished pulmonary function), gastrointestinal bleeding secondary to gastrointestinal neurofibromata, facial disfigurement from neurofibromata, and pseudarthroses. Death may result from some of these complications.

For unknown reasons, NF-1 is associated with an increased incidence of mental retardation, although it is usually not severe. Learning problems, speech retardation of a nonspecific nature, hyperactivity, seizures, and EEG changes are also commonly reported.12,13 If seizures are present, intracranial tumors must be excluded, although often no specific etiology for the seizure disorder is found. Persons with NF-1 tend to show subtle neurologic abnormalities involving fine coordination, balance, and gait.

The reported incidence of complications in NF-1

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed for children with neurofibromatosis, but are meant to supplement anticipatory guidelines available for treating the normal child provided in the AAP publication, "Guidelines for Health Supervision." They are intended to assist the pediatrician in helping the family seek appropriate medical care for a child with NF-1. The complications of NF-1 result from direct involvement of multiple systems by neurofibromata, an increased risk for malignancy (mostly fibrosarcomas but also other malignancies, including leukemia), and poorly understood associations such as mental retardation, short stature, and neurologic and vascular changes unassociated with neurofibromatosis.

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The reported incidence of complications in NF-1
varies from study to study mostly because of biased patient selection by age and specialty referral, but also because of inconsistent diagnostic criteria and variable utilization of imaging techniques. Generally complications are overestimated because most studies involve patients in hospitals or referral clinics. About one third of patients with NF-1 show serious complications, and about one half are mildly affected. However, because of the extreme degree of variability even within a family, it is not possible to predict the clinical features in a specific person.

GENETICS

Transmission of NF-1 is by an autosomal dominant mode of inheritance. In about half of the patients, the condition is due to a new mutation. In such instances the parents (both phenotypically normal in regard to NF-1) are not at increased risk compared with the normal population to have another child affected with this disorder. However, the persons with new mutations are at 50% risk to transmit the gene to their offspring. The mutant NF-1 gene has a high penetrance rate, and only rarely does a person known to have this mutation show no clinical manifestations.

The NF-1 gene has been localized to chromosome 17 at band q11.2. Neurofibromin, the protein product of the nonmutated gene locus, is thought to act as a tumor suppressor under normal conditions by down-regulating another cell protein that enhances cell growth and proliferation. Point mutations and deletions have been identified within the NF-1 gene, giving rise to diminished function of neurofibromin in affected persons. DNA analysis for the neurofibromatosis mutation is not yet commercially available, but linkage studies using DNA markers have been accurate in 95% to 99% of the patients studied. Linkage analysis, however, requires study of several family members and is not applicable to all patients.

CLINICAL MANAGEMENT

The multiorgan occurrence of neurofibromas and their complications often requires care from a variety of medical and surgical specialists. The pediatrician should coordinate such care. Patients with more than minimal manifestations of NF-1 may benefit from referral to a multidisciplinary neurofibromatosis (NF) clinic for primary or specialty care. Such clinics are a valuable consultation resource for pediatricians caring for patients with NF-1.

Treatment is aimed at the complications as they occur. Some of the problems, such as renal artery stenosis, if detected early, can be managed successfully. Enlarging tumors can sometimes be managed by observation and surgery. However, surgical removal of a neurofibroma compromising an essential organ system may not be possible because of an inaccessible site or infiltration into surrounding tissue. If malignancies (including leukemia) develop, treatment is the same as for children without NF-1.

In the medical supervision of a child with NF-1, a number of areas require ongoing assessment and periodic review throughout life (Table), including the following:

1. Evaluate the child for new neurofibromas and progression of lesions. Examine the skin carefully for signs of plexiform neurofibromas that may impinge on or infiltrate underlying structures.
2. Check the child's blood pressure. Because renal disease (particularly renal artery stenosis), aortic stenosis, pheochromocytomas (more common in adults) and adrenal tumors may occur, regular and careful blood pressure measurements are important. A variety of vascular hypertrophic lesions may be found.
3. Evaluate neurodevelopmental progress.
4. Evaluate the child for skeletal changes. Look for scoliosis, vertebral angulation, and limb abnormalities. Sometimes localized hypertrophy of a leg, arm, or other part of the body results from plexiform neurofibromata.
5. If any complications occur or if neurocutaneous lesions appear to be rapidly advancing, refer to the appropriate specialist.
6. Recommend available resources for patients with NF-1 (eg, NF clinics, support groups, and individual NF-1 families). Supply books and pamphlets (obtainable from the National NF Foundation). The National NF Foundation can also provide further information and clinic locations. The address of this organization appears in the Acknowledgments section.

THE PRENATAL VISIT

At times the pediatrician may be called on to counsel a family when one of the parents-to-be is affected and the fetus has been diagnosed to have NF-1 by DNA studies. In this situation, the family most likely already has been counseled about the disorder and its inheritance pattern. However, the pediatrician may be called upon to review the information and to assist the family in the decision-making process. As appropriate, the pediatrician may discuss the following issues with the family:

1. Review the prenatal diagnosis.
2. Explain the mechanism for occurrence of the disorder in the fetus and the recurrence rate.
3. Review the prognosis, manifestations, variability, and progressive nature of the disorder.
4. Review the treatments and interventions that are currently available. This discussion should include the efficacy, complications, side effects, and cost or other burdens of these treatments.
5. Discuss the options available to the family for management and rearing of the child. In cases of early prenatal diagnosis, this may include discussion of pregnancy termination, as well as continuation of the pregnancy and rearing the child at home, adoption, etc.
6. When appropriate, consider referring to a clinical geneticist for a more extended discussion of clinical findings, recurrence rates, future reproductive options, and evaluation of the risks of disease for other family members.
7. Inform them that in many parts of the country there are specialty NF clinics that are available for guidance, therapy, and consultation.

HEALTH SUPERVISION FROM BIRTH TO 1 MONTH—NEWBORNS

Examination
1. Confirm the diagnosis by the presence of cutaneous manifestations. Use of a Wood’s lamp may be helpful in identifying CLS. Axillary freckling is sometimes present at birth. 
2. Be aware that normal examination results do not exclude NF-1. 
3. All first-degree relatives should be advised to have a physical examination, including a slit lamp examination of the irides for Lisch nodules, which are found in >90% of adults with this disorder but are uncommon in children under 3 years of age. 
4. Some specialists advise an initial imaging study for optic glioma when the diagnosis of NF-1 is made. The NIH Consensus Development Conference did not recommend computed tomography or magnetic resonance imaging studies for asymptomatic patients with NF-1, however, and generally recommended special studies only when clinically indicated.

Anticipatory Guidance
1. Review the natural history and genetics of NF-1. 
2. Advise the parents to report any unusual or new symptoms. 
3. Stress the need for regularly scheduled visits, including careful neurologic and blood pressure evaluations.

HEALTH SUPERVISION FROM 1 MONTH TO 1 YEAR-INFANCY

Examination
1. Compare the infant's growth and development with figures on growth charts. As a group, children with NF-1 are shorter than average but have larger heads.
2. Examine the patient for the presence of CLS. Inform the family that new ones may appear and...
preexisting CLS often increase in size. Reassure the family that CLS have no clinical significance.
3. Check for proptosis, a rapidly increasing head size, and focal neurologic signs.
4. Perform a careful physical examination for skeletal abnormalities, especially in the spine and legs. This is particularly important before the child begins to bear weight.
5. Refer the infant to appropriate specialists, as indicated.
6. Check the infant’s neurodevelopmental progress at each visit.

Anticipatory Guidance
1. Review the family’s psychological support and intrafamilial relationships.
2. Advise the parents to use sun protection (sunscreen) on the infant. Sun exposure deepens pigment in CLS. Although this is usually of cosmetic significance only, melanoma and basal cell carcinoma have been reported in adults with NF-1.1,2
3. If necessary, review future pregnancy planning for parents.

HEALTH SUPERVISION FROM 1 TO 5 YEARS—EARLY CHILDHOOD

Examination
1. Examine the child for neurofibromata and new freckling (which can appear in any intertriginous area). Assure parents that CLS and freckling have only cosmetic significance.
2. Consider taking photographs to document lesion size for future reference.
3. Evaluate the child’s vision.
4. Recommend that the child receive an ophthalmological examination annually.
5. If there are visual changes, persistent headaches, seizures, a marked increase in head size, or a plexiform neuroma of the head, obtain computed tomography or magnetic resonance imaging of the head.
6. Assess the child’s speech.

Anticipatory Guidance
1. Provide anti-pruritic medication as necessary. Pruritis may be found with cutaneous neurofibromata.
2. Review the child’s preschool program.
3. Obtain a psychological evaluation of the child for assessment of learning abilities. The child may benefit from special preschool education programs and speech therapy.
4. Refer the child for an audiogram before he or she enters a preschool or school program.
5. Discuss indications for surgery, as appropriate. If there is a change in the size of superficial neurofibromata or evidence of a space-occupying internal lesion, refer the child to an NF clinic or other appropriate specialists.
REFERENCES

5. Obringer AC, Meadows AT, Zackai EH. The diagnosis of neurofibromatosis-1 in the child under the age of 6 years. AJDC. 1989;143:717–719
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