Neurofibromatosis

Neurofibromatosis (NF) (von Recklinghausen disease) has a variety of manifestations, which may affect nearly every system and organ. Distinctive features may be present at birth but the development of complications is often delayed for decades. It is a common autosomal dominant disorder affecting approximately 1 in 4,000 of the population. Neurofibromatosis is the consequence of an abnormality of neural crest differentiation and migration during the early stages of embryogenesis, possibly related to the influence of nerve or glial growth factor.

CLINICAL MANIFESTATIONS AND DIAGNOSIS. There are two distinct forms of neurofibromatosis. NF-1 is the most prevalent type of neurofibromatosis and is diagnosed if any two of the following signs are present: (1) At least five café-au-lait spots over 5 mm in greatest diameter in prepubertal patients or at least six café-au-lait spots over 15 mm in postpubertal patients. Café-au-lait spots are the hallmark of neurofibromatosis and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the first few years of life. The spots are scattered throughout the body surface with predilection for the trunk and extremities and sparing of the face. (2) Axillary or inguinal freckling consists of multiple hyperpigmented areas 2–3 mm in diameter. (3) Two or more iris Lisch nodules. Lisch nodules are hamartomas located within the iris and are best identified with a slit lamp examination. They are present in more than 90% of patients with NF-1 but are not a component of NF-2. (4) Two or more neurofibromas or one plexiform neurofibroma. Neurofibromas typically involve the skin, but they may be situated along peripheral nerves and blood vessels and within viscera including the gastrointestinal tract. These cutaneous lesions appear characteristically during adolescence or pregnancy, suggesting a hormonal influence. They are usually small, rubbery lesions with a slight purplish discoloration of the overlying skin. Plexiform neurofibromas are usually evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of the face. The skin overlying a plexiform neurofibroma may be hyperpigmented to a greater degree than a café{acute-e}-au-lait spot. Plexiform neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. (5) A distinctive osseous lesion. Abnormalities of the skeleton are a common feature of neurofibromatosis. Kyphoscoliosis is reported in approximately 40% of patients. Dysplasia of the sphenoid wing causes a pulsating exophthalmos, whereas bowing of the tibula and fibula is often associated with pathologic fractures that have a propensity to develop pseudoarthroses. (6) Optic gliomas are present in approximately 15% of patients with NF-1. These relatively benign tumors consist of glial cells and a mucinous material. Most patients with optic gliomas are asymptomatic and have normal or near-normal vision, but approximately 20% have visual disturbances or evidence of precocious sexual development secondary to tumor invasion of the hypothalamus. Children rarely are aware of unilateral visual loss, thus diagnosis may be delayed. Patients with a unilateral optic glioma typically display an afferent pupillary defect. To test for this, each eye is alternatively stimulated by a bright light source (swinging flashlight test). The affected pupil dilates rather than constricts, whereas light in the unaffected eye causes both pupils to constrict equally. Patients with NF-1 and a plexiform neuroma of the eyelid have a high association with an ipsilateral optic glioma. The CT findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm. (7) A first-degree relative with NF-1 whose diagnosis was based on the aforementioned criteria. The NF-1 gene is assigned to chromosome 17q11.2.

Children with NF-1 are susceptible to neurologic complications. Magnetic resonance imaging (MRI) studies in selected children have shown abnormal signals in the globus pallidus, thalamus, and internal capsule, which probably represent low-grade glioma or hamartoma that is not detected by computed tomography (CT) scanning. These findings may account for the high incidence of learning disabilities, attention deficit disorders, and abnormalities of speech among affected children. Complex partial and generalized tonic-clonic seizures are a frequent complication. Hydrocephalus is a rare manifestation secondary to aqueductal stenosis, whereas macrocephaly with normal-sized ventricles is a common finding. The cerebral vessels may be occluded owing to the neurofibromatosis, resulting in hemiparesis and intellectual deficits. Not surprisingly, psychologic disturbances are

prevalent owing to the seriousness and uncertainty of the disease. Malignant neoplasms are also a significant problem in patients with NF-1. A neurofibroma occasionally differentiates into a neurofibrosarcoma or malignant schwannoma. The incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. However, tumors of the CNS (including optic gliomas, meningiomas of the brain and spinal cord, neurofibromas, astrocytomas, and neurilemmomas) account for significant morbidity and mortality because of their increased frequency in patients with NF-1.
NF-2 accounts for 10% of all cases of neurofibromatosis and may be diagnosed when one of the following is present: (1) bilateral eighth nerve masses consistent with acoustic neuromas as demonstrated by CT scanning or MRI. (2) A parent, sibling, or child with NF-2 and either unilateral eighth nerve masses or any two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacities. Bilateral acoustic neuromas are the most distinctive feature of NF-2. Symptoms of hearing loss, facial weakness, headache, or unsteadiness may appear during childhood, although signs of a cerebellopontine angle mass are more commonly present in the 2nd and 3rd decades of life. Although café-au-lait spots and skin neurofibromas are classic findings in NF-1, they are much less common in NF-2. Posterior subcapsular lens opacities are identified in approximately 50% of patients with NF-2. As with NF-1, CNS tumors, including schwann-cell and glial tumors, and meningiomas are common in patients with NF-2. Linkage analysis has shown that the gene for NF-2 is located near the center of the long arm of chromosome 22q1.11.

TREATMENT. As there is no specific treatment for neurofibromatosis, the management includes genetic counseling and early detection of treatable conditions or complications. The evaluation of a child with neurofibromatosis should include several baseline studies, such as an audiogram, auditory brain stem and visual evoked potentials, an electroencephalogram (EEG), psychologic testing (including studies predictive for learning disorders), a roentgenographic skeletal survey, and CT scanning or MRI of the brain and optic nerves. The asymptomatic patient should be re-examined annually with a neurologic assessment, including blood pressure, auditory and visual screening, and a thorough search for the complications of neurofibromatosis. A parent with neurofibromatosis has a 50% chance of transmitting the disease with each pregnancy. The type of neurofibromatosis (NF-1 and NF-2) "breeds true" for successive generations. Because approximately one half of all cases of neurofibromatosis result from fresh mutations, each parent should be carefully examined (including a search for Lisch nodules) before counseling for the risk of affected future pregnancies. Standard DNA diagnostic analysis is not practical for the prenatal diagnosis of the NF-1 gene because of the large size of the gene and the significant number of mutations. However, prenatal diagnosis is feasible if the mutation causing the condition is known in the affected parent. The majority of NF-2 cases are the result of a mutation. Examination of fetal DNA for the characteristic single-strand conformational polymorphism of an altered DNA sequence provides accurate prenatal testing. In familial cases, where affected and unaffected family members are available, linkage can be established, making prenatal diagnosis available with a certain degree of accuracy.