Neurofibromatosis Type 1, also known as von Recklinghausen disease, was first described by Frederick von Recklinghausen, who proposed that the characteristic dermal tumors that he observed in patients with NF1 arose from the fibrous tissue surrounding peripheral nerves (hence the term neurofibroma). This disease is a common genetic disorder, with an incidence of one per 3500 live births and without a preference for sex or race. An autosomal-dominant disorder, NF1 results from mutation of the NF1 gene, which has been mapped to chromosome 17. This gene spans more than 350 kb of genomic DNA, encoding an RNA of 11 to 13 kb with at least 59 exons. Its protein product, called neurofibromin, contains 2818 amino acids with an estimated molecular mass of 220 kD and shows close homology to the proteins of the guanosine 5'-triphosphatase–activating family, which act as tumor suppressors. Neurofibromatosis Type 1 has virtually 100% penetrance by the age of 5 years. Approximately 50% of cases represent new mutations, and the mutation rate is one of the highest recorded in humans.

Clinical Diagnosis of NF1

The diagnosis of NF1 is based on clinical criteria established by the National Institutes of Health Consensus Development Conference on Neurofibromatosis (Table 1). Many of these signs may not appear until late childhood or adolescence. Café-au-lait spots and plexiform neurofibromas are usually recognized within the 1st year of life, whereas optic pathway gliomas and axillary freckling may not appear until 3 to 5 years of age. Dermal neurofibromas usually are first observed during adolescence, and often increase throughout puberty. The clinical manifestations of NF1 include cutaneous, ophthalmological, musculoskeletal, and neurological lesions. Among these, ocular and cutaneous lesions are the most common.

Cutaneous Manifestations

Some of the most common and earliest manifestations of NF1 are café-au-lait macules, axillary freckling, and Lisch nodules. Café-au-lait macules are apparent in most affected children. These macules are characterized by homogeneous pigmentation with a smooth regular border, varying in size from a few millimeters to a few centimeters. These “spots” do not evolve into tumors and often fade during adulthood. They may be found anywhere on the body except on the scalp, eyebrows, palms, or soles. Histologically, café-au-lait spots represent increased numbers of melanocytes as well as giant pigmented granules (macromelanosomes).

Freckling in regions that are not exposed to the sun, such as axillary and inguinal regions, is also a common manifestation of NF1, occurring in 80% of children by 6 years of age. In addition, freckling can be observed under the neck and breast in areas where skin folds exist.

Lisch nodules are iris hamartomas that do not have any

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effect on visual function. They are uncommon in young children, and are found in approximately 30% of individuals with NF1 by the age of 6 years. They are highly characteristic of NF1 and are best detected by slit lamp examination. Less common ocular findings in NF1 include congenital glaucoma, conjunctival and orbital neurofibromas, retinal astrocytomas, and sectorial retinitis pigmentosa.

Musculoskeletal Abnormalities

Distinctive bone abnormalities, including skeletal dysplasia (particularly sphenoid wing dysplasia), scoliosis, and tibial pseudarthrosis are observed in patients with NF1. Scoliosis affects 10 to 20% of children with NF1 and may occur at an earlier age than in the general population (Fig. 1). When associated with paravertebral neurofibromas, scoliosis may present with an abrupt angle curvature (dystrophic scoliosis). This type of scoliosis is difficult to correct surgically. Short stature is estimated to affect between 25 and 35% of patients. A repeated pathological fracture with incomplete healing secondary to cortical thinning of the long bones is also seen in patients with NF1. Rarely, musculoskeletal malignancies such as rhabdomyosarcoma may arise in patients with NF1, hence the need to recognize quickly and diagnose fast-growing soft tissue lesions in the context of this disorder.

Neurological Manifestations

The neurological manifestations of NF1 include a wide variety of lesions in both the peripheral nervous system and the CNS, including macrocephaly, epilepsy, spinal meningocoeles, neurofibromatosis, and peripheral neuropathy. Hydrocephalus can result from aqueductal stenosis associated with nonprogressive proliferation of subependymal glial cells around the aqueduct and may require surgical diversion when symptomatic. Abnormalities of the intracranial vasculature, although rare, have been reported in patients with NF1.

Optic pathway tumors are the most frequently identified CNS neoplasm in young patients with NF1. They were initially reported in less than 5% of NF1 cases, but this was before the advent of computerized tomography and MR imaging. More recent estimates made using modern neuroimaging techniques have stated that the prevalence of OPTs is between 11 and 19% of NF1 cases, which approximates the lifetime risk of suffering an optic glioma. When associated with paravertebral neurofibromas, 1st-degree relative (parent, sibling, offspring) w/ NF1 according to these criteria

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<td><strong>Diagnostic criteria of NF1</strong></td>
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<td>≥6 café-au-lait macules &gt; 5 mm in greatest diameter in prepubertal individuals or &gt; 15 mm in greatest diameter postpuberty</td>
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<tr>
<td>≥2 neurofibromas of any type or ≥ 1 plexiform neurofibroma freckling in axillary or inguinal regions</td>
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<td>≥2 Lisch nodules</td>
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<tr>
<td>distinct oseous lesion, such as sphenoid wing dysplasia or thinning of cortex of long bones (w/ or w/o pseudarthrosis)</td>
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<tr>
<td>1st-degree relative (parent, sibling, offspring) w/ NF1 according to these criteria</td>
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* Diagnosis is NF1 if two or more of these signs are present. Modified from “Neurofibromatosis. Conference statement” released by the National Institutes of Health Consensus Development Conference.

The period of greatest risk for the development of symptomatic OPTs in NF1 is during the first 6 years of life. The OPTs found in the chiasm of children younger than 3 years of age often have a very aggressive course (Fig. 3). After the age of 6 years, the appearance of symptomatic OPTs, as well as the progression of known OPTs requiring therapy, is extremely unusual. Some studies suggest, however, that symptomatic OPTs can appear as late as the third decade of life. Most OPTs are low-grade pilocytic astrocytomas.

The natural history of OPTs reveals that they are clinically indolent tumors and may regress spontaneously or remain static. Interestingly, as a general rule, the growth of optic gliomas in patients with NF1 is less aggressive than in patients without this disorder. The National Institutes of Health guidelines for patients with newly diagnosed NF1, who have no known OPT, recommend a complete ophthalmological examination at diagnosis, followed by annual examinations until the age of 6 years. For children older than 6 years, periodic eye screening is recommended at longer intervals. These guidelines also recommend neuroimaging only when clinically indicated rather than as a routine screening procedure. For children with newly diagnosed OPTs, regular ophthalmic examinations accompanied by neuroimaging are suggested.

The principal aim of treatment for children with OPTs and NF1 is to prevent visual loss. This can be accomplished by judicious use of surgery, radiation therapy in children older than 3 years of age, and chemotherapy. In general, children younger than 3 years of age who have progressive, symptomatic lesions involving the chiasm will undergo a trial of chemotherapy. In this age group, surgery is reserved for large tumors causing a mass effect or in children in whom chemotherapy has failed. Caution is now used in recommending radiation therapy for patients with NF1. Chemotherapy cycles, generally well tolerated by most patients, are conducted in sequence for time periods longer than 1 year.

Plexiform Neurofibroma

Plexiform neurofibromas are a common manifestation of NF1. They can be classified as benign PNSTs that involve multiple nerve fascicles or branches of major nerves. They may arise from cranial or upper cervical nerves. Plexiform
neurofibromas can vary from a few millimeters in diameter to massive overgrowths several centimeters in size (Fig. 4). They can cause hyperpigmentation or hypertrophy of the overlying skin. These neurofibromas can be cosmetically disfiguring, not to mention the psychological discomfort that arises when the lesions are found in and around the facial area. Plexiform neurofibromas can grow quickly either in early childhood or during times of hormonal change such as those occurring during puberty or pregnancy.

On MR images, plexiform neurofibromas display a high signal intensity on T2-weighted images with central areas of low signal. The treatment of these lesions remains a surgical challenge because of the potential for extensive growth and invasion of surrounding normal structures. Accordingly, conservative management is recommended for asymptomatic lesions, whereas symptomatic lesions may require excision to minimize morbidity. For all lesions, the specter of recurring neurofibromas that will require repeated excision exists. It is hoped that future therapy with drugs such as 13-cis retinoic acid or interferon-alpha may have a role to play in treating these problematic tumors.

Individuals affected with NF1 have a 2 to 5% risk of malignant transformation of their plexiform neurofibroma. Malignant PNSTs or neurofibrosarcomas are the main lesions that result from malignant transformation. These lesions often occur during adolescence and young adulthood. Malignant PNSTs present as a marked neurological deficit, persistent pain, or rapid growth of a plexiform neurofibroma. Individuals with internal plexiform neurofibromas are 18 times more likely to suffer malignant PNSTs than patients without internal plexiform neurofibroma. The 5-year survival of patients with malignant PNSTs is approximately 40%. The general treatment of malignant PNSTs includes diagnostic biopsy sampling followed by extensive excision to achieve wide margin resection, radiation, and chemotherapy.

**Spinal and Paraspinal Tumors**

Intraspinal tumors occur in approximately 2% of patients with NF1. These lesions can occur in all spinal segments (Fig. 5). On the other hand, paraspinal neurofibromas are the most common tumors to affect patients with NF1. The tumors arise generally from the dorsal roots in the cervical and lumbar regions of the spine, and can cause radicular symptoms, the most common of which is pain. Most of these lesions are intracanalicular and intraforaminal and demonstrate extension into the spinal canal with growth. Over time, enlargement of the spinal canal and widening of the interpeduncular distance can occur, resulting in instability and scoliosis. These lesions appear on MR images as dumbbell-shaped tumors in the foramina. If they extend into the spinal canal toward the spinal cord, they can displace or compress the cord. The histopathological findings are usually neurofibroma, rarely astrocytoma, and sometimes ependymoma. Resection is indicated for lesions causing mass effect. The goal is to achieve complete removal of the tumor whenever it is safe to do so, because the recurrence rate is high in partially resected tumors.

**Tumors of the CNS**

Tumors of the CNS occur in 5 to 11% of patients with NF1, and 30% of these will be optic pathway lesions. Several studies suggest that individuals with NF1 are at increased risk for the development of brain tumors during their lifetimes. The tumors appear in the cerebral cortex, basal ganglia, cerebellum, brainstem, and pineal region. Although many of these lesions will be symptomatic, some of them will be discovered during the MR imaging screening in the context of NF1. These lesions appear as areas of high signal intensity on T2-weighted images. They can also show focal contrast enhancement. In some studies MR spectroscopy has been used to investigate CNS lesions in patients with NF1 to distinguish between hamartomas and neoplasms, with modest success. The most common CNS tumor in NF1 is a pilocytic astrocytoma; however, there are reported cases of high-grade gliomas in older children. Other rare types of tumors include ependymomas, ganglioglioma, medulloblastoma, and dysplastic neuroepithelial tumors. Because the frequency of malignant change in these tumors was found to be high-
er than for tumors at comparable sites in patients without NF1. Surgical removal should be proposed whenever possible, especially for symptomatic, enhancing lesions. Surgery should be combined with radiation therapy or chemotherapy where indicated.

**Tectal Glioma**

Tectal glioma in patients with NF1 is a benign subgroup of brainstem lesions that most often cause symptoms as a result of increased intracranial pressure due to obstructive hydrocephalus. Magnetic resonance imaging is the modality of choice for visualizing these lesions. They appear as low-signal-intensity lesions on T1-weighted images and as high-signal-intensity areas on T2-weighted images in as many as 60% of children with NF1. The histopathological finding in most instances is a low-grade glioma. Because the clinical course is usually indolent as far as the mass lesion is concerned, treatment of hydrocephalus as it develops is the cardinal rule. Endoscopic third ventriculostomy is the best form of therapy for the hydrocephalus that develops in these patients. Direct surgery can be performed on radiologically and clinically progressive lesions. Radiation therapy and chemotherapy can also be

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Fig. 2. A: Axial MR image with contrast added, demonstrating a right-sided intraorbital optic glioma. B: Coronal MR image demonstrating a large mass lesion occupying the orbital apex.

Fig. 3. Sagittal MR image obtained in a 2.5-year-old girl with visual failure and macrocephaly. A large midline optic chiasmatic/hypothalamic glioma is seen, with accompanying obstructive hydrocephalus.

Fig. 4. Coronal MR image of the abdomen obtained in a patient with NF1, demonstrating bilateral plexiform neurofibromas emanating from the spinal nerve roots and extending peripherally along the course of the nerves.
used for residual, clinically aggressive lesions.\textsuperscript{13,15} Spontaneous regression or involution of these lesions has been reported.\textsuperscript{32,33}

Other Manifestations of NF1

Cognitive impairments are prevalent in children with NF1 and can result in specific learning disabilities in 30 to 65\% of patients.\textsuperscript{34} Defects in learning affect visual spatial and visual motor integration skills. Some studies have demonstrated a correlation between focal areas of signal hyperintensity on MR images, so-called unidentified bright objects, and cognitive dysfunction.\textsuperscript{10,34} Unidentified bright objects are found mostly in the brainstem, basal ganglia, thalamus, and cerebellum, and have been observed in 60 to 70\% of children with NF1 (Fig. 6). Currently, the relationship between these objects and cognitive dysfunction in NF1 remains controversial.

CONCLUSIONS

In general the life expectancy of a child with NF1 is shorter than that of a member of the general population unaffected by the disease. Factors associated with excess mortality in patients with NF1 include malignant transformation, vasculopathy, hydrocephalus, and cognitive dysfunction.

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