The neurofibromatoses, including neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis, comprise a group of genetically distinct disorders of the nervous system characterized by predisposition to nerve sheath tumors. All 3 types of NF have tumor manifestations (consistent with tumor-suppressor status) and nontumor manifestations. In the second part of this 2-part series, the manifestations of NF2 and schwannomatosis are reviewed. NF2 is characterized by bilateral vestibular schwannomas, meningiomas, ependymomas, cataracts, and epiretinal membranes. The combination of complete hearing loss from vestibular schwannomas and blindness from bifacial weakness is a devastating potential outcome of NF2. Schwannomatosis is characterized by multiple nonvestibular, nonintradermal schwannomas and chronic pain. Recently, germline alterations in the SMARCB1/INI1 gene have been implicated in both familial and sporadic forms of this disorder. Neurologists play an important role in the diagnosis and management of the neurofibromatoses.


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Key words: Neurofibromatoses • Schwannomatosis • Tumor-suppressor, neurogenetic • Nerve sheath tumors
distinguished schwannomatosis from NF2 based on its clinical characteristics; this distinction was confirmed genetically in 2003. This article, the second in a 2-part series, will discuss NF2 and schwannomatosis. The first article in the series focused on NF1 and appeared in the Spring 2009 issue of Reviews in Neurological Diseases.

Neurofibromatosis 2

Epidemiology and Diagnostic Criteria

NF2, previously known as central neurofibromatosis, is less common than NF1, with a birth incidence of 1 in 25,000 to 1 in 40,000. Similar to NF1, it is an autosomal disorder with full penetrance, and about 50% of patients harbor de novo mutations in the NF2 gene. The disease is characterized by the development of bilateral vestibular schwannomas, meningiomas, ependymomas, neurofibromas, nonvestibular schwannomas (Figure 1), and posterior subcapsular lens opacity. The average age of diagnosis, 17 to 24 years, is older than that in NF1; symptoms precede a formal diagnosis by about 5 to 8 years. Various diagnostic criteria have been proposed to improve sensitivity without sacrificing specificity (Table 1).

Clinical Features

Unlike NF1, most of the clinical features of NF2 involve the nervous system (Table 2). The hallmark tumor in NF2 is the schwannoma, a benign encapsulated tumor arising from Schwann cells. These tumors typically grow eccentric to the nerve and cause symptoms by compression rather than direct invasion. Malignant transformation of schwannomas does not occur in NF2, except in the setting of prior irradiation. The most common presenting symptoms in adults include hearing loss, tinnitus, or imbalance—due to involvement of the eighth cranial nerve—which typically occur in the second or third decade of life. Clinicians should be aware that pediatric patients with NF2 often present without these classic symptoms. Instead, presenting symptoms often include cutaneous tumors, seizures, myelopathy, visual loss, and peripheral nerve dysfunction. These tumors are usually asymptomatic and detected incidentally. About 50% of patients with NF2 have evidence of intracranial meningiomas on magnetic resonance imaging (MRI). Although histologically benign, these tumors are associated with a 2.5-fold increase in the relative risk of death as compared with patients without an intracranial meningioma. Spinal cord tumors,
Neurofibromatosis 2 and Schwannomatosis

Consisting of ependymomas, schwannomas, and meningiomas, are also commonly seen in patients with NF2. Between 67% to 90% of patients will demonstrate at least 1 spinal cord tumor on MRI, but many patients never manifest clinical symptoms.13 Although schwannomas and meningiomas are extramedullary in location, fewer than half of patients show radiographic evidence of cord compression.14 Spinal cord gliomas, consisting of ependymomas and astrocytomas, arise as intramedullary lesions in about 50% of patients (Figure 2), although radiographic and neurologic progression is rare.14 Finally, mononeuropathies/polynuropathies have become increasingly recognized as features of NF2. Often, they manifest as a facial palsy or hand or foot drop, and they are thought to not be directly related to the mass effect of the tumors.15 Dermatologic manifestations occur in NF2, although they are less pronounced than in NF1. Skin tumors occur in 60% to 70% of patients, with the vast majority consisting of schwannomas (Figure 3) and a minority consisting of neurofibromas.16 Cutaneous abnormalities are more common in pediatric NF2 patients but are seldom present in sufficient numbers to raise suspicion for NF1.16 Ophthalmic abnormalities are common in NF2 and represent a valuable diagnostic sign in pediatric cases. Posterior lens opacities (ie, cataracts) are seen in up to 75% of patients but rarely cause visual disturbance. Optic sheath meningiomas, although rare, constitute a disproportionate cause of decreased visual acuity in these patients.5 Other abnormalities include epiretinal membranes and retinal hamartomas. Unlike NF1, optic pathway gliomas do not occur with increased frequency in NF2.

**Table 2**

**Clinical Features of Neurofibromatosis 2**

<table>
<thead>
<tr>
<th>Neurologic Clinical Features</th>
<th>Non-Neurologic Clinical Features</th>
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<tr>
<td>• Schwannoma</td>
<td>• Dermatologic</td>
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<tr>
<td>• Meningioma</td>
<td>– Café au lait spots</td>
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<td>• Spinal cord tumors</td>
<td>– Cutaneous tumors (schwannomas,</td>
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<td>• Mono/polyneuropathy</td>
<td>neurofibromas)</td>
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<td>• Ocular</td>
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<td>– Posterior lens opacities</td>
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<td>(cataracts)</td>
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<td></td>
<td>– Retinal hamartoma</td>
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<td>– Epiretinal membrane</td>
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<td>– Orbital meningiomas</td>
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**Genetics and Molecular Biology**

NF2 is an autosomal dominant genetic disorder in which 50% of cases arise from a de novo NF2 gene mutation. Studies suggest that 25% to 33% of sporadic patients with bilateral vestibular schwannomas are mosaic for the NF2 mutation and may present with an attenuated phenotype.17,18 Mosaic NF2 should also be suspected in individuals with multiple schwannomas, meningiomas, or ependymomas who do not meet formal criteria for diagnosis of NF2.17 Genotype/phenotype correlation studies have found that variability within families is less than between families, suggesting a strong correlation between the underlying genotype and the expressed phenotype.

The NF2 gene maps to chromosome 22q11.2.19,20 It is 110 kilobase pairs and is composed of 17 exons. The predominant gene product is a 595 amino acid protein known as Merlin.21,22 This protein links membrane-associated proteins to the actin cytoskeleton. It is believed that the NF2 protein acts as a tumor suppressor gene, regulating Schwann cell and arachnoid cap cell growth. More recent evidence suggests that
Neurofibromatosis 2 and Schwannomatosis continued

Merlin plays a role in the regulation of receptor tyrosine kinases and in the maintenance of contact-dependent inhibition of proliferation.23

Similar to NF1, the diagnosis of NF2 is based on clinical criteria. Genetic counseling is a critical component to the care of the NF2 patient. The use of molecular genetic testing via mutational and linkage analysis has advanced our ability to facilitate genetic counseling and early detection of at-risk individuals. Mutational analysis in patients with NF2 is about 60% sensitive in patients with sporadic mutations and about 90% sensitive in familial cases.24 Currently, linkage analysis is reserved for the rare families with NF2 in which a causative mutation cannot be found.

Management and Treatment
A medical history should probe for auditory and vestibular function, focal neurologic symptoms, skin tumors, visual symptoms, seizures, and headaches. Patients who present with unilateral vestibular schwannomas before age 20 should be closely monitored for NF2 because 20% of these patients will subsequently develop a contralateral vestibular schwannoma (and meet diagnostic criteria for NF2).25 In comparison, 0.12% to 5.7% of patients who present after age 20 will develop a contralateral vestibular schwannoma.25 Ten percent of young patients with multiple cranial meningiomas will meet diagnostic criteria for NF2.15 MRI of the brain with thin (3 mm) axial and coronal cuts through the internal auditory canal and MRI of the spine, both with gadolinium, are recommended to identify vestibular schwannomas and spinal cord gliomas, especially ependymomas. A comprehensive ophthalmologic examination is essential to identify characteristic lesions, such as lens opacities, epiretinal membranes, or retinal hamartomas. In addition, patients with facial weakness from cranial nerve schwannomas or secondary to surgical resection are at risk of exposure keratopathy and blindness. The combination of complete hearing loss from vestibular schwannomas and blindness from bifacial weakness is a devastating potential outcome of NF2. Thus, close ophthalmologic follow-up is essential for health maintenance of the eye. Audiology and brainstem evoked responses serve to document eighth nerve dysfunction, with abnormalities of pure tone threshold present in 90% of NF2 patients between ages 10 and 72. After the initial diagnosis, patients should be followed closely until the behavior of the tumors is established. During these visits, a full neurologic examination, MRI scan of the brain and extracranial symptomatic areas, and audiology should be performed.

Treatment of NF2-related tumors is primarily surgical. The goal is to preserve function and maximize quality of life. Due to the multiplicity of the tumors, it is not feasible to resect every lesion. Patients who are asymptomatic or who have little neurologic dysfunction related to their tumors should be managed conservatively and followed closely to preserve neurologic function. Indications for surgical resection include rapid tumor growth and worsening neurologic symptoms. Stereotactic radiotherapy for vestibular schwannomas has been advocated by some groups to avoid the complications of surgery. Actuarial control rates of 80% to 85% have been reported in NF2 patients, with hearing-preservation rates of 40% to 64%.26-28 The role of radiation therapy for other tumors is not established. At this time, many clinicians opt for surgical resection for those tumors that are surgically accessible, reserving the use of radiation treatment for those patients who are not good surgical candidates. Importantly, radiation therapy may render subsequent resection of vestibular schwannoma more difficult and may increase the risk of secondary malignancy or malignant transformation of schwannomas.29 Traditionally, there has been little to no role for chemotherapy in the treatment of NF2-related tumors. However, a recent report demonstrated the potential benefit of erlotinib for progressive vestibular schwannoma in NF2.30 Further investigation is warranted in regard to the role of chemotherapy for NF2 patients.

Schwannomatosis
Schwannomatosis is the third major form of neurofibromatosis. At this time, there is no estimate of the prevalence of schwannomatosis. Its annual incidence of 0.58 cases per 1,000,000 persons is believed to be similar to that of NF2.31 Unlike NF1 and NF2, only 15% of cases are familial.32 Schwannomatosis is characterized by the development of multiple schwannomas in the absence of vestibular or intradermal schwannomas. Symptoms commonly develop in the second or third decade of life, with pain as the initial complaint. The diagnostic criteria for schwannomatosis exclude patients who fulfill the NF2 diagnostic criteria and individuals with vestibular schwannoma on MRI, a constitutional NF2 mutation, or a first-degree relative with NF2 (Table 3).33

There is ongoing research into the pathogenesis of schwannomatosis. Recently, mutations in the SMARCB1/INI1 gene have been associated with familial schwannomatosis, although the exact mechanism remains to be elucidated.33 In the vast majority of schwannomatosis-
associated schwannomas, truncating mutations in the NF2 gene are present. However, multiple tumors from the same patient do not share a common mutation, which thereby excludes germline mutations in the NF2 gene as the cause for schwannomatosis. At this time, it is not known what causes the instability of the NF2 gene in schwannomatosis.

During the initial evaluation of patients who have or are at risk of schwannomatosis, testing to exclude NF1 and NF2 should be performed. A thorough medical history should include questions about auditory and vestibular function, neurologic symptoms, dermatologic signs, and visual symptoms. A careful family history regarding unexplained neurologic, dermatologic, and audiologic symptoms in first-degree relatives should be obtained. MRI of the brain with thin cuts (3 mm) through the internal auditory canal is necessary to rule out vestibular schwannomas. Finally, management of patients with schwannomatosis should be symptomatically driven, with a focus on pain management and treatment of depression due to chronic pain.

**Conclusion**

The neurofibromatoses comprise a group of complex disorders with a wide range of clinical manifestations and phenotypic variability. Although...
there are similarities between NF1, NF2, and schwannomatosis, they are distinct diseases with unique clinical and molecular features. It is important that a multidisciplinary team plays a role in the care of these complex neurocutaneous disorders.

References