Neurofibromatosis: A Review of NF1, NF2, and Schwannomatosis

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Abstract

The neurofibromatoses are a heterogeneous group of hereditary cancer syndromes that lead to tumors of the central and peripheral nervous systems, as well as other organ systems. By far the most common form is neurofibromatosis 1 (96%), followed by neurofibromatosis 2 (3%), and a more recently recognized, lesser known form, schwannomatosis. The diagnostic criteria, pathogenesis, molecular considerations, and clinical manifestations are discussed in this review article.

Keywords
- neurofibromatosis
- NF1
- von Recklinghausen disease
- NF2
- schwannomatosis

Neurofibromatosis

Neurofibromatosis is a heterogeneous group of hereditary cancer syndromes that lead to tumors of the central and peripheral nervous systems. By far the most common form is neurofibromatosis type 1 (NF1, 96%), followed by neurofibromatosis type 2 (NF2, 3%), and a lesser known form, schwannomatosis. Neurofibromatosis has no gender or racial predilection.

Neurofibromatosis Type 1

Introduction

NF1, also known as von Recklinghausen disease or peripheral neurofibromatosis, is an autosomal dominant tumor predisposition syndrome most readily characterized by the development of multiple neurofibromas of the peripheral nerves. The incidence of NF1 is approximately 1 in every 2,500 to 3,000 births.[1] Life expectancy is shortened to an average of 54 years, often on account of malignancy.[2] Malignancies associated with NF1 include malignant peripheral nerve sheath tumors, gliomas, leukemia, pheochromocytomas, gastrointestinal (GI) stromal tumors, and others. NF1 is caused by a mutation in the neurofibromin tumor suppressor gene located on chromosome 17. It has a high rate of penetrance and the mutation rate of the *NF* gene is high with 80% being of paternal origin.[3] The earliest known depiction of presumed neurofibromatosis dates back to the 13th century with sketches by a Cistercian monk.[4] In 1862, Virchow made reference to the hereditary component when he described a man in which the "body was quite covered with lumps from pinhead-sized to pigeon egg-sized" and he noted that the "peculiarities have existed in an inherited manner already over three generations." However, it was Virchow student, Friedrich von Recklinghausen, in 1882 that gave the most thorough clinical and histological account of the disease and who coined the term "neurofibroma."

Diagnostic Criteria

The symptoms of NF1 can vary significantly among affected patients and thus a timely and specific diagnosis can be difficult to ascertain. Though the clinical diagnosis may be suspected very early in childhood or infancy, the cardinal features may not be entirely present until an older age. Approximately 30% of NF1 patients will meet one of the below criterion by the age of 1 year, 97% of patients will meet two criteria by the age of 8 years and, in a retrospective review of NF1 patients, all patients met the criteria by the age of 20 years.[1] In 1987, the National Institutes of Health (NIH) developed a consensus for diagnosis due to clinical variation.

The clinical diagnosis can be established if the criteria listed in ►**Table 1** are met without cause by an alternate diagnosis.[5]

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Table 1 Clinical diagnostic criteria for neurofibromatosis type 1

Diagnostic criteria of NF1
Two or more of the following:
• At least six café-au-lait macules ($>$ 5 mm diameter in prepubertal individuals and $>$ 15 mm in postpubertal individuals)
• Freckling in axillary or inguinal regions
• Optic glioma
• At least two Lisch nodules (iris hamartomas)
• At least two neurofibromas of any type, or one plexiform neurofibroma
• A distinctive osseous lesion (sphenoid dysplasia or tibial pseudarthrosis)
• A first degree relative with NF1

Pathogenesis and Genetic Considerations

The causative gene for NF1, was identified in 1990 and it was found to be one of the largest genes in the human genome encompassing 280 kbp of DNA.[6] The *NF1* gene is located on chromosome 17q11.2, which encodes for a protein known as neurofibromin.[7] Neurofibromin belongs to the GTPase-activating family of tumor suppressor proteins that regulate the function of the RAS/MAPK signaling and mechanistic target of rapamycin (mTOR) pathways. Approximately 50% of mutations are de novo, occurring in patients with no family history. For families with an inherited mutation, there is complete penetrance; however, clinical manifestations among family members can vary greatly. The variability in phenotypic expression is likely a result of epigenetic modification.[8] Studies addressing the genotype–phenotype correlation have found that deletion of the entire gene, known as 17q11.2 microdeletion, is associated with a more severe form of the disease, while mosaicism can lead to a mild or even segmental presentation.[6,7]

Nearly 1,500 different mutations of the *NF1* gene have been identified and these mutations have been found throughout the entire length of the large gene locus.[6] Nonsense, frameshift, and point mutations have all been identified with the majority of the mutations leading to a truncated form of the protein. Genetic testing is often reserved for family members of a patient whose pathological mutation has been identified, and thus the exact mutation can be screened for in their relatives. Otherwise, given the remarkably high degree of mutation susceptibility and the lack of "hotspots" on the gene, NF1 does not lend itself to mutational analysis as a practical diagnostic tool.[6] The diagnosis of NF1 is most often made on the clinical grounds discussed above.

Clinical Manifestations

Neurofibromas

Neurofibromas, the namesake of the disease, are the most common tumor of NF1, occurring in approximately 60% of the patients. Histologically, neurofibromas of NF1 are indistinguishable from sporadic tumors, albeit the former are often larger. Neurofibromas may be cutaneous or internal, involving deep soft tissues. The cutaneous forms may be pedunculated, nodular, or plaque-like developing in late childhood and increasing in numbers into adulthood.[2] The internal or deep neurofibromas can occur throughout the body including periorbital, retroperitoneal, GI tract, and mediastinal locations.[9] Pathognomonic of NF-1, plexiform neurofibromas are internal neurofibromas that, rather than growing intraneurally within a single nerve, grow to involve multiple fascicles or branches of a nerve or plexus. This growth pattern lends itself to the characteristic "bag of worms" description given on palpation or surgical examination of these tumors. Plexiform neurofibromas often develop in childhood and grow rapidly, exerting mass effect on adjacent structures. Unlike the cutaneous form, plexiform neurofibromas have an increased risk of transformation into malignant peripheral nerve sheath tumors (MPNST). MPNSTs are rare aggressive spindle-cell sarcomas, accounting for only approximately 5% of all soft tissue sarcomas. About 50% of MPNSTs occur in the setting of NF1 as these patients have an 8 to 13% risk of developing one in their lifetime.[3] Sudden change or growth of a plexiform neurofibroma on imaging surveillance, as well as increased uptake on fluorodeoxyglucose-positron emission tomography (PET scan), should raise suspicion for malignant transformation. Treatment for neurofibromas includes surgical resection and laser therapy, while the goal of plexiform neurofibroma surgery is often for debulking. Recent clinical trials involving tyrosine kinase inhibitor imatinib have shown a decrease in tumor volume by greater than 20% in a subset of patients.[10] Further studies addressing this therapy, as well as mTOR inhibitors, are underway.[10] MPNSTs are a significant cause of mortality in NF1 patients and despite radical excision with wide surgical margins, followed by chemoradiation, 5-year survival rates are poor due to frequent lung and bone metastases as well as local recurrence.[2]

Pigmentary Abnormalities

Café-au-lait spots are benign tan-brown pigmented macules that can occur anywhere on the body, and are often the presenting sign of NF1. By the age of 1 year, 99% of the patients with the diagnosis of NF1 will have six or more café-au-lait macules greater than 5 mm (prepubertal criteria as per NIH).[1,9] Though a common feature of NF1, café-au-lait spots are a nonspecific finding as they can be se seen in approximately 10% of the general population as well as in other genetic syndromes—Silver Russell dwarfism, MEN IIb, Legius syndrome, and McCune Albright syndrome. The numeric cutoff used in the diagnostic criteria is based on a study by Crowe et al in 1956 in which 78% of the 203 NF1 patients analyzed had at least six café-au-lait spots greater than 15 mm.[11] This quantity is greater than those reported for the general population. In a retrospective review of infants with birthmarks, Mihm et al showed that 1.8% of African American infants will have three or more café-au-lait spots, while nonsyndromic Caucasian infants rarely have two or more.[12] Histologically, these lesions show hyperpigmentation of the basal epidermis with macromelanosomes present.[9] Although there is no potential for malignant

transformation, cosmetic treatment is sometimes sought. Case reports show that some patients may have a good response with dermatologic laser therapy for depigmentation; however, it may take several treatments for a response and a subset of patients will have repigmentation of the lesion within 6 months.[13]

Freckling in the axilla and groin are another defining symptom of NF1. Only approximately 40% of patients will be noted to have freckling in infancy and 90% of NF1 patients will have freckling by the age of 7 years.[1] Melanocytic nodules can also occur in the irises of NF1 patients. These small, often multiple, hamartomatous lesions, known as Lisch nodules, are found in 93% of adults with NF1. They are asymptomatic.[14]

Gliomas

Patients with NF1 are at an increased risk of developing low- and high-grade gliomas. The most commonly encountered glioma in the setting of NF1 is a low-grade glioma of the optic nerve. These optic nerve gliomas occur in about 15% of NF1 patients and usually present by the age of 7 years.[2] Generally, these tumors are pilocytic astrocytomas, World Health Organization grade I, and are histologically equivalent to pilocytic astrocytomas of the general population with a biphasic growth pattern, hair-like processes, and Rosenthal fibers. Given the indolent nature of these tumors, management usually consists of imaging surveillance. When visual acuity declines, chemotherapy may be employed.[2] The location of these tumors does not allow for surgical intervention and radiation therapy is avoided in NF1 patients due to increased risk of developing radiation-induced malignancies.[15] Brainstem gliomas are the second most frequent glioma of NF1 and again, these tumors are usually pilocytic astrocytomas. For the same reasons as optic gliomas, chemotherapy is the only treatment available with a goal of symptomatic relief and prolonged survival. Finally, NF1 patients have a fivefold risk of developing malignant gliomas, particularly glioblastomas, over the general population with an average survival of about 1 year.

Musculoskeletal Manifestations

Children with NF1 have a significantly increased risk for developing rhabdomyosarcomas with an approximately 20-fold increase over the general population.[2] These rhabdomyosarcomas may arise from any site; however, a large review found a predominance of bladder and prostate sites of origin.[16] The treatment protocols followed for nonsyndromic rhabdomyosarcomas may also be applied to NF1 patients.

Variable skeletal abnormalities are frequently noted in NF1 patients, including osteopenia, scoliosis, and sphenoid wing or congenital tibia dysplasia. In addition, many patients with NF1 will be of short stature; though their body proportions remain normal.[17] The mechanistic association of NF1 and skeletal deformities is largely unknown; however, NF1 patients have been reported to have low-bone mineral densities and low concentrations of vitamin D.[2] Studies have indicated a threefold increase fracture risk in NF1-affected children increasing to a fivefold increased risk in adults.[17,18] Repeat fractures in these patients may lead to pseudoarthrosis.

Gastrointestinal Manifestations

The GI tract can be involved by neurofibromas and malignant peripheral nerve sheath tumors similar to other sites of the body; however, also there are various other GI malignancies associated with neurofibromatosis. As for neurofibromas, the GI tract can be involved by focal neurofibromas or diffusely by a neurofibromatous proliferation expanding the lamina propria. In both instances, ganglion cells may be intermixed without clinical significance. GI stromal tumors (GIST) are not uncommon occurrences in NF1 patients and have been reported in up to 25% of patients.[19] In contrast to GISTs in the general population, NF1-associated GISTs rarely harbor mutations in KIT or PDGFRA. In a majority of cases, the GIST is small, asymptomatic, and follows a benign course. Histologically, the GISTs are similar to nonsyndromic tumors composed of spindle cell and skeinoid fibers. Endocrine tumors of the GI tract are also seen in NF1 patients and these have a predilection for the periampullary region. The most common endocrine tumor reported is a somatostatinoma; however, gastrinoma, insulinoma, carcinoids, and paragangliomas have also been described in this setting.[19]

Other Malignancies

Patients with NF1 also have a significant predisposition to malignancies outside of the nervous system. Children with NF1 have a sevenfold increased risk of hematopoietic malignancies, especially myeloid leukemia, compared with their age-matched counterparts. The treatment and prognosis are similar for the syndromic and general populations. NF1 patients are also at an increased risk for the development of breast cancer, particularly in women under the age of 50 years. Again, the treatment is the same for both the groups of patients. Finally, although a rare occurrence, pheochromocytomas of the adrenal gland are seen more frequently in NF1 patients than in the general population with a reported incidence up to 5% compared with less than 1%.[2] The presentation for pheochromocytomas often involves flushing, palpitations, and hypertension and surgery is often curative.

Neurofibromatosis 2

Introduction

NF2, also known bilateral acoustic neurofibromatosis or central neurofibromatosis, is a hereditary tumor syndrome characterized predominantly by the development of schwannomas, along with meningiomas, ependymomas, and ocular abnormalities. Despite the name, neurofibromas are relatively infrequent. NF2 is inherited in an autosomal dominant pattern with an estimated incidence of 1 in 25,000, prevalence of 1 in 60,000, and a penetrance of approximately 0.95.[20] Patients usually present around age 20 and prognostic considerations include age at diagnosis, meningioma status, and access to specialty medical centers.[21] The disease is caused by a mutation in the *NF2* gene on chromosome 22, which encodes for a protein, merlin. Over half of the cases are caused by de novo gene mutations in patients with no family history of the disease.

Table 2 Clinical diagnostic criteria for neurofibromatosis type 2

Main criteria	Additional criteria
Bilateral vestibular schwannomas *or*	Unilateral vestibular schwannoma *plus* any two of the following: meningioma, glioma, schwannoma, or juvenile posterior lenticular opacities *or*
First-degree relative with neurofibromatosis type 2 *plus* 1. Unilateral vestibular schwannomas *or* 2. Any two of the following: Meningioma, glioma, schwannoma, or juvenile posterior lenticular opacities	At least two meningiomas *plus* 1. Unilateral vestibular schwannoma *or* 2. Any two of: glioma, neurofibroma, schwannoma, and cataract

Diagnostic Criteria

Bilateral schwannomas of the superior vestibular branch of the eighth cranial nerve (vestibular schwannoma or acoustic neuroma) are pathognomonic for NF2. However, since 41% of patients eventually proven to have NF2 do not have bilateral vestibular schwannomas at the initial time of presentation, there have been several diagnostic standards created for NF2. These include the widely recognized Manchester criteria as well as additional NIH criteria shown in ►**Table 2**. Baser et al recently proposed a scoring system to replace the Manchester criteria with reportedly increased sensitivity while maintaining 100% specificity.[21,22]

Pathogenesis and Genetic Considerations

NF2 was proven to be genetically distinct entity from NF1 when linkage studies discovered a novel proven in 1993.[23,24] These studies found the disease to be caused by abnormalities of a gene located on the q12 band of chromosome 22. This *NF2* gene codes for the protein merlin (also known as schwannomin), which is a tumor suppressor protein impacting PI3 kinase/Akt, Raf/MEK/ERK, and mTOR signaling pathways. Merlin is named for its relationship to the moesin (membrane organizing extension spike protein)—erzin (cytovillin)—radixin family of cytoskeleton-associated proteins,[23] which suggests that it may be influential in communication between surface signaling and the cytoskeleton matrix. Mutations in merlin can be found in approximately 93% of patients with clinical evidence of NF2 and a positive family history.[25] A molecular diagnosis is more elusive to find in patients with de novo mutations, 59%, due to somatic mosaicism,[26] which is present in 30 to 60% of de novo cases. In mosaic cases, the mutation is harbored within the tumor itself and only a subset of circulating lymphocytes picked up on a routine blood test. Recent studies have found that, while penetrance levels will be different for the offspring of a mosaic patient than for a fully penetrant familial patient, there is still a risk of transmission of the disease in the setting of a nondetectable mutation in the blood. It has been estimated that the risk of transmission drops from the autosomal dominant 50% to around 8 to 12% depending on initial clinical presentation.

The phenotype of NF2 can have varying degrees of severity. Within an affected family, the natural history and phenotypic expression of NF2 is usually similar between its members. However, interfamily variations can be striking. The differences can be attributed to differing abnormalities within the *NF2* gene. For instance, the most severe clinical manifestations have been associated with frameshift or nonsense mutations, which also happen to be the most common mutation types, in which the mutation causes truncated protein expression. An analysis of 268 NF2 patients by Selvanathan et al found that patients who harbored mutations leading to truncated protein expression were diagnosed at a younger age and had a higher prevalence of meningiomas, spinal tumors, and cutaneous tumors.[27] The younger age of diagnosis was found attributable to earlier symptomatic presentations, especially tinnitus, wasting, and weakness. In contrast, mutations resulting in large deletions or missense mutations lead to a milder disease presentation. Smith et al reported that, in addition to mutation type, the position of the mutation within the gene also had phenotypic implications. Mutations toward the 5′ end of the gene are associated with a higher prevalence of intracranial meningiomas, whereas mutations in exons 14 and 15 confer a lower risk.[28] It was also noted in this study that, while there is a female predominance of developing meningiomas in the general population, there is no gender predilection for meningiomas within NF2 patients.

Clinical Manifestations

NF2 predisposes patients to the development of nervous system tumors, including predominantly schwannomas followed by meningiomas, and ependymomas. In addition, patients are also affected by ocular manifestations. The hallmark and pathognomonic finding of NF2 is bilateral vestibular schwannomas, which can be found in 90 to 95% of NF2 patients.

Vestibular Schwannomas

Vestibular schwannomas, also known as acoustic neuromas, present with tinnitus, gradual hearing loss, and balance dysfunction. Usually present by the age of 30 years, these tumors arise from the superior division of the eighth cranial nerve within the internal auditory meatus. Histologically, vestibular schwannomas in NF2 are similar to sporadic schwannomas by displaying characteristic alternating Antoni A and B regions, Verocay bodies, and hyalinized vessels. In contrast to sporadic schwannomas, vestibular schwannomas of NF2 are often multifocal, as evidenced by radiographic studies[29] and appear multilobulated or botryoid at the time of surgery. In fact, a recent study has found that each of these tumors or "lobules" harbors admixed cell populations with various somatic NF2 mutations, supporting polyclonality

with multiple distinct tumor clones.[30] This finding may explain the disparities observed in treatment outcomes when comparing with sporadic cases. Treatment is usually reserved for cases with significant impact on quality of life, particularly hearing preservation, or for instances when the tumor grows medially and causes brainstem compression. For sporadic tumors, surgery and radiosurgery have been the mainstays of therapeutic intervention; however, both options are more complex in the setting of NF2. Surgery has a similar hearing preservation rate of approximately 50% between both sporadic and NF2 tumors, however, recurrence rates for NF2 vestibular schwannomas are about 44% compared with 1.3% for their sporadic counterparts.[31] This discrepancy is attributable to the multifocal growth pattern as well as the tendency of the tumor to involve the facial nerve. Thus, there is also increased risk of facial nerve injury and consequential eyelid and lacrimal gland dysfunction. If surgical resection yields an intact cochlear nerve, cochlear implantation can be utilized for further improvement in hearing outcomes.[32] Stereotactic radiation has a significantly poorer hearing preservation rate for NF2 tumors compared with sporadic, and this may be in part due to histological tendency of NF2 schwannomas to invade nerve fibers, rather than displace them as sporadic tumors do, which leads to inevitable nerve damage when targeting with radiation or surgery.[33] Also, there appears to be a greater risk of malignant transformation following radiation in vestibular schwannomas of NF2 patients.[31] Finally, chemotherapy with bevacizumab, a vascular endothelial growth factor inhibitor, has recently been utilized with promising success showing a clinical response of hearing improvement in 57% of cases and tumor shrinkage in 53%; however, toxicities including hypertension and proteinuria are not uncommon.[34,35]

Peripheral Schwannomas

Schwannomas of other cranial and peripheral nerves, especially paraspinal and cutaneous nerves, are encountered in up to 70% of patients with NF2.[36] Symptoms attributable to peripheral schwannomas are most often pain, sensory loss, and weakness. As with the vestibular schwannomas, the histology of peripheral schwannomas of NF2 and sporadic schwannomas are similar with the exception of the tendency of NF2 schwannomas to infiltrate the associated nerve. Also, immunohistochemical study for INI1 (SMARCB1) displays a mosaic pattern of expression in syndromic tumors as opposed to intact positivity in sporadic cases.[36] The finding of SMARCB1 alterations in these schwannomas raises the possibility of a diagnosis of schwannomatosis rather than NF2 (see "Schwannomatosis" discussion below), however in most cases, the other clinical or molecular criteria of NF2 are present.

Minute Schwann cell neoplasms, called tumorlets, are not uncommon in NF2 patients and are often found studded along the paraspinal nerve roots. These tumorlets are believed to be schwannoma precursors in these patients.[37] Similar to plexiform neurofibromas of NF1, plexiform schwannomas involving more than one nerve fascicle are more commonly seen in NF2 patients and the finding of a plexiform schwannoma confers a 10 to 50% chance that the patient in fact has NF2.[38,39] Plexiform schwannomas are most often cutaneous or subcutaneous with a predilection for the head and neck region. In contrast to the neurofibromas of NF1, schwannomas of NF2 rarely undergo malignant transformation. Excision is the treatment of choice for peripheral schwannomas and surgical outcomes are reportedly varied. Some authors report a worse postsurgical outcome for NF2-associated schwannomas in comparison to sporadic schwannomas, as may be expected due to their infiltrative nature and plexiform subtypes, while others report great improvement in neurologic deficits among both the patient groups.[40]

Meningiomas

Meningiomas occur in about 50% of NF2 patients and are associated with significant morbidity and mortality in this population. Most are intracranial meningiomas and frequently multiple, though spinal meningiomas also occur. Symptoms from an intracranial meningioma, such as headache or seizure, are the presenting symptom in up to 30% of patients eventually found to have NF2.[20] Meningiomas occur at a younger age in NF2 patients than in the general population, and in fact, approximately 20% of pediatric patients diagnosed with a meningioma will be found to have NF2.[41]

Ependymomas

Glial neoplasms are relatively uncommon in NF2 with the exception of intramedullary spinal ependymomas. Spinal ependymomas in NF2 have a predilection for the cervical and cervicomeduallry junction, with about 85% occurring in this region,[42] and commonly present as multiple tumors with a "string of pearl" appearance in the cord. Histologically, the tumors are often low-grade classic or tanycytic ependymomas. Ependymomas of NF2 patients are often asymptomatic and are only identified by routine imaging surveillance and thus the mainstay of therapy is monitoring.

Ocular Manifestations

Ophthalmic complications are found in a majority of patients with NF2. The most common ocular manifestation is a cataract caused by posterior subcapsular lenticular opacities which is present in up to 80% of NF2 patients.[43] Additional ocular findings include epiretinal membranes, retinal hamartomas, optic nerve gliomas, and meningiomas, and intraocular schwannomas.

Schwannomatosis

Introduction

Schwannomatosis, as the name implies, is a syndrome characterized by the development of multiple peripheral nerve schwannomas, without concomitant involvement of the vestibular nerve. Since the schwannoma is the predominant tumor in both NF2 and schwannomatosis, there can be considerable overlap in the phenotypes of these syndromes and as such schwannomatosis is often categorized as the third form of neurofibromatosis. However, genetically they are two distinct entities. The prevalence of schwannomatosis is

Table 3 Diagnostic criteria for schwannomatosis

Clinical criteria	Molecular criteria
• At least two nondermal biopsy-proven schwannomas *plus* no radiographic evidence of bilateral vestibular schwannomas on high-quality MRI *or*	• Biopsy-proven schwannoma or meningioma *plus* a germline SMARCB1 mutation *or*
• One biopsy-proven nondermal schwannoma or intracranial meningioma *plus* a first-degree relative with schwannomatosis	• At least two biopsy-proven schwannomas or meningiomas harboring a shared SMARCB1 mutation and differing NF2 mutations

Abbreviations: NF2, neurofibromatosis type 2; MRI, magnetic resonance imaging.

difficult to assess given the clinical similarities to NF2 and lack of a reliable genetic test in all cases, though it is speculated to be about as common as NF2.[36]

Pathogenesis and Genetic Considerations

Schwannomatosis is caused by a mutation in the *SMARCB1* gene, also known as the *INI1*, *BAF47*, or *hSNF5* gene, located on chromosome 22q11.2, centromeric to the *NF2* gene. The majority of the cases of schwannomatosis are caused by de novo mutations, though familial cases exist with an autosomal dominant inheritance pattern.[44] Even in the familial forms, a germline SMARCB1 mutation is only identified in 40 to 50% of cases,[26] suggesting involvement of other genetic loci yet to be identified. Genetic testing is complicated by the presence of somatic NF2 mutations found in many tumors of patients with schwannomatosis. Therefore, molecular studies performed on several tumors may be required before a definitive diagnosis can be made. SMARCB1 mutations are also responsible for the rhabdoid tumors of rhabdoid predisposition syndrome, however, rarely do these two syndromes overlap clinically. The differences in tumorigenesis, outcome, and presentation for these two syndromes with a shared mutation is not completely understood, though may be a result of truncated versus nontruncated proteins or epigenetic factors.[26]

Diagnostic Criteria

Diagnostic criteria for schwannomatosis are not yet as standardized as they are for the other two neurofibromatoses. Currently, the diagnosis can be made on a molecular or clinical basis. Clinically, a patient can be diagnosed with schwannomatosis with the following stipulations: (1) at least two nondermal biopsy-proven schwannomas with no radiographic evidence of bilateral vestibular schwannomas on high-quality magnetic resonance imaging or (2) one biopsy-proven nondermal schwannoma or intracranial meningioma and a first-degree relative with schwannomatosis. It has also been proposed that a patient with two or more nondermal tumors that are suspicious for schwannomas, but without histological confirmation, be considered "possible" for a diagnosis of schwannomatosis.[26] Finally, as bilateral vestibular schwannomas of NF2 may occur in the third decade of life, an age cutoff of at least 30 years may be employed to ensure an accurate diagnosis of schwannomatosis.[26] Molecularly, the diagnosis can be made if a patient (1) has a biopsy-proven schwannoma or meningioma and a germline SMARCB1 mutation, or (2) has at least two biopsy-proven schwannomas or meningiomas with a shared SMARB1 mutation and differing NF2 mutations, as outlined in ►**Table 3**.

Clinical Manifestations

Schwannomas

Though schwannomas are common to both schwannomatosis and NF2, there are clinical differences. The age at presentation for schwannomatosis peaks in adulthood, usually between the ages of 30 and 60 years,[44] and often with chronic debilitating pain. In contrast, NF2 can be reliably diagnosed in early childhood and more commonly presents with neurological deficits. Histologically, sporadic schwannomas and syndromic schwannomas are indistinguishable; however, similar to NF2, the schwannomas of schwannomatosis tend to have an intraneural growth pattern, peritumoral edema, myxoid change, and a mosaic INI1 staining pattern by immunohistochemistry.[26,45] Management is clinical observation for asymptomatic patients. In cases of spinal cord compression or bothersome symptoms, surgery is performed to improve quality of life.

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