A General Introduction to Neurofibromatosis

25

Sumit Sinha, Nishant Yagnick, and Harsh Deora

25.1 Introduction

Neurofibromatosis (NFM) is a relatively common condition characterized by neurological and cutaneous lesions and present with a wide variety of clinical manifestations, which constitute a diagnostic and a therapeutic challenge. The term NFM comprises of at least four distinct sets of disorders (see below): neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), segmental schwannoma, and schwannomatosis. All of them are genetically determined autosomal dominant disorders, each characterized by the presence of distinct nerve sheath tumors and other clinical features. This chapter will review the pathogenesis, diagnosis, and management of each of these forms of NFM.

25.2 Classification of NFM

Riccardi et al. classified NFM into eight types with peculiar clinical features and patterns of inheritance (Table 25.1) [1]. However, soon after it was proposed that NFM can be classified into five broad subtypes, based on clinical presentation and genetic implications for the patients: NF1, classical; NF2, acoustic; NF3, segmental; NF4, familial; and NF5, Noonan phenotype [2].

More recently, there have been at least four distinct types of NFM recognized, with the probability of other variant forms existing [3]:

1. Neurofibromatosis 1 (NF1)—also called as von Recklinghausen's disease or peripheral neurofibromatosis—is the most common form of NFM (85%). NF1 is an autosomal dominant disorder affecting 1 in 3500–5000 individuals. It is the most common single-gene disorder in humans. The genetic locus of NF1 has been localized to the long arm of chromosome 17. However, there is no positive family history in 35–50% of patients. These sporadic cases usually arise from (paternal) germ cell mutations.
2. Neurofibromatosis 2 (NF2)—or central neurofibromatosis—is also an autosomal dominant disorder and affects 1 in 40–50,000 individuals, with a prevalence of 1 in 2,10,000 in population. Sporadic gene mutations occur in 50% of cases. NF2 is characterized by the presence of bilateral schwannomas of the eighth cranial nerve, causing progressive hearing loss and the presence of multifocal meningiomas.
3. Segmental neurofibromatosis is characterized by café au lait macules dispersed in bands on

S. Sinha (✉)
Neurosurgery and Spine Services, Paras Hospital, Gurugram, Harayana, India

N. Yagnick
Paras Hospital, Gurugram, Harayana, India

H. Deora
Department of Neurosurgery, NIMHANS, Bangalore, India

F. Guedes et al. (eds.), *Diagnostic Assessment and Treatment of Peripheral Nerve Tumors*,
https://doi.org/10.1007/978-3-030-77633-6_25

Table 25.1 Riccardi classification of NFM

Type	Inheritance	Remarks
Neurofibromatosis (NF1)	AD	Café au lait spots, neurofibroma, Lisch nodules, axillary freckling, osseous and neurological involvement, and benign and malignant tumors
Acoustic (NF2)	AD	Bilateral acoustic neuromas, few café au lait spots, and neurofibromas
Mixed (NF3)	AD	Mixed NF1 and NF2
Variant (NF4)	Unknown	Variations of CNS tumors, café au lait spots, neurofibroma, and Lisch nodules
Segmental (NF5)	Non-inheritable	Segmental neurofibromas and café au lait spots
Familial (NF6)	Unknown	Café au lait spots
Late onset (NF7)	Unknown	After third decade-neurofibroma, few café au lait spots
Unspecified (NF8)	Unknown	Variable manifestations

the skin and limited to one or a few body segments.

4. Schwannomatosis is a condition sharing the presentation and phenotype with NF2, albeit with a distinct clinical and molecular signature, and presenting with multiple deep and intensely painful schwannomas.

25.3 Neurofibromatosis 1 (NF1)

NF1 was first described by Friedrich von Recklinghausen in 1882 [4]. Since then, there has been much genetic and clinical research on this multi-system, age-penetrating disorder with a predilection for the nervous system. It is also known as von Recklinghausen's disease or peripheral neurofibromatosis and characterized by the development of multiple neurofibromas of peripheral nerves. The incidence of NF1 is approximately 1 in 2500–3000 births [5]. The average life expectancy of patients with NF1 is 54 years, often due to associated malignancies [6].

25.3.1 Genetics of NF1

Neurofibromatosis is an autosomal dominant Mendelian disorder with complete penetrance. However, it can have variable expressivity in terms of the major manifestations and severity of the disease. This is exemplified by the microdeletion phenotype as it involves the entire NF1 gene vs the intragenic mutations. Another reason for this observation is that some of those genes co-deleted with NF1 exert an influence on the clinical manifestation of the disease in patients with NF1 microdeletions. Approximately 50% of the affected individuals don't have any affected parent and represent new mutations of the NF1 gene.

NF1 is inherited from parents in 50% of cases and is consequent to a spontaneous mutation in the remaining 50% [7, 8]. More than 1500 mutations have been identified in patients with NF1. Usually, NF1 is due to the loss of a function dominant mutation of NF1 gene (neurofibromin), which is a tumor suppressor gene located on chromosome 17q11.2. However, only a single "microdeletion" (equivalent to a loss of 1.5 MB), found in only 5–10% of cases, has been identified as a consistent prognostic indicator of the disease manifestation. Moreover, the wide spectrum of clinical pictures associated with the same mutation suggests that other factors determine the phenotype, yet their nature has not been identified [9–14].

The gene responsible for NF1 is more than 300 kb in size, located on chromosome 17, and includes 60 exons. All types of mutations are scattered throughout the gene, including nucleotide changes, insertion or deletions, splicing mutations, and whole gene mutations. A comprehensive genetic testing and direct sequencing for NF1 is able to detect the causative mutation in 95% of individuals fulfilling the diagnostic

criterion and may be useful to confirm a diagnosis in an individual with only one clinical feature, especially in sporadically affected young children and for prenatal diagnosis.

25.3.2 Pathogenesis

The NF1 gene encodes for the "neurofibromin" protein which is a GTPase-activating protein (GAP) that promotes the conversion of Ras-GTP to Ras-GDP. The gene is involved with the control of response of the cells to growth stimuli [15]. Several pathways are known to be involved in the development of tumors associated with NF1. Loss of neurofibromin increases rat sarcoma viral oncogene homolog (RAS) activity, which causes unopposed cell growth and activation of downstream intermediates such as mitogen-activated protein kinase (MAPK) and the mammalian target of rapamycin (mTOR) pathways [16]. Neurofibromin is also involved in the regulation of cyclic adenosine monophosphate levels, which has been shown to affect the CNS, especially optic pathway glioma (OPG) formation [17–19].

The target cell for the mutations is Schwann cells in a neurofibroma and a melanocyte in café au lait macules. The neurofibroma contains a mixed population of fibroblasts, perineural cells, and mast cells. All of these cells proliferate due to the secretion of cytokines secreted by the mast cells. Some phenotypic characteristics, especially the cognitive deficits, are explained on the basis of haploinsufficiency.

The recognition of the role of Ras signaling pathway in the pathogenesis of NF1 has led to the development of ongoing preclinical trials of candidate therapies including Ras, downstream effectors of Ras, mTOR, cytokines, and angiogenesis factors.

25.3.3 Diagnostic Criterion

There are several diagnostic criteria developed to diagnose NF1, but the most commonly used one was developed by the Consensus Development Conference at the National Institutes of Health (NIH) in 1987 which concluded that the diagnosis of NF1 could be assigned to a person with two or more of the following criteria:

1. The presence of more than six café au lait spots measuring at least 15 mm in diameter in adults or five café au lait spots of 5 mm in children
2. Two or more neurofibromas of any type or at least 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 (sphenoid dysplasia or tibial pseudoarthrosis)
7. A first-degree relative with NF1 by the above criteria

While these criteria can be applied to adults, the same cannot be applied to children or at an early stage of the disease. This is because only about half of children with NF1 and no known family history of NF1 meet the NIH criteria for diagnosis by age 1 year. However, by 8 years of age, almost all cases will exhibit features of the same.

In case a child is born to a known NF parent, then they need only one criterion to fulfill the diagnosis, which is usually identified early in the form of cafe au lait spots, which develop in infancy in >95% of individuals with NF1. The young children with multiple café au lait spots and no other NF1 features whose parents do not show signs of NF1 on careful physical and ophthalmologic examination should be strongly suspected of having NF1 and followed clinically. A definite diagnosis of NF1 can be made in most of these children by age 4 years using the NIH criteria. The young children who present with six or more café au lait macules and freckling in axillary or inguinal regions but have no known family history of NF1 also meet the diagnostic criteria for NF1. However, the diagnoses of Legius syndrome or constitutional mismatch repair syndrome need to be considered in such cases, especially if no additional findings of NF1 develop with increasing age.

25.3.4 Clinical Manifestations

There seem to be two age peaks in the occurrence of severe clinical problems for NF1 patients: one from 5 to 10 years of age and the second from 36 to 50 years of age. At the second peak, 75% of the clinical problems are related to malignancy. There is extreme variability in features and complications of NF1 among affected individuals. Approximately one-third of patients with NF1 will suffer serious medical and cosmetic complications over their lifetime; the remaining two-thirds will have mild to moderate involvement.

NF1 can have varied manifestations, and the lifespan of these individuals is typically 15 years shorter than an average individual [20]. Apart from the increased risk of having neurofibromas, these patients can develop a plethora of other malignant and benign tumors which can contribute to an early demise and considerable morbidity. Although the peripheral nervous system is the focus of the disease in NF1, NF1-associated neoplasms can occur elsewhere in the body including the central nervous system, skin, the gastrointestinal tract, bone marrow, breast and soft tissues.

25.3.4.1 Neurofibromas

Neurofibromas (NF) are benign tumors arising from the Schwann cells and are a hallmark of NF1, present in all the patients older than 30 years. They may occur anywhere in the body, involving either a discrete length of an individual nerve or multiple nerve fascicles. They may appear typically on the skin surface or within the dermis and increase in number during puberty and pregnancy. Internal or deep NF may occur throughout the body including the periorbital, retroperitoneal, GI tract, and mediastinal locations or present with pain or neurological deficits, as are the spinal NF (Figs. 25.1 and 25.2). There are multiple types of neurofibromas that exist with a varying capacity to become malignant peripheral nerve sheath tumors. The WHO classification scheme defines five distinct neurofibroma subtypes (Table 25.2). The plexiform NF is pathognomonic of NF1, which grow along multiple fascicles or branch of a nerve.

The morbidity associated with plexiform NF is twofold. They can lead to cosmetic disfigurement, bony destruction, and pain and have 8–13% lifetime risk of malignant transformation

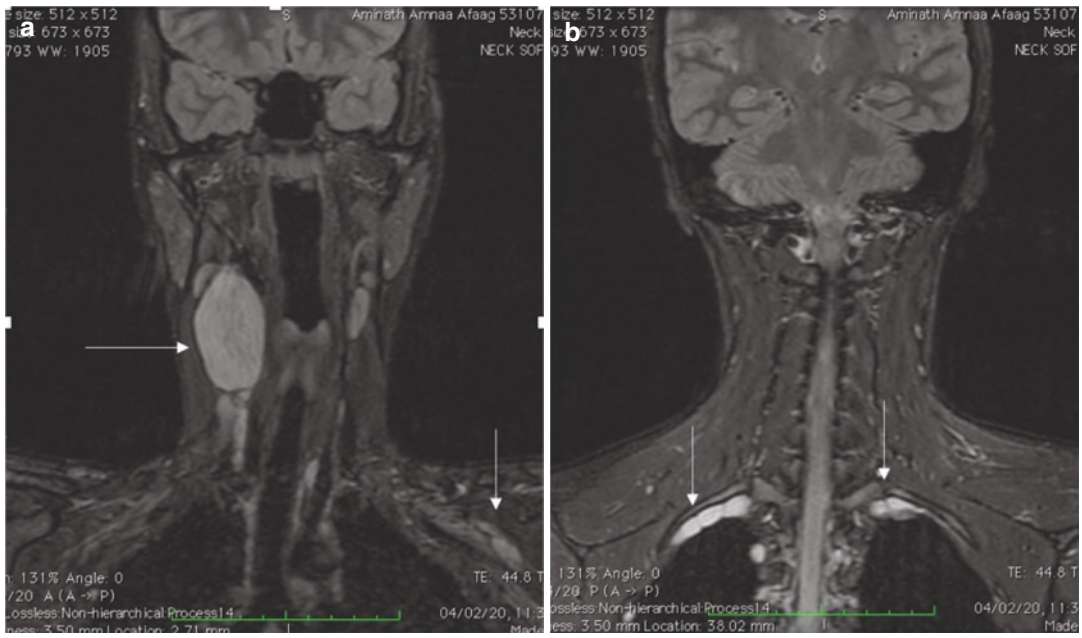

Fig. 25.1 (**a**) T2 weighted MRI coronal images showing hyperintense lesion involving the right carotid sheath/vagus nerve (white arrow); (**b**) T2 weighted MRI coronal images showing hyperintense lesion involving the bilateral intercostal nerves (white arrow)

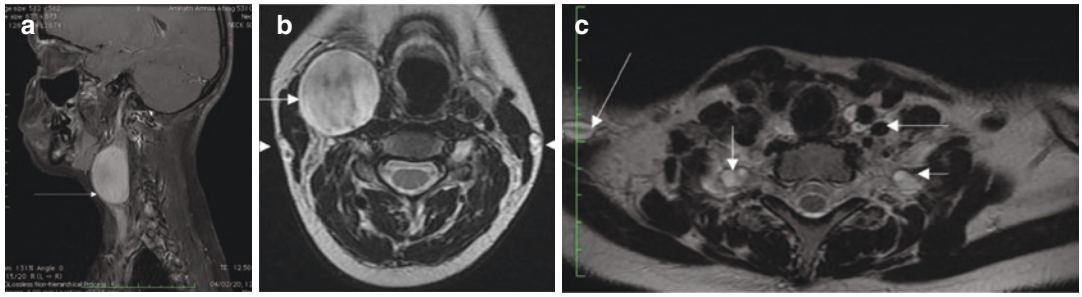

Fig. 25.2 (**a**) T1 weighted contrast-enhanced fat-suppressed sagittal images and (**b**) T2 weighted axial images showing a large enhancing and T2 hyperintense lesion involving the carotid sheath/vagus nerve (white arrows) (**c**) T2 weighted axial images in the same case showing other multiple subcutaneous and brachial plexus neurofibromas (white arrows)

Table 25.2 Types of Neurofibromas and their association with Neurofibromatosis

Type	Location	NF1 incidence	Malignant potential	Remarks
Localized cutaneous	Skin	10% NF1 90% sporadic	None	Most common, hidden under café au lait spots
Diffuse cutaneous	Skin	10% NF1 90% sporadic	Very low	Uncommon lesions that present as plaque-like lesions
Localized intraneural	Cranial, spinal, autonomic nerve plexus	Can be NF1 or sporadic	Intermediate	Second most common
Plexiform	Cranial, spinal, autonomic nerve plexus	Exclusively NF 1	Highest	Diagnostic of NF1
Massive soft tissue	Extremities, extensive soft tissue expansion with underlying large nerve	Exclusively NF 1	Intermediate	Less common called elephantiasis neuromatosa

into malignant peripheral nerve sheath tumor (MPNST).

25.3.4.2 CNS Tumors

In the central nervous system, astrocytoma is the most common manifestation. Gliomas can present throughout the CNS in patients with NF1. The relative risk of having a brain tumor is 100 times higher in children (<10 years) with NF1 than those without NF1. Most of these tumors are low-grade (WHO I–II grade) tumors. These patients also carry a chance of developing high-grade neoplasms like diffuse astrocytomas (WHO grade II–III) and glioblastomas (WHO grade IV), many of which occur in the brainstem. The Cancer Genome Atlas Research Network concluded that 18% of sporadic glioblastomas have a homozygous deletion or mutation of NF1 gene, underscoring the important role that NF1 loss plays in glioblastoma pathogenesis [21].

The patients develop optic pathway gliomas (OPG) during childhood or adolescence. NF1-associated optic gliomas can occur anywhere along the optic nerves, the optic chiasm, or the optic tracts and are found in ~15% of children with NF1 [22]. As the World Health Organization (WHO) grade I neoplasms (pilocytic astrocytomas), OPG typically follow a benign clinical course, involving optic nerve, chiasma, and/or hypothalamus. However, they can be clinically problematic as nearly half of NF1 patients with OPG develop moderate to severe visual impairment [23, 24]. Precocious puberty also occurs in a small fraction of NF1 patients whose OPG involve the optic chiasm and adjacent hypothalamus. OPG usually present before the age of 6 years with a loss of visual acuity, proptosis, or strabismus, but they may not become symptomatic until later in childhood or even in adulthood. Symptomatic OPG in NF1 are frequently stable

and indolent for many years or are only very slowly progressive, and some of these tumors even regress spontaneously.

25.3.4.3 Café Au Lait Macules and Other Skin Manifestations

The café au lait spots occur in nearly all NF1 cases, and intertriginous freckling shall develop in 90% cases. By the age of 1 year, 99% of children with the diagnosis will have 6/>6 café au lait macules >5 mm. These spots are characteristically ovoid in shape with well-defined borders and usually about 1–3 cm in size. They are uniform in color, being a little darker than the background pigmentation of the individual (Fig. 25.3a, b). The pigmentation may also be irregular, with freckling or a more deeply pigmented smaller café au lait spot within a larger more typically colored lesion. The café au lait spots are flat and flush with the surrounding skin; however, if the skin of the lesion is raised or has an unusually soft or irregular texture in comparison to the surrounding skin, an underlying plexiform neurofibroma is more likely. The darker pigmentation of café au lait spots may be difficult to see in people with very dark skin, where the color of the lesions is similar to that of the rest of the skin. A Wood's light is useful in such cases to demonstrate the pigmented macules. Café au lait spots are not seen on the palms or soles in patients with NF1 but can occur almost anywhere else on the body. The size, number, and location of café au lait spots do not correlate with the severity of NF1 or the location of future neurofibromas.

The skin fold freckling appears first in the inguinal region and later in the axillae. This is often the next sign to appear, usually at 3–5 years of age. Only 40% will have freckling in infancy, while 90% of NF1 patients will have this by the age of 7 years. The freckles are frequent in sun-exposed areas and may also be seen diffusely over the trunk, proximal extremities, and neck in patients with NF1. Similar freckling is common in fair-skinned people who do not have NF1. However, patients with NF1 also develop freckles in areas where the skin rubs against the skin, i.e., in the axilla, groin, and under the breasts in women. These freckles look like any others; however, it is only their location that is unusual.

Other skin manifestations include juvenile xanthogranulomas which are small, tan, or orange-colored papules that may occur in clusters.

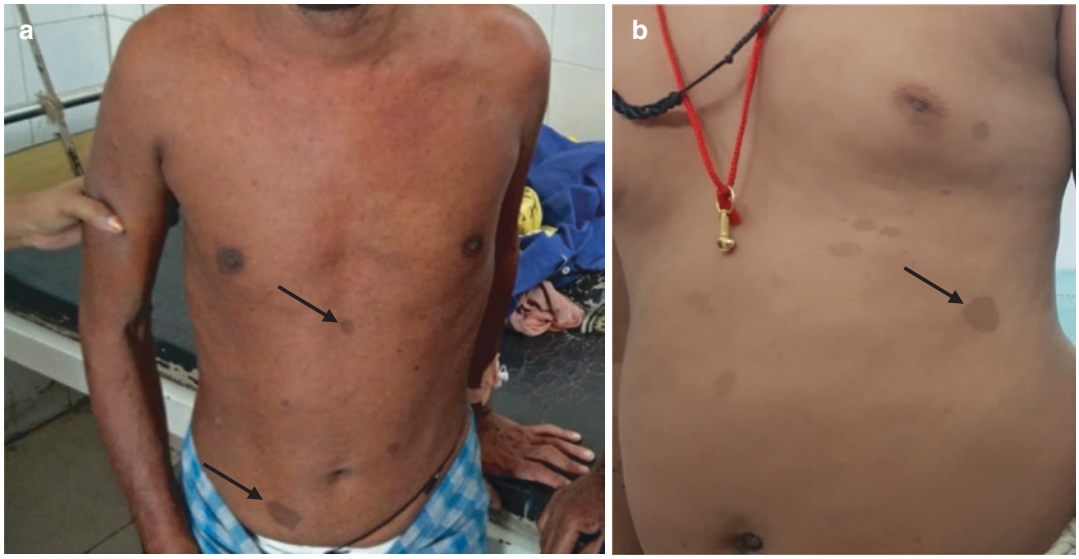

Fig. 25.3 (**a**, **b**) Photograph of patients with NF1 showing cafe au lait macules on the abdomen (black arrows)

Nevus anemicus is another such lesion which is an irregularly shaped macule, paler than the surrounding skin, and that does not get red when rubbed, as the skin surrounding it does.

25.3.4.4 Ocular Findings

Ocular manifestations include iris Lisch nodules. These are melanocytic hamartomas and are asymptomatic and highly specific for NF1. They are demonstrable in adults and half of the children <5 years with the help of a slit lamp [25]. Choroidal freckling cannot be seen on standard ophthalmologic examination but can be visualized by scanning laser ophthalmoscopy with infrared or near-infrared light, infrared reflectance imaging, or optical coherence tomography. Other infrequent ocular manifestations of NF1 include retinal vasoproliferative tumors and neovascular glaucoma [26, 27].

25.3.4.5 Neurological Manifestations

These can be divided as central and peripheral. NF1 patients have psychiatric and neuropsychological abnormalities with IQ scores which may be normal or slightly below normal. The learning disabilities have been reported in up to 80% of these children [28, 29]. This is more so in cases with microdeletion. Frank intellectual disability can be seen in 6–7% cases which is twice that of the general population. Further, nearly 40% of these children have attention-deficit/hyperactivity disorder, 30% have autism spectrum disorder [30], and many have visual-spatial deficits [31]. Deficits in visual-spatial performance, social competence, and attention are most commonly seen in people with NF1, but problems with motor function, executive function, memory, and language are also frequent. T2-weighted magnetic resonance imaging often identifies "unidentified bright objects" (UBOs) in the basal ganglia, thalamus, brainstem, cerebellum, or subcortical white matter of these children [32–34]. These UBOs, which have variously been interpreted as hamartomas [35], regions of abnormal myelination [36], heterotopias [37], or vacuolated myelin [38], are potentially related to the learning disabilities seen in children with NF1 [39]. UBOs can also be confused with the radiologic abnormalities associated with glioma.

Seizures are also more common than the general population which may be due to the presence of tumors or infarct [40]. Other central manifestations include sleep disturbances and headaches (migraines). The pain in association with plexiform neurofibromas is also common and must be distinguished from the pain that may be the first sign of transformation to a malignant peripheral nerve sheath tumor.

25.3.4.6 Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

MPNSTs are aggressive spindle cell neoplasms derived from the Schwann cell lineage [41] with a 5-year survival of up to 60%. As a group, MPNSTs represent ~2 to 5% of all soft tissue sarcomas. However, MPNSTs are encountered in three very different clinical settings, which raise the question of whether there are distinct MPNST subtypes that arise via different pathogenic mechanisms. About 40–50% of MPNSTs arise in NF1 patients. MPNSTs are the most common malignancy encountered in NF1 patients, and the lifetime risk of developing an MPNST has been estimated at 5.9–10.3%. Another 40–47% of MPNSTs are sporadic, with the remaining 10–13% occurring at sites of previous radiation therapy. MPNST usually arise from a pre-existing plexiform NF. The signs of a malignant change are unexplained persistent pain, rapid growth, change in texture from soft to hard, and an increased uptake on FDG-PET scan.

25.3.4.7 Musculoskeletal Manifestations

The presence of skeletal abnormalities such as scoliosis, vertebral scalloping, unilateral sphenoid wing dysplasia, decreased bone mineral density, and tibial pseudoarthrosis has been found in nearly half of NF1 patients [42]. The serum 25-hydroxy vitamin D levels are reduced in individuals with a large number of dermal neurofibromas [43]. 25-Hydroxy vitamin D levels are inversely proportional to the burden of these tumors.

Osteopenia and osteoporosis are both more frequent in NF1 than in general population. The hypothesis is that there is a lower-than-expected serum 25-hydroxy vitamin D concentration, elevated serum parathyroid hormone levels, and evidence of increased bone resorption in patients with NF1. The neurofibromin gene plays a critical role in regulating the mesenchymal stem/progenitor cell differentiation into osteoblasts, affecting collagen synthesis and mineralization. The function of both osteoblasts and osteoclasts appears to be abnormal in NF1. Dysplasia can occur in long bones, most commonly in the tibia and fibula, which is infrequent but characteristic of NF1. This usually presents in infancy as unilateral anterolateral bowing of the lower leg, which is quite different from the common physiologic bowing seen in children when they begin to walk. Early recognition of tibial dysplasia permits bracing, which may prevent fracture. The initial radiographic changes consist of narrowing of the medullary canal with cortical thickening at the apex of the bowing. In contrast, sphenoid wing dysplasia can be incidental and can cause strabismus or even progressive pulsating enophthalmos.

Scoliosis can be seen in the dystrophic variety which occurs at a young age (6–8 years) and is characterized by an acute angle over a short segment of the spine and can be rapidly progressive. Non-dystrophic variety commonly presents with adolescent scoliosis and is not associated with vertebral anomalies.

Orbital dysplasia may occur due to the presence of a plexiform NF in trigeminal nerve.

25.3.4.8 Vascular Manifestations

Vascular abnormalities ranging from renal, coronary and cerebral artery stenosis to pulmonary stenosis, valvular malformations, and coarctation of the abdominal aorta occur in nearly 10% [44–47] and are some other factors contributing to mortality in these patients, particularly those who die before 30 years of age [48].

Hypertension and stroke are the most common manifestation of NF1 in the vascular system. Hypertension can be essential or associated with renal artery stenosis, coarctation of the aorta, or other vascular lesions associated with hypertension. A renovascular cause is often found in children with NF1 and hypertension. Stroke in young is a common manifestation with the involvement of both the brain and heart. Stenosis or ectasia of the cerebral and intracranial arteries are much more common in NF1 than the general population. Moyamoya disease is three times as common as the general population.

Cardiovascular abnormalities such as valvular pulmonic stenosis, congenital heart defects, or hypertrophic obstructive cardiomyopathy are more common in these cases. They can develop pulmonary hypertension in the adult age group which is often in association with parenchymal lung disease [49].

There is an increased risk of hemorrhagic and ischemic strokes in adult and pediatric population as compared to general population. The various associations include moyamoya angiopathy, cerebral aneurysm, and ectatic cerebral vessels.

25.3.4.9 Non-CNS Tumors

Apart from the involvement of the nervous system, patients with NF1 can also have systemic neoplasms. There is a 0.1–5.7% risk of NF1 patients developing pheochromocytomas, typically in the fifth decade of life [50–52].

The endocrine tumors of gastrointestinal tract (GIT) are also seen in NF1 with a predilection for periampullary region. The most common of these is a somatostatinoma. Gastric carcinoids are also associated with NF1, although this is a rare manifestation of the disorder [53]. NF1 patients are at increased risk (45-fold higher than that of the general population) for the development of gastrointestinal stromal tumors (GISTs) [54], with 60% of them occurring in the small intestine, whereas sporadic GISTs are most commonly gastric [55].

Young children with NF1 are prone to develop juvenile myelomonocytic leukemia, with boys being particularly susceptible to this malignancy

[56]. Glomus tumors, which are small benign but exquisitely painful tumors that develop at the end of digits, have also been suggested to be a feature of NF1 [57].

NF1 patients have a 20-fold increased risk for the development of embryonal rhabdomyosarcomas as compared with the general population [58–60]; this is, however, one of the less common manifestations of NF1, occurring in <1% of individuals with this disorder. Likewise, leiomyosarcomas and osteosarcomas occur rarely in NF1 but still at a rate higher than that of the general population [61]. The lifetime risk of developing breast cancer is found to be double in women with NF1, and the survival of NF1 patients with breast cancer is poorer than that of other breast cancer patients [62].

25.3.4.10 Other Manifestations

NF1 may present with dysmorphic features and overgrowth in childhood. Child overgrowth has been defined as any child with NF1 under the age of 18 years who has height and/or head circumference at least two standard deviations above the age- and sex-matched population. Facial dysmorphism is defined as having two or more of the following features: coarse face, flat occiput/brachycephaly, facial asymmetry, prominent forehead, frontal bossing, ptosis, down slanting deep-set eyes, eversion of the lateral eyelid, epicanthic folds, high and broad nasal bridge, bulbous nasal tip, large and low-set ears, malar hypoplasia, wide and prominent philtrum, micrognathia, small pointed chin, and low posterior hairline.

Macrocephaly and short stature are variably seen in NF1 cases [63–65].

25.3.5 Management

The management of NF1 consists of the following:

1. Surveillance
2. Surgery of progressive lesions
3. Genetic counseling

The important surveillance points depend upon the age of the patient. The presence of plexiform NF or orbital or long bone dysplasia should be sought for in the clinical examination in an infant suspected of having NF1. In children, besides plexiform NF, the presence of high blood pressure (due to renal artery stenosis), curved spine (due to scoliosis), and learning disability should be screened, as also the presence of optic glioma by performing an ophthalmological examination and assessment of growth and head circumference. The adults should be screened for the presence of NF, high blood pressure, neurological function (for the presence of hydrocephalus, optic glioma, spinal cord or peripheral nerve compression), and tumor growth for the possibility of MPNST.

The treatment of various lesions in NF1 depends upon their presentation and is summarized in Table 25.3. The development of newer therapies targeting MEK inhibitors and mTOR pathways is currently under research trials [66]. Anti-angiogenesis factors like bevacizumab have shown objective responses in vision testing in cases with refractory optic gliomas [67, 68].

The biopsy of the suspected tumors is not necessary as the imaging is diagnostic. Surgery is recommended for optic gliomas with deteriorating vision or proptosis.

Table 25.3 Treatment of various lesions in NF1

Dermal NF	Plastic surgery, CO_2 laser, electro-desiccation	To improve appearance or discomfort
Plexiform NF	Debulking	For cosmesis or neurological decompression. Complete removal not possible
Optic gliomas	Usually stable and do not require treatment. Surgery recommended for deteriorating vision or proptosis	Postoperative chemotherapy with carboplatin and vincristine. Five-year progression free survival is 70%
Learning disabilities	Neuropsychological assessment	
MPNST	Surgery and/radiation	

25.4 Neurofibromatosis 2 (NF2)

NF2, also known as bilateral acoustic neurofibromatosis or central neurofibromatosis, is a hereditary tumor syndrome characterized predominantly by the development of schwannomas, with meningiomas, ependymomas, and ocular abnormalities. Posterior subcapsular cataract is the only non-tumor manifestation.

NF2 is inherited in an autosomal dominant pattern with an estimated incidence of 1 in 25,000, a prevalence of 1 in 60,000, and penetrance of almost 100% [69]. Patients usually present around age 20, and prognostic considerations include age at diagnosis, meningioma status, and access to specialty medical centers. Over half of the cases are caused by de novo gene mutations in patients with no family history of the disease. The life expectancy of patients with NF2 is reduced as compared with unaffected individuals (69 vs 80 years) [70].

25.4.1 Genetics and Pathogenesis of NF2

The disease is caused by a germline mutation in the NF2 gene, which can be identified in 70–90% of affected individuals. NF2 was proven to be a genetically distinct entity from NF1, caused by abnormalities of a gene located on the q12 band of chromosome 22. This NF2 gene is composed of 17 exons spanning 110 kb and codes for the protein named "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, which suggests that it may be influential in communication between surface signaling and the cytoskeleton matrix.

The NF2 protein is a true tumor suppressor as biallelic loss results in tumor formation. Mutations in Merlin can be found in approximately 93% of patients with clinical evidence of NF2 and positive family history, in 90% of sporadic vestibular schwannoma and in 50–60% of sporadic meningiomas.

The phenotype of NF2 can have varying degrees of severity. Within an affected family, the natural history and phenotypic expression of NF2 are 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.

25.4.2 Diagnostic Criterion

NF2 is diagnosed using clinical criteria. There is a paucity of cutaneous stigmata in NF2, and cafe au lait macules are not a regular feature. Bilateral schwannomas of the superior vestibular branch of the eighth cranial nerve (vestibular schwannoma or acoustic neuroma) are pathognomonic for NF2. There have been several diagnostic criteria for NF2 as 41% of patients eventually proven to have NF2 do not have bilateral vestibular schwannomas at the initial time of presentation. These include the widely recognized Manchester criteria as well as additional NIH criteria as shown in Table 25.4.

Table 25.4 Diagnostic criteria of NF2

Main criteria	Additional criteria
Bilateral vestibular schwannomas	Unilateral vestibular schwannoma plus any two of the following: meningioma, glioma, schwannoma, or juvenile posterior lenticular opacities
First-degree relative with NF2 plus: 1. Unilateral vestibular schwannomas 2. Any two of the following: meningioma, glioma, schwannoma, or juvenile posterior lenticular opacities	At least two meningiomas plus: 1. Unilateral vestibular schwannoma 2. Any two of the following: glioma, neurofibroma, schwannoma, and cataract

25.4.3 Clinical Presentation

NF2 is known to have nervous system tumors including schwannomas followed by meningiomas and ependymomas (Fig. 25.4a–f). The patients can also have non-neoplastic ocular manifestations. The pathognomonic hallmark finding of bilateral vestibular schwannoma is found in >95% of NF2 patients.

25.4.3.1 Vestibular Schwannomas

These tumors arise from the superior division of the vestibular nerve and present with sensorineural hearing loss, tinnitus, and imbalance while walking (Fig. 25.5a–c). They histologically resemble sporadic tumors with the presence of alternating Antoni A and B bodies, Verocay bodies, and hyalinized blood vessels. However, in contrast to the sporadic schwannomas, the schwannomas in NF2 tend to be multifocal and multilobulated and invade the nerve fibers, rather than displacing them (as in sporadic NF) [71]. This accounts for the high recurrence rates for NF2 tumors as compared to sporadic tumors (44% vs 1.3%) with surgery or radiotherapy. The risk of malignant transformation after radiation is more in NF2 vestibular schwannomas as compared to sporadic ones [71].

25.4.3.2 Peripheral Schwannomas

Schwannomas of other cranial and peripheral nerves, especially paraspinal and cutaneous nerves, are encountered in up to 70% of patients with NF2 [72] (Fig. 25.6a–h). Symptoms attributable to peripheral schwannomas are most often pain, sensory loss, and weakness. These schwan-

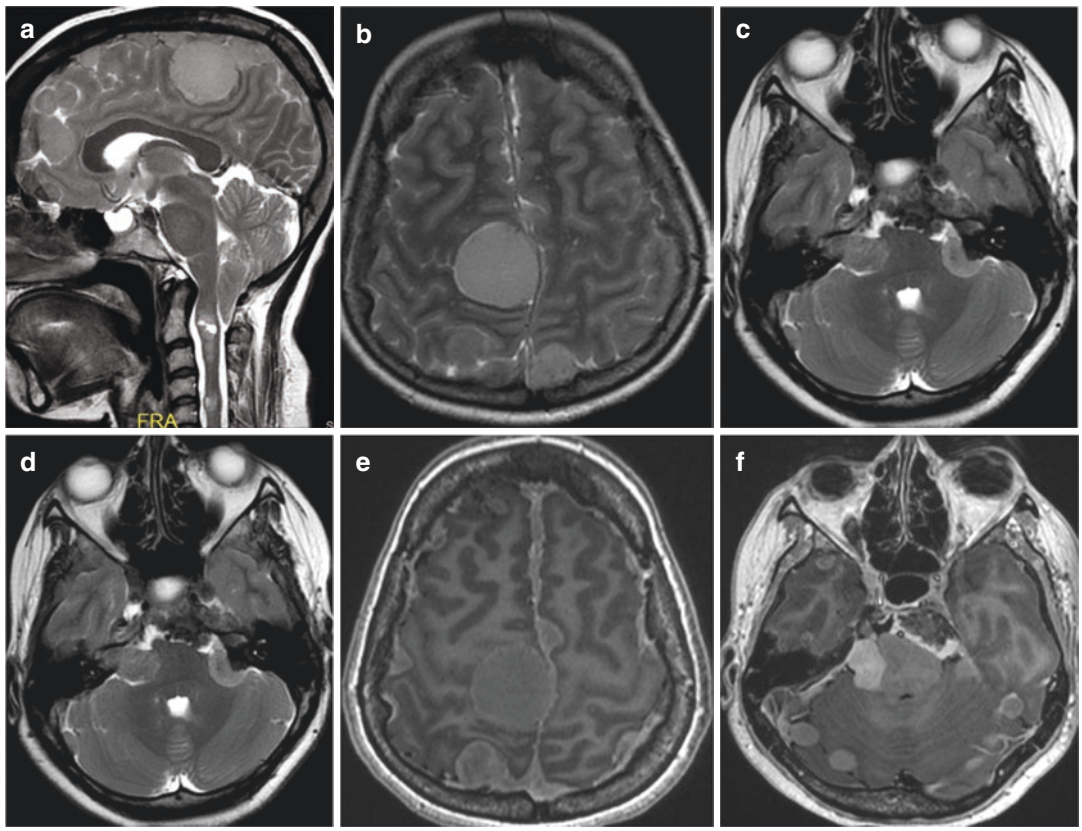

Fig. 25.4 (**a**–**f**) MRI of a patient with NF2 showing multiple meningiomas along the falx and bilateral acoustic neuroma

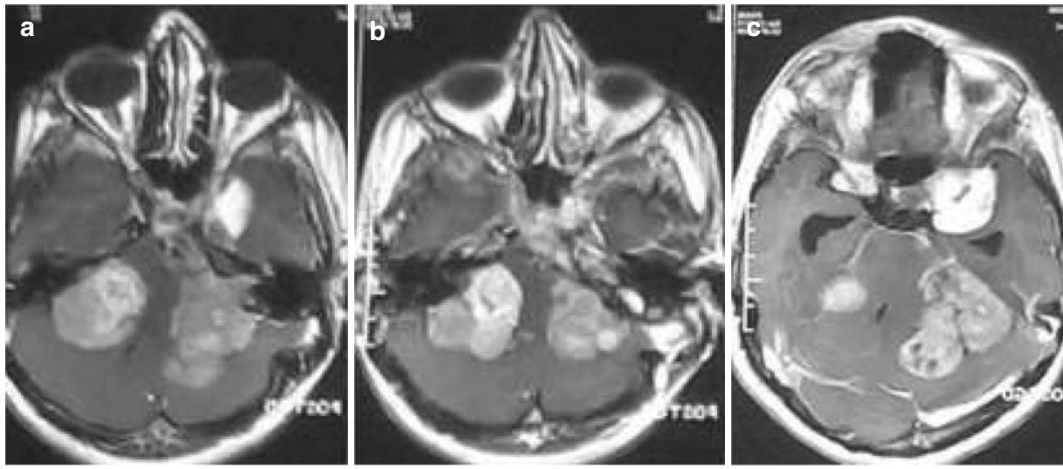

Fig. 25.5 (**a**–**c**) Contrast MRI of the brain of a patient with NF2 showing bilateral acoustic neuromas and left-side sphenoid wing meningioma and right-side optic nerve sheath meningioma

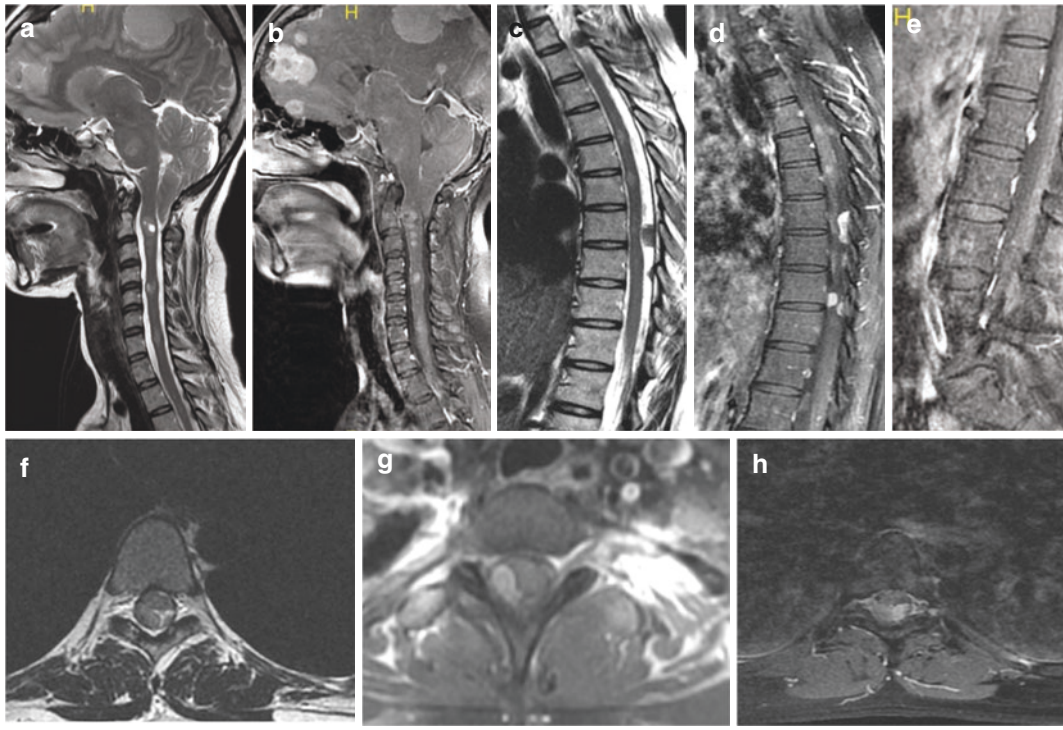

Fig. 25.6 (**a**–**h**) MRI of a patient with NF2 showing multiple intracranial (frontal convexity and falcine) meningiomas along with multiple intradural schwannomas

nomas also have a multifocal infiltration of the associated nerve as the NF2-associated vestibular schwannomas.

Small schwannomas are often found studded along the paraspinal nerve roots in NF2. These tumors are believed to be schwannoma precursors in these patients. The finding of a plexiform schwannoma confers a 10–50% chance that the patient has NF2. Plexiform schwannomas are most often cutaneous or subcutaneous with a pre-

dilection for the head and neck region. The schwannomas of NF2 are benign and rarely undergo malignant transformation in contrast to the neurofibromas of NF1.

25.4.3.3 Ependymomas

Intracranial ependymomas are not found in NF2. The spinal ependymomas are present in 50% of patients as intramedullary tumors. The intramedullary ependymomas in NF2 are most commonly found in cervical and cervico-medullary regions of the spinal cord (63–82%), followed by thoracic spine (36–44%), and present as multiple tumors in the form of a "string of pearl" appearance. These tumors are mostly asymptomatic and followed closely.

Ocular Manifestations:

These are found in a majority of NF2 patients in the form of posterior subcapsular lenticular opacities found in almost 80% of the patients. Other less common ocular findings include OPG, retinal hamartomas, epiretinal membranes, or schwannomas.

25.4.3.4 Meningiomas

These tumors are found at a younger age in NF2 than in the general population. About 20% of the children diagnosed with a meningioma will be found to have NF2. They are found in about 50% of patients with NF2 and are frequently multiple and intracranial. The intracranial meningiomas are most commonly found along the falx and convexity (70%) followed by skull base (25%) and intraventricular (3%). Spinal meningiomas also occur. The majority (>60%) of meningiomas in NF2 are stable and show no or little growth in the follow-up.

25.4.4 Management

The treatment strategy for NF2-associated tumors is different from sporadic tumors as the primary aim is to preserve the neurological function and quality of life.

The standard treatment of vestibular schwannomas is surgery, which is indicated for tumors with critical neural compression. However, a period of watchful waiting may be allowed in some patients with little or no neurologic dysfunction. In general, the schwannomas arising from other cranial nerves are slow-growing and are less symptomatic, and the surgical resection should be reserved for those with progressive neurological deficit or rapid tumor growth.

The radiation therapy is not encouraged in NF2-associated schwannomas because of the risk of malignant transformation, although the risk is absolutely low.

Several targeted therapies have been used in patients with NF2 and progressive vestibular schwannomas. The clinical trials with erlotinib (EGFR inhibitor) and lapatinib (EGFR/ErbB2 inhibitor) have been performed, although with low rates of radiologic response [73, 74]. A similar study with everolimus, an mTOR inhibitor, was associated with prolonged stable disease in NF2 patients with progressive vestibular schwannomas [75]. The treatment with anti-vascular endothelial growth factor, bevacizumab, has produced a durable hearing and radiologic response in patients with progressive vestibular schwannomas [76].

Surgery remains the standard treatment for progressive or symptomatic meningiomas or intramedullary ependymomas in NF2. The majority of these tumors have a benign histology and as such don't require radiation therapy after a good surgical excision.

25.5 Schwannomatosis

Schwannomatosis, as the name implies, is a syndrome characterized by the predisposition to development of multiple schwannomas (without concomitant involvement of the vestibular nerve) and much less commonly meningiomas (Fig. 25.7a–c). Schwannomatosis is distinct genetically from NF2; however, there is a considerable overlap in the phenotypes of these two syndromes. The true prevalence of schwannomatosis is 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. Unlike the patients with NF1 with characteristic dermatologic manifestations and patients with NF2 with bilateral acoustic neuromas, the patients with schwannomatosis have non-specific symptoms that may delay the diagnosis.

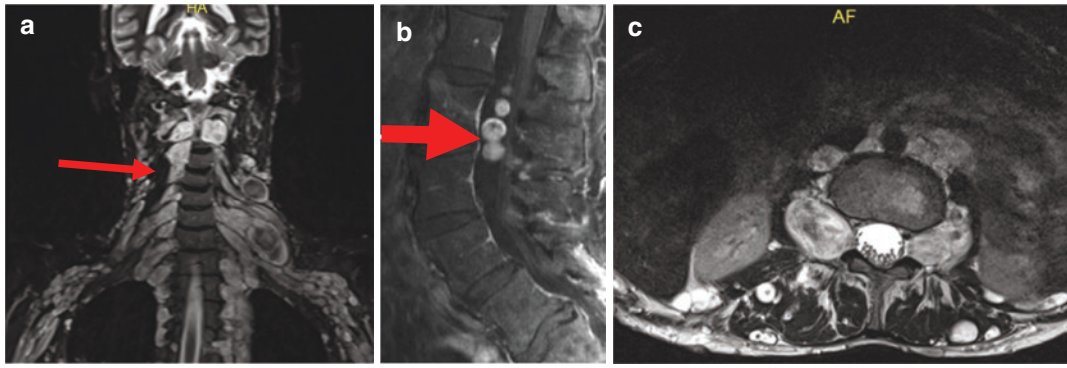

Fig. 25.7 (**a**–**c**) Cervical spine MRI of a patient with presumed schwannomatosis showing multiple cervical, mediastinal, and lumbar intra- and extra-dural schwannomas (red arrows). The patient did not have any evidence of vestibular schwannoma on brain MRI and had SMARCB1 positivity on genetic testing

25.5.1 Genetics and Pathogenesis of Schwannomatosis

Schwannomatosis is an autosomal dominant trait with incomplete penetrance, variable expression, and a high rate of mutation. Familial schwannomatosis accounts for 15% of the cases, while sporadic cases account for the rest 85%, with clinically unaffected parents. The germline mutations in the *SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member* (SMARCB1, also called hSNF5, INI1, BAF47) gene (located on chromosome 22q11.2, centromeric to the NF2 gene) have been found in 40–50% of families with familial schwannomatosis and in 10% of patients with sporadic schwannomatosis [77]. The SMARCB1 gene exerts its tumor suppressor function by regulating cell cycle, lineage-specific gene expression, and embryonic stem cell programming. The gene encodes for a protein involved in chromatin remodeling. It is also involved in the formation of rhabdoid and atypical teratoid tumors, and such tumors are found in some members of the families with schwannomatosis. The majority of the cases of schwannomatosis are caused by de novo mutations, though familial cases exist with an autosomal dominant inheritance pattern [78].

The mutations in the LZTR1 gene have also been identified fairly commonly in SMARCB1-negative schwannomatosis patients with NF2 loss in their tumors. The LZTR1 protein is involved in multiple cellular processes including regulation of chromatin and the cell cycle. The mutations in the second rhabdoid tumor locus, SMARCA4 (Brg1), which is also a component of SWI/SNF (AWItch/sucrose non-fermentable) complex, have also been reported in a small number of patients with schwannomatosis.

The clinical testing for both SMARCB1 and LZTR1 mutations is now available for schwannomatosis patients.

25.5.2 Clinical Presentation

Though schwannomas are common to both schwannomatosis and NF2, there are clinical differences [79]. The age at presentation for schwannomatosis peaks in adulthood, usually between the ages of 30 and 60 years, and often with chronic debilitating pain. In contrast, NF2 can be reliably diagnosed in early childhood and more commonly presents with neurological deficits [80]. 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 [81].

25.5.3 Diagnostic Criteria

The diagnostic criteria incorporate both clinical and molecular markers. These are elaborated in Table 25.5.

The most common symptom is pain (46%), presence of a mass (27%), or both (11%). The schwannomas in schwannomatosis commonly affect the spine (74%) and peripheral nerves (89%), while cranial nerve schwannomas (mostly trigeminal) are uncommon (8%). Vestibular schwannomas are rare, and meningiomas occur in 5% of the schwannomatosis patients, with a special predilection for the falx. There is a phenotypic overlap between schwannomatosis and NF2, although bilateral acoustic neuromas have not been reported in schwannomatosis. The neurologic manifestations related to schwannomas are rare and occur often as a consequence of surgical excision of these lesions.

25.5.4 Management

Management of patients with schwannomatosis is symptom-based, and clinical observation is recommended for asymptomatic patients. The pain is the hallmark of this disorder and is the most challenging feature to treat. In cases of spinal cord compression or bothersome symptoms, surgery is performed to improve quality of life [82]. The major risk of the surgery is the iatrogenic damage to the nerve because of the growth within the myelin.

Table 25.5 Diagnostic criteria for schwannomatosis

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

There has been a limited experience with radiation in the treatment of schwannomas related to schwannomatosis, and there have been reports of malignant transformation of schwannomas after the radiation treatment. Henceforth, most reserve the usage of radiation for enlarging schwannomas which cannot be treated with surgery. The role of chemotherapy in the treatment of painful schwannomas is unclear.

25.6 Conclusions

The NFM are a diverse set of conditions with a propensity for the development of nerve sheath tumors. These are classified as distinct tumor suppressor syndromes where loss of specific proteins due to mutations in tumor suppressor genes leads to dysregulation of pathways responsible for cell division and proliferation, thereby contributing to tumor formation at various sites in the body, including the central and peripheral nervous system. A multidisciplinary team effort with a deep understanding of the disorder and basic laboratory and clinical investigations with early implementation of the treatment can lead to excellent results. Genetic counseling is an important tool for the management of affected individuals and their families. Genetic testing is feasible and can identify patients with doubtful history and clinical manifestations.

Acknowledgments We thank the following for their contribution toward clinical photographs and MRI images for the manuscript: Dr. Nihar V Kathrani, Dr. Karthik Kulanthaivelu, Dr. Dattaraj Sawarkar, and Dr. Sunil Budappa.

References

1. Riccardi VM. Neurofibromatosis: clinical heterogeneity. Curr Probl Cancer. 1982;8:1–34.
2. Carey JC, Baty BJ, Johnson JP, Morrison T, Skolnik M, Kivlin J. The genetic aspects of neurofibromatosis. Ann N Y Acad Sci. 1986;486:45–6.
3. Stein DV, Crawford AH. Neurofibromatosis. Surgical management of spinal deformities.2009;211–231. https://doi.org/10.1016/b978-141603372-1.50018-4.

4. Von Recklinghausen F. Uber die multiple Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin: Hirschwald; 1882.
5. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000;105(3 Pt 1):608–14.
6. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. Lancet Neurol. 2014;13(8):834–43.
7. Huson SM, Compston DAS, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in South East Wales. 1—Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet. 1989;26:704–11.
8. Rasmussen A, Friedman JM. NF1 gene and neurofibromatosis 1. Am J Epidemiol. 2000;151:33–40.
9. Woodruff JM. Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. Am J Med Genet. 1999;89:23–30.
10. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. Acta Neuropathol. 2012;123:295–319.
11. Evans DG, Huson SM, Birch JM. Malignant peripheral nerve sheath tumors in inherited diseases. Clin Sarcoma Res. 2012;2:17.
12. King AA, Debaun MR, Riccardi VM, Gutmann DH. Malignant peripheral nerve sheath tumors in neurofibromatosis 1. Am J Med Genet. 2000;93:388–92.
13. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumors in neurofibromatosis 1. J Med Genet. 2002;39:311–4.
14. Jadayel D, Fain P, Upadhyaya M, et al. Paternal origin of new mutations in von Recklinghausen neurofibromatosis. Nature. 1990;343:558–9.
15. Helfferich J, Nijmeijer R, Brouwer OF, et al. Neurofibromatosis type 1 associated low grade gliomas: a comparison with sporadic low grade gliomas. Crit Rev Oncol Hematol. 2016;104:30–41.
16. Brems H, Beert E, de Ravel T, et al. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol. 2009;10:508–15.
17. Rodriguez F, Stratakis CA, Evans DG. Genetic predisposition to peripheral nerve neoplasia: diagnostic criteria and pathogenesis of neurofibromatoses, Carney complex, and related syndromes. Acta Neuropathol. 2012;123:349–67.
18. Buchanan ME, Davis RL. A distinct set of Drosophila brain neurons required for neurofibromatosis type 1-dependant learning and memory. J Neurosci. 2010;30:10135–43.
19. Warrington NM, Gianino SM, Jackson E, et al. Cyclic AMP suppression is sufficient to induce gliomagenesis in a mouse model of neurofibromatosis-1. Cancer Res. 2010;70:5717–27.
20. Williams VC, Lucas J, Babcock MA, et al. Neurofibromatosis type 1 revisited. Pediatrics. 2009;123:124–33.
21. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455:1061–8.
22. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44:81–8.
23. Balcer LJ, Liu GT, Heller G, et al. Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas: relation to tumor location by magnetic resonance imaging. Am J Ophthalmol. 2001;131:442–5.
24. Thiagalingam S, Flaherty M, Billson F, et al. Neurofibromatosis type 1 and optic pathway gliomas: follow-up of 54 patients. Ophthalmology. 2004;111:568–77.
25. Ragge NK, Falk RE, Cohen WE, Murphree AL. Images of Lisch nodules across the spectrum. Eye (Lond). 1993;7:95–101.
26. Hood CT, Janku L, Lowder CY, Singh AD. Retinal vasoproliferative tumor in association with neurofibromatosis type 1. J Pediatr Ophthalmol Strabismus. 2009;25:1–3.
27. Shields JA, Pellegrini M, Kaliki S, Mashayekhi A, Shields CL. Retinal vasoproliferative tumors in 6 patients with neurofibromatosis type 1. JAMA Ophthalmol. 2014;132:190–6.
28. Schwetye KE, Gutmann DH. Cognitive and behavioral problems in children with neurofibromatosis type 1: challenges and future directions. Expert Rev Neurother. 2014;14:1139–52.
29. Garozzo D. Peripheral nerve tumors in Neurofibromatosis 1: an overview of management and indications for surgical treatment in our experience. Neurol India. 2019;67:S38–44.
30. Garg S, Green J, Leadbitter K, et al. Neurofibromatosis type 1 and an autism spectrum disorder. Pediatrics. 2013;132:e1642–8.
31. Cutting LE, Levine TM. The cognitive profile of children with neurofibromatosis and reading disabilities. Child Neuropsychol. 2010;16:417–32.
32. Itoh T, Magnaldi S, White RM, et al. Neurofibromatosis type 1: the evolution of deep gray and white matter MR abnormalities. AJNR Am J Neuroradiol. 1994;15:1513–9.
33. Van Es S, North KN, McHugh K, et al. MRI findings in children with neurofibromatosis type 1: a prospective study. Pediatr Radiol. 1996;26:478–87.
34. Griffiths PD, Blaser S, Mukonoweshuro W, et al. Neurofibromatosis bright objects in children with neurofibromatosis type 1: a proliferative potential? Pediatrics. 1999;104:e49.
35. Braffman BH, Bilaniuk LT, Zimmerman RA. The central nervous system manifestations of the phakomatoses on MR. Radiol Clin North Am. 1988;26:773–800.
36. Smirniotopoulos JG, Murphy FM. The phakomatoses. AJNR Am J Neuroradiol. 1992;13:725–46.
37. Bognanno JR, Edwards MK, Lee TA, et al. Cranial MR imaging in neurofibromatosis. AJR Am J Roentgenol. 1988;151:381–8.

38. DiPaolo DP, Zimmerman RA, Rorke LB, et al. Neurofibromatosis type 1: pathologic substrate of high-signal-intensity foci in the brain. Radiology. 1995;195:721–4.
39. Torres Nupan MM, Velez Van Meerbeke A, Lopez Cabra CA, et al. Cognitive and behavioral disorders in children with neurofibromatosis type 1. Front Pediatr. 2017;5:227.
40. Brossier NM, Carroll SL. Genetically engineered mouse models shed new light on the pathogenesis of neurofibromatosis type I-related neoplasms of the peripheral nervous system. Brain Res Bull. 2012;88:58–71.
41. Pasmant E, Sabbagh A, Spurlock G, et al. NF1 microdeletions in neurofibromatosis type 1: from genotype to phenotype. Hum Mutat. 2010;31(6):E1506–18. https://doi.org/10.1002/humu.21271.
42. Elefteriou F, Kolanczyk M, Schindeler A, et al. Skeletal abnormalities in neurofibromatosis type 1: approaches to therapeutic options. Am J Med Genet A. 2009;149A:2327–38.
43. Lammert M, Friedman JM, Roth HJ, et al. Vitamin D deficiency associated with a number of neurofibromas in neurofibromatosis 1. J Med Genet. 2006;43:810–3.
44. Lin AE, Birch PH, Korf BR, et al. Cardiovascular malformations and other cardiovascular abnormalities in neurofibromatosis 1. Am J Med Genet. 2000;95:108–17.
45. Oderich GS, Sullivan TM, Bower TC, et al. Vascular abnormalities in patients with neurofibromatosis syndrome type I: clinical spectrum, management, and results. J Vasc Surg. 2007;46:475–84.
46. Rea D, Brandsema JF, Armstrong D, et al. Cerebral arteriopathy in children with neurofibromatosis type 1. Pediatrics. 2009;124:e476–83.
47. D'Arco F, D'Amico A, Caranci F, et al. Cerebrovascular stenosis in neurofibromatosis type 1 and utility of magnetic resonance angiography: our experience and literature review. Radiol Med. 2014;119:415–21.
48. Friedman JM, Arbiser J, Epstein JA, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascular task force. Genet Med. 2002;4:105–11.
49. Ennibi K, El Kassimi I, Asfalou I, Chaari J, Benyass A. Pulmonary hypertension and von Recklinghausen's disease: association and therapeutic difficulties. Pneumologia. 2015;64:55–7.
50. Bausch B, Koschker AC, Fassnacht M, et al. Comprehensive mutation scanning of NF1 in apparently sporadic cases of pheochromocytoma. J Clin Endocrinol Metab. 2006;91:3478–81.
51. Mannelli M, Castellano M, Schiavi F, et al.; Italian Pheochromocytoma/Paraganglioma Network. Clinically guided genetic screening in a large cohort of Italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. J Clin Endocrinol Metab. 2009;94:1541–1547.
52. Eisenhofer G, Lenders JW, Timmers H, et al. Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. Clin Chem. 2011;57:411–20.
53. Easton DF, Ponder MA, Huson SM, et al. An analysis of variation in expression of neurofibromatosis (NF) type 1 (NF1): evidence for modifying genes. Am J Hum Genet. 1993;53:305–13.
54. Barahona-Garrido J, Aguirre-Gutierrez R, Gutierrez-Manjarrez JI, et al. Association of GIST and somatostatinoma in a patient with type-1 neurofibromatosis: is there a common pathway? Am J Gastroenterol. 2009;104:797–9.
55. Miettinen M, Fetsch JF, Sobin LH, et al. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006;30:90–6.
56. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis, and childhood leukemia/lymphoma: a population-based UKCCSG study. Br J Cancer. 1994;70:969–72.
57. Brems H, Park C, Maertens O, et al. Glomus tumors in neurofibromatosis type 1: genetic, functional, and clinical evidence of a novel association. Cancer Res. 2009;69:7393–401.
58. McGaughran JM, Harris DI, Donnai D, et al. A clinical study of type 1 neurofibromatosis in northwest England. J Med Genet. 1999;36:197–203.
59. Patil S, Chamberlain RS. Neoplasms associated with germline and somatic NF1 gene mutations. Oncologist. 2012;17:101–16.
60. Crucis A, Richer W, Brugieres L, et al. Rhabdomyosarcomas in children with neurofibromatosis type I: a national historical cohort. Pediatr Blood Cancer. 2015;62:1733–8.
61. Afsar CU, Kara IO, Kozat BK, et al. Neurofibromatosis type 1, gastrointestinal stromal tumor, leiomyosarcoma, and osteosarcoma: four cases of rare tumors and a review of the literature. Crit Rev Oncol Hematol. 2013;86:191–9.
62. Uusitalo E, Kallionpaa RA, Kurki S, et al. Breast cancer in neurofibromatosis type 1: overrepresentation of unfavorable prognostic factors. Br J Cancer. 2017;116:211–7.
63. Clementi M, Milani S, Mammi I, et al. Neurofibromatosis type 1 growth charts. Am J Med Genet. 1999;87:317–23.
64. Szudek J, Birch P, Friedman JM. Growth charts for young children with neurofibromatosis 1 (NF1). Am J Med Genet. 2000;92:224–8.
65. Szudek J, Birch P, Friedman JM. Growth in North American white children with neurofibromatosis 1 (NF1). J Med Genet. 2000;37:933–8.
66. Avery RA, Fisher MJ, Liu GT. Optic pathway gliomas. J Neuroophthalmol. 2011;31:269–78.
67. Packer RJ, Jakacki R, Horn M, et al. Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan. Pediatr Blood Cancer. 2009;52:791–5.
68. Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-

grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. Neuro Oncol. 2016;19:1135–44.
69. Friedman JM. Neurofibromatosis 1. 1998 [Updated 2019 Jun 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle, : University of Washington; 1993–2020. https://www.ncbi.nlm.nih.gov/books/NBK1109/
70. Wilding A, Ingham SL, Lalloo F, et al. Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet. 2012;49(04):264–9.
71. Maniakas A, Saliba I. Neurofibromatosis type 2 vestibular schwannoma treatment: a review of the literature, trends, and outcomes. Otol Neurotol. 2014;35(5):889–94.
72. McCaughan JA, Holloway SM, Davidson R, et al. Further evidence of the increased risk for malignant peripheral nerve sheath tumor from a Scottish cohort of patients with neurofibromatosis type 1. J Med Genet. 2007;44:463–6.
73. Plotkin SR, Halpin C, McKenna MJ, Loeffler JS, Batchelor TT, Barker FG. Erlotininb for progressive vestibular schwannoma in neurofibromatosis 2 patients. Otol Neurotol. 2010;31(07):1135–14.
74. Karajannis MA, Legault G, Hagiwara M, et al. Phase II trial of lapatinib in adult an dpediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. Neuro Oncol. 2012;14(09):1163–70.
75. Karajannis MA, Legault G, Hagiwara M, et al. Phase II study of everolimus in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas. Neuro Oncol. 2014;16(02):292–7.
76. Plotkin SR, Merker VL, Halpin C, et al. Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients. Otol Neurotol. 2012;33(06):1046–52.
77. Plotkin SR, Blakeley JO, Evans DG, et al. Update from the 2011 international schwannomatosis workshop: from genetics to diagnostic criteria. Am J Med Genet A. 2013;161A(03):405–16.
78. Longo JF, Weber SM, Turner-Ivey BP, Carroll SL. Recent advances in the diagnosis and pathogenesis of neurofibromatosis type 1 (NF1)-associated peripheral nervous system neoplasms. Adv Anat Pathol. 2018;25(5):353–68.
79. Trofatter JA, Mac Collin MM, Rutter JL, et al. A novelmoesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell. 1993;72(5):791–800.
80. Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. Nature. 1993;363(6429):515–21.
81. Evans DG, Ramsden RT, Shenton A, et al. Mosaicism in neurofibromatosis type 2: an update of risk based on uni/bilaterality of vestibular schwannoma at presentation and sensitive mutation analysis including multiple ligation-dependent probe amplification. J Med Genet. 2007;44(7):424–8.
82. Kresak JL, Walsh M. Neurofibromatosis: a review of NF1, NF2, and Schwannomatosis. J Pediatr Genet. 2016;5(2):98–104. https://doi.org/10.1055/s-0036-1579766.