Review Article

The Neurofibromatoses

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Summary

Background: Neurofibromatosis of types 1 and 2 (NF1, NF2) and schwannomatosis are the diseases that make up the neurofibromatosis spectrum. With respective incidences of 1 in 3000, 1 in 33 000, and 1 in 60 000 births, they form part of the group of rare tumor-suppressor syndromes. They give rise to a greater tumor burden for the nervous system than any other type of neoplastic disease. New approaches to symptomatic treatment are emerging.

Method: This review is based on articles retrieved by a selective literature search on the pathogenesis, diagnosis, and treatment of the neurofibromatoses.

Results: NF1 and NF2 are monogenic diseases, while the genetics of schwannomatosis is complex. The three entities are clinically and pathophysiologically distinct. An important aspect of their tumor biology is the alternation of growth phases and growth pauses. Correlations between genotypes and phenotypes are variable, while new mutations and genetic mosaics are common. Ninety-nine percent of patients with NF1 have six or more café-au-lait spots by the age of 12 months; 90–95% of patients with NF2 develop bilateral vestibular schwannomas. In schwannomatosis, pain is the most prominent symptom; two-thirds of those affected develop spinal schwannomas. The severity and prognosis of these disorders are not closely correlated with the radiological findings; rather, neurologic deficits, malignant transformation, and psychosocial stress are of greater clinical importance. Advances in knowledge of pathophysiology have led to the development of targeted treatment approaches. Examples include the off-label treatment of vestibular schwannomas with bevacizumab and of plexiform neurofibromas with MEK inhibitors.

Conclusion: Patients with neurofibromatoses need individualized care. They should be treated in centers of expertise where interdisciplinary consultation is available and new types of pharmacotherapy can be provided.

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Neurofibromatosis types 1 and 2 (NF1, NF2) and schwannomatosis (SWN) constitute the neurofibromatosis disease spectrum. The neurofibromatoses are rare, but they give rise to a greater tumor burden for the nervous system than any other neoplastic disease (1). The three entities differ fundamentally from one another (e1–e3): NF1 and NF2 are inherited in an autosomal dominant pattern, with an approximately 50% rate of de novo mutations in each. The genetic mechanism of SWN is more complex; the rate of new mutations probably lies between 50% and 80% (2, e4).

In this review, we present the definition and pathophysiology of the neurofibromatoses and discuss the current diagnostic and therapeutic strategies in the light of the relevant international literature.

Type 1 neurofibromatosis (NF1)

NF1 (von Recklinghausen's disease) is a genetic tumor-disposition syndrome associated with malformations and tumor growth in the nervous system and other organ systems (1–7). Its frequency is approximately 1 per 3000 neonates, regardless of sex or ethnic background (8). The diagnosis is made on clinical grounds with the aid of the criteria defined by the National Institutes of Health (NIH) (*Table*). The life expectancy of the affected persons is approximately 15 years less than normal, mainly because of malignancies, but also due to heart attack and stroke (3, e5).

Diagnostic criteria

Some 70% of persons with NF1 (95% confidence interval [55; 82]), fulfill two of the criteria listed in the *Table* before their first birthday, thereby establishing the diagnosis. Two criteria are met by the eighth birthday in 97%; all patients have marked, characteristic features of NF1 by the time they are 20 years old (4).

Genetics and molecular pathophysiology

The NF1 gene *(17q11.2)* encodes the tumor suppressor protein neurofibromin (e6, e7), which stabilizes the proto-oncogene Ras in its inactive form (e8) and thereby inhibits cellular proliferation. The disorder is inherited in autosomal dominant fashion, with complete penetrance and variable expression. Genotype–phenotype correlations have been established for a small number of mutations: for example, a deletion of the entire gene (*17q11.2* microdeletion) is associated with a severe disease course (5), and splice-site mutations are associated with spinal tumors in particular. Genetic mosaics generally lead to a mild form of the disease (e6, e7).

TABLE

Diagnostic criteria for the neurofibromatoses (1, e64, e65)

Type 1 neurofibromatosis (NF1) [3,4]	Type 2 neurofibromatosis (NF2) [e66]	Schwannomatosis [e67]
Two or more of the following features		
– ≥ 6 café-au-lait spots (> 5 mm before puberty, > 15 mm after puberty) – ≥ 2 neurofibromas or ≥ 1 plexiform neurofibroma – axillary or inguinal freckling – ≥ 2 Lisch nodules (iris hamartomas) – optic nerve glioma – typical bony changes (dysplasia of sphenoid bone, thinning of cortex in long bones [with or without pseudarthrosis]) – first-degree relative with NF1	Definite: bilateral vestibular nerve schwannomas (VS) or – NF2 in a first-degree relative **and** – unilateral VS and age < 30 or – two of the following: meningioma, glioma, schwannoma, juvenile posterior lens opacification/juvenile cortical cataract Possible or probable: – unilateral VS and age < 30 **and** at least one of the following: meningioma, glioma, schwannoma, juvenile posterior lens opacification/juvenile cortical cataract – > 2 meningiomas and VS and age < 30 or one of the following: glioma, schwannoma, juvenile posterior lens opacification/juvenile cortical cataract	Definite: age > 30 **and** ≥ 2 non-intradermal schwannomas, of which at least one has been histologically confirmed, **and** no evidence of VS on high-resolution MRI **and** no constitutional NF2 mutation or 1 histologically confirmed non-vestibular schwannoma **and** a first-degree relative who meets the above criteria Possible: age < 30 and 2 non-dermal schwannomas, of which at least one has been histologically confirmed, **and** no evidence of VS on high-resolution MRI **and** no constitutional NF2 mutation or age > 45 **and** ≥ 2 non-dermal schwannomas, of which at least one has been histologically confirmed, **and** no manifestations of eighth cranial nerve dysfunction **and** no constitutional NF2 mutation or radiological evidence of a non-vestibular schwannoma **and** a first-degree relative who meets the criteria for definite schwannomatosis
Genetic tests [1]: blood analysis for constitutional mutations and tumor analysis (if tumor material is available, fixed or frozen) for somatic mutations (mosaics)		
NF1 gene analysis	NF2 gene analysis	NF2 gene analysis—*SMARCB1/INI1, LZTR1*

Prenatal diagnosis of NF1 is possible in principle, as the disease causes severe manifestations before the patient reaches the age of 18 in more than just isolated cases. In Germany, preimplantation diagnosis (PID) must be approved by the local ethics committee. Prenatal diagnosis and PID are used only exceptionally, not routinely.

Clinical manifestations

Neurofibroma

Most patients with NF1 have cutaneous neurofibromas (CNF) *(Figure 1a)*. These usually first appear in adolescence and become more numerous in adulthood (3). In addition, 30–50% of NF1 patients have subcutaneous and plexiform neurofibromas (PNF) *(Figures 1a, b)*. PNF are already present in the embryo; they are benign at first and grow in reticular fashion, displacing normal tissue. In around 8–13% of NF1 patients, PNF degenerate into malignant peripheral nerve sheath tumors (MPNST); these tend to metastasize early and are the main cause of the lower life expectancy of persons with NF1 (9).

Other tumors

Children with NF1 have an approximately sevenfold elevation of the lifetime risk of hematopoietic malignancies, particularly myeloid leukemia. NF-associated and sporadic tumors carry the same prognosis and are treated identically. In women under age 50 in particular, the risk of breast cancer is significantly elevated (approximately fivefold) (3). Benign pheochromocytoma of the adrenal glands is much more common in NF1 patients than in the general population, although still rare (incidence 5% vs. < 1%) (3). Children with NF1 are also at elevated risk of rhabdomyosarcoma, predominantly in the bladder and the prostate gland (3, e9). Gastrointestinal stroma tumors (GIST) have been found at elevated frequency in some study populations (6); endocrine tumors have also been described occasionally (6).

Central nervous system

Patients with NF1 have an elevated risk of developing both low-grade and high-grade gliomas. The most common type is pilocytic astrocytoma of the optic nerve, seen in 15% of NF1 patients of whom approximately half are asymptomatic (3). The brainstem is the second most common site. The most important element of the care of patients with low-grade glioma is monitoring the progression of the disease. Optic nerve gliomas can grow

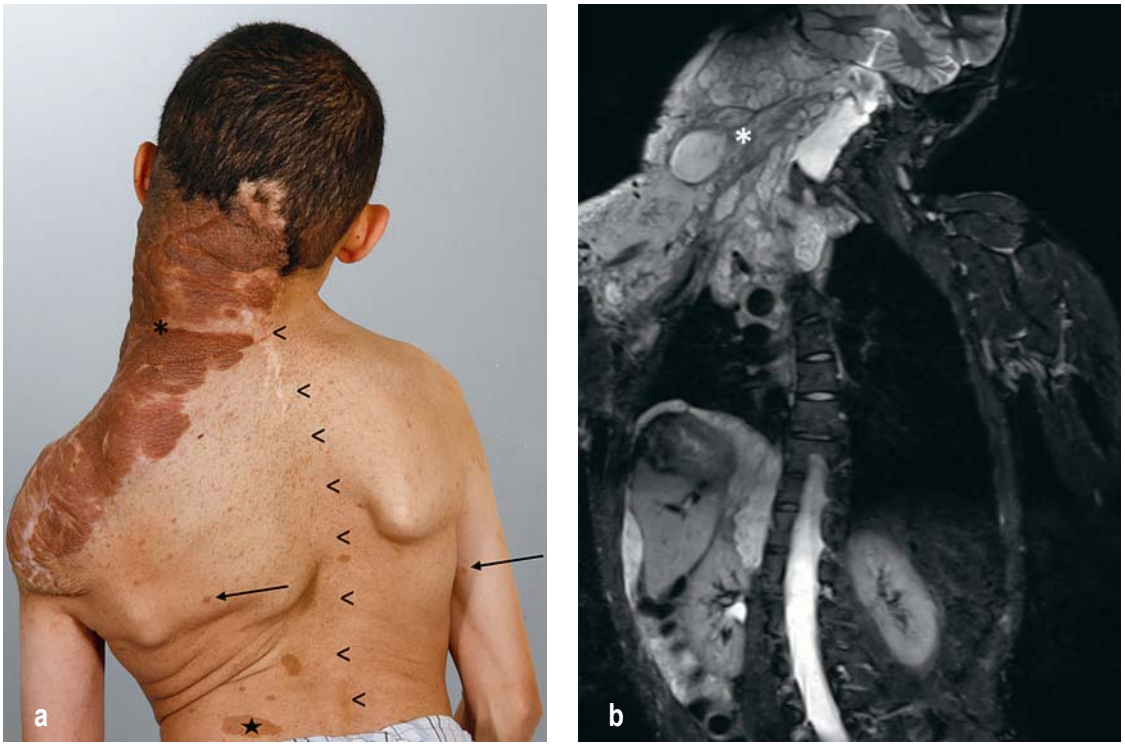


Figure 1: Features of type 1 neurofibromatosis (NF1)

a) There are small, nodular cutaneous neurofibromas (arrows) and changes of skin pigmentation. A large plexiform neurofibroma (*) extends across the right side of the neck to the back and arm. Scoliosis (arrowheads) and café-au-lait spots (star) are also seen, but are not specific and occur in other genetic syndromes as well (Silver–Russell syndrome, multiple endocrine neoplasia type IIb [MEN IIb], Legius syndrome, McCune–Albright syndrome, etc.).

b) MRI reveals the nodular-infiltrative growth pattern of the plexiform neurofibroma (PNF). Further tumor manifestations are seen around the thoracic and abdominal organs.

markedly in early childhood but often remain stable from age 7 years onward (7). The lifetime risk of high-grade glioma is elevated at least fivefold. Focal areas of T2-signal intensity (FASI) are seen in the cerebral MRI scans of at least 60% of children with NF1, but their clinical significance remains unclear (e10–e14). The affected children are of mildly lower intelligence on average, and 60–81% have specific partial performance deficits (dyslexia, dyscalculia, etc.) or an attention deficit disorder (AD[H]D) (10, e15–e18). Approximately 11% have a disorder from the autism spectrum, a markedly higher prevalence than in the general population (1%); these frequency figures cannot, however, be considered representative of the totality of children with NF1, because of a preselection effect (e19).

Pigmentation anomalies

Pigmentation anomalies are not diseases in and of themselves, but they are diagnostically useful. Café-au-lait spots are often the initial clinical manifestation of NF1. Ninety-nine percent of NF1 patients have six or more such spots measuring at least 5 mm in diameter by the end of their first year of life *(Table)* (4, e20, e21). Axillary and inguinal freckling is a further sign seen in only 40% of toddlers with NF1, but in 90% of patients by age 7 (4). Small, melanocytic iris hamartomas (Lisch nodules) are seen in 93% of adults with NF1 (e22).

Musculoskeletal manifestations

The typical skeletal abnormalities are scoliosis, sphenoid wing dysplasia, and congenital tibial dysplasia and osteopenia. Children with NF1 have a 3.4-fold elevation of the fracture risk, and adults over age 41 have a 5.2-fold elevation (33.3% vs. 6.3% fracture rate, $p < 0.001$); this is correlated, among other things, with a significantly lower vitamin D3 level (11, e23).

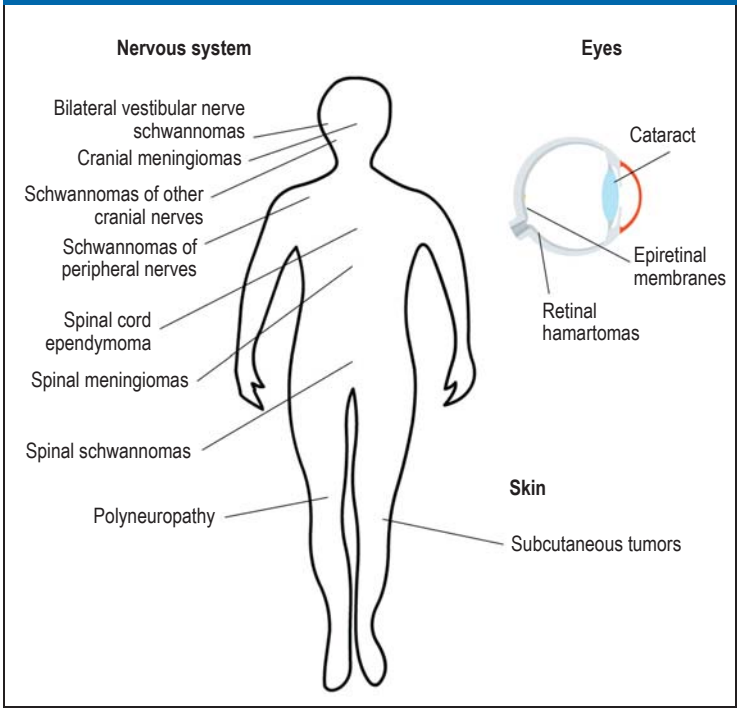
Treatment

No causally directed treatment of NF1 is yet available. The most important elements of management are early diagnosis and symptom-oriented treatment. Genetic counseling is especially important. Cognitive deficits and developmental delays should be recognized early and addressed with suitable special-needs education. AD(H)D can be specifically treated with stimulants (methylphenidate) in both childhood and adulthood; randomized, placebo-controlled trials have shown that this improves attentiveness (a 3.9 ± 1.1 point reduction on the simplified Conners scale, $p = 0.0003$) (e24). Moreover, long-term effects on the development of intelligence and

on the quality of life have been demonstrated (e25, e26). Cutaneous neurofibromas can be surgically resected for either esthetic or medical reasons (pain, inflammation).

The surgical treatment of PNF is an interdisciplinary challenge. MRI and PET are indispensable for risk stratification. Regressive changes in the tumor, growth acceleration, and changes in glucose utilization can constitute evidence of malignant transformation. For malignant peripheral nerve sheath tumors (MPNST), complete surgical resection is the single treatment approach offering a chance of cure; the 5-year survival rate with chemotherapy is less than 20%. Annual ophthalmological examinations are more sensitive than imaging studies for the detection of symptomatic optic nerve glioma. For patients with impaired visual acuity, chemotherapy is indicated (carboplatin and vincristine; SIOP-LGG). Radiotherapy is controversial because of the elevated risk of second malignancies and higher-grade gliomas. Vitamin D3 deficiency, if present, should be substituted. For inoperable PNF, a currently available option is off-label treatment with MEK inhibitors. These drugs work by inhibiting the molecule MEK, which plays a role in the Ras downstream signaling pathway and thus affects the cell proliferation in NF1-associated tumors. In an initial trial, tumors were reduced in size in 17 of the 24 children so treated (12).

FIGURE 2



Clinical features of type 2 neurofibromatosis:
bilateral vestibular nerve schwannomas are pathognomonic.

Type 2 neurofibromatosis (NF2)

NF2 is a tumor disposition syndrome of autosomal dominant inheritance that is found in approximately 1 per 33,000 births *(eTable 1)* (13, e27). Half of all cases arise through de novo mutations (14).

The mortality of the disease has steadily declined in recent years because of early detection, treatment in multidisciplinary centers, and innovative therapies aimed at the preservation of neurological function. The mean life span of persons with NF2 in industrialized countries is now over 60 years (15).

Diagnostic criteria

The growth of schwannomas (also known as neurinomas) on both vestibulocochlear nerves, i.e., bilateral vestibular nerve schwannoma, is pathognomonic for NF2 (5). "Acoustic neuroma" is an older term for vestibular nerve schwannoma (5).

As 41% of patients initially presenting with NF2 do not yet have pronounced bilateral vestibular nerve schwannoma, a number of diagnostic standards have been developed, including the well-established Manchester criteria, which serve as the basis for the NIH criteria *(Table)*. Other types of benign tumor are common in NF2 as well *(eTable 2)*. The reported frequencies of the main clinical criteria (neurological, ocular, and cutaneous manifestations) *(Figure 2)* are variable, sometimes markedly so (16).

Genetics and molecular pathophysiology

The NF2 gene *(22q11.2)* was identified in 1993 (e28, e29). It encodes the tumor suppressor protein merlin. Persisting repair processes by Schwann cells in an altered axonal microenvironment probably contribute to schwannoma formation (17).

Loss of merlin leads to the activation of proliferative signal pathways by way of Ras modulation, which affects targets that have also been identified in NF1 (18, e30). Sporadic schwannomas and meningiomas also arise through changes in these signal pathways (19, e31–e34).

NF2 mutations can be demonstrated in the blood of approximately 91% of all patients with a positive family history (20). In patients with de novo mutations, mutation analysis yields less clear results (59%) (20, e35–e36). Genetic mosaics are found in 30–60% of all de novo cases. The mutation is then clearly demonstrable only in tumor tissue. NF2 genetic mosaics can also be passed on to the offspring of affected patients, with a elevated risk of 8–12% (14). The regulatory framework for prenatal diagnosis and PID in NF2 is the same as in NF1.

Clinical grades of severity

Historically, a distinction was made between the Wishart phenotype of NF2 (early onset, rapid progression, neuropathy, poor prognosis) and the (Feiling-)Gardner phenotype (initial diagnosis after age 20, low tumor burden). Nowadays, mild, moderate, and severe phenotypes are distinguished, and radiological criteria (clinician-rated severity, ClinSev) are also applied that are, in part, correlated with genetic severity (GenSev)

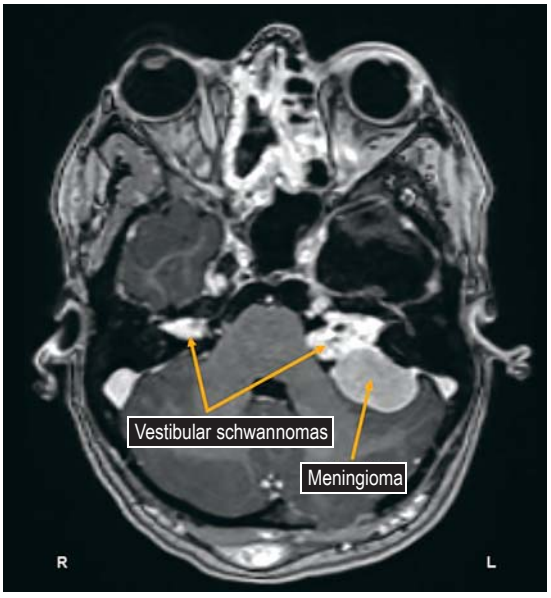


Figure 3: Typical MRI findings: bilateral vestibular nerve schwannomas (VS) in a patient with type 2 neurofibromatosis. Collision of a VS with a meningioma, as seen here on the patient's left side, is also not unusual.

(e37). The assessment of disease severity in everyday clinical practice is a complex matter *(eTable 3)*.

Clinical manifestations

Vestibular nerve schwannoma

Bilateral vestibular nerve schwannomas (VS) arise in 90–95% of patients with NF2 *(Figure 3)*. Histologically they resemble sporadic vestibular nerve schwannomas (90 % of all VS, lifetime risk 1 in 1000), but they often grow multifocally (21). Each of these tumors or tumor lobules can contain a mixed cell population with different somatic NF2 mutations (polyclonality) (22).

Management options: The main goal of the treatment of bilateral vestibular schwannoma is to prevent impending loss of function, especially hearing loss *(eFigure)*. Surgical interventions are more challenging than in the management of sporadic VS. The opportunity to spare the patient's hearing on the side of a small, favorably located lesion in a patient with good hearing in both ears should not be missed (23, 24). If adequate residual hearing is present after surgery, auditory rehabilitation can be carried out with a conventional hearing aid at first, and then later with a cochlear implant or an auditory brainstem implant (ABI) (e38, e39).

Growth arrest of vestibular nerve schwannomas by means of stereotactic radiosurgery is less commonly achieved in NF2 patients than in sporadic tumors, and higher radiation doses can accelerate hearing loss (25). The reported 5-year tumor control and hearing preservation rates vary from 66% to 100% and from 33% to 57%, respectively (e40–e46).

Off-label treatment with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab has now become an important therapeutic option. At least over the intermediate term (according to retrospective studies with follow-up intervals of 1–3 years), it is associated with hearing improvement in 57% and tumor shrinkage in 55% of patients , although there is a risk of side effects including hypertension and proteinuria (26, e47).

Other schwannomas

Schwannomas of other cranial nerves are found in 24–51% of NF2 patients (13). Tumors affecting the lower cranial nerves are most likely to cause severe disease with marked impairment of the patient's quality of life, as they are associated with vocal cord paralysis (35%) and dysphagia (50%) (27). Schwannomas of peripheral nerves (most commonly paraspinal and subcutaneous schwannomas) are found in 70% of NF2 patients *(eTable 2)* (13, e48). In contrast to schwannomatosis, they generally become symptomatic with sensory or motor disturbances, rather than pain. Unlike PNF in NF1, schwannomas in NF2 hardly ever undergo malignant transformation. Resection is the treatment of choice for symptomatic peripheral schwannomas; preservation of function is very important here as well (e49).

Meningiomas

Approximately 50% of patients with NF2 have meningiomas; these tumors are associated with high morbidity (28). One-fifth of all children with meningiomas have NF2 (29). Convexity meningiomas can generally be totally resected without complication, but this is indicated only when their further growth would threaten neurologic function or cerebral perfusion. The risk of postoperative morbidity is much higher with meningiomas of the skull base. The progression-free 5-year survival rate after stereotactic radiosurgery for meningioma is approximately 86% (30). A combined microsurgical and radiosurgical strategy is helpful primarily in the treatment of parasagittal meningiomas and of petroclival tumors that extend into the cavernous sinus. Patients with a heavy meningioma burden may develop malresorptive hydrocephalus.

Spinal tumors

Spinal schwannomas and meningiomas should be resected if they compress the spinal cord or become symptomatic.

Ependymomas

Nearly all intramedullary tumors in patients with NF2 are ependymomas (31, e50); these arise in 33–53% of all patients with NF2, and 85% are located in the cervical spine (32). If they progress, they should be microsurgically excised. Treatment with bevacizumab is an alternative (33).

The growth behavior of NF2-associated tumors

Intracranial vestibular nerve schwannomas and meningiomas have similar annual growth rates, ranging from 0.30 to 2.57 cm^3 per year (e51–e54). Non-vestibular schwannomas grow much more slowly (34). As a rule, the growth is "saltatory," with periods of growth separated by pauses that may last for years (34, e52). In their spontaneous course, VS

and meningiomas display a median progression-free interval of 18–21 months (34). For intramedullary ependymomas, the median progression-free interval is 24 months (35).

Peripheral neuropathy

Approximately 47% of patients with NF2 suffer from neuropathy (e55). The peripheral nerve lesions are due to non-compressive microlesions (<5 mm) (36). It is unclear whether these microlesions represent a tumor precursor stage (37, e56). Merlin loss in peripheral axons also plays a role (38).

Ocular complications

Subcapsular cataracts arise in nearly 80% of patients with NF2 (e57). Other ocular complications include epiretinal membranes, retinal hamartoma, optic nerve glioma and meningioma, and intraocular schwannoma. Facial nerve palsy puts the cornea at risk of ulceration.

Key messages

- The neurofibromatoses are genetically and clinically distinct diseases with variable course.
- Their clinical severity is primarily a function of the time of appearance of the first symptoms, the overall tumor burden, the symptoms, the underlying genetic mutation, and the patient's individual coping strategy.
- Most tumors affecting the central nervous system in type 2 neurofibromatosis grow irregularly, with interspersed growth pauses.
- The life expectancy of patients with neurofibromatosis is improved by early detection of disease and by the coordination of medical care at a specialized center, in collaboration with the family physician.
- The key elements of medical management are the preservation of neural function and the treatment of pain (schwannomatosis), together with the reinforcement of cognitive resources and self-image in patients with type 1 neurofibromatosis.

Schwannomatosis (SWN)

Only since about 2005 has schwannomatosis been considered to constitute a separate entity. It has a similar clinical presentation to NF2, without fulfilling the diagnostic criteria. It is said to be present in approximately 1 in 69 000 births (39), but its prevalence may well be much higher, as many cases are oligosymptomatic. Chronic pain is generally the most prominent symptom.

Diagnostic criteria

This entity is defined by the occurrence of multiple schwannomas without any other stigmata of NF2 (bilateral vestibular nerve schwannomas, subcapsular cataract, NF2 mutation in the blood) *(Table)*.

Genetics and molecular pathophysiology

In schwannomatosis, various NF2 mutations can be found in tumor tissue that are not seen in the DNA of blood cells. A small proportion of patients have mutations in the *SMARCB1* gene (e58). Mutations in the *LZTR1* gene are more common (2, e59); it seems that somatic NF2 mutations arise secondarily (40). Schwannomatosis affects multiple members of a family in fewer than 20% of cases. The inheritance pattern is unclear. Genetic NF2 mosaics and segmental courses of SWN are common.

Clinical manifestations

Schwannomas

Histologically, the schwannomas of schwannomatosis are hardly distinguishable from those seen in sporadic disease or in other tumor syndromes (NF2, Carney complex). In SWN, just as in NF2, there are intrafascicular microlesions in the peripheral nerves.

Pain

Chronic neuropathic pain is a further central feature of SWN. The severity of the pain is not correlated with either the quantitative tumor burden or the distribution of the tumors. SWN, unlike NF2, rarely causes sensorimotor deficits.

Other tumors

Spinal schwannomas are seen in nearly two-thirds of patients (e60). Meningiomas and unilateral vestibular schwannomas can be seen as well (e61, e62). There is debate over whether malignancies are more common in patients with SWN (e63).

Treatment

Painful or functionally limiting schwannomas can be surgically resected. Genetic investigation of the resected tumor material is of high prognostic relevance, in particular when the diagnosis is initially unclear. Co-analgetic drugs (amitriptyline, gabapentin, pregabalin) have been found especially useful in the treatment of the associated neuropathic pain.

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Conflict of interest statement

The authors state that no conflicts of interest exist.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref2020

eTables and eFigure:
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Questions concerning the article in Issue 20/2020:

The Neurofibromatoses

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Please select the answer that is most appropriate.

Question 1

What accompanying diseases are mainly responsible for the markedly reduced life expectancy of persons with type 1 neurofibromatosis?

a) Type 2 diabetes and peripheral arterial occlusive disease
b) Gastrointestinal tumors and generalized epilepsy
c) Malignant tumors, heart attack, and stroke
d) Melanoma and non-Hodgkin lymphoma
e) Hypertriglyceridemia and hypertension

Question 2

What is the function of the neurofibromatosis 1 gene?

a) It activates MAP kinase signal transduction and thereby regulates cellular proliferation.
b) It inhibits JAK kinase, which regulates the division of Schwann cells.
c) It is primarily expressed during fetal development and leads postnatally to an accumulation of p53 protein.
d) It regulates the activity of the EGFR gene and thereby triggers the development of cutaneous and glial tumors.
e) It encodes the tumor suppressor protein neurofibromin and suppresses the activity of the proto-oncogene Ras.

Question 3

What are the diagnostic criteria for type 1 neurofibromatosis?

a) Six or more café-au-lait spots and first-degree relatives with NF1
b) Radiological demonstration of a non-vestibular schwannoma and of at least two non-cutaneous schwannomas
c) At least one grand mal seizure and ≥ 2 meningiomas before puberty
d) Polyneuropathy and cataract in young adulthood
e) Cardiac valvular disease and eighth cranial nerve dysfunction

Question 4

What type of hematopoietic malignancy is more commonly diagnosed in persons with type 1 neurofibromatosis?

a) Acute lymphocytic leukemia
b) Chronic lymphocytic leukemia
c) Prolymphocytic leukemia
d) Myeloid leukemia
e) Hairy-cell leukemia

Question 5

Which of the following findings secures the diagnosis of type 2 neurofibromatosis?

a) Sphenoid wing dysplasia
b) Optic nerve glioma
c) Bilateral vestibular schwannomas
d) Two or more plexiform neurofibromas
e) Juvenile posterior lens opacification

Question 6

What type of tumor can arise from a plexiform neurofibroma?

a) Glioma
b) Malignant peripheral nerve sheath tumor
c) Meningioma
d) Ependymoma
e) Medulloblastoma

Question 7

Which of the following is a sign of schwannomatosis?

a) Chronic neuropathic pain and non-vestibular schwannomas
b) Bilateral vestibular vertigo and hearing loss
c) Astrocytomas and epileptic seizures
d) Neurofibromas and organ compression
e) Meningiomas and anosmia

Question 8

Persons with type 1 neurofibromatosis are at increased risk of developing a glioma. What type of tumor most often affects the optic nerve?

a) Subependymal giant-cell astrocytoma
b) Anaplastic astrocytoma
c) Pleomorphic xanthoastrocytoma
d) Pilocytic astrocytoma
e) Gliosarcoma

Question 9

Which of the following substances has been found useful to relieve pain caused by a schwannoma?

a) Acetylsalicylic acid
b) Metamizole
c) Ibuprofen
d) Oxycodone
e) Gabapentin

Question 10

Approximately what proportion of patients with type 2 neurofibromatosis have neuropathic symptoms?

a) 10%
b) 30%
c) 50%
d) 70%
e) 90%

► **Participation is possible only via the Internet: cme.aerzteblatt.de**

Supplementary material to:

The Neurofibromatoses

by Said Farschtschi, Victor-Felix Mautner, Anna Cecilia Lawson McLean, Alexander Schulz, Reinhard Friedrich, and Steffen K. Rosahl

Dtsch Arztebl Int 2020; 117: 354–60. DOI: 10.3238/arztebl.2020.0354

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eTABLE 1

Incidence and new mutation rates of the neurofibromatoses

	Incidence (per number of births)	Hereditary cases/ new mutations
NF1	1:3000	50:50
NF2	1:33 000	50:50
SWN	1:60 000	20:80

NF1/2, Types 1 and 2 neurofibromatosis; SWN, schwannomatosis

eTABLE 2

The frequency of tumors in patients with NF2 (11, 14)

Tumor entity	Frequency
Vestibular nerve schwannoma	90–95%
Schwannoma of other cranial nerves	24–51%
(Sub-)cutaneous schwannoma	59–68%
Intracranial meningioma	45–58%
Peripheral nerve schwannoma	43–48%
Ependymoma	33–53%
Mesothelioma	Rare (associated with asbestos)
Malignant schwannoma	Rare

NF2, Type 2 neurofibromatosis

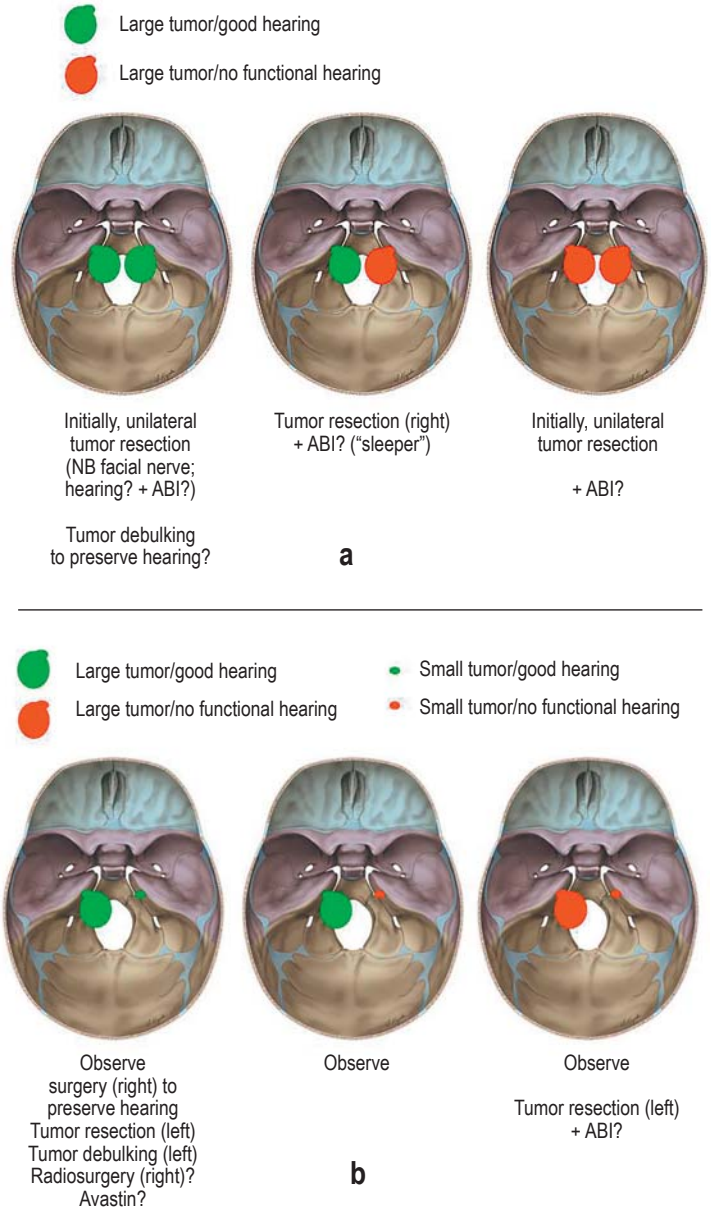
eTABLE 3

Grades of clinical severity in type 2 neurofibromatosis (NF2)
The disease is categorized as moderate whenever its classification as either mild or severe seems clinically inappropriate.*[1]

Mild	Severe
Age at onset >30 years + no more than two further tumors (symptomatic or >1.5 cm)*[2]	Age at onset ≤ 20 years + at least two further tumors (symptomatic or > 1.5 cm) aside from the bilateral vestibular nerve schwannomas or demonstration of a tumor of the central nervous system before the 11th birthday and at least one further symptomatic tumor with positive genetic findings for NF2
– Retained good functional hearing – No dizziness – No impairment of verbal expression – No more than mild bilateral visual impairment – No more than mild gait impairment – No more than mild pain	– Total deafness – Incapacitating vertigo – Dysphagia necessitating tube feeding – Phonation disturbance – Severe visual impairment – Facial nerve palsy, HB grade 3 or worse – Wheelchair-bound because of paraparesis/paraplegia or severe ataxia – Incontinence necessitating catheterization – Severe orientation disturbance – Severe memory impairment – Additional conditions with moderate or severe manifestations (e.g., postoperative syringomyelia, pseudotumor cerebri due to venous sinus occlusion by a parasagittal meningioma, medically intractable depression) – Severe chronic pain

*[1] The listed disease manifestations are to be considered a starting point for the categorization of clinical severity. The assessment should be performed by an experienced physician and updated at each follow-up examination.
*[2] Including vestibular nerve schwannomas and tumors that have already been resected
HB, House and Brackmann

eFIGURE



Treatment options for vestibular nerve schwannomas (VS) in type 2 neurofibromatosis (NF2). Possible constellations in the management of VS in NF2, depending on tumor size and residual auditory function:
a) large tumor on both sides
b) asymmetrical tumor distribution
A "sleeper" is an inactive brainstem implant that is only activated in the event that the patient also loses hearing in the other ear.
ABI, Auditory brainstem implant