Spinal Cord Tumors in Neurofacomatosis

12

Frederick A. Boop, Jimmy Ming-Jung Chuang, and Chenran Zhang

12.1 Introduction

Neurofacomatosis (phakomatoses) are a group of neuro-oculocutaneous disorders characterized by involvement of structures that arise from the embryonic ectoderm—thus, the central nervous system (CNS), skin, and eyes. The phakomatoses concept was formulated in 1923 by an ophthalmologist Van Der Hoeve to describe three disorders (neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau syndrome), according to their ophthalmologic manifestations (Greek *phakos* means birthmark) [1, 2]. However, it has been subsequently noted that mesodermal and

F. A. Boop
Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA

Department of Neurosurgery, Le Bonheur Children's Hospital, Memphis, TN, USA

Semmes Murphey, Memphis, TN, USA
e-mail: fboop@semmes-murphey.com

J. M.-J. Chuang (✉)
Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA

Department of Neurosurgery, Le Bonheur Children's Hospital, Memphis, TN, USA

Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

C. Zhang
Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA

Department of Neurosurgery, Le Bonheur Children's Hospital, Memphis, TN, USA

Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Changzheng Hospital, Second Military Medical University, Shanghai, China

K. I. Arnautović, Z. L. Gokaslan (eds.), *Spinal Cord Tumors*,
https://doi.org/10.1007/978-3-319-99438-3_12

endodermal tissues are also involved. A number of genetic and acquired diseases come in this category and may affect one or more organ systems. They tend to form tumors in various organs, particular the nervous system. Now neurofacomatosis are also termed as "neuroectodermatoses" or "neurocutaneous syndrome."

Intramedullary spinal cord tumors are rare. They account for only 4–6% of all CNS tumors [3]. In this chapter, we mainly survey the neurocutaneous tumor syndrome and intramedullary spinal cord tumor associated with the three major neurofacomatosis: Neurofibromatosis type I (NF1), Neurofibromatosis type 2 (NF2) and von Hippel-Lindau syndrome (VHL). Table 12.1 lists the summary of neurocutaneous tumors and intramedullary tumors associated with all neurofacomatosis.

12.2 Neurofibromatosis Type 1

12.2.1 Epidemiology and Genetics

NF1, known as von Recklinghausen disease or peripheral neurofibromatosis, was first described by von Recklinghausen in 1882 [4]. It is the most common of the neurofacomatoses with a prevalence of 1 per 3000; it has equal sex distribution and no obvious ethnic predilection [5, 6]. NF1 is transmitted as an autosomal-dominant trait but half of patients get sporadic mutations without a family history of the disease [7]. Penetrance is nearly 100% by 8 years of age, whereas expressivity is extremely viable [8, 9].

The NF1 locus maps to chromosome 17q11.2 and consists of 57 constitutive exons spread over 350 kb of genomic deoxyribonucleic acid (DNA) [10]. Using cDNA-SSCP/HD analysis, Pros et al. identified 282 different mutations in 374 independent patients with NF1 [11]. The NF1 gene encodes for a 2818-amino-acid protein referred to as neurofibroma [12]. Neurofibromin plays a pivotal regulatory role in the Ras pathway of cellular proliferation. Loss of neurofibromin function will cause to excessive Ras activation and creating a tendency toward cell proliferation and tumor development [13]. Neurofibromin is expressed in many different cell types especially in Schwann cells and neurons [14]. Therefore, neurofibromin functions as a tumor suppressor gene with respect to neurofibroma and glioma formation [15, 16]. Recently, the mechanistic target of rapamycin (MTOR) pathway has also been implicated in NF1-related tumors [17].

12.2.2 Diagnostic Criteria and Screening

Diagnostic criteria are summarized in Table 12.2, which were outlined in an earlier National Institutes of Health (NIH) meeting (NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988) [18]. Two or more criteria must be present to establish the diagnosis. These criteria are extremely sensitive and specific for the disease, but genetic testing for confirmation is strongly recommended in controversial cases. However, DeBella et al. concluded that the

Table 12.1 Neurofacomatosis and Allied Tumors

Syndrome	Classic features	Associated tumor	Associated spinal cord tumor
Neurofibromatosis Type 1	Café au lait spots	Neurofibroma, Optic Glioma, Iris hamartoma	Intramedullary astrocytoma
Neurofibromatosis Type 2	Juvenile lens opacity	Vestibular Schwannoma, Meningioma, Spinal schwannoma and meningioma	Intramedullary ependymoma
Von Hippel-Lindau Disease		Retinal, cerebellar and spinal hemangioblastoma, Endolymphatic sac tumors Pheochromocytoma, Renal cell carcinoma	Intramedullary hemangioblastoma
Tuberous Sclerosis Complex	Cortical tubers, seizure, hypopigmented macules, autism, Shagreen patch	Angiofibroma, Renal angiomyolipoma, Subependymal giant cell astrocytoma, Cardiac rhabdomyoma	
Schwannomatosis		Cranial and spinal nerve schwannomas (except acoustic neuroma)	
L'hermitte-Duclos Disease	Seizure, CNS abnormalities	Cerebellar gangliocytomas	
Ataxia-Telangiectasia	Ataxia, Sclera telangiectasia CNS abnormalities	Leukemia, Lymphoma	
Li-Fraumeni Syndrome		Sarcoma, cancers of the breast, brain and adrenal glands	
Sturge-Weber Syndrome	Port-wine stain, seizure, glaucoma	Ipsilateral leptomeningeal angioma	
Maffucci's Syndrome	Hyperpigmented patches and nevi	Multiple enchondromas with secondary hemangiomas, Glioma	
Epidermal Nevus Syndrome	Seizure, CNS abnormalities	Patchy cutaneous hamartomatous lesions	
Neurocutaneous Melanosis	Pigmented cutaneous area	Leptomeningeal melanoma	
Klippel-Trenaunay-Weber Syndrome	Unilateral limb hypertrophy, Macrocephaly	Subcutaneous hemangiomas	
Incontinentia Pigmenti	Hypopigmented skin lesions, CNS abnormalities		
Cowden Disease	Seizure, CNS abnormalities	Multiple facial trichilemmomas	
Wyburn-Mason Syndrome	Retinal and cerebral arteriovenous malformation		

Table 12.2 Diagnostic Criteria for NF1

The presence of two or more of the following is diagnostic:
• ≥6 cafe´ au lait spots >5 mm in prepubertal individuals or > 15 mm in postpubertal individuals
• ≥2 neurofibromas of any type or 1 plexiform neurofibroma
• Axillary or inguinal freckling
• Optic gliomas
• ≥2 hamartomas of the iris (Lisch nodules)
• Distinctive osseous lesion (ie, sphenoid wing dysplasia or thinning of long bone cortex with or without pseudoarthrosis)
• First-degree relative with NF1

diagnosis of NF1 cannot always be made in young children using the NIH diagnostic criteria [8]. Modification of these criteria may be necessary for children under 8 years old.

The diagnostic and health supervision guidelines for patients with NF1 have been published by the Committee on Genetics of the American Academy of Pediatrics [19]. Screening magnetic resonance imaging (MRI), electroencephalogram (EEG,) and X-rays are no longer routinely recommended unless specific problems arise. Neurologic and ophthalmologic assessments, as well as blood-pressure monitoring (for pheochromocytoma and renal arterial abnormalities), are required. Behavior and development should be evaluated carefully, and formal neuropsychometric evaluation may be necessary if concerns arise. Genetic counseling and screening with targeted testing of the NF1 mutation identified in the patient should be considered in first degree relatives [18].

12.2.3 Neurocutaneous Tumor Syndromes and spinal tumors in Neurofibromatosis type 1

Symptoms within and between families can vary extremely, and signs generally develop by 10 years of age [18]. By puberty, more than 80% of NF1 patients develop neurofibromas that can be cutaneous, subcutaneous, or deep [8]. Plexiform neurofibromas can experience malignant transformation (Fig. 12.1). The incidence of optic pathway gliomas, brain stem gliomas, cerebellar gliomas, and meningiomas is increased in patients with NF1 [20]. A prospective study of NF1 cancer incidence in the United Kingdom (UK) showed NF1 carries a 2.7-fold increase in overall risk of cancer, with a cumulative risk of a malignancy at 20% by age 50 years [21].

Spinal neurofibromas: Spinal neurofibromas (Fig. 12.2) are benign tumors of the peripheral nerves, originating from the nerve sheath, and generally encasing the nerve roots as a result of an asymmetric growth pattern [22, 23]. Their common anatomical locations are intradural extramedullary, and dumbbell type. Familial

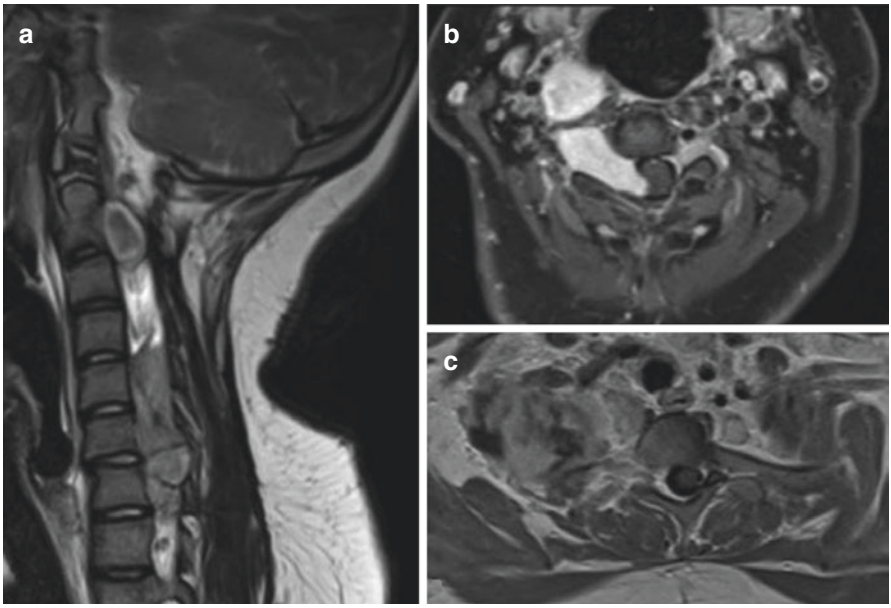

Fig. 12.1 Sagittal (**a**) and axial (**b**, **c**) MRIs of plexiform neurofibromas undergoing malignant transformation

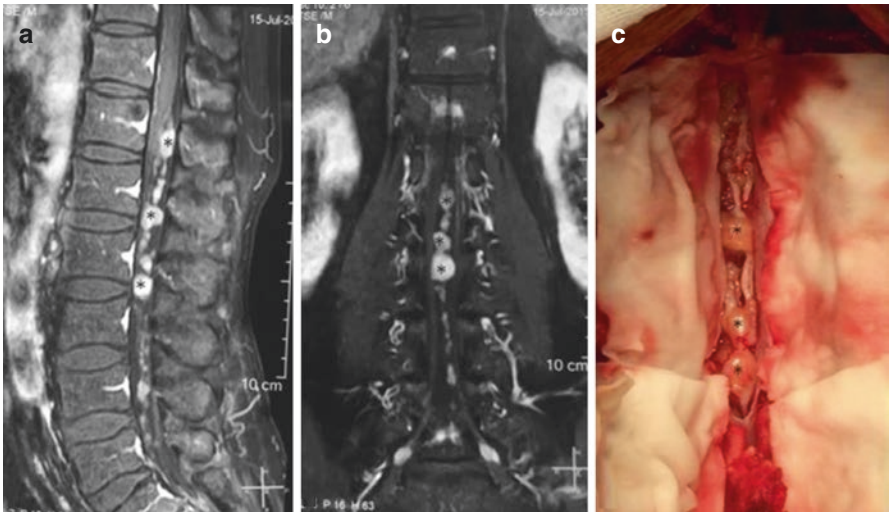

Fig. 12.2 Sagittal (**a**) and coronal (**b**) MRI with gadolinium identifies multiple lesions in the lumbar spinal canal. Intraoperative view of the neurofibromas (**c**)

spinal neurofibromatosis is an alternate form of neurofibromatosis that is classified by numerous neurofibromas symmetrically affecting the whole axial spine [24, 25]. Spinal cord compression is seldom found but can occur [23]. So far, the largest systematic study by Nguyen et al. that describes spinal MRI findings of patients with NF1 and associated symptoms demonstrates that 80% of patients with NF1 had spinal neurofibromas, with ascending frequency from 70% in patients younger than 10 years to 80% in patients aged 10–18 years to 89% in individuals older than 18 years of age [22]. Meanwhile, symptoms are reported among 60% of patients at presentation. At baseline, 34% of patients had MRI changes consistent with spinal cord compression that was most prevalent at the cervical (43%) and lumbar (40%) spine region. Some of the patients with progression of their spinal neurofibromas developed cord compression. Paraspinal plexiform neurofibromas (PNs) were present in 79% of patients, of which 88% had accompanied spinal neurofibromas. However, other reported frequency of asymptomatic spinal neurofibromas on MRI ranges from 13% in children to 40% in children and adults with NF1. The higher incidence of spinal neurofibromas as described in the study by Nguyen et al. probably results from a more severe phenotype patient cohort and its clinical trials nature.

Surgical resection is a safe and effective treatment for spinal nerve sheath tumors. Approximately 30% of patients developed a postoperative complication, most commonly new or worsening sensory deficits. Complications were more common in cervical and lumbosacral tumors but had no association with patient age, clinical presentation, symptom duration, tumor size, or tumor pathology. Intradural and dumbbell tumors were associated with higher rates of cerebrospinal fluid (CSF) leak, pseudomeningocele, and wound infection. Complications are an inevitable consequence of spinal nerve sheath tumor surgery given the intimacy of these lesions with functional neural elements. There was no difference in the use of intraoperative neuro-monitoring when comparing cases with surgical complications and those without. However, the use of neuro-monitoring was associated with a significantly higher rate of gross-total resection.

Plexiform neurofibromas: PN is another tumor type that can be found in up to 50% of patients with NF1 who undergo an MRI [26]. PNs occur along any peripheral nerve but if located in the paraspinal area, they can grow and extend laterally along the spinal nerves with or without involvement of the neural foramina [27, 28].

12.2.4 Spinal Cord Tumor in Neurofibromatosis Type 1

Gliomas are often associated with NF1, most being low-grade. They mainly involve the optic pathways—especially in children [29, 30]—and only 1% are found in the spinal cord [18]. The incidence of intramedullary gliomas in NF1 patients may be far more than their sporadic counterparts according to similar works [31]. So far, there are several case series reporting intramedullary gliomas in NF1 patients. Lee et al. reported 3 intramedullary astrocytomas with NFI (1 low grade astrocytoma and 2 anaplastic astrocytomas) [32]. On pathologic

examination, most are pilocytic astrocytomas (PAs) World Health Organization (WHO) Grade I [33]. However, patients with NF1 may also develop diffusely infiltrating astrocytomas (DAs) (WHO grades II–IV), particularly with an onset later in life [34]. Rodriguez et al. included 100 patients with NF1: there were four intramedullary astrocytoma cases, two PAs, and two low-grade astrocytoma, subtype indeterminate (LGSI) [35]. The prognoses of the PA and LGSI gliomas overall were generally favorable.

Pilomyxoid Astrocytoma (PMAs) usually occur in young children and are frequently located in the hypothalamic/chiasmatic region. They are seldom found in the spinal cord. Spinal PMAs affect pediatric age group more than adult patients with a female preponderance, mostly the cervical and thoracic spinal regions. Most of the lesions are intramedullary with only one case report being an intradural extramedullary lesion [36]. The association of intramedullary PMA with NF1 is even less common. Dunn-Pirio et al. reported so far the first case of a spinal cord PMA in an adult patient with NF1 [37]. The patient underwent a partial surgical resection of the spinal cord tumor followed by adjuvant carboplatin 560 mg/m^2 every 4 weeks. Radiation was avoided due to risks associated with NF 1. Single agent carboplatin was effective and well-tolerated.

Ependymomas have been reported with a higher incidence in NF2 rather than in NF1 and are preferentially located in the spinal cord [38]. Ependymoma with NF1 has rarely been reported, not to mention spinal cord ependymoma with NF1. To date, only four cases of ependymoma with NF1 have been reported in English literature, and only 2 of them were spinal cord ependymoma with NF1: thoracic cord ependymoma (WHO II) in a 5-year-old boy and 1 cervical spinal cord ependymoma in a 49-year-old female [39, 40]. There were no differences found between ependymomas in NF1 patients and those found in their sporadic counterparts in terms of clinical course. Therefore, the management modality is similar with total surgical resection remaining the treatment of choice whenever possible. Moreover, as NF1 is a multisystem disease, the cooperation between multidisciplinary clinicians and scientists is essential.

12.3 Neurofibromatosis Type 2

12.3.1 Epidemiology and Genetics

NF2 is significantly less common than NF1 with an incidence of 1 per 33,000 [41]. Although the disease is classified as "neurofibromatosis," neurofibromas are relative infrequent. Actually, NF2 is a unique clinical and pathological entity, entirely distinct both phenotypically and genotypically from NF1. The hallmark of NF2 is the development of bilateral vestibular schwannomas (VS). It is an autosomal dominant inheritance pattern with nearly 100% penetrance, although 50% of patients have sporadic mutations [42]. Affected patients with no gender predilection typically present in late adolescence; those who present in childhood often have atypical and more severe clinical manifestations [43].

The NF2 gene maps to the long arm of chromosome 22 (22q11.1-22q13.1), which encodes a 595-amino-acid protein referred to as merlin or schwannomin [44]. Merlin is a cytoskeletal protein that appears to play a role in the control of cell growth, affecting signaling pathways connected with contact inhibition and tumor suppression [45]. Merlin is widely expressed in Schwann cells, arachnoid cells, and the ocular lens. The gene product is considered to be a tumor suppressor and regulator of Schwann cell and arachnoidal cell proliferation [46]. Merlin functions as a tumor suppressor gene with respect to schwannoma and meningioma formation [42]. Some genotype-phenotype correlations have been identified with NF2. Missense or splicing mutations tend to predict milder disease than do mutations that lead to protein truncation [47]. Somatic mosaicism for NF2 gene mutation may produce localized disease severity [42]. Therefore, genetic testing for NF2 is valuable in some cases for diagnostic purposes.

12.3.2 Diagnostic Criteria and Screening

There are multiple diagnostic criteria for NF2. The most recent and sensitive criteria to be used are Baser criteria or Manchester criteria, which have been shown to have a sensitivity of 79% and a specificity of 100% [48]. The criteria are shown in Table 12.3.

Accepted criteria for NF2 screening include having a first-degree relative with NF2, the presence of VS before the age of 30 years, the presence of meningioma before the age of 20 years, the presence of cutaneous schwannomas, and the

Table 12.3 Diagnostic Criteria for NF2 (Manchester Criteria)

The presence of two or more of the following is diagnostic:
Bilateral vestibular schwannomas
• First-degree family relative with NF2 and unilateral vestibular schwannoma or any two of the following: – Meningioma – Schwannoma – Glioma – Neurofibroma – Posterior subcapsular lenticular opacity
• Unilateral vestibular schwannoma and any two of the following: – Meningioma – Schwannoma – Glioma – Neurofibroma – Posterior subcapsular lenticular opacity
• Two or more meningiomas and unilateral vestibular schwannoma, or any two of the following: – Schwannoma – Glioma – Neurofibroma – Posterior subcapsular lenticular opacity

presence of multiple spinal tumors [49]. The NF2 screening includes detailed personal and family history, cutaneous and ocular examination, and MRI of the neural axis. For patients with a confirmed diagnosis of NF2, regular following should consist of annual hearing test, brainstem auditory evoked potential response, visual exam, and dermatologic exam. MRI of neural axis should begin at age 10, repeated every 2 years up to age 20, and then repeated every 3-to-5 years afterward [42]. Closer follow-up is required for patients in whom lesions are identified.

12.3.3 Neurocutaneous Tumor Syndromes and spinal tumors in Neurofibromatosis type 2

Patients with NF2 harbor a wide spectrum of nervous system tumors, including cranial (vestibular, facial, and trigeminal) and peripheral nerve schwannomas, as well as meningiomas and intramedullary ependymomas [50].

Vestibular Schwannoma. VS or acoustic neuromas are benign tumors that are pathognomonic for NF2 when present bilaterally. Bilateral VSs are seen in up to 95% of patients with NF2 (Fig. 12.3) [51]. VS cause the typical symptoms of hearing loss, tinnitus, and vestibular dysfunction. Hydrocephalus and brainstem dysfunction can result from mass effect in severe cases. Management options include observation, surgical resection, radiosurgery, or chemotherapy [52]. The decision to treat requires a consideration of the patient's age, medical condition, hearing status, neurological function, and size of tumor. Surgical timing presents challenges to neurosurgeons. Symptomatic and large tumors usually are treated surgically; however, the treatment of smaller bilateral tumors is less clear due to unpredictable tumor growth. Stereotactic radiosurgery also has been applied for local control [53]. Surgical approach and planning are required to take into account the likelihood of

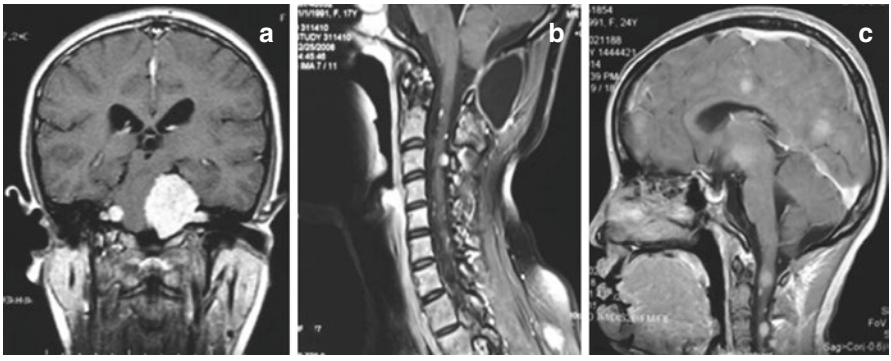

Fig. 12.3 The cranial (**a**) and cervical spinal cord (**b**) MRI of a 17-year-old girl with NF2, which clearly show bilateral vestibular schwannomas and multiple spinal schwannomas, respectively. Image from 7 years later (**c**), which shows multiple intracranial meningiomas and progress of the spinal schwannomas

preservation of hearing and whether the tumors are bilateral. In addition, VSs in NF2 are often multifocal and may grow to involve facial nerve fibers [42]. Therefore, microsurgical resection is associated with significant tumor recurrence in NF2 patients, as well as with high risk of hearing loss and facial dysfunction. Radiosurgery is a valuable alternative treatment offering tumor control or delaying the need for surgery; however, there is a price in terms of hearing function. These results may compare favorably with the progressive deafness associated with the natural history of the disease, or with surgery [53]. Targeted chemotherapy is currently being explored but the data are still lacking.

Intracranial meningioma. Meningiomas are the second-most common tumor associated with NF2. Intracranial meningiomas (Fig. 12.3) are observed in 45–58% of people with NF2, where spinal meningiomas are found in 20% of affected patients. Intracranial meningiomas tend to be multiple in number and often develop at a younger age than sporadic patient [47]. In the pediatric age group, meningiomas are often the first sign of NF2 [54]. Malis reported a series of 41 NF2 patients with long-term follow-up [55]. His series highlights the clinical burden of meningiomas in NF2. Most of the deaths in patients from NF2-related disease was attributable to overwhelmingly rapid growth of multiple meningiomas, not vestibular schwannomas [55]. Clinical symptoms from meningiomas are usually related to their size and location. Surgery remains the mainstay of treatment for growing and/or symptomatic meningiomas in NF2. Usually most meningiomas can be safely and fully resected. However, meningiomas involving the optic sheath and skull base are associated with higher rates of surgical sequela [56]. In situations where there is residual tumor from a partial resection, stereotactic radiosurgery has been used for local control [57]. At present, there are no defined medical treatments for NF2-associated meningiomas, and clinical studies using molecularly targeted drug therapies are currently being investigated [58].

Spinal schwannoma and spinal meningioma. Research has identified that NF2 patients have a predilection for multiple spinal nerve sheath schwannomas and spinal meningioma [59]. Spinal schwannomas are intradural, extramedullary neoplasms, arising from dorsal nerve roots (Fig. 12.3). In Malis's series treated over a 30-year period, he found that tumors of the spine were nearly as common as VS on MRI [55]. Among 41 NF2 patients, all of whom were initially referred due to bilateral VS, a total 99 extra-medullary spinal tumors were treated surgically. Of these, 58 were spinal schwannomas and 41 were meningiomas [55]. Previous reports have indicated that symptomatic spinal schwannomas in NF2 are likely to grow faster, more likely infiltrating nerve roots and progressing to serious deficits sooner [60]. Li et al. found that patients with NF2 were the youngest at the first spinal schwannoma operation and had the shortest duration of preoperative symptoms [61]. These intradural-extramedullary NF2 schwannomas did not have a preferred spinal location and only a slight predominance in the lumbar area [62]. Small cauda equina nodular schwannomas were common in NF2 (86.9%). They were usually small in size and showed a relatively stable behavior over time [63]. On the contrary, large extramedullary tumors (>5 mm) in NF2 were prone to progression. If small cauda equina nodules progressed into larger tumors, they would be difficult to treat

surgically. Meanwhile, most patients with NF2 tend to have significant problems related to bilateral vestibular schwannomas as well as other intracranial neoplasms. In such cases, a conservative approach is usually adopted towards these small spinal tumors. In addition, it was much more difficult to totally resect tumors in NF2 patients with higher rate of neurological deficits, and tumor recurrence [60].

For patients with NF2, approximately 10% of meningiomas requiring resection are located in the spine [64]. Spinal meningiomas is more prevalent in the female and elderly populations [65]. Early surgery remains the main treatment of growing and/or symptomatic meningiomas in NF2.

12.3.4 Spinal Cord Tumor in Neurofibromatosis Type 2

More than 75% of intramedullary spinal cord tumors associated with NF2 are ependymomas. Intra-medullary ependymomas are present in 33–53% of patients with NF2. Cervical cord and cervicomedullary junction are the most common location of involvement (Fig. 12.4) [55]. They are usually multiple and present with typical appearance of a "string of pearls" in neuroimaging, being hyperintense on T2, hypointense to isointense on T1, and mostly enhancing after contrast [62]. Clinical

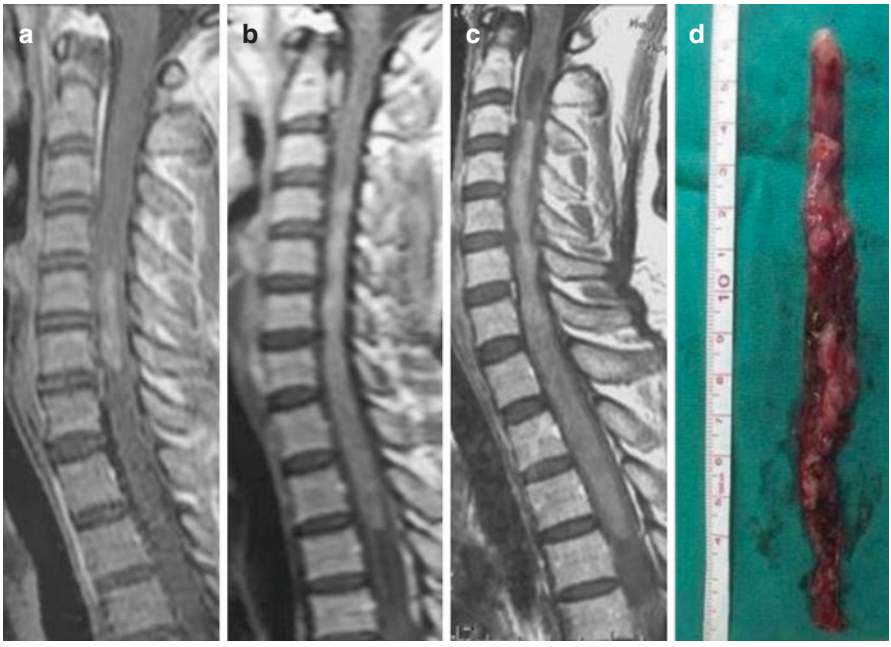

Fig. 12.4 The progress of a multiple-segment cervical intramedullary ependymoma with NF2. The spine MRI were taken on the year of 2005 (**a**), 2008 (**b**), and 2009 (**c**). The lesion was removed en bloc in 2009 (**d**)

signs and symptoms are variable and depend on the size and anatomic location of the tumor. In contrast to sporadic tumors, the majority of NF2-associated spinal tumors are asymptomatic. Accordingly, fewer than 20% of patients with these tumors are symptomatic. The most common symptoms of the patients with intramedullary spinal cord tumors are back pain, weakness, or sensory disturbances [66]. The management of NF2-associated ependymomas has not been firmly established. Although observation is often used to follow asymptomatic tumors, surgical resections are frequently effective and curative. Kalamarides et al. retrospectively reviewed two NF2 centers: Manchester, UK and Paris/Lille, France [67]. They found a significantly improved outcome in patients cared for in specialty centers. Spinal ependymomas produce morbidity. Surgery can prevent or improve this in selected cases but can itself result in morbidity. Surgery should be considered in growing/symptomatic ependymomas, particularly in the absence of overwhelming tumor load where bevacizumab is the preferred option [67].

The timing of the resection is best determined by detailed neurologic surveillance to assess for early onset of symptoms [68]. Because most NF2-associated spinal cord ependymomas are grade II tumors, gross total resection is often the curative (Fig. 12.4), with radiation therapy reserved for recurrent or residual tumors. WHO grade I myxopapillary ependymoma has also been reported in patients with NF2, and these tumors are usually treated with surgery alone [69]. Given that NF2 is a genetic tumor syndrome, there are concerns about the extra risks of radiation therapy in this patient cohort. For this reason, chemotherapy is the desirable choice for the patients with recurrent and unresectable tumors. The evaluation of molecularly targeted therapies for these tumors is currently ongoing. Small series of patients treated with bevacizumab have reported improvement with NF2-associated ependymomas [70].

12.4 Von Hippel-Lindau Disease

12.4.1 Epidemiology and Genetics

Von Hippel-Lindau (VHL) disease was attributed to Eugen von Hippel's descriptions of the retinal angiomatosis in 1904 and Arvid Lindau's descriptions of the hemangioma in the cerebellum and spinal cord in 1927 [71, 72]. The term von Hippel-Lindau disease was first used in 1936 and has been in common use since the 1970s. VHL is an autosomal dominant disease found in approximately 1 per 36,000 people [73]. It is familial in around 80% of cases, and the penetrance rate is up to 90% [74]. VHL is characterized by hemangioblastomas, usually involving retina, cerebellum, and spinal cord. It is also associated with non-CNS lesions, such as pancreatic neuroendocrine tumors, pheochromocytomas, renal cell carcinomas, endolymphatic sac tumors, and cystic tumors in multiple organs. Although VHL is grouped in the neurofacomatosis or neurocutaneous syndromes, it does not typically involve cutaneous manifestations, in contrast with other phakomatoses.

VHL disease as an autosomal dominant inheritance pattern is caused by loss of the tumor suppressor gene located at 3p25–26 [75]. The VHL gene encodes for a protein referred to as pVHL, which coordinates multiple aspect of the cell cycle and facilitates angiogenesis through regulatory control over hypoxia-inducible factor-1 alpha (HIF-1α) and hypoxia-inducible factor-2 alpha (HIF-2α) [76]. Dysfunction or absence of the pVHL leads to constitutive overexpression of HIF-1α and HIF-2α, which leads to increased level of vascular endothelial growth factor (VEGF) and other pro-angiogenic signals [76, 77]. These insults combine to cause the spectrum of tumors found in VHL disease.

12.4.2 Diagnostic Criteria and Screening

Clinical diagnostic criteria of VHL, summarized in Table 12.4, are used for referral to specialists for genetic counseling and testing. For individuals who have a family history of VHL, detection of only one type of tumor specific to VHL may be sufficient to make a diagnosis. For those patients without a family history of the disease, at least two types of VHL tumors should be identified to confirm a diagnosis [78, 79]. The definite diagnosis of VHL is typically confirmed by genetic testing to identify a germline mutation of the VHL gene.

The loss of vision is one of the more common presentations with VHL due to retinal hemangioblastoma (angiomas). Patients with cerebellar hemangioblastoma may present with ataxia, dysmetria, and coordination difficulties. Patients with spinal cord hemangioblastomas present with motor or sensory problems based on the tumor's location. Patients with pheochromocytomas can present with paroxysmal or sustained hypertension. Hearing loss is often associated with endolymphatic sac tumors.

Screening protocols have been developed for early diagnosis of typical lesions. The protocol includes annual ophthalmic examinations from early childhood, MRI of the head every 12–36 months from adolescence onward, ultrasound (or MRI) of the abdomen every 12 months, beginning at the age of 16 years. Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites should be considered in high-risk families [80]. Patients also need regular evaluations for

Table 12.4 Diagnostic Criteria for VHL

Without VHL family history: Present with two or more of the following characteristic lesions
With VHL family history: Present with one or more of the following characteristic lesions
• Spinal or cerebellar hemangioblastoma
• Retinal angioma
• Adrenal or extra-adrenal pheochromocytoma
• Renal cell carcinoma
• Multiple renal and pancreatic cyst

neurologic symptoms, visual impairment, and hearing loss. As a result, all patients with VHL require lifelong monitoring for associated tumors.

12.4.3 Neurocutaneous Tumor Syndromes in von Hippel–Lindau disease

The disease is classified into type 1, the result of a nonsense mutation or deletion, and type 2, the result of a missense mutation. Based on adrenal involvement and risk of pheochromocytoma, type 2 carries risk of pheochromocytoma and type 1 does not [81]. Type 1 typically carries high risk for renal involvement, high risk for CNS hemangioblastomas, and low risk for the development of pheochromocytomas [82].

Hemangioblastomas are the lesions most frequently observed in VHL disease. Sporadic hemangioblastomas tend to be solitary in older patients, whereas VHL disease-related hemangioblastomas tend to be multiple in young adults with mean age of 29 years [73]. Woodward et al. examined 188 patients with solitary hemangioblastoma and without VHL family history [83]. Of these, 5% were found to have germline mutations in the VHL gene, and another 5% ultimately progress to additional VHL-related lesions. VHL-related hemangioblastomas have been reported to harbor germline mutation (94%) and loss of heterozygosity (62%) at the VHL gene. Over 150 different germline mutations have been identified [84, 85].

Hemangioblastomas in retina and central nerve system. Retinal hemangioblastoma is one of the earliest manifestations of the disease, and it has been reported in early childhood [86, 87]. More than 50% of patients with VHL disease have retinal hemangioblastoma. The retinal lesion has the appearance of aneurysmal dilatation which will manifest to tortuous vessels and lead to retinal detachment with progressive vision loss [88]. Other VHL-associated hemangioblastomas are circumscribed vascular tumors usually found in posterior fossa (80%) and spinal cord (20%) and rarely in the cerebral hemispheres. These tumors usually are found in patients after the third decade of life. They are benign but become symptomatic due to mass effect caused by adjacent cyst progression or tumor hemorrhage. 80% of patients with hemangiomas in medulla or spinal cord are associated with syringomyelia [89].

VHL disease is suggested to account for approximately a third of patients with CNS hemangioblastomas. On the other hand, overall CNS hemangioblastomas occur in 60–80% of VHL patients [73, 90]. The growth of VHL associated hemangioblastomas in central nerve system is variable. Some tumors tend to grow rapidly and others remain quiescent even in the same patient. Surgery for hemangioblastomas in VHL disease in indicated for patients who become symptomatic. Radiological progression without symptoms should not be an absolute indication for surgical resection [91]. Radiation therapy, in particular radiosurgery, can provide sustained control in patients with multiple or surgically inaccessible solid hemangioblastomas. Radiosurgery does not control the growth of associated cysts [92].

Chemotherapy to date has not yielded good tumor control rates. Targeted therapy, such as vascular endothelial growth factor (VEGF) inhibitors, and gene replacement therapy are under investigation.

Renal cell carcinoma and pheochromocytoma in VHL. Renal cell carcinoma (RCC) is the most common malignancy in VHL patients occurring in 24–45% of cases. In contrast to sporadic RCC, VHL-related RCC tends to be multifocal, bilateral and highly recurrent, although its metastatic potential is low. It has a clear cell appearance and is an important cause of death in VHL patients [90, 93]. Once identified, surgery is the treatment of choice with partial nephrectomy or radio frequency ablation when there is limited tumor involvement. Total nephrectomy or even bilateral nephrectomy is reserved for those patients with extensive tumor involvement, recognizing that renal dialysis is possibly required after surgery to sustain life [94]. Although the risk of RCC varies in different subtypes of VHL disease, in the most common forms the lifetime risk is 70% with 40 years of age being the mean age at clinical diagnosis.

Pheochromocytoma is a rare tumor and is present in about 0.2% of patients presenting with hypertension [95]. The majority of pheochromocytomas are sporadic; however, 15–20% are inherited as a part of the familial disorder. Familial pheochromocytoma are associated with von Hippel-Lindau (VHL) disease and multiple endocrine neoplasia II (MEN II) [96]. VHL disease accounts for 50% of patients with apparently isolated familial pheochromocytoma and 11% of patients with an apparently sporadic pheochromocytoma [93]. Mean age at diagnosis of pheochromocytoma in VHL disease is around 30 years. Both adrenal and extra-adrenal pheochromocytoma can occur in VHL disease. Pheochromocytoma differ from hemangioblastoma and clear cell renal cell carcinoma in that they are not richly vascularized and they are involved in several other tumor syndromes [93]. Genetic testing for VHL gene and radiological screening tests may be considered to establish early diagnosis in other members of familial pheochromocytoma [97].

12.4.4 Spinal Cord Tumor in von Hippel-Lindau disease

VHL disease accounts for approximately 10% of patients with an intramedullary spinal hemangioblastoma. On the other hand, up to 25% of patients with intramedullary hemangioblastomas will have evidence of VHL [98]. The tumor tends to occur in dorsal or dorsolateral parts of the spinal cord with pial attachment. They show a cervical predominance when they occur in association with VHL and typically present with progressive sensory deficits or proprioceptive deficits. Patients with VHL tend to become symptomatic at an earlier age [99].

MRI is the diagnostic test of choice for intramedullary hemangiomas (Fig. 12.5). MRI findings demonstrate “flow-void” phenomenon that reflects prominent feeding arteries or draining veins. Heterogeneous enhancement pattern also represents a vascular tumor parenchyma, comprising closely packed blood vessels interspersed

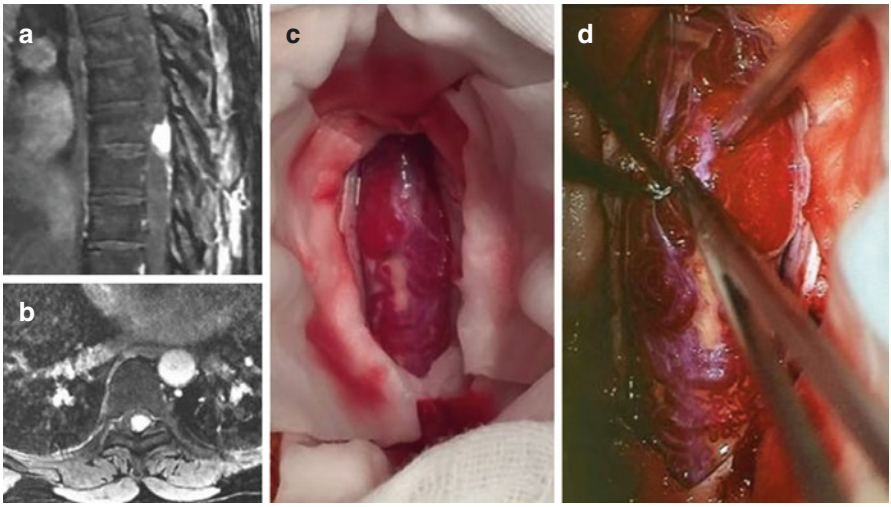

Fig. 12.5 Coronal (**a**) and axial (**b**) MRI with gadolinium identifying intramedullary hemangioblastomas of the thoracic spinal cord. Intraoperative view of the hemangioblastomas (**c**, **d**)

with stromal cells [100]. Regardless of tumor size, they are often associated with significant edema and syrinx formation [101].

Microsurgical resection is the primary treatment for intramedullary hemangioblastomas of the spinal cord (Fig. 12.5). The indications for surgical resection in the setting of sporadically occurring spinal cord hemangioblastomas differ from those occurring in VHL patients. Resection is necessary in patients with sporadic tumors both for diagnosis and to ameliorate symptoms. In the VHL patients with intramedullary hemangioblastomas, the surgical indications are based on the presence of symptoms and signs. Therefore, asymptomatic tumors may be followed clinically/radiographically and should be resected only when they become symptomatic. Preoperative spinal angiography can be of value prior to surgery in helping to determine the location and the nature of the feeding artery and delineate vascular supply [102]. Preoperative embolization may serve as an adjunct to surgery for those associated with arteriovenous shunt, for cord dysfunction related to venous congestion, or in cases harboring the risk of torrential intraoperative bleeding [103].

Clinical series have demonstrated that these lesions can be resected safely with preoperative neurological function serving as the best predictor of neurological outcome after surgery. Anatomically, hemangioblastomas arise from the pial layer and are considered juxta-medullary, but can exhibit an encapsulated component [104]. Surgical resection is complicated by the risk by of bleeding and local ischemia during surgery [105]. Complete resection is possible with the use of microsurgical techniques [106]. Targeted therapies, such as SU5416 (VEGF inhibitor), thalidomide, and bevacizumab (pan-VEGF inhibitor), have been reported to stabilize the disease in small case series [107–109].

12.5 Conclusion

Our understanding of VHL has come a long way since Van Der Hoeve described these three disorders (neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau syndrome) according to their ophthalmologic manifestations in 1923, and the later discovery of the NF1, NF2, and VHL genes in the early 1990s. Now, advanced techniques of microsurgical technique and stereotactic radiosurgery set a high bar for tumor treatment. New targeted therapies are showing promise for CNS tumors arising in this population of at-risk individuals. However, CNS tumors, including spinal cord tumors associated with the neurofacomatosis, comprise a group of tumors that are histologically benign, but have significant clinical consequences. Multidisciplinary management with early diagnosis is the mainstay of management. Hopefully a more advanced understanding of the molecular mechanisms will translate to new targeted therapies or perhaps gene replacement therapies which will revolutionize the outcomes in this group of patients.

References

1. Van Der Hoeve J. Les phacomatoses de Bourneville, de Recklinghausen at de von Hippel-Lindau. J Beige Neurol Psychiatr. 1933;33:752.
2. Van Der Hoeve J. Eye diseases in tuberous sclerosis of the brain and in Recklinghausen disease. Trans Ophthalmol Soc UK. 1923;43:534.
3. Russell DS, Rubinstein LJ. Pathology of Tumors of the Nervous System. 5th ed. London: Edward Arnold; 1989.
4. Von Recklinghausen F. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin: Verlag von August Hirschwald; 1882.
5. Korf BR. Clinical features and pathobiology of neurofibromatosis 1. J Child Neurol. 2002;17(8):573–7.; discussion 602-574, 646-551. https://doi.org/10.1177/088307380201700806.
6. Lammert M, Friedman JM, Kluwe L, Mautner VF. Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. Arch Dermatol. 2005;141(1):71–4. https://doi.org/10.1001/archderm.141.1.71.
7. North K. Neurofibromatosis type 1: review of the first 200 patients in an Australian clinic. J Child Neurol. 1993;8(4):395–402. https://doi.org/10.1177/088307389300800421.
8. 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.
9. Poyhonen M, Niemela S, Herva R. Risk of malignancy and death in neurofibromatosis. Arch Pathol Lab Med. 1997;121(2):139–43.
10. Farrell CJ, Plotkin SR. Genetic causes of brain tumors: neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and other syndromes. Neurol Clin. 2007;25(4):925–46., viii. https://doi.org/10.1016/j.ncl.2007.07.008.
11. Pros E, Gomez C, Martin T, Fabregas P, Serra E, Lazaro C. Nature and mRNA effect of 282 different NF1 point mutations: focus on splicing alterations. Hum Mutat. 2008;29(9):E173–93. https://doi.org/10.1002/humu.20826.
12. Cawthon RM, Weiss R, Xu GF, Viskochil D, Culver M, Stevens J, Robertson M, Dunn D, Gesteland R, O'Connell P, et al. A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. Cell. 1990;62(1):193–201.
13. Li Y, O'Connell P, Breidenbach HH, Cawthon R, Stevens J, Xu G, Neil S, Robertson M, White R, Viskochil D. Genomic organization of the neurofibromatosis 1 gene (NF1). Genomics. 1995;25(1):9–18.

14. Daston MM, Scrable H, Nordlund M, Sturbaum AK, Nissen LM, Ratner N. The protein product of the neurofibromatosis type 1 gene is expressed at highest abundance in neurons, Schwann cells, and oligodendrocytes. Neuron. 1992;8(3):415–28.
15. Zhu Y, Ghosh P, Charnay P, Burns DK, Parada LF. Neurofibromas in NF1: Schwann cell origin and role of tumor environment. Science. 2002;296(5569):920–2. https://doi.org/10.1126/science.1068452.
16. Gutmann DH, Donahoe J, Brown T, James CD, Perry A. Loss of neurofibromatosis 1 (NF1) gene expression in NF1-associated pilocytic astrocytomas. Neuropathol Appl Neurobiol. 2000;26(4):361–7.
17. Hutt-Cabezas M, Karajannis MA, Zagzag D, Shah S, Horkayne-Szakaly I, Rushing EJ, Cameron JD, Jain D, Eberhart CG, Raabe EH, Rodriguez FJ. Activation of mTORC1/mTORC2 signaling in pediatric low-grade glioma and pilocytic astrocytoma reveals mTOR as a therapeutic target. Neuro-Oncology. 2013;15(12):1604–14. https://doi.org/10.1093/neuonc/not132.
18. Daras M, Kaley TJ. Benign brain tumors and tumors associated with phakomatoses. Continuum (Minneap Minn). 2015; 21(2 Neuro-oncology):397–414. https://doi.org/10.1212/01.CON.0000464177.73440.44.
19. American Academy of Pediatrics Committee on Genetics. Health supervision for children with neurofibromatosis. Pediatrics. 1995;96(2 Pt 1):368–72.
20. Yohay K. Neurofibromatosis type 1 and associated malignancies. Curr Neurol Neurosci Rep. 2009;9(3):247–53.
21. Walker L, Thompson D, Easton D, Ponder B, Ponder M, Frayling I, Baralle D. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. Br J Cancer. 2006;95(2):233–8. https://doi.org/10.1038/sj.bjc.6603227.
22. Nguyen R, Dombi E, Akshintala S, Baldwin A, Widemann BC. Characterization of spinal findings in children and adults with neurofibromatosis type 1 enrolled in a natural history study using magnetic resonance imaging. J Neuro-Oncol. 2015;121(1):209–15. https://doi.org/10.1007/s11060-014-1629-5.
23. Abul-Kasim K, Thurnher MM, McKeever P, Sundgren PC. Intradural spinal tumors: current classification and MRI features. Neuroradiology. 2008;50(4):301–14. https://doi.org/10.1007/s00234-007-0345-7.
24. Carey JC, Viskochil DH. Neurofibromatosis type 1: A model condition for the study of the molecular basis of variable expressivity in human disorders. Am J Med Genet. 1999;89(1):7–13.
25. Riccardi VM. Neurofibromatosis, Phenotype, Natural History, and Pathogenesis. 2nd ed. Baltimore: Johns Hopkins University Press; 1992.
26. Nguyen R, Dombi E, Widemann BC, Solomon J, Fuensterer C, Kluwe L, Friedman JM, Mautner VF. Growth dynamics of plexiform neurofibromas: a retrospective cohort study of 201 patients with neurofibromatosis 1. Orphanet J Rare Dis. 2012;7:75. https://doi.org/10.1186/1750-1172-7-75.
27. Thakkar SD, Feigen U, Mautner VF. Spinal tumours in neurofibromatosis type 1: an MRI study of frequency, multiplicity and variety. Neuroradiology. 1999;41(9):625–9.
28. Jinnai T, Koyama T. Clinical characteristics of spinal nerve sheath tumors: analysis of 149 cases. Neurosurgery. 2005;56(3):510–5. discussion 510-515
29. Guillamo JS, Creange A, Kalifa C, Grill J, Rodriguez D, Doz F, Barbarot S, Zerah M, Sanson M, Bastuji-Garin S, Wolkenstein P, Reseau NFF. Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. Brain. 2003;126(Pt 1):152–60.
30. Rosenfeld A, Listernick R, Charrow J, Goldman S. Neurofibromatosis type 1 and high-grade tumors of the central nervous system. Childs Nerv Syst. 2010;26(5):663–7. https://doi.org/10.1007/s00381-009-1024-2.
31. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis 1: an analysis using U.S. death certificates. Am J Hum Genet. 2001;68(5):1110–8. https://doi.org/10.1086/320121.

32. Lee M, Rezai AR, Freed D, Epstein FJ. Intramedullary spinal cord tumors in neurofibromatosis. Neurosurgery. 1996;38(1):32–7.
33. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803–20. https://doi.org/10.1007/s00401-016-1545-1.
34. Gutmann DH, Rasmussen SA, Wolkenstein P, MacCollin MM, Guha A, Inskip PD, North KN, Poyhonen M, Birch PH, Friedman JM. Gliomas presenting after age 10 in individuals with neurofibromatosis type 1 (NF1). Neurology. 2002;59(5):759–61.
35. Rodriguez FJ, Perry A, Gutmann DH, O'Neill BP, Leonard J, Bryant S, Giannini C. Gliomas in neurofibromatosis type 1: a clinicopathologic study of 100 patients. J Neuropathol Exp Neurol. 2008;67(3):240–9. https://doi.org/10.1097/NEN.0b013e318165eb75.
36. Mendiratta-Lala M, Kader Ellika S, Gutierrez JA, Patel SC, Jain R. Spinal cord pilomyxoid astrocytoma: an unusual tumor. J Neuroimaging. 2007;17(4):371–4. https://doi.org/10.1111/j.1552-6569.2006.00101.x.
37. Dunn-Pirio AM, Howell E, McLendon RE, Peters KB. Single-Agent Carboplatin for a Rare Case of Pilomyxoid Astrocytoma of the Spinal Cord in an Adult with Neurofibromatosis Type 1. Case Rep Oncol. 2016;9(3):568–73. https://doi.org/10.1159/000449406.
38. Cheng H, Shan M, Feng C, Wang X. Spinal cord ependymoma associated with neurofibromatosis 1 : case report and review of the literature. J Korean Neurosurg Soc. 2014;55(1):43–7. https://doi.org/10.3340/jkns.2014.55.1.43.
39. Riffaud L, Vinchon M, Ragragui O, Delestret I, Ruchoux MM, Dhellemmes P. Hemispheric cerebral gliomas in children with NF1: arguments for a long-term follow-up. Childs Nerv Syst. 2002;18(1–2):43–7. https://doi.org/10.1007/s00381-001-0534-3.
40. Mittal A, Meena R, Samar N, Kumar S, Khandelwal A. A Case of Neurofibromatosis Type 1 Associated with Cervical Cord Ependymoma. Int J Curr Res Rev. 2017;9(23):22–4.
41. Evans DG, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. Otol Neurotol. 2005;26(1):93–7.
42. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet J Rare Dis. 2009;4:16. https://doi.org/10.1186/1750-1172-4-16.
43. Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. Arch Dis Child. 1999;81(6):496–9.
44. Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaze C, Plougastel B, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature. 1993;363(6429):515–21. https://doi.org/10.1038/363515a0.
45. Xiao GH, Chernoff J, Testa JR. NF2: the wizardry of merlin. Genes Chromosomes Cancer. 2003;38(4):389–99. https://doi.org/10.1002/gcc.10282.
46. Cooper J, Giancotti FG. Molecular insights into NF2/Merlin tumor suppressor function. FEBS Lett. 2014;588(16):2743–52. https://doi.org/10.1016/j.febslet.2014.04.001.
47. Parry DM, MacCollin MM, Kaiser-Kupfer MI, Pulaski K, Nicholson HS, Bolesta M, Eldridge R, Gusella JF. Germ-line mutations in the neurofibromatosis 2 gene: correlations with disease severity and retinal abnormalities. Am J Hum Genet. 1996;59(3):529–39.
48. Baser ME, Friedman JM, Wallace AJ, Ramsden RT, Joe H, Evans DG. Evaluation of clinical diagnostic criteria for neurofibromatosis 2. Neurology. 2002;59(11):1759–65.
49. Evans DG, Raymond FL, Barwell JG, Halliday D. Genetic testing and screening of individuals at risk of NF2. Clin Genet. 2012;82(5):416–24. https://doi.org/10.1111/j.1399-0004.2011.01816.x.
50. Campian J, Gutmann DH. CNS Tumors in Neurofibromatosis. J Clin Oncol. 2017;35(21):2378–85. https://doi.org/10.1200/JCO.2016.71.7199.
51. Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V, Harris R. A clinical study of type 2 neurofibromatosis. Q J Med. 1992;84(304):603–18.

52. Moffat DA, Quaranta N, Baguley DM, Hardy DG, Chang P. Management strategies in neurofibromatosis type 2. Eur Arch Otorhinolaryngol. 2003;260(1):12–8. https://doi.org/10.1007/s00405-002-0503-9.
53. Rowe JG, Radatz MW, Walton L, Soanes T, Rodgers J, Kemeny AA. Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. J Neurol Neurosurg Psychiatry. 2003;74(9):1288–93.
54. Ruggieri M, Iannetti P, Polizzi A, La Mantia I, Spalice A, Giliberto O, Platania N, Gabriele AL, Albanese V, Pavone L. Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. Neuropediatrics. 2005;36(1):21–34. https://doi.org/10.1055/s-2005-837581.
55. Malis LI. Neurofibromatosis type 2 and central neurofibromatosis. Neurosurg Focus. 1998;4(3):e1.
56. Nowak A, Dziedzic T, Czernicki T, Kunert P, Marchel A. Clinical course and management of intracranial meningiomas in neurofibromatosis type 2 patients. Neurol Neurochir Pol. 2015;49(6):367–72. https://doi.org/10.1016/j.pjnns.2015.08.007.
57. Wentworth S, Pinn M, Bourland JD, Deguzman AF, Ekstrand K, Ellis TL, Glazier SS, McMullen KP, Munley M, Stieber VW, Tatter SB, Shaw EG. Clinical experience with radiation therapy in the management of neurofibromatosis-associated central nervous system tumors. Int J Radiat Oncol Biol Phys. 2009;73(1):208–13. https://doi.org/10.1016/j.ijrobp.2008.03.073.
58. Perry A, Giannini C, Raghavan R, Scheithauer BW, Banerjee R, Margraf L, Bowers DC, Lytle RA, Newsham IF, Gutmann DH. Aggressive phenotypic and genotypic features in pediatric and NF2-associated meningiomas: a clinicopathologic study of 53 cases. J Neuropathol Exp Neurol. 2001;60(10):994–1003.
59. Halliday AL, Sobel RA, Martuza RL. Benign spinal nerve sheath tumors: their occurrence sporadically and in neurofibromatosis types 1 and 2. J Neurosurg. 1991;74(2):248–53. https://doi.org/10.3171/jns.1991.74.2.0248.
60. Klekamp J, Samii M. Surgery of spinal nerve sheath tumors with special reference to neurofibromatosis. Neurosurgery. 1998;42(2):279–89. discussion 289-290
61. Li P, Zhao F, Zhang J, Wang Z, Wang X, Wang B, Yang Z, Yang J, Gao Z, Liu P. Clinical features of spinal schwannomas in 65 patients with schwannomatosis compared with 831 with solitary schwannomas and 102 with neurofibromatosis Type 2: a retrospective study at a single institution. J Neurosurg Spine. 2016;24(1):145–54. https://doi.org/10.3171/2015.3.SPINE141145.
62. Mautner VF, Tatagiba M, Lindenau M, Funsterer C, Pulst SM, Baser ME, Kluwe L, Zanella FE. Spinal tumors in patients with neurofibromatosis type 2: MR imaging study of frequency, multiplicity, and variety. AJR Am J Roentgenol. 1995;165(4):951–5. https://doi.org/10.2214/ajr.165.4.7676998.
63. Aboukais R, Baroncini M, Zairi F, Bonne NX, Schapira S, Vincent C, Lejeune JP. Prognostic value and management of spinal tumors in neurofibromatosis type 2 patients. Acta Neurochir. 2013;155(5):771–7. https://doi.org/10.1007/s00701-012-1590-z.
64. Goutagny S, Kalamarides M. Meningiomas and neurofibromatosis. J Neuro-Oncol. 2010;99(3):341–7. https://doi.org/10.1007/s11060-010-0339-x.
65. Setzer M, Vatter H, Marquardt G, Seifert V, Vrionis FD. Management of spinal meningiomas: surgical results and a review of the literature. Neurosurg Focus. 2007;23(4):E14. https://doi.org/10.3171/FOC-07/10/E14.
66. Chang UK, Choe WJ, Chung SK, Chung CK, Kim HJ. Surgical outcome and prognostic factors of spinal intramedullary ependymomas in adults. J Neuro-Oncol. 2002;57(2):133–9.
67. Kalamarides M, Essayed W, Lejeune JP, Aboukais R, Sterkers O, Bernardeschi D, Peyre M, Lloyd SK, Freeman S, Hammerbeck-Ward C, Kellett M, Rutherford SA, Evans DG, Pathmanaban O, King AT. Spinal ependymomas in NF2: a surgical disease? J Neuro-Oncol. 2018;136(3):605–11. https://doi.org/10.1007/s11060-017-2690-7.

68. Hoshimaru M, Koyama T, Hashimoto N, Kikuchi H. Results of microsurgical treatment for intramedullary spinal cord ependymomas: analysis of 36 cases. Neurosurgery. 1999;44(2):264–9.
69. Plotkin SR, O'Donnell CC, Curry WT, Bove CM, MacCollin M, Nunes FP. Spinal ependymomas in neurofibromatosis Type 2: a retrospective analysis of 55 patients. J Neurosurg Spine. 2011;14(4):543–7. https://doi.org/10.3171/2010.11.SPINE10350.
70. Farschtschi S, Merker VL, Wolf D, Schuhmann M, Blakeley J, Plotkin SR, Hagel C, Mautner VF. Bevacizumab treatment for symptomatic spinal ependymomas in neurofibromatosis type 2. Acta Neurol Scand. 2016;133(6):475–80. https://doi.org/10.1111/ane.12490.
71. von Hippel E. Über eine sehr seltene Erkrankung der Netzhaut. Klin Beobachtungen Arch Ophthalmol. 1904;59(1):83–106.
72. Lindau A. Zur Frage der Angiomatosis Retinae und ihrer Hirnkomplikationen. Acta Ophthalmol. 1926;4(1–2):193–226.
73. Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, Ferguson-Smith MA. Clinical features and natural history of von Hippel-Lindau disease. Q J Med. 1990;77(283):1151–63.
74. Maher ER, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, Sampson J, Williams A, Ferguson-Smith MA, Morton N. Von Hippel-Lindau disease: a genetic study. J Med Genet. 1991;28(7):443–7.
75. Kley N, Whaley J, Seizinger BR. Neurofibromatosis type 2 and von Hippel-Lindau disease: from gene cloning to function. Glia. 1995;15(3):297–307. https://doi.org/10.1002/glia.440150310.
76. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol. 2004;22(24):4991–5004. https://doi.org/10.1200/JCO.2004.05.061.
77. Barry RE, Krek W. The von Hippel-Lindau tumour suppressor: a multi-faceted inhibitor of tumourigenesis. Trends Mol Med. 2004;10(9):466–72. https://doi.org/10.1016/j.molmed.2004.07.008.
78. Richard S, Graff J, Lindau J, Resche F. Von Hippel-Lindau disease. Lancet. 2004;363(9416):1231–4. https://doi.org/10.1016/S0140-6736(04)15957-6.
79. Butman JA, Linehan WM, Lonser RR. Neurologic manifestations of von Hippel-Lindau disease. JAMA. 2008;300(11):1334–42. https://doi.org/10.1001/jama.300.11.1334.
80. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011;19(6):617–23. https://doi.org/10.1038/ejhg.2010.175.
81. Banks RE, Tirukonda P, Taylor C, Hornigold N, Astuti D, Cohen D, Maher ER, Stanley AJ, Harnden P, Joyce A, Knowles M, Selby PJ. Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. Cancer Res. 2006;66(4):2000–11. https://doi.org/10.1158/0008-5472.CAN-05-3074.
82. Barontini M, Dahia PL. VHL disease. Best Pract Res Clin Endocrinol Metab. 2010;24(3):401–13. https://doi.org/10.1016/j.beem.2010.01.002.
83. Woodward ER, Clifford SC, Astuti D, Affara NA, Maher ER. Familial clear cell renal cell carcinoma (FCRC): clinical features and mutation analysis of the VHL, MET, and CUL2 candidate genes. J Med Genet. 2000;37(5):348–53.
84. Glasker S. Central nervous system manifestations in VHL: genetics, pathology and clinical phenotypic features. Familial Cancer. 2005;4(1):37–42. https://doi.org/10.1007/s10689-004-5347-6.
85. Glasker S, Bender BU, Apel TW, Natt E, van Velthoven V, Scheremet R, Zentner J, Neumann HP. The impact of molecular genetic analysis of the VHL gene in patients with haemangioblastomas of the central nervous system. J Neurol Neurosurg Psychiatry. 1999;67(6):758–62.
86. Ridley M, Green J, Johnson G. Retinal angiomatosis: the ocular manifestations of von Hippel-Lindau disease. Can J Ophthalmol. 1986;21(7):276–83.
87. Webster AR, Maher ER, Moore AT. Clinical characteristics of ocular angiomatosis in von Hippel-Lindau disease and correlation with germline mutation. Arch Ophthalmol. 1999;117(3):371–8.

88. Greenwald MJ, Weiss A. Ocular manifestations of the neurocutaneous syndromes. Pediatr Dermatol. 1984;2(2):98–117.
89. Salazar FG, Lamiell JM. Early identification of retinal angiomas in a large kindred von Hippel-Lindau disease. Am J Ophthalmol. 1980;89(4):540–5.
90. Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg. 2003;98(1):82–94. https://doi.org/10.3171/jns.2003.98.1.0082.
91. Ammerman JM, Lonser RR, Dambrosia J, Butman JA, Oldfield EH. Long-term natural history of hemangioblastomas in patients with von Hippel-Lindau disease: implications for treatment. J Neurosurg. 2006;105(2):248–55. https://doi.org/10.3171/jns.2006.105.2.248.
92. Hanakita S, Koga T, Shin M, Takayanagi S, Mukasa A, Tago M, Igaki H, Saito N. The long-term outcomes of radiosurgery for intracranial hemangioblastomas. Neuro-Oncology. 2014;16(3):429–33. https://doi.org/10.1093/neuonc/not201.
93. Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Altehoefer C, Zerres K, Januszewicz A, Eng C, Smith WM, Munk R, Manz T, Glaesker S, Apel TW, Treier M, Reineke M, Walz MK, Hoang-Vu C, Brauckhoff M, Klein-Franke A, Klose P, Schmidt H, Maier-Woelfle M, Peczkowska M, Szmigielski C, Eng C, Freiburg-Warsaw-Columbus Pheochromocytoma Study Group. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med. 2002;346(19):1459–66. https://doi.org/10.1056/NEJMoa020152.
94. Steinbach F, Novick AC, Zincke H, Miller DP, Williams RD, Lund G, Skinner DG, Esrig D, Richie JP, deKernion JB, et al. Treatment of renal cell carcinoma in von Hippel-Lindau disease: a multicenter study. J Urol. 1995;153(6):1812–6.
95. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. Medicine (Baltimore). 1991;70(1):46–66.
96. Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc. 1981;56(6):354–60.
97. Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA. Pheochromocytoma: a review. Maturitas. 2014;77(3):229–38. https://doi.org/10.1016/j.maturitas.2013.12.009.
98. Neumann HP, Eggert HR, Weigel K, Friedburg H, Wiestler OD, Schollmeyer P. Hemangioblastomas of the central nervous system. A 10-year study with special reference to von Hippel-Lindau syndrome. J Neurosurg. 1989;70(1):24–30. https://doi.org/10.3171/jns.1989.70.1.0024.
99. Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: a review. Curr Neurol Neurosci Rep. 2011;11(3):320–8. https://doi.org/10.1007/s11910-011-0190-2.
100. Baker KB, Moran CJ, Wippold FJ 2nd, Smirniotopoulos JG, Rodriguez FJ, Meyers SP, Siegal TL. MR imaging of spinal hemangioblastoma. AJR Am J Roentgenol. 2000;174(2):377–82. https://doi.org/10.2214/ajr.174.2.1740377.
101. Cristante L, Herrmann HD. Surgical management of intramedullary hemangioblastoma of the spinal cord. Acta Neurochir. 1999;141(4):333–9. discussion 339-340
102. Roonprapunt C, Silvera VM, Setton A, Freed D, Epstein FJ, Jallo GI. Surgical management of isolated hemangioblastomas of the spinal cord. Neurosurgery. 2001;49(2):321–7. discussion 327-328
103. Ohtakara K, Kuga Y, Murao K, Kojima T, Taki W, Waga S. Preoperative embolization of upper cervical cord hemangioblastoma concomitant with venous congestion--case report. Neurol Med Chir (Tokyo). 2000;40(11):589–93.
104. Mandigo CE, Ogden AT, Angevine PD, McCormick PC. Operative management of spinal hemangioblastoma. Neurosurgery. 2009;65(6):1166–77. https://doi.org/10.1227/01.NEU.0000359306.74674.C4.
105. Lonser RR, Weil RJ, Wanebo JE, DeVroom HL, Oldfield EH. Surgical management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. J Neurosurg. 2003;98(1):106–16. https://doi.org/10.3171/jns.2003.98.1.0106.

106. Selch MT, Tenn S, Agazaryan N, Lee SP, Gorgulho A, De Salles AA. Image-guided linear accelerator-based spinal radiosurgery for hemangioblastoma. Surg Neurol Int. 2012;3:73. https://doi.org/10.4103/2152-7806.98386.
107. Sardi I, Sanzo M, Giordano F, Buccoliero AM, Mussa F, Arico M, Genitori L. Monotherapy with thalidomide for treatment of spinal cord hemangioblastomas in a patient with von Hippel-Lindau disease. Pediatr Blood Cancer. 2009;53(3):464–7. https://doi.org/10.1002/pbc.22065.
108. Madhusudan S, Deplanque G, Braybrooke JP, Cattell E, Taylor M, Price P, Tsaloumas MD, Moore N, Huson SM, Adams C, Frith P, Scigalla P, Harris AL. Antiangiogenic therapy for von Hippel-Lindau disease. JAMA. 2004;291(8):943–4. https://doi.org/10.1001/jama.291.8.943.
109. Hrisomalos FN, Maturi RK, Pata V. Long-term use of intravitreal bevacizumab (avastin) for the treatment of von hippel-lindau associated retinal hemangioblastomas. Open Ophthalmol J. 2010;4:66–9. https://doi.org/10.2174/1874364101004010066.