Von Hippel-Lindau Disease

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C. Di Rocco et al. (eds.), *Textbook of Pediatric Neurosurgery*,
https://doi.org/10.1007/978-3-319-72168-2_46

Introduction

Von Hippel-Lindau disease is a dominantly inherited familiar cancer disease characterized by the development of a variety of neoplasms, either benign or malignant, as well as cysts in different organs of the body. The disease depends on the inactivation of the VHL gene in the short arm of chromosome 3 (3p25–26.6) with high penetrance and variable expression (Maddock et al. 1996; Neumann et al. 1992; Seizinger et al. 1991). The protein encoded by this gene is unique and inhibits transcription elongation resulting in unregulated growth of vascular tumors in multiple tissues. The cardinal tumors of the disease for the neurosurgeon – *hemangioblastomas* (HBs) and *retinoblastomas* – are due to the abnormal focal proliferation of newly formed vessels which may cause life-threatening complications in spite of their benign nature because of their common location in the brain and spinal cord. When involving the retina, these tumors may impair the visual function leading to visual loss when poorly managed. The *cysts*, typical of the disease, commonly involve the kidneys, pancreas, and genital tracts. Often these lesions are detected in asymptomatic subjects and require the differential diagnosis with other benign lesions that do not bear a similar increased risk to develop clear cell renal carcinomas or pancreatic neuroendocrine tumors.

Pheochromocytoma of the adrenal glands is a further usually benign tumor associated to the disease. This tumor also can be diagnosed in asymptomatic subjects but more often is associated to specific signs and symptoms, especially high blood pressure unresponsive to medical treatment.

Finally, *endolymphatic sac benign tumors* may occur in about 10% of the affected subjects. Impaired body balance, tinnitus, and progressive hearing loss, until deafness in untreated subjects, are the typical clinical manifestations.

There are only a few studies to evaluate the relative incidence of the various lesions. In a report based on a genetic registry in England, Maddock and coworkers analyzed 83 affected subjects: the cumulative occurrence of cerebellar hemangioblastoma was 60.2%, retinal hemangioblastoma 41%, RCC 25.3%, spinal hemangioblastoma 14.5%, and pheochromocytoma 14.5% (Maddock et al. 1996).

Historical Background

The first description of retinal hemangioblastomas (HBs) in two siblings is due to Collins, an English ophthalmologist, in 1884. Twenty years later, the German ophthalmologist von Hippel recognized a familiar relation transmission in retinal HBs. The association of retinal and cerebellar lesions was then described by the ophthalmologist Scandinavian Lindau in 1926. However, only in 1964, Melmon and Rosen introduced the eponym of "von Hippel-Lindau disease." Finally, the VHL suppressor gene was localized in the short arm of the chromosome 3 (3p.25.6) in 1993 (Shanbhogue et al. 2016; Kaelin 2002).

Generalities

The prevalence is estimated at 1/53,000 and annual birth incidence at 1/36,000 (Maddock et al. 1996; Lonser et al. 2003a). Men and women are equally affected. Mean age at diagnosis is 26 years. It has greater than 90% penetrance by 65 years of age (Maher et al. 1990). The natural

history of the disease varies both within and between families (Shanbhogue et al. 2016). In most cases, the onset of symptoms occurs at 24–26 years, and the diagnosis is obtained around 30 years (Maddock et al. 1996; Shanbhogue et al. 2016; Maher et al. 1990). In more than a third of the affected subjects, cerebellar hemangioblastomas are responsible for the initial clinical manifestations which lead to diagnosis (Maddock et al. 1996). They include headache, nausea, vertigo, nystagmus, hypertension, wide-based gait, and dysmetria (Friedrich 2001). Erythrocytosis has been reported in patients with VHL disease in about 5–20% (Choyke et al. 1995). Complications related to hemangioblastomas account for the primary cause of death in about half of the cases followed by those of renal cell carcinomas (32%) (Maddock et al. 1996; Neumann et al. 1992; Maher et al. 1990; Friedrich 2001). Survival before the implementation of modern treatment protocols was about 50 years. Earlier diagnosis and surveillance protocols have significantly improved the prognosis (Lonser et al. 2003a; Friedrich 1999).

Different lesions can involve the central nervous system (CNS), such as hemangioblastomas developing in the brain, in the retina, and in the spinal cord, as well as in the endolymphatic sac (ELS) tumors. Out of the CNS, lesions develop in the pancreas, in the kidneys, in the adrenal gland, and in reproductive organs (Shanbhogue et al. 2016).

Clinical Diagnosis

The diagnosis of VHL disease is based on clinical criteria. In those patients with a family history of VHL, the presence of a CNS hemangioblastoma (including retinal HBs) or a single visceral tumor is sufficient for the diagnosis. In those patients without a family history, the presence of two or more CNS HBs or one CNS HB and a visceral tumor (with the exception of epididymal and renal cysts, which are frequent in the general population) is required for the diagnosis (Shanbhogue et al. 2016; Lonser et al. 2003a; Winn 2011). Also the relevance of the presence of multiple pancreatic cysts is a matter of debate (Seizinger et al. 1991), due to their high frequency in the normal population. Unlike the other neurocutaneous diseases, VHL disease is not typically associated with skin findings; it has nonetheless been traditionally classified within the phakomatoses (Winn 2011).

Screening Recommended for Patients at Risk of Harboring VHL

Test	Age for starting the screening and frequency
Ophthalmoscopy	Infancy (yearly)
Plasma or 24 h urinary catecholamines and metanephrines	2 years of age (yearly)
MRI of cranioaxis (with and without contrast)	11 years (yearly)
CT and MRI of internal auditory canals	At the onset of symptoms
Abdomen ultrasound	8 years (yearly)
Abdomen CT (with and without contrast)	18 years (yearly)

Reference: Lonser et al. (2003a)

Genetic Diagnosis

A great variety of mutations can be found scattered throughout most of the VHL gene, and, although some recurrent mutations have been reported, most families have their own unique germline mutation (Hes et al. 2000). Molecular testing is the standard for evaluation of patients and families when VHL is suspected (Friedrich 2001). This genetic testing not only allows the identification of family members carrying the VHL mutation that may not yet present any clinical manifestations but also in those individuals that do not meet all the clinical criteria. In patients with unclear clinical diagnostic criteria, the young age, the presence of multicentric or bilateral tumors, the involvement of multiple organs, and a family history of VHL-associated tumors represent, according to Hes and coworkers, are the

main risk factors for finding a VHL mutation (Hes et al. 2001).

The genetic diagnosis is based on qualitative and quantitative Southern blotting test with a detection rate in peripheral blood leukocytes of nearly 100% (Lonser et al. 2003a; Stolle et al. 1998). However, the genetic testing can be a real challenge in the cases harboring genetic mosaicism as the mutation might not be carried in all peripheral leukocytes. Consequently, it is possible that a subject with the clinical signs of the disease could occasionally not have confirmed the diagnosis genetically (Lonser et al. 2003a; Sgambati et al. 2000). In an analysis of the VHL mutation in peripheral blood, actually, sporadic cerebellar hemangioblastomas were found associated to VHL in about 30% of the cases (Maher et al. 1990; Friedrich 2001; Winn 2011). Nevertheless, even those patients with sporadic cerebellar hemangioblastoma resulting negative at the standard genetic test should be evaluated with repeated CNS and abdominal exams to exclude false-negative results (about 5%) depending on genetic mosaicism. This is particularly true for the younger patients with negative mutation and screening which should undergo a long controlling period due to the higher risk of developing lesions as compared to older patients (Winn 2011).

Pathogenesis: Molecular Genetics

In the 1990s, several studies of the VHL disease demonstrated that the condition was due to a rearrangement, deletion, and mutation of the VHL gene, located at the 3p25–p26. The two most frequent mutations were arg238-to gln (608537.0005) and arg238-to typ (608537.0003). Subsequent studies identified an extensive variety of genetic mutations in the attempt to correlate the various phenotypes of the disease with specific genetic abnormalities (Latif et al. 1993; Crossey et al. 1994).

Most patients with the disorder inherit a germline mutation of the VHL gene from the affected parent and a normal (wild type) gene from the unaffected parent (Lonser et al. 2003a). According to the two-hit hypothesis model, the individual inherits a defective VHL allele from one of the parents. When a somatic inactivation or loss of the remaining wild-type VHL allele occurs, both VHL alleles are inactivated, and the formation of the tumor is started, due to a lack of suppression (Kaelin 2002). Mutations are present in all the cells of the affected patients. However, a tumor will be developed only when a mutation of the wild type (normal gene) occur in the cell of one of the susceptible organs (either CNS, kidneys, pancreas, adrenal glands, or reproductive adnexal organs) (Lonser et al. 2003a; Latif et al. 1993; Knudson 1986).

The VHL protein can be found in the nucleus or the cytoplasm of the cell where it will form a complex together with two transcription factors: elongins B and C (Lonser et al. 2003a; Friedrich 1999). The normal function of this protein involves an inhibition of hypoxia-inducible factor 1 α (HIF-1α) by ubiquitin-mediated proteasomal degradation (Shanbhogue et al. 2016; Friedrich 1999). Many of the suppressive effects of the protein result from the degradation of HIF (Lonser et al. 2003a). HIF increases glucose uptake and the expression of angiogenic growth and mitogenic factors including vascular endothelial growth factor (VEGF), platelet-derived growth factor β (PDGFβ), erythropoietin (causing the polycythemia occasionally seen in von Hippel-Lindau), transforming growth factor α (TGFα), and glucose transporter-1 genes (Shanbhogue et al. 2016; Kaelin 2002; Lonser et al. 2003a). Therefore the VHL mutations lead to an accumulation of HIF-1α that causes the production of VEGF, PDGFβ erythropoietin, and TGF-α stimulating proliferation of the cells within the tumor (Maxwell et al. 1999; Duan et al. 1995; Kibel et al. 1995; Pause et al. 1997).

Classification

VHL disease has been classified into distinct clinical subtypes (type 1 and types 2A/2B/2C) based on the presence of different tumors (Shanbhogue et al. 2016; Lonser et al. 2003a). Those families with a low risk of developing pheochromocytomas are grouped in type 1, and although the risk

for these tumors is low, they can suffer any of the other tumors that are generally associated to VHL. On the other hand, type 2 families will develop pheochromocytomas but will have different risks for the growth of renal cell carcinomas: type 2A families will have a low risk and families type 2B a high one, and those with no development of other tumors will be defined as type 2C (Lonser et al. 2003a). Several genotype and phenotype correlations have been described in the families affected by VHL. In a study performed by Chen and coworkers, it was observed that while in the type 1 families, 56% of the responsible mutations were microdeletions/insertions, nonsense mutations, or deletions in VHL, and in the type 2 families, the mutations were missense mutations in 96% of the cases. Moreover mutations in the codon 238 conformed 43% of the mutations responsible for VHL type 2 (Chen et al. 1995). Therefore, currently, the identification of mutations associated with different phenotypes can be useful for presymptomatic diagnosis and prognostic counseling (Friedrich 1999, 2001; Chen et al. 1995).

Genotype-Phenotype Correlation (Lonser et al. 2003a)

Type	Characteristics	
Type 1	Retinal hemangioblastomas	
No pheochromocytoma	CNS hemangioblastomas	
	Renal cell carcinoma	
	Pancreatic tumors/cysts	
Type 2 Pheochromocytoma	Type 2A	Pheochromocytomas
		Retinal hemangioblastomas
		CNS hemangioblastomas
	Type 2B	Pheochromocytomas
		Retinal hemangioblastomas
		CNS hemangioblastomas
		Pancreatic tumors/cysts
		Renal cell carcinoma
	Type 2C	Only presence of pheochromocytomas

Reference: Lonser et al. (2003a)

CNS Lesions

CNS Hemangioblastomas

Hemangioblastomas is defined in the WHO classification 2016 as a tumor histologically characterized by neoplastic stromal cells and abundant small vessels.

Hemangioblastoma is a benign slow-growing tumor of adults, typically occurring in the brain stem, cerebellum, and spinal cord. In VHL disease, central nervous system hemangioblastomas are the most common tumors affecting 60–80% of patients (Shanbhogue et al. 2016; Jagannathan 2008). The presenting symptoms vary, and the usual age at diagnosis is between 30 and 50 (Jagannathan 2008). The most frequent site is the cerebellum (44–72% of the patients), followed by the retina (25–60%), spinal cord (40–50%), and brain stem (10–25%) (Lonser et al. 2003a) and rarely in supratentorial structures such as the optic pathways, choroid plexus, anterior pituitary, and infundibulum (1%), but they can appear anywhere along the neuroaxis (Shanbhogue et al. 2016). Between 5% and 30% of the patients in the normal population that develop a cerebellar hemangioblastoma will be diagnosed with VHL (Shanbhogue et al. 2016; Richard et al. 1998). It has been found that these hemangioblastomas in the VHL disease context are frequently associated with peritumoral edema and/or cysts (Wanebo et al. 2003). Histologically, they consist of a rich vascular plexus that is surrounded by polygonal stromal cells that have a neoplastic origin (Lonser et al. 2003a).

The decision for surgical removal of CNS hemangioblastomas can be influenced by certain factors like the presence of neurological symptoms or signs, an increasing extent of the lesion, or the presence of an enlarging cyst or an enlarging syrinx (with spinal lesions). The goal is to avoid progressive neurological disability from these lesions (Lonser et al. 2003a).

Cerebellar Hemangioblastomas

The cerebellum is the most frequent location of CNS hemangioblastoma, and it develops in 84%

of patients with VHL disease by the age of 60 (Winn 2011).

Clinical and Imaging Features

Cerebellar hemangioblastomas are red, well-defined mass lesions intensively vascularized. In most cases, on computed tomography (CT), they present as a well-defined cystic mass with a contrast-enhancing nodule that can sometimes be in contact with the pial surface (Shanbhogue et al. 2016; Choyke et al. 1995; Leung et al. 2008). However, in about a third of the patients with cerebellar hemangioblastomas, a single lesion without any cystic component can be detected (Osborn et al. 2004). On T1-weighted sequences of MRI study, the nodule will appear as an iso-hypointense lesion with cystic portion that may sometimes be slightly hyperintense due to blood and protein product content (Fig. 1a). While the nodule will enhance significantly with gadolinium contrast, the cystic wall does not typically enhance (Fig. 1b). On T2-weighted

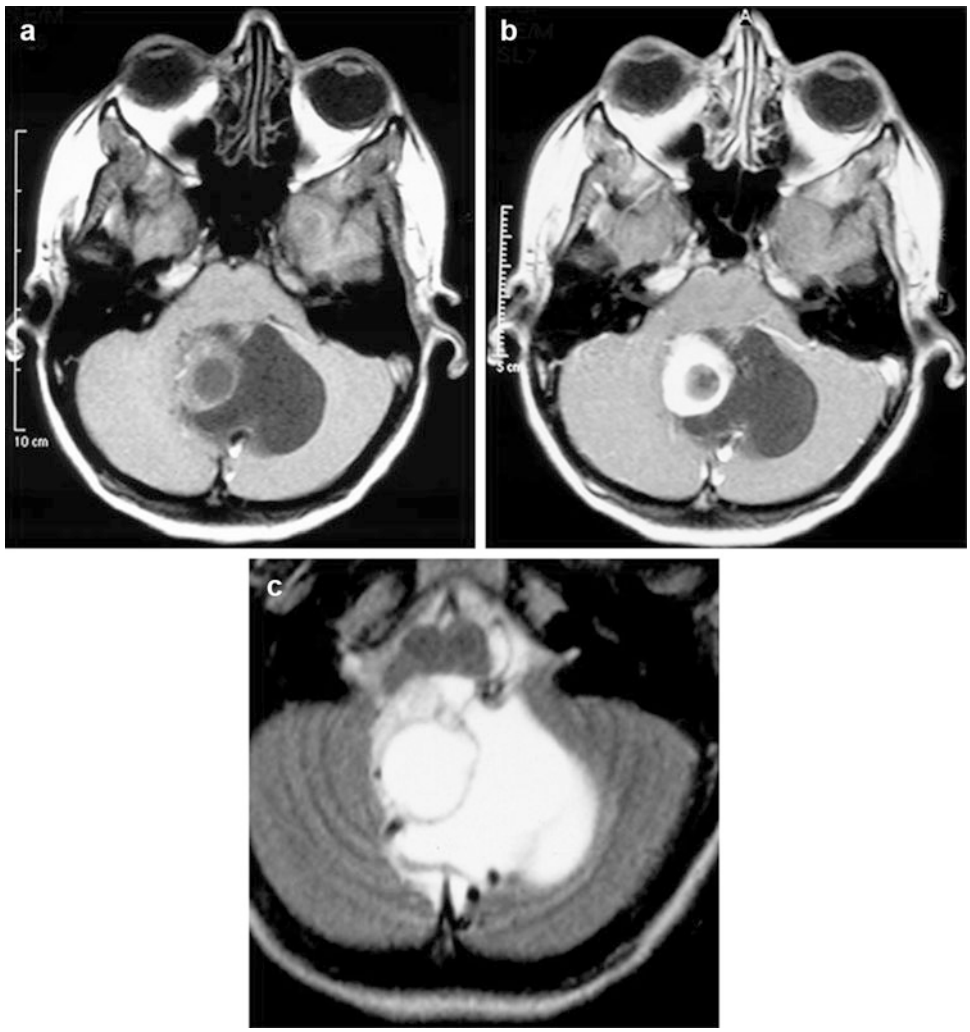

Fig. 1 Magnetic resonance imaging (*MRI*) of a cerebellar hemangioblastoma. (**a**) T1-weighted sequences, the nodule appears as an iso-hypointense lesion with cystic portion slightly hyperintense than the cerebrospinal fluid. (**b**) Contrast-enhanced images showing the enhancing of the solid part of the lesion. (**c**) T2-weighted sequences showing both the nodule and the cyst as hyperintense

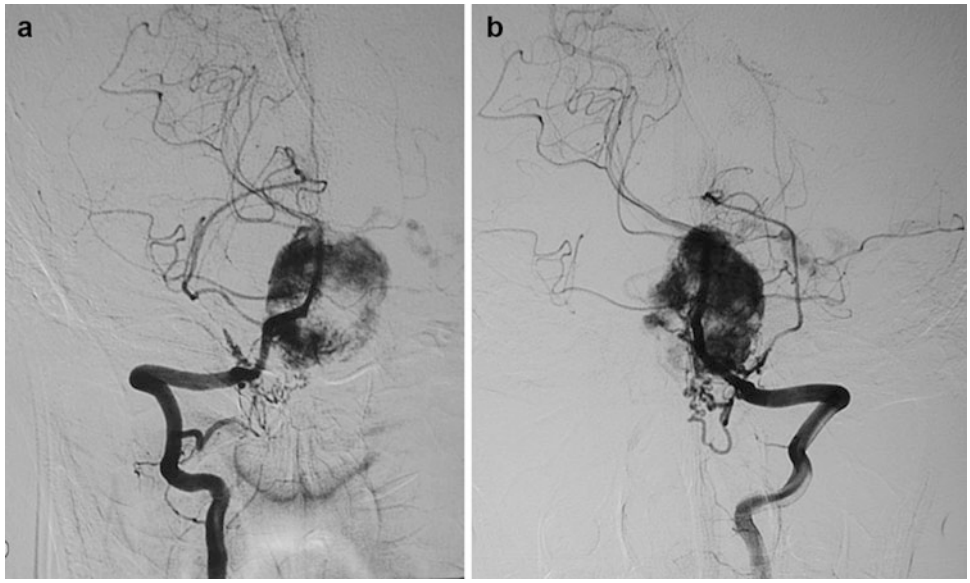

Fig. 2 Digital subtraction angiography of the case in Fig. 1 in anteroposterior (**a**) and lateral (**b**) view showing a very vascularized mass, with prolonged stain

sequences, both the nodule and the cyst and the lesion are normally hyperintense (Fig. 1c). Vessels within the cyst will appear as flow voids (normal flow-related signal loss in vessels that contain vigorously flowing blood) (Shanbhogue et al. 2016; Choyke et al. 1995; Leung et al. 2008; Osborn et al. 2004). The digital subtraction angiography shows a very vascularized mass, with prolonged stain and with possible A–V shunting (Fig. 2a, b).

The differential diagnosis includes solitary hemangioblastoma; pilocytic astrocytoma (usually in younger patients, lacking large flow voids and with the nodule often not abutting pial or ependymal surface); vascular metastasis of other tumors, like renal clear cell carcinoma (usually it will be a solid, not cystic lesion); and multiple AVMs in vascular neurocutaneous disease (small AVMs can angiographically mimic hemangioblastomas) (Osborn et al. 2004).

Most of the studies in the literature refer to sporadic cerebellar hemangioblastomas, while only few series of cerebellar hemangioblastomas and VHL disease have been described (Jagannathan 2008). However, it is important to make a differentiation between these two varieties of patients as they imply different management strategies. In the first group, the sporadic cerebellar hemangioblastomas constitutes the only lesion to be dealt with, whereas in the VHL group, the surgeon has to face frequently multiple lesions in other CNS locations such as the spinal cord and brain stem or other visceral tumors (Winn 2011; Jagannathan 2008).

Treatment

Although the gold standard of therapy for symptomatic sporadic and VHL-associated CNS hemangioblastomas is the surgical resection which can be safely performed in most patients (Lonser 2014), in many cases untreated tumors can remain stable without growth (Fig. 3a, b). Often, these tumors may alternate phases of growth to phases of arrest (Lonser et al. 2003a). Consequently, the surgical indication can be difficult in some circumstances.

Generally, the surgical resection of hemangioblastomas in patients with VHL disease is indicated only when the lesions produce symptoms. Nearly 75% of symptom-producing tumors have a cystic component, so the presence of cysts should be taken into account in the decision-making

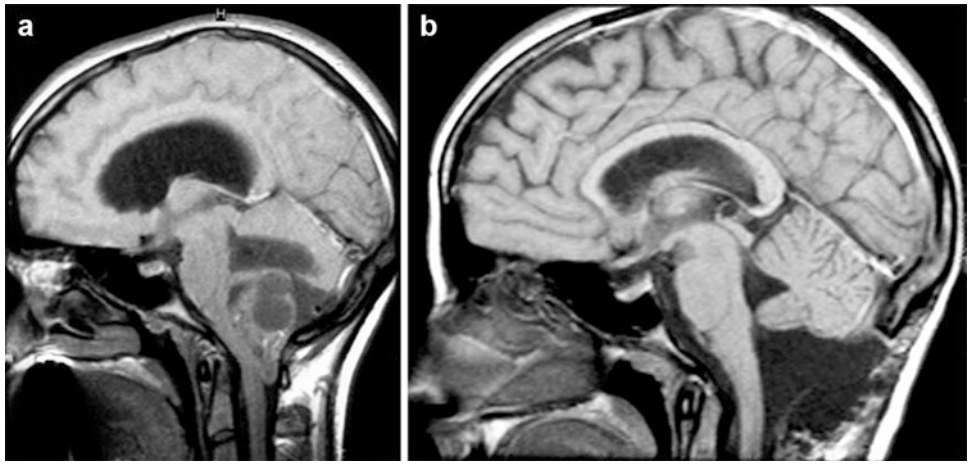

Fig. 3 Preoperative (**a**) MRI T1-weighted sequences in sagittal plane of a hemangioblastoma case. In the postoperative (**b**) images, a total removal of the lesion can been appreciated

process. Multiple or progressive tumoral cysts may also limit the application of alternative treatment, namely, stereotactic radiosurgery on the nodular component. On the other hand, such a treatment may represent a good therapeutic option in solid, small-sized (<3 cm in diameter), and deeply located hemangioblastomas in order to reduce the risk associated to the microsurgical resection. However, recurrence is frequent because of possible further growth of the residual tumor (Shanbhogue et al. 2016; Lonser et al. 2003a; Jagannathan 2008; Page et al. 1993).

Spinal Cord Hemangioblastomas

Unlike cerebellar hemangioblastomas, spinal hemangioblastomas are more specific to VHL (Lonser et al. 2003a; Choyke et al. 1995; Takai et al. 2010). They account for 2–6% of all spinal cord tumors and are the third most common intramedullary tumor (Mehta 2010).

Clinical and Imaging Features

Spinal cord HBs commonly appear on neuroimaging studies as lesions with a cystic component and enhancing nodule or small multiple enhancing nodules along the posterior pial surface of the cord (more rarely the anterior) (Shanbhogue et al. 2016). The administration of gadolinium avoids possible misdiagnoses with other tumors. The presence of a prominent draining vein may occasionally make difficult the differential diagnosis with a dural fistula, therefore requiring a careful radiological workup in addition to angiography. Embolization can be a feasible preoperative treatment for extensive spinal cord HBs (Shanbhogue et al. 2016).

The symptoms will vary from localizing pain to progressive myelopathy and/or tetraparaparesis (Shanbhogue et al. 2016). The lesions can occur anywhere along the spinal cord (including the cauda equina). Nevertheless the most frequent location will be the craniocervical junction and the conus medullaris (Shanbhogue et al. 2016; Mehta 2010).

Some clinical differences have been described between those sporadic cases and those lesions associated with VHL disease. Takai and coworkers (2010) compared two groups of patients: with sporadic HBs and VHL-related lesions. Spinal HBs associated with VHL disease were diagnosed a decade earlier ($p = 0.007$) and were more often associated with fewer and severe neurological symptoms and signs than sporadic tumors ($p = 0.004$). The majority of individuals with sporadic lesions had a single lesion at the cervical or thoracic spine, while patients with VHL HBs had multiple lesions as well as a broad distribution (at all spinal levels) ($p =$

0.04). Furthermore, while patients with sporadic disease improved significantly their neurological situation postoperatively ($p = 0.02$), the surgical outcomes were consistently less rewarding in the group of VHL patients ($p = 1.00$). Factors related with poor postoperative outcome were the number of removed lesions ($p = 0.03$) and the location in the lower spinal cord ($p = 0.05$). Interestingly, the same authors reported the occurrence of new lesions every 2 years in one third of the VHL patients.

Spinal cord hemangioblastomas can be localized along the entire spinal cord. However some frequently involved sites have been identified. Mehta and coworkers (Mehta 2010) analyzed 218 surgically removed spinal hemangioblastomas in patients with VHL disease and found that the great majority of them had developed dorsal to the dentate ligament (94%) and were primarily located either at the dorsal nerve root entry zone (51%) or on the posterior columns (44%). A location anterior to the dentate ligament was extremely rare (around 5% of the cases). These findings are confirmed by other publications (Wanebo et al. 2003; Mehta 2010; Lonser et al. 2003b). Only about one fifth of the spinal HBs develop completely within the spinal cord, the majority of them (two fifths of the cases) having both an intramedullary and extramedullary locations. Purely extramedullary HBs account for about a third of the cases. Because of the preferential posterior location of the tumor, the dorsal spinal roots are frequently involved. Consequently, the interruption of sensory nerve rootlets can be necessary in some cases to obtain the complete tumor excision. The presence of a syrinx cavity is also frequent in this kind of lesions. However, Mehta and coworkers (Mehta 2010) found that 127 (96%) out of the 132 syringes they encountered when dealing with spinal HBs either diminished or collapsed following the removal of the tumor. Such a result appeared to be not related to the direct opening of the syrinx cavity (favorable response in 51 out 52 cases (98%)) as it was obtained with a comparable frequency also in subjects whose syrinx had left intact during the operation (favorable response in 76 out 80 cases (95%)). Therefore, the authors highlighted that intentional syrinx drainage is unnecessary during hemangioblastoma resection (Mehta 2010; Lonser et al. 2003b).

Treatment

The surgical removal of spinal cord hemangioblastomas is considered the standard procedure in the management of these tumors (Mehta 2010). However, the treatment strategy may be complex due to the somewhat unpredictable progression pattern of the lesion and the high risk of the operation to worsen already existing symptoms (Vougioukas et al. 2006). Therefore, it is not surprising that the timing of surgery for patients with von Hippel-Lindau disease and spinal hemangioblastomas still remains a matter of debate, especially in subjects with multiple lesions (Van Velthoven et al. 2003). In general, in most instances, the indication for spinal cord HB removal in VHL requires the presence of symptoms (Mehta 2010; Lonser et al. 2003b). Actually, multiple operations in the course of time (four additional surgeries over a 10-year period) were necessary in patients undergoing surgical treatment based on the mere radiological progression of the lesion in patients asymptomatic at the first operation (Ammerman et al. 2006). Furthermore, it has been reported that only a little more than the half of subjects although there was some kind of measurable growth in 97% of the lesions followed, only 58 (41% of the patients) became symptomatic demonstrating how important the presence of symptoms is to indicate surgery in this group of patients. The surgical removal of spinal cord HBs in VHL disease should depend on the presence of symptomatic lesions (Mehta 2010; Lonser et al. 2003b; Ammerman et al. 2006).

Tumor volume, anterior location, and the presence of peritumoral edema have been previously considered as predictors of poor surgical outcome (Mehta 2010; Lonser et al. 2003b; Van Velthoven et al. 2003; Kanno et al. 2009). In terms of surgical outcome, up to 71% of the patients will improve immediately after the resection, and most patients (up to 96%) will have either stable or improved postoperative situation 6 months after surgery (Mehta 2010). Even in purely intramedullary

HBs, excellent long-term prognoses have been reported (Van Velthoven et al. 2003).

Retinal Hemangioblastomas

The retinal hemangioblastomas or retinal angiomas are seen in as many as 60% of the patients with VHL being one of the most common tumors in VHL disease. They have historically been called retinal angiomas or hemangiomas, but pathologically they are identical to any CNS hemangioblastomas (Shanbhogue et al. 2016). The mean age of presentation is 25 years but can present in younger ages. They can be found in or around the optic nerve and on the periphery, as well as bilateral and multifocal (Lonser et al. 2003a). About 85% will be located in the peripheral retina, causing no symptoms.

Clinical and Imaging Features

Usually they do not produce symptoms in the early stages; however, they can still cause partial or total loss of vision. While the number of retinal angiomas does not appear to increase with age, the probability of visual loss increases with age (Kreusel et al. 2006). To prevent this complication, an early diagnosis and treatment are mandatory. Ophthalmoscopy should be performed once a year starting at 1 year of age (Lonser et al. 2003a).

Treatment

Treatment of small lesions usually consists of laser photocoagulation, while larger lesions should be treated by cryotherapy, radiotherapy, or vitreoretinal surgery (Shanbhogue et al. 2016). Most peripheral retinal tumors will respond to laser photocoagulation or cryotherapy. Very high rates of regression have been reported in small retinoblastomas (90%), compared with 67% in larger lesions (Kim et al. 2014). Kim et al. describe better outcomes in peripheral retinoblastomas compared to those juxtapapillary lesions ($p = 0.01$) (Kim et al. 2014). Those tumors involving the optic disk should be managed conservatively under a wait-and-see policy due to the potential damage that laser photocoagulation and similar treatments can cause (Frantzen et al. 1993). In some cases with irreversible glaucoma and severe untreatable pain, enucleation might be necessary (Lonser et al. 2003a).

Endolymphatic Sac Tumors

The endolymphatic sac (ELS) is located at the end of the endolymphatic duct, where the vestibular aqueduct has its opening. It plays a major role in the production and resorption of endolymph that will be found inside that cochlea and semicircular canals.

Clinical and Imaging Features

Endolymphatic sac tumors (ELSTs) are benign tumors. Although they do not metastasize, they can be locally aggressive. When they grow, they can provoke a variety of symptoms like imbalance, tinnitus, aural fullness, or hearing loss (that can present in a sudden manner). Even in some cases, a facial nerve paresis can be present. Most of the patients will already have some degree of hearing loss when imaging is performed: partial or complete hearing loss (100%), tinnitus (77%), a sense of disequilibrium (62%), and facial paresis (8%). The presence of microscopic tumors can be higher than what is estimated by imaging, as patients often have vestibulocochlear symptoms with no evidence of tumor in the CT or MRI (Lonser et al. 2003a; Manski et al. 1997). ELSTs when they grow can invade the cerebellopontine angle and simulate other tumors. When they are greater in size, they can also erode into the facial nerve canal causing facial nerve paralysis (Shanbhogue et al. 2016; Choo et al. 2004).

To make a radiological examination and diagnosis, pre- and postcontrast CT and MRI of internal auditory canals should be performed (Lonser et al. 2003a). On the CT, the ELSTs are isodense with brain parenchyma and will provoke destructive changes in the petrous bone, eroding the bone with a "moth-eaten" appearance on the CT. MRI T1WI sequences can show a homogeneous and heterogeneous hyperintense (due to protein and hemorrhage) appearance with variable contrast-enhancing patchy patterns, and

T2WI and FLAIR will show a hyperintense mass (Shanbhogue et al. 2016; Lonser et al. 2003a).

Treatment

Gross total resection is the treatment of choice for primary and recurrent ELSTs. Those patients with small and less extensive lesions will have better outcomes in comparison with extended primary tumors or recurrent disease (Carlson et al. 2013). Usually the preoperative level of hearing will be preserved (Lonser et al. 2003a). On the other hand, those patients that undergo a subtotal resection will have a greater risk of multifocal recurrence. Stereotactic radiosurgery will be a feasible option in poor surgical candidates or in those cases of focal recurrence but when the surgical morbidity risk is elevated (Carlson et al. 2013).

In conclusion, surgery will be a curative treatment for those complete resections, and the preoperative level of hearing is usually preserved, being the role of radiation therapy still unclear (Lonser et al. 2003a).

Visceral Lesions

Pheochromocytomas

In the VHL disease, pheochromocytomas tend to develop in the adrenal gland or paraganglia in 10–20% of the patients (Lonser et al. 2003a). They can be bilateral in adrenal gland and may develop in glomus jugulare and periaortic tissue (Butman et al. 2008). They can be the only manifestation of the disease, and 5% of them are malignant (Walther et al. 1999).

Clinical and Imaging Features

Pheochromocytomas secrete various substances, the most important of which are adrenaline, noradrenaline, and dopamine (Florczak et al. 2013), but one third of the patients are asymptomatic (Walther et al. 1999). The usual beginning of symptoms may be a hypertensive crisis before the age of 10; frequent clinical findings are hypertension, palpitations, tachycardia, headaches, episodic sweating, agitation, and skin pallor or nausea (Butman et al. 2008). Because of the early appearance of these lesions, catecholamine dosage screening should be started in young children with a family history of VHL (Lonser et al. 2003a). The hypertension is usually episodic in adults while in pediatric patients has chronic feature (Bissada et al. 2008); this may led to hypertensive cardiomyopathy or retinopathy and retinal detachment. Other consequences may include myocardial infarction, arrhythmia, stroke, sudden cardiac death, and adrenergic myocarditis (Ben-Skowronek and Kozaczuk 2015). The diagnosis of pheochromocytoma is made by laboratory and imaging studies.

Functional tests are fundamentals to detect alteration even when imaging studies are not depicting any tumor. The determination of catecholamine and methoxycatecholamine levels in a 24-h urine collection is the commonly used method; in fact free metanephrine levels in plasma is very sensitive but still hardly available (Lonser et al. 2003a; Florczak et al. 2013). The tumor produces catecholamines periodically, and elevated levels thus can only be detected during episodes in which large amounts are released leading to the possibility of false negative; on the contrary the level of methoxycatecholamines is permanently elevated (Ben-Skowronek and Kozaczuk 2015).

The imaging techniques to depict pheochromocytomas include CT, MR, and iodine 131 metaiodobenzylguanidine (MIBG) scintigraphy. In CT studies, they appear as solid or complex cystic lesions with possible necrosis, hemorrhage, and calcifications (Taouli et al. 2003). Enhancement after contrast injection is typical, although small areas of the tumor may be hypodense (Choyke et al. 1995). At MRI studies, the tumor show low to intermediate signal intensity on T1-weighted and high signal intensity on T2-weighted images with enhancement after gadolinium (Choyke et al. 1995; Taouli et al. 2003). 131I MIBG is 75–95% sensitive and 98–100% specific for these tumors and is useful in case of clinical diagnosis with negative CT/MRI scans. Moreover it is also useful for the diagnosis of malignant pheochromocytoma metastases (Leung et al. 2008).

Treatment

The recommended treatment is surgical resection performing adrenalectomy. In recent years, there is a tendency to achieve a laparoscopic adrenal-sparing surgery with partial adrenalectomy/enucleation in order to preserve the function of the gland (Ikeda et al. 2001; Pavlovich et al. 2001). This strategy, performed in early phase, has shown good outcome of the patients in terms of recurrence rate and corticosteroid independence (Baghai et al. 2002). It is important to have a complete preoperative evaluation of the patient for detection of hidden pheochromocytomas and prevention of perioperative hypertensive crisis (Lonser et al. 2003a).

Renal Cyst and Renal Cell Carcinoma

Renal cysts are usually asymptomatic and diagnosed incidentally in approximately 15% of patients with VHL disease; they do not require any treatment in the majority of the patients (Ben-Skowronek and Kozaczuk 2015). These lesions, particularly complex cysts, require intensive controls because they may harbor clear cell renal cell carcinoma component (Butman et al. 2008).

Renal cell carcinoma (RCC) is the most common malignant tumor in VHL found in 24–45% of the patients (Lonser et al. 2003a). They appear at a younger age (fourth decade of life) in VHL disease than in the general population (Leung et al. 2008). The lesions are often multiple, and the rate of growth has a wide variability (Walther et al. 1999).

Clinical and Imaging Features

Because RCCs can remain asymptomatic for long periods of time, early diagnosis using planned imaging is important and can potentially positively influence the outcome. Infrequently, in more advanced cases, patients present with hematuria, flank pain, or mass (Lonser et al. 2003a; Butman et al. 2008).

Ultrasonography (US) is useful in determining the solid or cystic component of the lesion. It may be solid hypervascular or complex cystic with mural nodules and thick septa. CT is more sensitive than US for detection of small lesions, but the second method may be preferable for patient's follow-up to reduce the amount of radiation exposure (Leung et al. 2008).

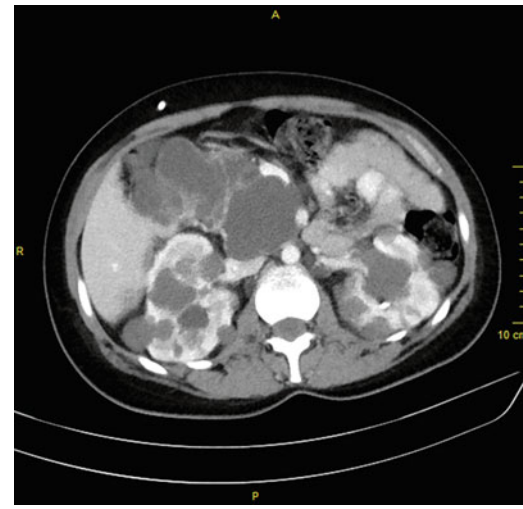

Fig. 4 Computed tomography study of a patient affected by von Hippel-Lindau disease showing multiple renal cysts, with distortion of the organ regular architecture

CT should be used in cases of unclear US findings and in cases of multiple renal cysts, where the organ architecture has been distorted (Fig. 4) (Levine et al. 1979). MR imaging may be used in young patients and those with renal failure. Simple cysts are hypointense on T1-weighted images and hyperintense on T2-weighted images, with no enhancement after administration of gadolinium contrast material. Complex or solid lesions enhance T1-weighted sequences with gadolinium (Leung et al. 2008).

Treatment

The treatment of choice for VHL disease-associated RCC is nephron-sparing surgery considering the high risk of recurrence and risks associated with renal replacement. A study regarding this method has shown no evidence of tumor metastasis and no need for dialysis (Walther et al. 1999). Radiofrequency ablation may be an option in poor surgical candidates, cases of tumor

<3 cm, or between 3 and 5 cm that would be difficult to treat with partial nephrectomy (Leung et al. 2008).

Pancreatic Cysts and Neuroendocrine Tumors

Pancreatic cysts/cystadenomas and neuroendocrine tumors occur, respectively, in 17–56% and 8–17% of patients affected by VHL. The mean age of diagnosis is 35–37 years (Libutti et al. 1998).

Clinical and Imaging Features

Pancreatic cysts in VHL are generally asymptomatic. Pancreatic neuroendocrine tumors are usually nonfunctional and asymptomatic but can have malignant behavior in up to 8% of cases (Butman et al. 2008).

Routine imaging of patients with VHL disease is fundamental for the diagnosis of these lesions.

Cysts are usually detected with US and CT that are similar in terms of sensitivity and specificity (Neumann et al. 1991).

Regarding tumors, US shows benign lesions as well-defined, round or oval masses hypoechoic relative to parenchyma.

Similarly, CT scan features are homogeneous and hypo- or isodense in comparison with pancreas (Fig. 5). Lesions smaller than 2 cm can be clearly depicted by contrast-enhanced CT, where intense enhancement in the arterial phase is demonstrated (Hough et al. 1994).

MRI can be used to confirm the diagnosis: the lesion is hypointense on T1- and hyperintense on T2-weighted images (Leung et al. 2008).

Treatment

Treatment of neuroendocrine tumors is surgical and decided depending on the location of the lesion. It includes pancreas-sparing procedures, such as distal pancreatectomy if the lesion is located in the pancreas tail or enucleation if it is in the head (Leung et al. 2008). Tumors of the pancreas body and tail have been also successfully managed using laparoscopy (Lonser et al. 2003a).

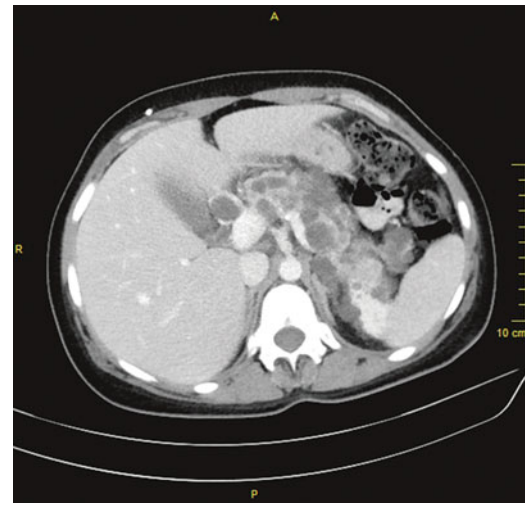

Fig. 5 Computed tomography study of the patient showed in Fig. 4 depicting multiple pancreatic cysts

However, larger masses may require more aggressive surgery. Criteria for resection have been defined by Libutti et al. (1998): no evidence of metastatic tumor >3 cm in the body or tail and >2 cm in the head of the pancreas or patient undergoing laparotomy for other lesions.

Papillary Cystadenomas

Epididymal papillary cystadenomas occur in approximately 20–60% of men with VHL (Leung et al. 2008). They arise from the epididymal duct and, when bilateral, are probably pathognomonic of VHL disease (Lonser et al. 2003a; Leung et al. 2008). These lesions are usually benign and typically appear in young age.

Papillary cystadenoma of the epididymis is frequently located in the head of the epididymis but may involve the spermatic cord. Lesions have usually a diameter of 2–3 cm. Patients are usually asymptomatic and may present with a hard "nugget" in the scrotum; bilateral cystadenoma may lead to infertility due to obstructive azoospermia (Leung et al. 2008). US can be used for monitoring of the lesion, and it shows masses with mixed echogenicity, with both solid and cystic elements. Usually only conservative management is

indicated, and treatment is reserved only in cases with severe local pain (Lonser et al. 2003a).

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