VON HIPPEL-LINDAU DISEASE

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ABSTRACT

Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumor syndrome. The incidence of VHL disease is assessed about one in 36,000 livebirths and the penetrance is higher than 90%. Similar to other tumor suppressor gene disorders, VHL disease is characterized by frequent development of specific types of tumors in selective organs.

The disease is named after the German ophthalmologist Eugen von Hippel, who identified and described characteristic retinal manifestations, and the Swedish Pathologist Arvid Lindau, who discovered the frequent co-occurrence of retinal and cerebellar hemangioblastoma with tumors and cysts in visceral organs. He described the clinical spectrum of VHL disease in detail in a large series of cases from Sweden but also from other European countries.

A clinical classification system divides individuals who are affected by VHL disease into two groups: Those predominantly without pheochromocytoma are classified as VHL type 1, and those predominantly with pheochromocytoma classified as VHL type 2. VHL type 2 is further subdivided into type 2A (with renal cancer) and type 2B (without renal cancer). In type 2C affected patients develop solely pheochromocytomas.

Tumorigenesis in patients with VHL disease shares fundamental principles in the different affected organ systems: germline VHL inactivation leads to persistence of microscopic developmentally arrested structures. These microscopic cell clusters already reveal biallelic VHL inactivation and consequent up-regulation of hypoxia inducible factor and down-stream targets like VEGF, EPO.
Current research for pharmacotherapy of VHL disease targets proteins of the HIF cascade and compounds that lead to upregulation and refunctionalization of mutated VHL protein.

INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumor syndrome. The incidence of VHL disease is assessed about one in 36,000 livebirths [1, 2] and the penetrance is higher than 90 % [3]. Similar to other tumor suppressor gene disorders, VHL disease is characterized by frequent development of specific types of tumors in selective organs.

The disease is named after the German ophthalmologist Eugen von Hippel, who identified and described characteristic retinal manifestations [4], and the Swedish Pathologist Arvid Lindau, who discovered the frequent co-occurrence of retinal and cerebellar hemangioblastoma with tumors and cysts in visceral organs. He described the clinical spectrum of VHL disease in detail in a large series of cases from Sweden but also from other European countries [5, 6].

A clinical classification system divides individuals who are affected by VHL disease into two groups [7]: Those predominantly without pheochromocytoma are classified as VHL type 1, and those predominantly with pheochromocytoma classified as VHL type 2. VHL type 2 is further subdivided into type 2A (with renal cancer) and type 2B (without renal cancer). In type 2C affected patients develop solely pheochromocytomas [8].

VON HIPPEL-LINDAU DISEASE MANIFESTATIONS

VHL disease targets a highly selective subset of organs by the frequent development of specific types of heavily vascularized tumors. Multiple and bilateral tumors occur frequently. Affected organs and tumors are listed in **table 1** [9-12].

Tumor	Frequency	Mean age of onset
Retinal hemangioblastomas	60%	25y
Cerebellar and spinal hemangioblastomas	65%	33y
Endolymphatic sac tumors	10%	22y
Renal clear cell carcinomas and cysts	45%	39y
Pheochromocytomas	20%	30y
Pancreatic cysts, microcystic serous adenomas, neuroendocrine tumors	35-70%	36y
Epididymal and broad ligament cystadenomas	> 50% of male	unknown

Table 1: Manifestations of VHL disease [9-12].

CNS HEMANGIOBLASTOMAS in VHL SYNDROME

Hemangioblastomas are the index tumors of VHL disease and are frequently the earliest manifestation of the disease. Multiple hemangioblastomas occur frequently in patients with VHL disease. In one major study 127 of 160 patients with VHL-associated hemangioblastomas had multiple tumors [13]. The central nervous system hemangioblastoma burden in VHL disease is associated with partial germline deletions and male sex [14]. The benign slow growing highly vascularized tumors cause neurologic symptoms depending on their size and location [13, 14]. A spinal hemangioblastoma may lead to focal neurologic deficits such as weakness and paresthesias. Posterior fossa tumors may present with ataxia, dysmetria, nystagmus, and slurred speech. Symptoms may also evolve due to CSF obstruction causing signs of increased intracranial pressure or brain stem herniation [3, 11, 15]. Symptoms are usually not caused by the tumor itself but rather by an associated pseudocyst or syrinx, which is caused by vascular leakage from the tumor [16] and which is usually larger than the tumor itself [13]. Polyglobulia has been reported in patients with hemangioblastomas [17]. It occurs in 10% of patients [18] and may cause thrombosis. Removal of the largest hemangioblastoma usually resolves polyglobulia [18].

Diagnosis is established by contrast enhanced MRI of the head and spine [19, 20], which typically identifies a solid enhancing nodule associated with a pseudocyst or syrinx (**figure 1**).

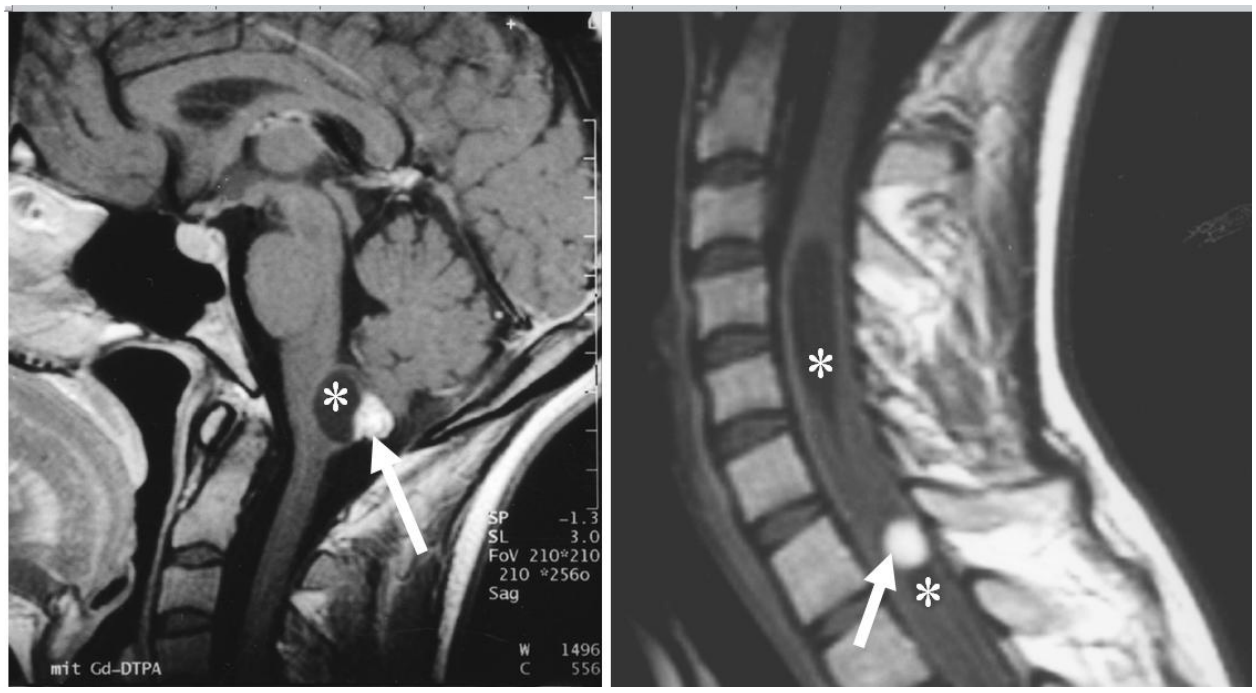

Figure 1: On contrast-enhanced MRI, hemangioblastoma is identified as solid enhancing nodule; the tumor is typically associated with extratumoral cyst (left) or syrinx (right).

Patients with VHL disease frequently develop several CNS hemangioblastomas but not all of the tumors need to be removed. Surgery is needed for all symptomatic tumors and for all tumors causing CSF obstruction [13, 21, 22]. Once symptoms occur, they can usually not be reversed by surgery; therefore, surgery may be recommended in a subset of asymptomatic tumors with radiographic progression [22]. Complete surgical removal of the solid tumor is the treatment of choice. If surgery is not possible, radiation therapy may be considered. However, a long-term control of hemangioblastomas by radiation could not be convincingly demonstrated in large series to date [23-27]. Prophylactic radiation of CNS hemangioblastomas is not recommended [28]. There is currently no established chemotherapy for hemanigoblastomas. Different cases of medical therapies have been published [29-33].

Currently studied substances include:

- PTK787/ZK 222584
- Avastin
- Vorinostat (NIH)
- Dovitinib (MD Anderson Cancer Center)

Surgical resection of hemangioblastomas requires careful dissection in the plane between tumor and CNS tissue. If the tumor is entered, major bleeding will occur. Hemangioblastoma patients harbor a risk for spontaneous or perioperative hemorrhage [34] and preoperative embolization has been recommended for large solid tumors [35, 36]. The tumors can usually be completely removed and permanent new neurologic deficit due to surgery is rare in experienced hands. Intraoperative ultrasound allows for identification of small tumors and control of complete resection of the tumors [37].

Recently intraoperative ICG angiography has been used by different groups. Some of them find it helpful in understanding the vascular anatomy of the lesions, whereas others find it of limited value [38-43]

Hemangioblastomas are composed of a dense capillary network with “stromal” cells in between. Microdissection and genetic deletion analysis revealed the “stromal” cells to represent the neoplastic component of these tumors [44], while the capillary network predominantly represents reactive VEGF-driven angiogenesis. The histogenesis of the neoplastic “stromal” cells has been controversial. Tumor cells stain consistently positive for neuron specific enolase [45-47], neural cell adhesion molecule [48, 49] and vimentin [47-51]. Recent studies suggest the “stromal” cells to represent developmentally arrested VHL-deficient hemangioblast progenitor cells with hematopoietic differentiation potential [52-56], based on the observation of expression of pre-hemangioblastic markers like scl and brachyury [56-59] and the ability of primitive blood island formation and differentiation into early red blood cells [58, 60-62]. Furthermore, anatomic studies on spinal cord and cerebellum of VHL patients revealed numerous developmentally arrested structural elements [63] that serve as potential precursor material for hemangioblastic tumors [64]. In addition to hematopoietic differentiation capacity the tumor cells are also capable of primitive vasculogenesis[65, 66]. It has remained unresolved, however, whether the tumor cells are of mesodermal or neuroectodermal

origin. A subset of patients with CNS hemangioblastomas develop polyglobulia as paraneoplastic effect, which resolves after removal of the tumor [18].

RETINAL HEMANGIOBLASTOMAS in VHL SYNDROME

Retinal hemangioblastomas are benign tumors that can occur as sporadic entity as well as in patients with VHL disease. Tumors frequently occur in multiplicity and bilaterally (in about 50 %). Histologically, retinal hemangioblastomas are identical to CNS hemangioblastomas [67]. High expression of VEGF in these tumors causes vascularization, vascular leakage and exsudation and eventually retinal detachment in the eye.

Annual fundoscopic screening and early treatment of asymptomatic lesions is recommended for VHL patients starting at one year of age. Most peripheral retinal hemangioblastomas are well controlled by laser photocoagulation or cryotherapy [68, 69]. Vitrectomy may be performed in larger tumors [70]. Tumours in the optic disc should be monitored without treatment. Alternative treatments are in experimental stages and include VEGF inhibition [71-73] and radiation therapy [74].

With screening and early treatment of detected lesions, visual prognosis for VHL patients is good: In one major study approximately 8% of the eyes of VHL patients had poor visual acuity of 20/200 or worse with approx. 8% of these eyes requiring enucleation [75].

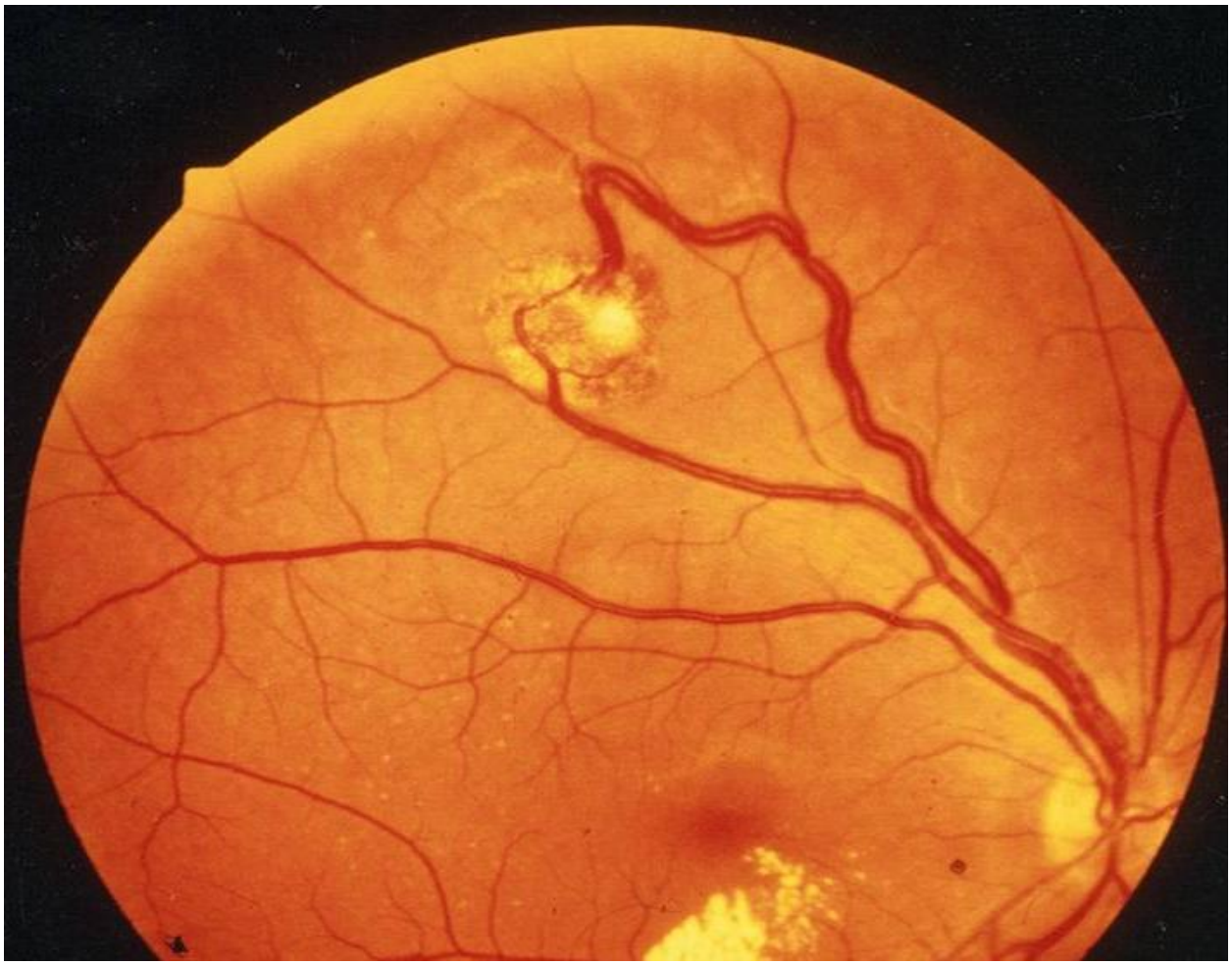

Figure 2: Fundoscopic photograph illustrating a retinal hemangioblastoma (arrows).

RENAL MANIFESTATIONS in VHL SYNDROME

Patients with VHL disease can develop renal cysts and renal cell carcinomas [76-81]. Renal cell carcinomas are malignant tumors. The pathogenetic relationship between renal cysts and renal cell carcinoma has remained unclear. One study suggests rare transition from a cyst to a solid lesion [82]. Histologically, renal cell carcinomas in VHL disease are always of clear-cell type (**figure 3**), and small carcinomas tend to be low grade [83]. While small renal tumours in VHL disease tend to be low grade and minimally invasive [83], their rate of growth varies widely [84, 85].

Renal manifestations are usually multiple and bilateral in patients with VHL disease. They remain asymptomatic for a long time. Advanced cases of renal cell carcinoma may present with hematuria, flank pain, or a flank mass.
Renal cysts in VHL disease usually do not require treatment. Therapy of renal cell carcinoma is targeted towards prevention of metastasis and preservation of kidney function. In contrast to sporadic renal cell carcinoma, nephrectomy is not recommended as primary therapy for VHL-disease-associated renal cell carcinomas. Most specialized centers recommend nephron-sparing surgery for carcinomas that exceed 3 cm in size

[77, 86]. Recent work supports the hypothesis, that a diameter of 4 cm is also acceptable [87]. Although the gold standard for treating renal tumors are open and laparoscopic partial nephrectomy, alternative therapies including cryotherapy and radiofrequency ablation are presently utilized [88]. Possible substances for treatment of metastasized disease include pazopanib [89].

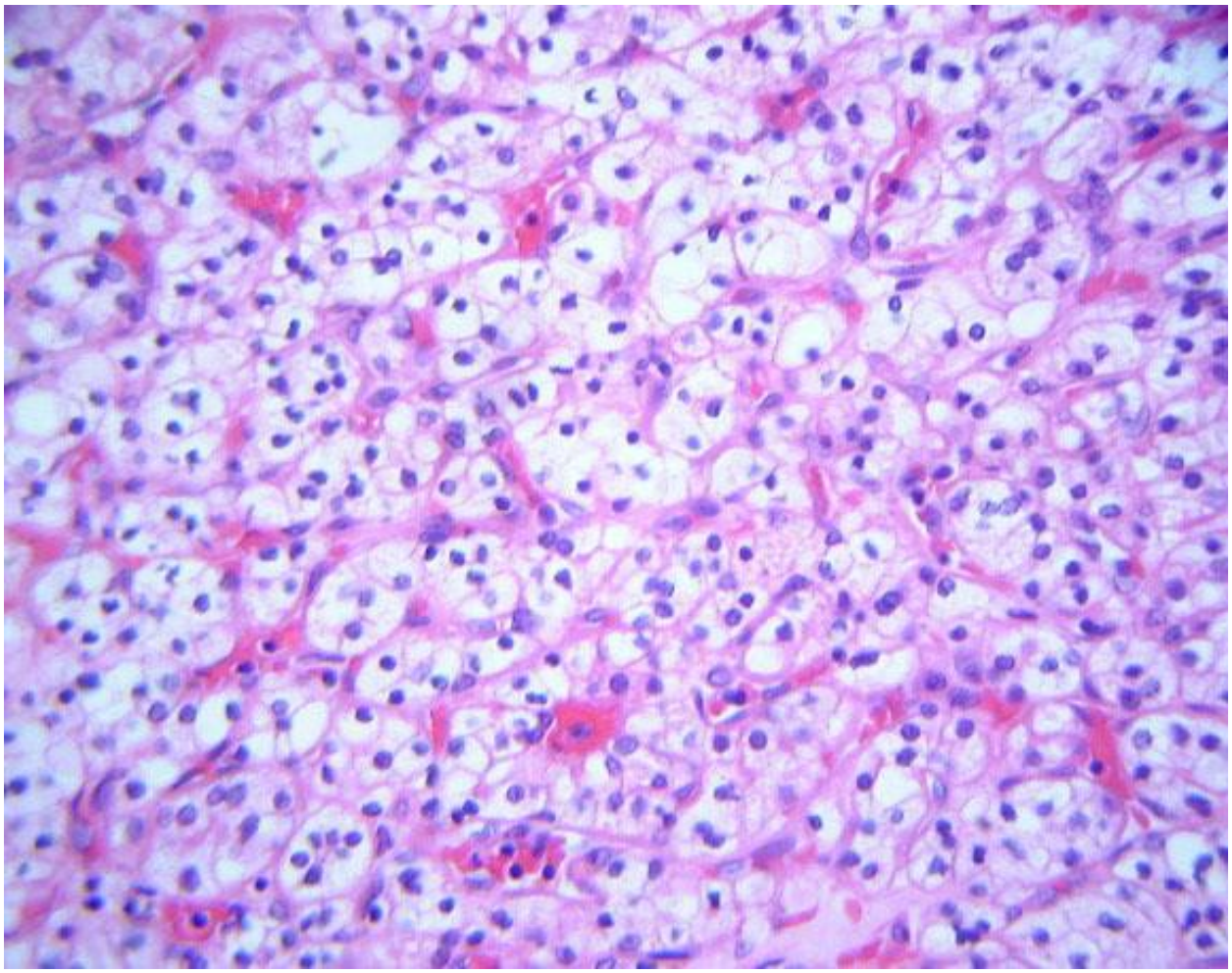

Figure 3. VHL disease associated renal cell carcinomas are of clear cell type (H&E stain).

PHEOCHROMOCYTOMAS in VHL SYNDROME

As mentioned in chapter 34 in this section (Editor: George P. Chrousos) and in chapter 7 in the section "Endocrine Testing Protocols" (Editor: Christian A. Koch), pheochromocytomas usually are sporadic but in more than 33% of patients can occur in a familial syndrome such as the VHL syndrome [90, 91]. Pheochromocytomas predominantly occur in patients with VHL disease type 2 (A,B,C) (**Figure 4**, modified from [92]).

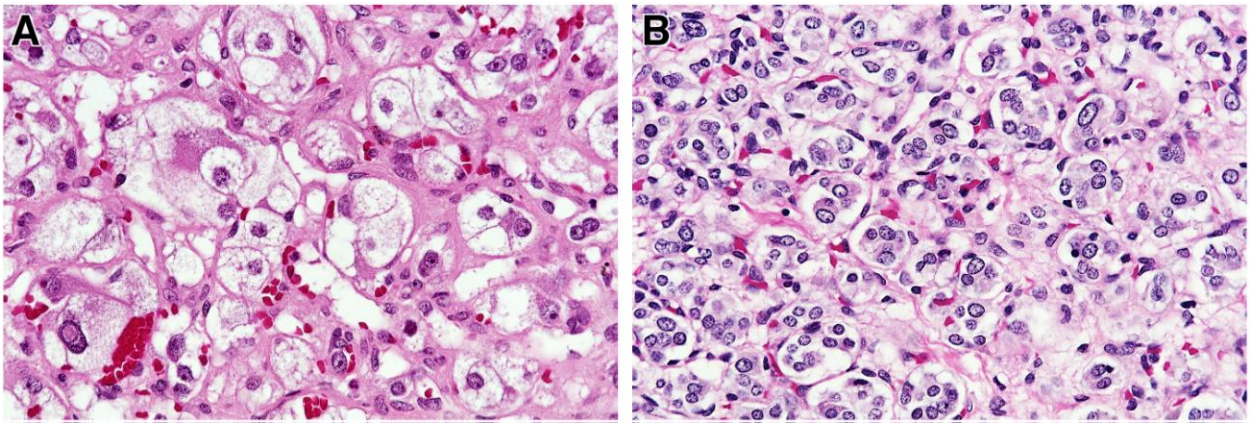

Figure 4. VHL-associated pheochromocytoma

In a series of 246 patients with VHL syndrome, 64 patients (26%) were found to have a pheochromocytoma [93]. In one third, these tumors were “nonfunctional” and did not cause symptoms of catecholamine excess such as hypertension. Utilizing 18F-DOPA functional imaging in 52 patients with von Hippel-Lindau disease, 4 of 10 patients with positive adrenal uptake had elevated catecholamine levels, i.e. 6 of 10 pheochromocytomas were “silent” [94]. Asymptomatic patients with pheochromocytoma have also been reported in 15 of 150 patients seen at the Mayo Clinic [95] and in 19 of 33 patients with adrenal pheochromocytomas that were incidentally discovered [96]. The mean age at diagnosis of VHL patients reported by Walther et al. 1999 [93] was 29 years with a range from age 6 to age 54 years. Bilateral pheochromocytomas in this group were found in 39% of patients. Extraadrenal pheochromocytomas or paragangliomas in patients with VHL disease can be sympathetic or parasympathetic and, if located in the head and neck, are mostly unable to produce and secrete catecholamines [91, 97-100].

In general, extraadrenal pheochromocytomas have a higher frequency and potential of malignancy than pheochromocytomas located in the adrenal gland [101]. Malignant pheochromocytomas (defined as the presence of chromaffin tissue at locations where such tissue should not be present, i.e. lungs, liver, bone, lymph nodes) are uncommon in patients with VHL syndrome [84, 91, 92, 102, 103]. Unfortunately, there are no markers yet that can reliably distinguish a benign from a malignant pheochromocytoma.

The detection of a pheochromocytoma in patients with VHL syndrome is particularly important, given the possible need for surgical interventions for other tumors such as CNS hemangioblastomas. Just like in any patient with an undetected pheochromocytoma, surgery and other factors can lead to life-threatening hypertensive attacks intraoperatively. Screening for pheochromocytoma in at high risk patients (VHL type 2A,B,C) should include measurements of urinary catecholamines and fractionated metanephrines, as well as of plasma free metanephrines, acknowledging that normetanephrine is the predominant biochemical marker for adrenal and extraadrenal VHL-associated pheochromocytomas, and that methoxytyramine a helpful marker for head and neck paragangliomas [104, 105]. Determining the screening age for pheochromocytoma should likely be made dependent on potential beneficial and negative sequelae that could occur if screening were not performed, i.e. malignancy

(lower than 5% in VHL disease!), hypertension, radiation exposure from frequent imaging. There is marked intrafamilial variation, and the penetrance of pheochromocytoma may be as late as age 54 years [93, 106]. At present, experts recommend pheochromocytoma screening be started already in childhood at the age of 8 years [91, 107] [9]. The adrenal glands (suprarenal) can be visualized while undergoing an MRI to look for renal abnormalities in patients with VHL disease. More than 70% of pheochromocytomas presenting in children are due to VHL disease. The diagnosis can further be established by abdominal computed tomography and/or magnetic resonance imaging [9].

Given the low frequency rate of extraadrenal pheochromocytomas (approx. 15%) and malignant pheochromocytomas (< 5%) in patients with VHL disease, only selected patients should undergo 123I-MIBG scanning to search for extraadrenal or metastatic lesions, before operation [101, 108]. Importantly, (isolated) pheochromocytoma can be the presenting manifestation of VHL syndrome [3, 109]. Approximately 50% of patients with apparently isolated familial pheochromocytoma have VHL disease and approx. 10% of patients with apparently sporadic pheochromocytoma [91, 110, 111], acknowledging that a family history is not always present or reliably obtainable [112] and that even if VHL germline mutations were detected by certified laboratory testing in patients with non-syndromic pheochromocytoma (i.e. in 3 of 182 patients, [113], misdiagnoses can occur.

Treatment of nonmetastatic adrenal pheochromocytoma consists of adrenal sparing (partial) tumor removal, either uni- or bilateral, depending on whether one or both adrenal glands are affected [114-116]. Endoscopic adrenal sparing removal of the pheochromocytoma should be performed in most if not all patients. [117].

Whether nonfunctional pheochromocytomas (clinically only remarkable as adrenal masses on imaging with normal fractionated urinary metanephrines and/or normal plasma free metanephrines) require treatment/surgery remains unclear. Important aspects in this context are the questions how fast such tumors grow, if and when they cause symptoms, and if and when (at what size) they metastasize [118, 119].

EPIDIDYMAL CYSTADENOMAS in VHL SYNDROME

These non-malignant tumors occur in about half of all male VHL patients [120]. Epididymal cystadenomas consist of cystic and adenomatous areas and arise typically in the caput epididymidis (**figure 5**). The tumors have been suggested to arise from microscopic precursor structures, which are abundantly observed in the efferent ductules of the caput epididymidis of VHL patients [121, 122]. Epididymal cystadenomas rarely cause symptoms and have no potential for malignant transformation. In rare cases bilateral obstruction of efferent ductules and spermatic cords may occur resulting in sterility. Epididymal cystadenomas are well visible on ultrasound.
Women who are affected by VHL disease develop cystadenomas of the broad ligaments, which play no major clinical role.

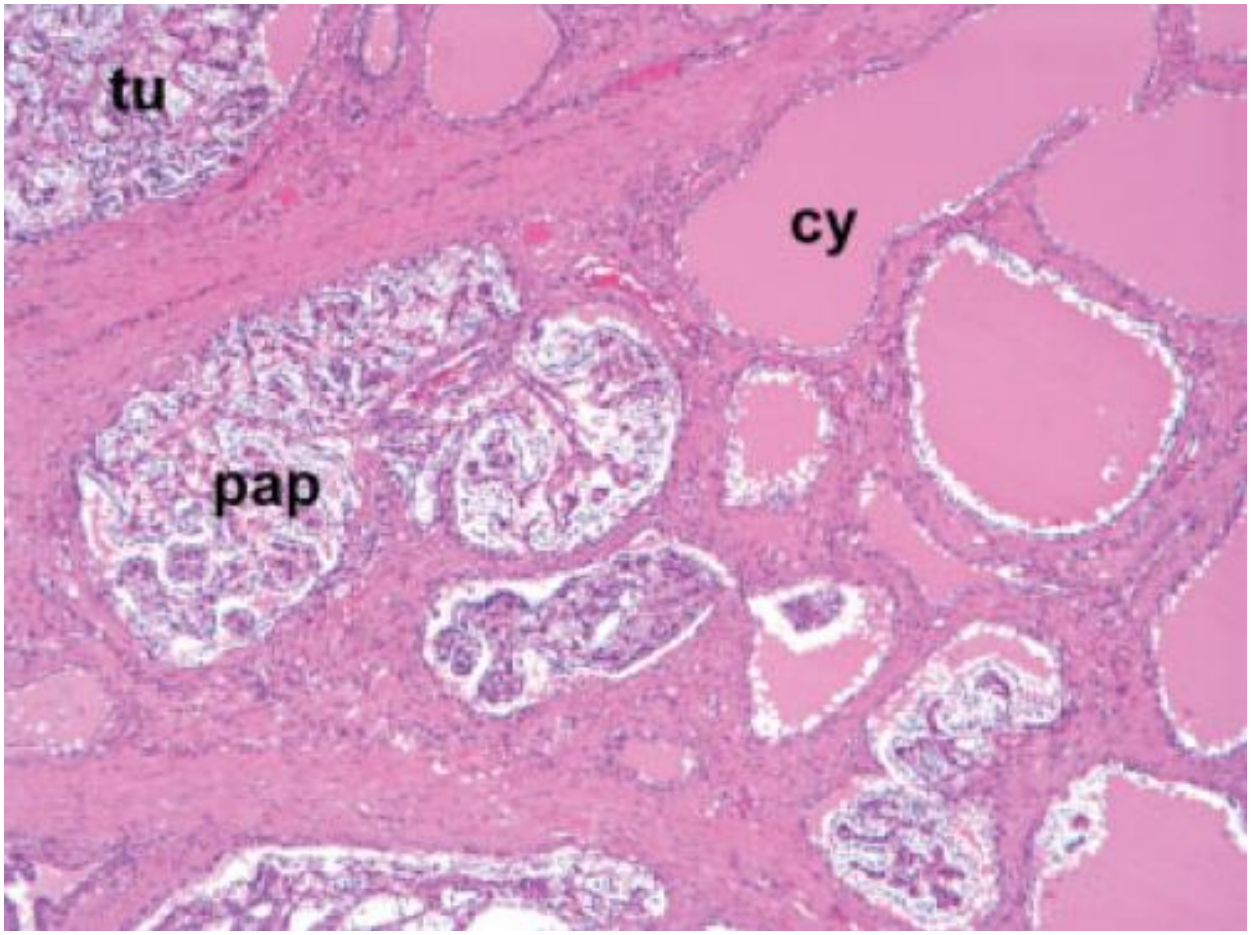

Figure 5. VHL disease associated epididymal cystadenomas consistently reveal papillary (pap), tubular (tu) and cystic (cy) architecture [121].

PANCREATIC MANIFESTATIONS in VHL SYNDROME

Pancreatic manifestations include pancreatic neuroendocrine tumors, cysts and cystadenomas. Overall, 35–70% of VHL patients develop a pancreatic manifestation [123-125]. Distinguishing between a benign microcystic adenoma and a pancreatic neuroendocrine tumor can be difficult. Similar to hemangioblastomas, pancreatic neuroendocrine tumors reveal a staggering growth pattern [126].

Most pancreatic tumors in VHL disease are asymptomatic. Extremely rare – and depending on size and location – are bile duct obstruction and/or pancreatic insufficiency. Most patients do not need any treatment. This is important for patients with pancreatic cysts and/or microcystic adenomas. All patients should be investigated by MRI with intravenous contrast administration. It is very important that imaging is performed in the early arterial phase. In contrast to the multicystic appearance of microcystic adenoma, neuroendocrine pancreatic tumors present as solid lesions and need to be considered for surgical removal. However, most VHL associated pancreatic neuroendocrine tumors are small and slowly growing. Metastases are virtually only

observed in patients with tumors of more than 3 cm diameter. In general, VHL associated pancreatic neuroendocrine tumors have a favorable prognosis compared to sporadic tumors [129]. Treatment has to be recommended for tumors larger than 3 cm [127, 128]. Resection of pancreatic tumors may also be performed if the patient is undergoing laparotomy for other lesions [127, 128]. In cases of biliary obstruction and/or pancreatic insufficiency treatment consists of placing biliary stents and/or replacing pancreatic enzymes. A new option is organ-sparing endoscopic resection which can be applied to tumors in the tail and the body of the pancreas [130].

ENDOLYMPHATIC SAC TUMORS in VHL SYNDROME

Endolymphatic sac tumors are benign cystadenomas that arise in the vestibular aquaeduct and may extend into the extraosseous portion of the endolymphatic sac, into the petrous bone, and into the inner ear [131, 132]. Large tumors have been reported to extend into the brain (Heffner 89). The vestibular aquaeduct connects the inner ear with the extraosseous portion of the endolymphatic sac, a dural fold at the posterior surface of the petrous bone. Despite their benign nature these lesions grow locally invasive into the temporal bone due to their origin in the osseous portion of the vestibular aqueduct.

Patients may present with hypakusis or hearing loss (100%), tinnitus (77%), dysequilibrium (62%), and facial paresis (8%) [133]. Hearing loss and vestibulopathy may occur suddenly due to tumor-associated intralabyrinthine hemorrhage, or insidiously, consistent with endolymphatic hydrops [134].

Diagnosis is established by MRI, which shows homogeneous or variable patterns of patchy enhancement and CT (bone window) revealing widening of the osseous portion of the vestibular aqueduct (**figure 6**).

Radical resection allows for complete excision of the tumors. The preoperative level of hearing can usually be preserved. The timing of surgery depends on the severity of symptoms, the slow but variable growth of the tumors, the possibility of injury to the 7^{th} and 8^{th} cranial nerves and possible bilateral occurrence. The role of radiation therapy in the treatment of these tumors remains unclear.

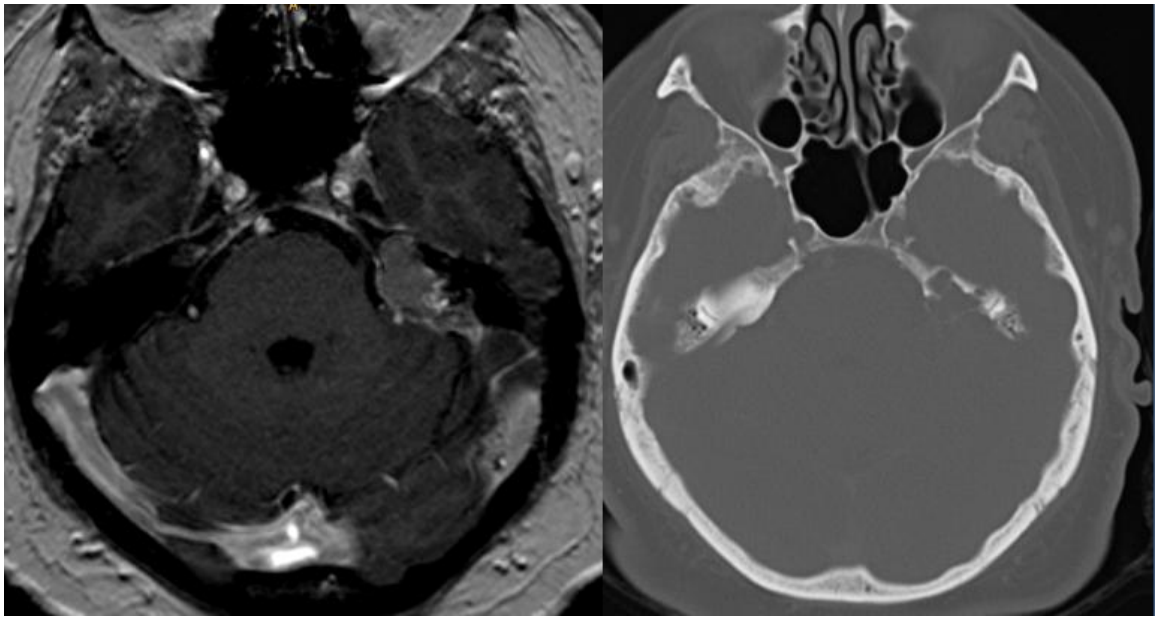

Figure 6. VHL-associated ELST (endolymphatic sac tumor). MRI reveals an inhomogenously enhancing mass in the left temporal bone, CT shows osteolysis.

PROGNOSIS in VHL SYNDROME

Before the introduction of clinical screening programs and timely prophylactic treatment of VHL associated lesions, the life expectancy of affected patients used to be impaired with a median survival around 50 years [2, 11]. Nowadays, life expectancy may be significantly improved by clinical screening programs with early detection and treatment of VHL manifestations [135] Modern management of VHL has meanwhile achieved a life expectancy of additional 10 years [136].

VHL SCREENING

All patients with hemangioblastoma, the index tumor of VHL disease, should receive a careful family history, screening for detection of other lesions associated with VHL (**table 2**), and should undergo genetic testing for VHL disease [137, 138].

Once the diagnosis of VHL disease is established, patients should undergo an annual screening program in order to identify manifestations early before deficits or metastasis occur. The screening programs vary slightly between different centers. A typical program is presented in **table 2**:

Screen for retinal hemangioblastoma: Annual ophthalmic examinations (direct and indirect ophthalmoscopy), beginning at age 1.
Screen for CNS hemangioblastoma: MRI scans of the head for every 12–36 months, beginning at age 12

Screen for renal cell carcinoma and pancreatic tumors: MRI (or ultrasound) examinations of the abdomen every 12 months, beginning from the age of 12 years
Screen for pheochromocytoma: Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites starting at age 6. MRI starting at age 12
Screen for epididymial cystadenoma: Ultrasonography of the testes starting at 18 years
Additional investigations may instigate in response to symptoms or signs of specific complications (eg, ELSTs)

Table 2. Example of a routine surveillance protocol for von Hippel–Lindau disease (modified from Maher [139])

MOLECULAR ASPECTS in VHL SYNDROME

Patients with VHL disease carry a germline mutation of the VHL tumor suppressor gene (VHL). The VHL gene had originally been linked to chromosome 3p25 in 1988 [140] and was subsequently cloned in 1993 [141]. The evolutionarily conserved VHL gene encodes two protein products, a 30-kDa full-length form (p30) and a 19-kDa form (p19).

The protein product of the VHL gene (pVHL) interacts with elongins B, C and Cullin-2 to form the VBC complex, an E3 ubiquitin ligase [142]. This multiprotein complex targets proteins for ubiquitin-mediated degradation, analogous to the S. cerevisiae SCF (Skp1/Cdc53/F-box) ubiquitination machinery [143-145]. Major targets of the VBC complex include the regulatory subunits of the heterodimeric transcription factor, hypoxia inducible factor (HIF). Therefore, VHL inactivation causes an up-regulation of HIF and downstream proteins under normoxic conditions. Many of the HIF targets are involved in the adaptation to acute or chronic hypoxia and include genes involved in the uptake and metabolism of glucose (GLUT-1), angiogenesis (VEGF, PDGF), control of extracellular pH (CA9), mitogenesis (TGFα), and erythropoiesis (erythropoietin) [146-149].

In addition to HIF degradation, the VHL protein is involved in HIF-independent cellular processes. It directs the proper deposition of fibronectin and collagen IV within the extracellular matrix [150]. Furthermore, it works to stabilize microtubules and foster the maintenance of primary cilium. The VHL protein also promotes the stabilization and activation of p53 and, in neuronal cells, promotes apoptosis by downregulation of Jun-B [150]. It was furthermore shown that acute VHL inactivation causes a senescent-like phenotype independently of HIF but dependent on the retinoblastoma protein (Rb) and the SWI2/SNF2 chromatin remodeller p400 [151].

Biallelic inactivation of the VHL tumor suppressor gene is suspected as initiating step of tumorigenesis. In general, two genetic events or “hits” are thought to occur to the two alleles of a tumor suppressor gene: The first hit is represented by a germline mutation and the second hit is characterized by inactivation of the wild-type allele [152]. More recent work suggests, that the biallelic VHL inactivation is only a first step in VHL tumorigenesis.

Tumorigenesis in VHL disease shares fundamental principles in the different affected organ systems: Germline VHL inactivation leads to persistence of microscopic

developmentally arrested structures. These microscopic cell clusters already reveal biallelic VHL inactivation and consequent up-regulation of hypoxia inducible factor and down-stream targets like VEGF, EPO etc. This principle has been shown for CNS hemangioblastomas [54, 55], renal cell carcinomas [153], endolymphatic sac tumors [131] and epididymal cystadenomas [121] and is most likely valid for all VHL associated tumors.

Current research for pharmacotherapy of VHL disease targets proteins of the HIF cascade [30]. Additionally investigated are compounds that lead to upregulation and refunctionalization of mutated VHL protein [154].

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