Management of von Hippel-Lindau Disease: An Interdisciplinary Review

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Keywords

Review · Von Hippel-Lindau disease · Disease entities · Interdisciplinary management · Screening programs · St. Gallen VHL multidisciplinary group

Summary

Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumour predisposition syndrome with an incidence of 1:36,000 newborns, the estimated prevalence in Europe is about 1–9/100,000. It is associated with an increased risk of developing various benign and malignant tumours, thus affecting multiple organs at different time points in the life of a patient. Disease severity and diversity as well as age at first symptoms vary considerably, and diagnostic delay due to failure of recognition is a relevant issue. The identification of a disease-causing VHL germline mutation subsequently allows family members at risk to undergo predictive genetic testing after genetic counselling. Clinical management of patients and families should optimally be offered as an interdisciplinary approach. Prophylactic screening programs are a cornerstone of care, and have markedly improved median overall survival of affected patients. The aim of this review is to give an overview of the heterogeneous manifestations of the VHL syndrome and to highlight the diagnostic and

therapeutic challenges characteristic for this orphan disease. A comprehensive update of the underlying genetic and molecular principles is additionally provided. We also describe how the St. Gallen VHL multidisciplinary group is organised as an example of interdisciplinary cooperation in a tertiary hospital in Switzerland.

Introduction

The von Hippel-Lindau (VHL) hereditary tumour syndrome is caused by germline mutations in the *VHL* tumour suppressor gene. The pattern of inheritance is autosomal dominant. De novo mutations occur in about 20% of the cases. The VHL syndrome is associated with an increased risk of developing various benign and malignant tumours. These include retinal capillary haemangioblastomas (RCH) – sometimes also called retinal angiomas – and central nervous system haemangioblastomas (CNS HB), pheochromocytomas (PHEO), renal cysts and clear cell renal cell carcinomas (ccRCC), endolymphatic sac tumours (ELST) as well as pancreatic cysts, pancreatic neuroendocrine tumours (PNET) and cystadenomas of the epididymis and the broad ligament (table 1, fig. 1, pictures 1–7). The VHL syndrome is an orphan disease with an incidence of 1:36,000 newborns, the estimated prevalence in Europe is about 1–9/100,000 (www.orpha.net, ORPHA892).

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The disease penetrance is high, and more than 90% of patients harbouring a *VHL* mutation develop clinical symptoms before the age of 65 years. Tumour location and dynamics of development, disease severity and diversity, as well as age at first symptoms vary considerably [1–4]. Due to its rarity, physicians often fail to recognize the underlying disease (supplement 1). Hence, diagnostic delay is a relevant issue as it impedes the implementation of a prophylactic screening program which markedly improved median overall survival well beyond the age of 50 years [5]. Major causes of death are metastatic ccRCC and CNS HB. Patients are also prone to the risk of unnecessary and extensive surgery with serious consequences in the long run (i.e. nephrectomy and haemodialysis).

Table 1. Von Hippel-Lindau (VHL)-associated tumours

Location	Tumour
Central nervous system	haemangioblastomas (HB)
Eyes	retinal capillary haemangioblastomas (RCH)
Petrosal bone	endolymphatic sac tumours (ELST)
Pancreas	pancreatic cysts, neuroendocrine tumours (PNET)
Kidney	renal cysts, clear cell renal cell carcinomas (ccRCC)
Adrenal glands	phaeochromocytomas (PHEO)
Epididymis, broad ligament	cystadenomas

Fig. 1. Picture 1. T1-weighted image of the cerebellum with bilateral cystic haemangioblastomas (HB). **Picture 2.** Sagittal magnetic resonance imaging (MRI) of the cervical spine shows 4 small HB at the 4th ventricle, medulla oblongata, and cervical cord (white arrows in B). No tumour-associated cysts or syringomyelia are present. Minimal oedema of 1 tumour can be seen on T2-weighted images (black arrow in A). **A** T2-weighted, **B** enhanced T1-weighted MRI, sagittal view. **Pictures 3 and 4.** Fundus photography (3) and fluorescein-angiography (4) of a retinal capillary haemangioblastoma (RCH). **Picture 5.** A small strong enhancing phaeochromocytoma of the left adrenal gland can be identified after the application of gadolinium (arrow). Enhanced T1-weighted MRI in arterial phase, coronal view. **Picture 6.** Endolymphatic sac tumour of the left side (thick arrows) with typical destruction of the posterior wall of the petrosal bone. At the posterior margin of and contralateral to the tumour, parts of the sigmoid sinus are visible after gadolinium application (thin arrows). **A** T2-weighted, **B** enhanced T1-weighted MRI, axial view. **Picture 7.** Clear cell renal cell carcinoma (ccRCC) in 2 different patients. A small early and strong enhancing carcinoma can be seen in the upper part of the left kidney (white arrow in A), showing similar contrast to the normal kidney during parenchymal phase (white arrow in B). Simple kidney cysts can be depicted best during parenchymal phase (open arrows A and B). C shows multifocal ccRCC of the lower part of the left kidney with inhomogeneous contrast enhancement (white arrows in C). Note multiple pancreatic cysts in the same image (open arrow in C). **A** and **C** Enhanced T1-weighted MRI, arterial phase, **B** enhanced T1-weighted MRI, parenchymal phase, coronal view.

The aim of this comprehensive review is to raise awareness of the VHL syndrome as an orphan disease to enable early diagnosis and ameliorate patient management. In addition, we would like to describe our single centre experience of a VHL caregiver model: the St. Gallen VHL Specialist Group (SG-VHL-SG).

Genetic Background

The *VHL* gene (Ensembl ID: ENSG00000134086), located on the short arm of chromosome 3 (3p25.3), comprises 3 exons and encodes 2 different mRNA transcripts of 213 and 172 amino acids, respectively (RefSeq ID: NM_000551 and NM_198156). As demonstrated in *Caenorhabditis elegans*, the VHL tumour suppressor protein (pVHL) and its homologues date back to the start of metazoan evolution and have been highly conserved among species [6, 7]. Its multifaceted roles range from targeting hypoxia inducible factor α (HIF α) for degradation and suppression of aneuploidy to microtubule stabilization [8, 9].

Molecular genetic testing of the coding sequence by DNA sequencing and gene dosage analysis detects pathogenic *VHL* germline mutations in nearly 100% of patients fulfilling the clinical criteria for VHL disease [1]. Thus far, more than 500 different *VHL* alterations have been described (Human Gene Mutation Database, www.hgmd.org) with about 20% of them having occurred de novo, i.e. without an affected parent. Detailed gene mutation information for as many as 945 VHL families were recently published [10]. Based on results from genotype-phenotype studies, the specific mutation can further hint at the risk of certain tumour types to occur (e.g. patients with loss of function *VHL* mutations like deletions, truncating and splice-site mutations have a lower risk for PHEO, also referred to as VHL type 1 disease).

The identification of a disease-causing *VHL* germline mutation in a patient subsequently allows family members at risk to undergo presymptomatic/predictive genetic testing after genetic counselling, and to clarify if they actually require regular close meshed clinical and imaging screening measures. Due to autosomal dominant inheritance, there is a 50% probability for the offspring to have inherited the *VHL* mutation from their parent. Since early recognition of clinical manifestations (e.g. RCH) is pivotal and screening recommendations thus start at a young age (i.e. fundoscopy in infancy or early childhood) [1], genetic testing is already recommended in children. The disorder does not affect intelligence, shows considerable intra-familial variability in disease expression, and has a number of surveillance and treatment measures; hence, requests for prenatal diagnosis are rare although technically feasible. Preimplantation genetic diagnosis, which has been successfully performed in VHL disease, is currently legal in most European countries with the exception of Austria, Italy, and Switzerland [11, 12].

Molecular Biology

Over the last years, major advances have been made in our understanding of the molecular mechanisms underlying the tumour suppressor functions of the *VHL* gene product, pVHL. Multiple distinct pVHL-regulated pathways have

been identified and linked to specific aspects of VHL-associated pathology [13]. It is now widely appreciated that pVHL acts as the substrate recognition component of an ubiquitin ligase that targets the transcription factor HIF for ubiquitin-mediated destruction in a prolyl hydroxylation-dependent manner when oxygen is present [14]. Accordingly, hypoxic tumour cells or VHL-deficient kidney cancers overproduce HIF and HIF target genes whose products play key roles in cellular processes such as growth factor signalling, angiogenesis, invasion and metastasis, and cell metabolism [15]. Among the HIF family members, HIF2 α appears to be a key driver in pVHL-defective ccRCC [16], while HIF1 α serves tumour suppressor functions in this context [17]. These molecular insights also provided the rationale for treating ccRCC. Drugs that inhibit HIF2 α or its downstream targets such as vascular endothelial growth factor (VEGF) are transforming the treatment of ccRCC [18].

Growing evidence indicates that tumour suppression by VHL involves the control of a variety of HIF-independent processes [19]. One such mechanism and route relates to a role for pVHL in the suppression of renal cysts. The latter represent a feature of VHL disease. Renal cyst development has been linked to defects in primary cilia, microtubule-based organelles that function to perceive environmental cues [20]. pVHL localizes to primary cilia and protects them from precipitous resorption in response to growth factor cues [21–23]. The PI3K-Akt and mTOR pathways are activated in human renal cysts, and in keeping with this finding, *VHL* and *PTEN* loss cooperate to promote renal cysts in mouse models [24]. These studies underscore the importance of pVHL's microtubule-regulatory function in the context of primary cilia maintenance and the suppression of kidney cell proliferation and renal cyst formation.

Renal cysts are believed to be pre-neoplastic, and it is presumed that additional mutations affecting other genetic loci are required to convert them into ccRCC. In this regard, ccRCC display high rates of aberrant chromosome numbers, referred to as aneuploidy. Several mechanisms have been implicated in the generation of numerical chromosomal instability, among them are defects in the mitotic checkpoint that normally prevents mitotic progression if a single chromatid is not attached to the mitotic spindle [25]. A key mediator in halting mitotic progression in response to checkpoint activation is Mad2 [26]. The protein levels of Mad2 vary significantly in human cancers [27, 28], and studies in mice have shown either increasing or decreasing Mad2 levels to cause abnormal mitotic checkpoint function, resulting in chromosome instability and tumour progression [28, 29]. Interestingly, *VHL*-deficiency in ccRCC is associated with low Mad2 expression. Consistent with this finding, *VHL*^{-/-} renal carcinoma lines display low levels of Mad2 and a weakened mitotic checkpoint [30, 31]. This implies that part of the normal function of pVHL is to maintain normal Mad2 protein levels in order to suppress aberrant mi-

Table 2. Criteria for referral to a von Hippel-Lindau (VHL) clinic: MGH (Massachusetts General Hospital) criteria

Any blood relative of an individual diagnosed with VHL disease
Individuals with 1 VHL-associated lesion ^a
AND a positive family history (FH) of VHL-associated lesion(s)
Any individual with 2 VHL-associated lesions
Individual with any of the following:
– ccRCC in a patient < 40 years
– Bilateral and/or multiple ccRCC
– ccRCC with a positive FH
– HB in a patient < 30 years
– > 2 central nervous system HB (any age at diagnosis)
– 1 HB + ccRCC or PHEO or pancreatic neuroendocrine tumour
– PHEO in a patient < 40 years
– Bilateral and/or multiple PHEO
– PHEO with a positive FH
– >1 Pancreatic serous cystadenoma
– >1 Pancreatic neuroendocrine tumour
– Multiple pancreatic cysts + any VHL-associated lesion
– ELST
Epididymal papillary cystadenoma

^aHaemangioblastoma (HB), clear cell renal cell carcinoma (ccRCC), pheochromocytoma (PHE), endolymphatic sac tumour (ELST), epididymal papillary cystadenoma, pancreatic serous cystadenomas, pancreatic neuroendocrine tumours.

otic checkpoint behaviour and the development of aneuploidy.

In summary, pVHL has multiple distinct functions, and its inactivation leads to dysregulation of diverse cellular processes which endow susceptible cells with attributes aiding progression towards a malignant phenotype. Unravelling the precise functions of pVHL in these processes and further definition of signalling pathways that cooperate with *VHL* mutation in hereditary and sporadic tumour formation remains a challenge of central importance.

Diagnostic Criteria and Classification

The diagnosis of VHL disease can be made based on characteristic clinical features. Either 1 index tumour (HB, PHEO, ccRCC) and a positive family history or the finding of 2 or more CNS HB or 1 CNS HB in combination with 1 visceral manifestation is sufficient to diagnose VHL disease regardless of a positive family history. Even though the clinical diagnosis can be based solely on the presence of typical lesions, genetic testing to establish and/or confirm the definite diagnosis is indicated for all patients with suspected VHL disease. Recommendations for comprehensive testing are listed in detail in the Massachusetts General Hospital (MGH) Criteria (table 2).

Table 3. Clinical subtypes of von Hippel-Lindau (VHL) disease

VHL Subtypes	Tumour type		
	haemangioblastoma	renal cell carcinoma	phaeochromocytoma
Type 1	+	+	–
Type 2A	+	–	+
Type 2B	+	+	+
Type 2C	–	–	+

Various studies on genotype-phenotype correlations have led to a subtype classification dependent on the absence (type 1) or presence (type 2) of PHEO. VHL type 2 has been further divided into 3 groups defined by the presence of ccRCC (table 3) [3]. Important differential diagnoses of VHL include other hereditary syndromes such as multiple endocrine neoplasia type 2 (MEN2), polycystic kidney disease, and hereditary pheochromocytoma-paraganglioma syndrome.

Characteristic Disease Manifestations

Central Nervous System Haemangioblastomas

About 70% of VHL patients exhibit HB of the central nervous system (CNS) [32, 33]. They constitute a frequent and early disease manifestation, and typically arise in the second decade of life. They are mostly multiple and frequently found in the cerebellum (52 %), the spinal cord (44 %), and the brainstem (18 %) [33]. Supratentorial localization is extraordinarily rare. HB are vascular tumours often accompanied by a cyst which may evolve to a space-occupying lesion being the major cause of neurological symptoms. CNS HB often constitute the first clinical manifestation of VHL disease. Their biological behaviour is unpredictable. Phases of stability alternate with phases of rapid tumour or cyst growth [32, 34]. Pregnancy can accelerate the growth of HB [35]. Multiplicity and recurrences of CNS HB make it mandatory to regularly assess the neurological status in combination with pre-planned radiological follow-ups. The imaging methods of choice are cerebral (including a focus on the temporal bone to disclose ELST) and spinal magnetic resonance imaging (MRI) scans. HB show strong contrast enhancement on T1-weighted images. Tumour-related cysts and oedema can be optimally detected on T2-weighted images. This screening allows good timing of surgical treatment as prophylactic removal of pre-symptomatic lesions prevents irreversible neurological deterioration [36, 37].

Radical yet tissue-sparing resection of the solid tumours can be achieved with modern microsurgical techniques. The accompanying cystic component usually resolves after resection of the solid lesion [34, 36]. Intraoperative neuromonitoring [38] and ultrasound [36] are recommended to

prevent postoperative neurological deficits. In general, the necessity of multiple surgeries during a patient's lifetime calls for minimally invasive approaches. In surgically non-resectable HB, stereotactic radiotherapy might be an option. However, it should only be used as a salvage therapy due to cyst enlargement and insufficient long-term local tumour control [39, 40].

Retinal Capillary Haemangioblastomas

RCH are found in 70% of VHL patients over the age of 60 years. Their histology and biological behaviour are similar to their CNS counterparts. They can be asymptomatic for years. RCH are found typically either in the peripheral retina or in the juxtapapillary location, and can progress to vision loss with retinal oedema, lipid deposition, and exudative retinal detachments [41]. Impaired vision occurs if the lesions are in proximity to the macula or lead to retinal detachment [42]. Early treatment of these complications carries a better prognosis [43]. Thus, screening from early childhood is recommended. The diagnostic method of choice is ophthalmologic examination including dilated fundoscopy and retinal angiography if needed.

The indication for laser photocoagulation or cryotherapy depends on the location, size, and secondary effects of the lesions. Small RCH can be treated successfully with argon laser photocoagulation in most locations. Cryotherapy is the treatment of choice for larger or peripheral tumours. Main complications of these 2 strategies are accumulation of retinal hard exudates and retinal oedema in the macula, contributing to decreased vision [43]. Vascular lesions are often accompanied by fibrous proliferation and contraction leading to retinal detachment. In these cases and in the case of vitreous haemorrhage, vitrectomy is recommended [42].

Endolymphatic Sac Tumour

ELST represent rare, slow growing tumours arising from the endolymphatic sac located on the posterior surface of the temporal bone. They are low-grade adenocarcinomas but with a locally aggressive and infiltrative growth pattern. They do not metastasise [44] and can often be asymptomatic for a long time. Most ELST are sporadic, and only one fifth of ELST are hereditary and occur in association with VHL disease. Bilateral occurrence is pathognomonic for VHL disease. The most common primary symptom is hearing loss. Other symptoms are vertigo, tinnitus, and aural fullness.

MRI is the diagnostic imaging method of choice. For early ELST depiction, a thin sliced sequence (≤ 3 mm) should be acquired covering the temporal bone. High resolution computed tomography (CT) of this region might also be helpful in the early diagnosis.

Early radical resection of ELST through a transmastoid approach is considered standard of care. It can be safely performed with a high probability of complete tumour removal. If performed prior to hearing loss, auditory function can be preserved in the majority of cases. Surgery is indicated in asymptomatic patients to prevent hearing loss and in patients suffering from vertigo irrespective of the hearing status. Subtotal resection carries a high risk of multifocal recurrence and should be avoided. The role of external beam radiation in the primary or postoperative setting is controversial. It can be considered in poor surgical candidates or intracranial recurrences with potentially high surgical morbidity [45–47]. Recurrences after surgery may be closely followed by MRI in patients without preservable hearing and in the absence of vertigo, reserving revision surgery and/or radiation for cases with tumour growth or imminent intracranial complications.

Clinical assessment of audiovestibular symptoms and a baseline pure tone audiogram are recommended at the time of diagnosis and anytime during follow-up when new symptoms appear or an ELST is diagnosed.

Renal Cell Carcinoma

The most frequent malignant tumour entity in VHL disease is ccRCC. On histopathology, clear cell type is found in the majority of cases. Microscopic analysis of grossly normal kidney parenchyma in VHL patients may reveal innumerable (up to 600) microscopic tumour foci as well as benign or atypical cysts with clear cell lining [48]. Mean age at diagnosis is 40 years with a lifetime incidence for the most common phenotypic forms of VHL disease (subtypes 1 and 2B) of around 70% [1].

Similar to sporadic ccRCC, VHL-associated tumours exhibit considerable variations in growth behaviour [49]. However, there is almost no metastatic potential at a diameter below 3 cm [50–52]. Therefore, active surveillance with MRI is recommended in tumours below 3 cm, as early surgical removal may deteriorate renal function. Adherence to a strict surveillance protocol is necessary to minimize metastatic risk.

The imaging method of choice is MRI. Plain cysts of the kidneys are usually depicted on T2-weighted images; complex cysts often show variable signal intensities depending on their content. A multiphasic acquisition of the abdominal organs with gadolinium is necessary to detect solid tumours, with ccRCC being best identified in the arterial or parenchymal phase.

Nephron-sparing surgery (NSS) and percutaneous focal ablation methods, in particular CT-guided radiofrequency ablation (RFA), are the appropriate therapy of ccRCC in VHL patients [53]. Local control is properly achieved by percutaneous ablation in lesions of up to 3 cm but is suboptimal in larger tumours. Surgery should remove as many tumours as possible during the same procedure as reoperation bears a

higher risk of functional renal impairment. If feasible, NSS should be performed under non-ischemic conditions (so-called 'zero ischemia'). Equal to sporadic ccRCC, minimal surgical resection margins are sufficient and lead to better preservation of renal function without compromising oncological outcome. Radical nephrectomy is the ultimate procedure and is exclusively limited to very large tumours. For optimal timing of interventions and reducing the risk of nephrectomy, regular screening and follow-up examinations of the kidneys in VHL patients are mandatory. Despite nephron-sparing approaches, progressive renal function loss may occur over time necessitating renal replacement therapy or kidney transplantation. In the 1990s, 1 in 4 patients with VHL was expected to reach end-stage renal disease [50, 54]; a more widespread use of a nephron-sparing strategy should reduce or delay this proportion.

Management of chronic kidney disease also applies to VHL patients, including optimal treatment of hypertension and prevention of secondary complications such as anaemia or hyperparathyroidism. Interdisciplinary management by oncologists, urologists, and nephrologists is essential for an optimal strategy which should also include transplant physicians once the prospect of bilateral nephrectomy or advanced loss of renal function is reached. 2 main questions arise when considering transplantation in VHL patients: the right time to transplant after tumour nephrectomy and the choice of post-transplant immunosuppression.

As a rule, patients with tumours require a latency of 2–5 years between complete remission and transplantation to avoid administering immunosuppression with a potentially recurrent or uncontrolled tumour. The situation is different in the case of VHL mainly due to the long-term follow-up of tumour progression prior to nephrectomy, the regular assessment of metastasis, the sequential resection of larger lesions, and the fact that ccRCC does not seem to be promoted by immunosuppression.

Some authors [54] express caution regarding the latency time between tumour nephrectomy and transplantation mainly due to the risk of local recurrence, residual malignancy, or undiagnosed metastasis. Nonetheless, in a series of 32 VHL patients rendered anephric, Goldfarb et al. [55] reported no difference in the duration of pre-transplant dialysis between patients who developed metastasis and those who did not. In particular, there was no recurrence in selected patients who underwent transplantation immediately after nephrectomy. Furthermore, the patients and grafts outcomes were not different compared to matched cases [55]. If living donor kidney transplantation is possible, a pre-emptive transplantation (i.e. without dialysis) can thus be considered simultaneously with the transplantation.

An important issue to address in living donor kidney transplantation in VHL patients is the risk of gene mutation in the related donor. The presence of the mutation could put the donor at risk for subsequent development of ccRCC in the re-

sidual kidney and put the transplanted kidney at risk for developing a tumour. Therefore, genetic testing is highly advisable in a blood-related donor even in the absence of clinical VHL manifestations.

The current practice is to use standard immunosuppression protocols especially at induction and in the initial post-transplantation period. Thereafter, the use of mTOR inhibitor-based immunosuppression can be considered with the aim of providing both, antiproliferative and anti-tumour effects. Overall, kidney transplantation is a valid option for selected VHL patients, but interdisciplinary management in the case of progressive renal failure or of an expected anephric status is essential for an optimal outcome of kidney transplantation in VHL patients.

Phaeochromocytoma

According to Neumann et al. [56], up to 11% of assumed sporadic cases of PHEO could be attributed to *VHL* gene mutations. As mentioned before, the risk for developing PHEO in VHL depends on the underlying germline mutation and affects predominantly patients with VHL type 2 [57].

The biochemical diagnosis of PHEO is based on increased plasma concentrations of free metanephrine and normetanephrine or excess urinary output of catecholamines and fractionated metanephrines. The distinct pattern of catecholamine excess in VHL, revealing almost exclusively norepinephrine production, may be helpful to discriminate individuals with *VHL* mutations from patients with MEN2 or neurofibromatosis type 1 (NF1) (combination of increased plasma concentration of metanephrine and normetanephrine) [58]. After establishing the biochemical diagnosis of PHEO, CT or MRI (showing early enhancement in the arterial phase), and additionally meta-iodobenzylguanidine (MIBG) scintigraphy or F-DOPA positron emission tomography are used for anatomical localization.

Compared to sporadic or other hereditary forms of PHEO, the risk of malignant transformation is not elevated (approximately 5%) [1]. In VHL disease, PHEO may be detected during routine imaging follow-up, and therefore is frequently asymptomatic at diagnosis [1]. The therapy of choice is laparoscopic tumour resection [59]. Depending on tumour size, partial adrenal-sparing adrenalectomy is pursued especially in patients with bilateral PHEO to preserve adrenocortical function [60]. Preoperative therapy with an alpha-adrenergic blocker agent (preferably phenoxybenzamine) or calcium channel blocker as well as expansion of the contracted blood volume are mandatory to prevent intraoperative hypertensive crisis or arrhythmia. Due to these potential intraoperative adverse events, PHEO has to be excluded before any surgical intervention in VHL disease [1]. Due to an increased risk of relapse, even patients having been successfully surgically treated for PHEO should undergo long-lasting surveillance.

Pancreatic abnormalities occur in up to 70% of patients with VHL disease [3]. Most frequently, simple pancreatic cysts are seen, but also serious cystadenomas and PNET are associated with VHL disease. Even rare cases of pancreatic HB and ccRCC metastasis have been described [61]. Usually, pancreatic cysts remain silent; they rarely become symptomatic due to compression of surrounding organs or due to exocrine/endocrine pancreatic insufficiency. Treatment strategies for symptomatic pancreatic cysts should be individualized. Radiologically guided percutaneous aspiration and/or hypertonic saline application as well as endoscopic biliary stent placement in cases of symptomatic biliary obstruction are used [62]. Cystectomy/enucleation in patients with only a few cysts seems feasible [63].

PNET can be detected in 12–17% of patients with VHL and harbour a malignant potential [63]. In 1998, Libutti et al. [63] were the first to recommend treatment guidelines based on tumour size in patients affected by a familial cancer syndrome including PNET to minimize the risk of metastasis while preserving pancreatic function. In a large single-centre analysis of 633 patients with VHL disease, 108 patients with PNET were enrolled on a prospective protocol to investigate the risk of metastasis. After a median follow-up time of 53 months, 3 prognostic factors emerged: neoplasm size > 3 cm, presence of a mutation in *VHL* gene exon 3, and a tumour doubling time of less than 500 days [64]. Another study of VHL-associated PNET (n = 35) could not confirm the correlation of VHL gene mutation and malignant phenotype [65]. Hence, a small slow-growing PNET should be closely followed by regular MRI [66, 67]. It is also recommended to resect even small lesions if abdominal surgery is conducted for other reasons [66].

Tumour-to-Tumour Metastasis

Tumour-to-tumour metastasis associated with VHL disease refers to the spread of malignant cells from ccRCC, PNET, or possibly PHEO to existent HBs. Case series and reports have been published on this phenomenon of indolent slow-growing recipient tumours which are available as hosts for metastases over extended time periods [68–70]. This should be taken into consideration when assessing VHL patients especially when disproportionate growth of CNS HB and RCH occurs.

Systemic Treatment Approaches

Primary treatment of all VHL-related tumours is local (i.e. surgical resection, RFA, radiotherapy). However, repeated local interventions at multiple sites or repeated recurrences in 1

area can increase morbidity [71]. Therefore, in individual patients systemic treatment may be an option. This includes cases of progression of inoperable and previously irradiated cerebral HB, RCH, PHEO, PNET, or ccRCC. Systemic treatment is recommended in the metastatic setting, addressing the same therapeutic principles as in sporadic malignancies. Due to the rarity of VHL, data about systemic treatment are sparse. VEGF-targeting agents seem to be a reasonable choice with regard to pathophysiology in most tumours. High levels of VEGF are found in HB, and it has been hypothesized that blocking the VEGF pathway might result in disruption of tumour angiogenesis and consequently tumour regression [72]. In a pilot study, 15 VHL patients were treated with the small-molecule VEGF receptor inhibitor, sunitinib. 9 of the 15 patients completed all planned 4 cycles of treatment, whereas 6 patients stopped early due to intolerance or disease progression. Significant responses were seen in ccRCC, in contrast to other VHL-related tumours where no effect was seen [73]. The reason for this difference in organ-specific response is unclear. There are also case reports showing efficacy of sunitinib in PHEO [74].

In addition, findings suggest that fibroblast growth factor (FGF) pathway inhibition may affect the growth of HB [73]. Efficacy was demonstrated in a patient with cerebellar HB treated with the multi-tyrosine kinase inhibitor pazopanib following progression on sunitinib. Pazopanib inhibits multiple growth factors including FGF receptor and VEGF receptor [75].

Bevacizumab, a humanized monoclonal antibody, binds to the soluble VEGF and inhibits its interaction with the VEGF receptor [76]. Indeed, efficacy of bevacizumab has been demonstrated in patients with HB and RCH [77–80].

The majority of sporadic ccRCC lack functional VHL protein, and this loss of function may occur via *VHL* gene mutations or epigenetic silencing via promoter hypermethylation [81, 82]. Patients with metastatic ccRCC related to VHL receive the same systemic treatment as patients with sporadic ccRCC [83]. Since 2007, several new treatments became available: sunitinib [84], bevacizumab in combination with interferon [85, 86], temsirolimus in patients with poor prognosis [87], and pazopanib [88] which was recently shown to have similar efficacy as sunitinib with less toxicity [89]. In conclusion, VEGF-, platelet-derived growth factor (PDGF)-, and FGF-targeted salvage treatments are also available for localized tumours which cannot be treated with local procedures.

Specific Paediatric Issues

To be a carrier of the *VHL* gene mutation has an enormous lifelong impact on quality of life. To confirm or exclude VHL disease, early molecular genetic testing of the children of an affected parent is therefore strongly recommended. Nearly all VHL tumours may occur in childhood and adolescence; hence a comprehensive paediatric screening programme should be started as early as possible. Yet, the spe-

cific needs of a young child have to be taken into account in terms of compliance as well as physical and psychological distress. An MRI scan, for instance, being the imaging method of choice to screen for intra-abdominal tumours, in a young child requires general anaesthesia and stringent medical and logistic management. An abdominal ultrasound performed by a skilled paediatric radiologist may be a reliable substitute.

The state of the art laboratory tests to screen for PHEO require a fasting intravenous blood sample taken with the patient in supine position – not easy to perform on a child. It is an important part of the caring paediatrician's responsibility to keep the balance between necessary (invasive) procedures and acceptable distress in order to maintain the required life-long screening and therapy adherence throughout all developmental stages.

Keeping the specific needs of an infant, a child, an adolescent, and a young adult in mind, the screening schedule should be adjusted accordingly. There are several surveillance protocols available, differing mainly in onset of screening and frequency of tests. It is important to emphasize that these schedules are only approximate recommendations with respect to age. All necessary diagnostic procedures have to be done instantly in the case of clinical suspicion, independent of the child's age.

Multidisciplinary Treatment

VHL disease is a systemic disease with pronounced interindividual heterogeneity. Continuous medical care and treatment of VHL patients is a long-lasting challenge which is best approached in an interdisciplinary fashion. Active teamwork of the various medical and surgical specialists is crucial. In addition, the transfer from paediatric to adult care is a delicate point.

The chronicity and the unpredictable course of the disease have major implications on matters of daily life like career choice and employment, health insurance, and family planning. Psychological stress and insecurity should not be underestimated and properly managed. In Switzerland, the Association for Families Affected by VHL founded in 2004 provides invaluable services giving advice on legal, psychosocial, and many other matters (www.vhl-europa.org/switzerland/). Similar organisations exist in many European countries. Family doctors and community services are important partners in the comprehensive care of a patient with VHL disease. We advise patients to seek professional psychological support.

Perspectives

Apart from early diagnosis and screening procedures, a major goal in VHL disease is the improvement of interdisciplinarity within institutions to ensure integral care of these

Table 4. Annual screening investigations in patients with von Hippel-Lindau (VHL) disease

Clinical neurological examination
Nephrology consultation in patients with clear cell renal cell carcinoma (ccRCC) following kidney surgery/interventions
Endocrinology consultation including measurement of plasma metanephrines
Ophthalmologic examination including dilated funduscopy
Abdominal magnetic resonance imaging (MRI) scan
Cerebral and spinal MRI scan

complex patients. We describe our single-institution network as a possible model:

In St. Gallen, a specialist group consisting of members from oncology, neurology, nephrology, surgery, neurosurgery, radiology, endocrinology, paediatrics, ophthalmology, and otorhinolaryngology has been set up to ensure adherence to regular screening examinations and to offer optimal individual care. Currently, 13 families are under our care. Close cooperation and communication with family doctors is also part of this network. VHL patients are enrolled into a schedule with annual screening examinations and specialist consultations (table 4), synchronized for maximal medical and patient efficiency. A strong and active interaction with the VHL Family Alliance (section Switzerland) is established.

The members of our group meet regularly on a 3-monthly basis and discuss complex situations of single patients and the optimal treatment approach. Experts from abroad as well as specialists from other medical fields like gastroenterology and dermatology are consulted if necessary.

In addition, monthly genetic consultations have been set up where patients and families are counselled and genetic testing can be arranged. Importantly, genetic testing should always be accompanied by comprehensive genetic counselling before and after testing.

Patients with a high suspicion of or a new diagnosis of VHL syndrome, who are being referred to our institution, are first seen by a medical oncologist who acts as the triage person. Available medical data are collected and pooled with the help of the general practitioner and the patient. Most urgent measures are taken, medical data is completed, and initial staging is performed. A detailed medical and family history as well as imaging and laboratory data of new VHL patients are presented to the interdisciplinary group at the following meeting. Genetic counselling and/or testing, an individual treatment plan, and a regular annual screening plan are subsequently discussed with the patient. The same procedure is followed in patients who are referred from one of the specialists within the network or are transferred from paediatric to adult care. Results of medical interventions or annual screening are discussed at the network meetings to ensure interdisciplinary decision-making at all times (see also table 4). Continuous information from the experts to the VHL patient organisation is also provided.

Conclusion

In conclusion, we would like to emphasize the importance of an interdisciplinary approach in specialized centres for patients with VHL – a complex and orphan disease. Early diagnosis and application of the recommended screening program is of utmost importance to prevent early morbidity and mortality. Local therapeutic approaches are the mainstay of tumour treatment and should be provided by experienced physicians with a widespread knowledge of VHL disease. Further understanding of the pathophysiology and consequences of VHL gene mutations may guide future targeted therapies.

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Supplemental Material

Case Report

To access the online supplemental material please refer to www.karger.com/?DOI=000369362.

Disclosure Statement

Dr. Christian Rothermundt declares the following potential conflict of interest: Pfizer advisory board. Prof. Silke Gillesen declares the following potential conflict of interest: Pfizer, Novartis and Bayer advisory board. Dr. Thomas Hundsberger declares the following potential conflict of interest: honoraria for lectures or advisory board participation from Roche and MSD. All other authors declare no conflict of interest.

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