Von Hippel-Lindau Syndrome

Iwona Ben-Skowronek Sylwia Kozaczuk

Department of Pediatric Endocrinology and Diabetology, Medical University of Lublin, Lublin, Poland

Key Words

Von Hippel-Lindau disease · Pheochromocytoma ·
Haemangioblastoma · Cystadenomas

Abstract

Von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome characterized by the development of multiple vascular tumours. The syndrome is caused by inactivation of the VHL protein (pVHL) and increased production of VEGF, PDGF, and TGF- α . The course of VHL syndrome is associated with the development of multiple vascular tumours. Most frequently, these include retinal and central nervous system haemangioblastomas, clear cell renal cell carcinoma, pheochromocytomas, pancreatic islet tumours, endolymphatic sac tumours, and additionally, renal and pancreatic cystadenomas and epididymal cystadenomas in men. VHL syndrome is a highly complex disease; hence, the diagnosis is often difficult. The diagnosis of any of the characteristic tumours, particularly in children, is an implicit indication for the necessity of diagnosis and genetic tests in the patient and family members and for intensive supervision of carriers of the mutated gene, thereby improving early diagnosis and successful treatment of the malignancies.

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Introduction

Von Hippel-Lindau (VHL) syndrome is a rare autosomal dominantly inherited genetic disorder [1]. The disease was first described separately by von Hippel in 1911 [2] and by Lindau in 1926 [3]. Its incidence is estimated at approximately 1/36,000 live births [4]. It is associated with a mutation of both alleles of the *vhl* gene located on the short arm of chromosome 3. To date, over 150 mutations responsible for the development of VHL syndrome have been discovered [5]. The aim of this review is to describe the clinical features, investigations, as well as diagnosis and treatment of VHL syndrome in the paediatric age range.

Molecular Basis

VHL disease is a hereditary cancer syndrome characterized by the development of multiple vascular tumours. The syndrome is caused by inactivation of the VHL protein (pVHL). Through its β -domain, pVHL binds directly to a hypoxia-inducible factor (HIF) [6]. HIF is a transcriptional complex participating in the regulation of gene expression by oxygen. HIF- α subunits are rapidly

Table 1. Classification of VHL syndrome*VHL type 1 (without pheochromocytoma)*

Retinal haemangioblastoma
CNS haemangioblastoma
Clear cell renal cell carcinoma

VHL type 2 (with pheochromocytoma)

Type 2a

Phaeochromocytoma
Retinal haemangioblastoma
CNS haemangioblastoma
Pancreatic islet tumour

Type 2b

Phaeochromocytoma
Retinal haemangioblastoma
CNS haemangioblastoma
Pancreatic islet tumour
Clear cell renal cell carcinoma

Type 2c

Phaeochromocytoma

Chuvash polycythaemia (VHL gene inactivation)

CNS = Central nervous system.

Fig. 1. Pheochromocytoma in the right and left adrenals. CT scan in a patient with VHL syndrome.

destroyed in oxygenated and iron-replete cells by a mechanism of ubiquitylation by the VHL tumour suppressor (pVHL) E3 ligase complex. The process is suppressed by hypoxia and iron chelation. The interaction between human pVHL and a specific domain of the HIF-1 α subunit is regulated through hydroxylation of a proline residue (HIF-1 α P564) by the enzyme HIF- α prolyl hydroxylase [7]. The loss of the functional VHL protein results in a high level of HIF, which causes increased production of VEGF, PDGF and TGF- α . This explains cell growth and proliferation of microvascular vessels. Additionally, HIF contributes to overproduction of tyrosine hydroxylase and catecholamines in pheochromocytomas. It is the cause of inhibition of apoptosis of neural crest cells and development of pheochromocytoma and paraganglioma [1].

Clinical Classification

VHL syndrome has been divided into 2 types depending on the risk of development of pheochromocytoma (table 1). According to different sources, in type 1, the tumours do not occur [5, 8, 9] or the risk is lower than 10% [4]; in turn, the risk of pheochromocytoma development in type 2 is estimated at approximately 40–60% [4]. Type 2 of the VHL syndrome is additionally classified

into 3 subtypes associated with the risk of clear cell renal cell carcinoma development. Type 2a is associated with development of retinal and central nervous system haemangioblastomas and pheochromocytomas, whereas clear cell renal cell carcinoma is extremely rare, and the mortality rate is close to the population average [10–13]. Type 2b, which is most common in European countries (except Germany), is characterized by the occurrence of clear cell renal cell carcinoma, which may be accompanied by the same neoplasia as in type 2a [14]. In turn, type 2c is connected to the occurrence of pheochromocytomas only [15]. The spectrum of VHL syndrome additionally comprises Chuvash polycythaemia, otherwise known as familial erythrocythaemia type 2. It is a rare form of the disease characterized by the absence of tumours with a particularly high incidence in the Chuvash population inhabiting the Volga river region [1, 10].

The course of VHL syndrome is associated with the development of multiple tumours, the most common of which include retinal and central nervous system haemangioblastomas, clear cell renal cell carcinoma, pheochromocytomas (fig. 1), pancreatic islet tumours, endolymphatic sac tumours, renal and pancreatic cystadenomas, as well as epididymal cystadenomas in men and cystadenomas of the broad ligament of the uterus in women [16]. Tumours that develop in VHL syndrome are usually bilateral and multifocal but rarely malignant [2,

17]. Sporadic neoplasms, cerebellar haemangioblastoma, and renal cell carcinoma occurring in VHL syndrome are diagnosed in very young patients and result from somatic mutation of both alleles of the VHL gene [18].

Haemangioblastomas in the Central Nervous System

Haemangioblastomas are the most typical feature of VHL syndrome and they occur in about 40% [19] to 60–80% of cases [20, 21]. The first symptoms usually comprise haemangioblastomas in the retina, cerebellum, and other parts of the central nervous system [22]. Because of germline mutation, haemangioblastomas of the central nervous system sometimes develop before birth and are diagnosed early – often before the age of 10 years. The signs and symptoms include weakness, pain in the arms and legs, back pain, headaches, numbness, and dizziness. In laboratory investigations, polycythaemia may be observed as a result of erythropoietin overproduction (caused by a high level of HIFs – major transcription factors under hypoxic conditions). Haemangioblastoma is diagnosed by MRI. In patients over the age of 10 years with VHL syndrome, MRI is recommended once a year. Small and asymptomatic tumours need only to be carefully watched. Symptomatic tumours or those located in important regions, e.g. in the cerebellum and near optic nerves, as well as large haemangioblastomas should be removed by surgical resection or by treatment with the gamma knife. Haemangioblastomas and postoperative morbidity are important causes of physical disability in VHL patients [23].

Retinal Haemangioblastoma

Visual loss remains one of the major complications of VHL disease; hence, early ophthalmologic screening is very important. Similarly to haemangioblastoma in the central nervous system, the neoplasm develops early in the foetal period and before the age of 10 years. Only one tumour develops in one eye. No symptoms are observed in most patients. Retinal haemangioblastomas are detected by ophthalmoscopy or fluorescein angiography. A screening examination of the retina should be carried out at least once a year. The treatment of choice is laser photocoagulation in the early stage. In large tumours with vision loss, removal of the affected eye should be considered.

Another cause of vision defects is retinopathy connected with arterial hypertension in the course of phaeochromocytoma development [24–26] (fig. 2).

Phaeochromocytoma

Pathophysiology

In the course of VHL syndrome, phaeochromocytomas tend to develop in the adrenal gland or paraganglia in children and young patients [11]. They secrete various substances, the most important of which are adrenaline, noradrenaline, and dopamine [27, 28].

Clinical Features

The most common symptoms of phaeochromocytoma include headaches, drenching sweats, bouts of anxiety and agitation, palpitations, and skin pallor often regarded as pathognomonic symptoms [29]. Some studies claim that paroxysmal hypertension and persistent arterial hypertension are the major symptoms of phaeochromocytomas. The literature provides information that arterial hypertension in paediatric patients usually is chronic, unlike in adults, who are affected by periodic hypertension episodes [30, 31]. Persistently high levels of arterial blood pressure may lead to the development of complications such as hypertensive cardiomyopathy or retinopathy and retinal detachment. Other complications that may occur in the course of phaeochromocytoma include myocardial infarction and heart failure, arrhythmia, stroke, sudden cardiac death, and, less frequently, Takotsubo cardiomyopathy and adrenergic myocarditis [32–38].

Investigation and Diagnosis

Phaeochromocytomas are diagnosed with biochemical and imaging analyses in patients aged between 10 and 40 years [1, 39–42]. The presence of hormonally active tumours can be detected by determination of catecholamine and methoxycatecholamine levels in plasma or 24-hour urine collection. Currently, determination of methoxycatecholamine levels in plasma is regarded as the most useful although hardly available method; therefore, determination of methoxycatecholamine levels in 24-hour urine collection is the method of choice [27]. The high sensitivity of this method is related to the fact that catecholamines (adrenaline and noradrenaline) are secreted by the tumour periodically, and elevated levels thereof can only be detected during episodes in which large amounts of the substances are secreted by the tumour. In turn, the level of methoxycatecholamines is permanently elevated, which is associated with the internal conversion of catecholamines to methoxycatecholamines within the tumour [43–52].

The proposals for a surveillance protocols for VHL syndrome in mutation-positive children with and without clinical manifestations are presented in tables 2 and 3.

Table 2. Proposal for a surveillance protocol for VHL syndrome in children according to Maher et al. [21]

Screening	Methods	Start of screening	Time
Retinal angioma	Ophthalmic examination	Infancy or early childhood; since the first year of life in children with genetically diagnosed VHL syndrome [1]	Every 12 months
CNS haemangioblastoma	CNS MRI	Since the first year of life in children with genetically diagnosed VHL syndrome [1] especially in adolescents	Every 12–36 months
Renal carcinoma and pancreatic tumours	Ultrasound and/or MRI of the abdomen	Since 16 years of life	Every 12 months
Phaeochromocytoma	Blood pressure monitoring 24-hour urine samples Catecholamine metabolites MRI of the abdomen Scintigraphy	Since 8 years of life	Every 12 months

CNS = Central nervous system.

Fig. 2. Development of hypertensive retinopathy in a patient with VHL. Optical coherence tomography before and after phaeochromocytoma surgery.

Table 3. Proposal of a surveillance protocol for VHL syndrome in mutation-positive children without clinical manifestations

Methods	Screening	Start of screening	Time
Ophthalmic examination	Retinal angioma	Infancy or early childhood; since the first year of life in children with genetically diagnosed VHL syndrome [1]	Every 12 months
CNS MRI	CNS haemangioblastoma	Since the first year of life in children with genetically diagnosed VHL syndrome [1], especially in adolescents	Every 36 months
Ultrasound of the abdomen	Phaeochromocytoma, renal carcinoma, and pancreatic tumours	Since 8 years of life [1, 21]	Every 12 months
Blood pressure monitoring	Phaeochromocytoma	Since 8 years of life	Every 12 months
24-hour urine samples catecholamine metabolites	Phaeochromocytoma	Since 8 years of life [1, 21]	Every 12 months
MRI of the abdomen	Phaeochromocytoma, renal carcinoma, and pancreatic tumours	Since 8 years of life [1, 21]	Every 36 months

CNS = Central nervous system.

Treatment

In the course of VHL syndrome, phaeochromocytomas are assumed to secrete mainly noradrenaline and methoxynoradrenaline [53–55]. This is important in the premedication of patients before surgery, as in this case the use of a beta-receptor blocker as a sole drug could cause a sudden increase in blood pressure. Noradrenaline secreted by the tumour stimulates alpha-1 receptors causing severe vasoconstriction, while vasodilating beta-receptors would be blocked. Therefore, the noncompetitive alpha-receptor antagonist phenoxybenzamine is a drug of choice. Selective alpha-blockers, e.g. prazosin and doxazosin, and calcium channel blockers can also be applied with good clinical outcome. In the case of persistent tachycardia, beta-receptor blockers can be used to lower the heart rate only after alpha-adrenergic receptor blockade, but never as monotherapy [29, 49]. Laboratory tests often indicate carbohydrate metabolism disorders, leucocytosis, and hypocalcaemia. The occurrence of hypocalcaemia in the course of phaeochromocytoma seems to be a common or regular phenomenon resulting from increased sequestration of calcium ions in the tumour, which utilizes them in the process of catecholamine release [56].

In the treatment of phaeochromocytoma, particularly in the paediatric population, laparoscopic partial adrenalectomy is the method of choice, which usually involves subsequent glucocorticosteroid substitution [42]. Malignant

phaeochromocytomas in VHL syndrome are rather rare, with an incidence of approximately 2.5%. However, a serious diagnostic problem is related to the fact that it is impossible to identify the benign or malignant nature of the tumours by histopathological examination, and the sole indicator of their malignancy is the development of metastases [41, 42]. Metastasis is referred to as the presence of phaeochromocytoma in body parts where chromaffin cells do not occur physiologically (e.g. lungs, bones). Infiltration of the tumour capsule does not indicate a malignant type, since this can be found in benign tumours as well. In order to identify potential malignant tumours, a PASS index has been devised, in which 10 microscopic characteristics are characterized by assigning 0, 1, or 2 points (max. score: 20). The PASS index for tumours with potentially high proliferative activity and hence possible malignancy is at least 4. An index below 4 indicates a benign nature of the tumour [27].

Both imaging diagnostics and follow-up after surgery involve scintigraphic analyses, adrenal CT, and possibly MRI of body parts with foci of increased isotope uptake in scintigraphy. The examinations should be repeated once a year for at least 10 years [52].

Renal Cell Carcinoma and Renal Cysts

As already mentioned, besides tumour-like lesions, numerous cystic lesions may occur in different localisations in the course of VHL syndrome. These are usually

asymptomatic changes detected incidentally or through targeted diagnostics. In an investigation conducted by Taylor et al. [49] of 21 patients with VHL syndrome confirmed by genetic tests, cystic lesions were found in 6 of the examined patients (29%); the changes included renal cysts in 4 patients, pancreatic cysts in 3, and an epididymal cyst in 1 patient [43]. Renal cysts are usually diagnosed incidentally in approximately 15% of patients with VHL syndrome; most frequently, they are asymptomatic and do not require treatment. Nevertheless, this type of lesions, particularly complex cysts, requires intensive supervision, as a solid mass with a clear cell renal cell carcinoma component may appear, although the phenomenon is not common [43, 49].

Pancreatic Cysts and Islet Cell Tumours in the Pancreas

Pancreatic cysts or cystadenomas are usually asymptomatic. Patients sometimes complain of pain in the abdomen. Islet cell tumours in the pancreas are malignant with metastases to regional lymph nodes. Tumour cells may produce various neuroendocrine substances. However, the prognoses after partial resection of the pancreas are relatively good [1].

Antiangiogenic Therapy for VHL-Related Tumours

Recently, clinical trials of antiangiogenic therapies have been performed. In renal cell carcinoma, thalidomide with interferon or SU5416 was used [53, 56]. In clinical trials, VEGF receptor kinase inhibitors in renal cell carcinoma

reached a partial response in more than 40% of cases and stabilisation of the disease in 90% of cases [54, 55].

Because VHL syndrome is a lifelong disease, transfer of patients or mutation-positive children to the care of adult endocrinologists with experience in this syndrome is highly important. The patient should be transferred with complete genetic documentation, surgical documentation, and full information about laboratory investigations. Extremely important is the information about monitoring methods and previous treatment. Full care of difficult patients is possible in specialist centres with a wide diagnostic base and cooperative surgeons and endocrinologists (tables 2, 3).

Conclusions

VHL syndrome is a highly complex disease, and the diagnosis is often difficult. This implies that the diagnosis of any of the characteristic tumours, particularly in children, is an implicit indication for the necessity of diagnosis and genetic tests in the patient and family members and for intensive supervision of carriers of the mutated gene, thereby improving early diagnosis and successful treatment of the malignancies. VHL is a lifelong disease. The very expensive diagnostics and, frequently, surgical treatments are a serious problem for patients and their families. Patients with VHL syndrome should be cared for by well-trained specialists and in genetic centres, and they need psychological support by psychologists and familial support groups. Very important issues are government care and financial support.

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