REVIEW ARTICLE

Von Hippel Lindau Disease: A Review Article

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Abstract

Von Hippel Lindau (VHL) disease is an inherited disease, multisystem cancer syndrome owing to genetic mutation of the VHL tumor suppressor gene located at chromosome 3. It is inherited as highly penetrant autosomal dominant trait with affected individuals at risk of developing various benign or malignant lesions of central nervous system, retina, kidney, adrenal glands, pancreas, and reproductive system. The diagnosis of VHL can be made clinically based on the characteristic history and clinical findings. Genetic testing of germline VHL mutation may also be used to confirm the diagnosis of VHL. Treatment should be based on multidisciplinary approach as there are many complexities associated with the management of various tumors manifesting at different time frames.

Keywords: Endocrine surgery, Pancreatic mass, Pheochromocytoma, Von Hippel Lindau disease.

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Introduction

Von Hippel Lindau (VHL) is a rare autosomal dominant inherited disease comprising different neoplasms, affecting various systems of the body including the central nervous system, kidney, adrenal, pancreas, and reproductive system (Flowchart 1) having a reported incidence of 1 in 35,000–50,000 worldwide.[1–3] It occurs as a result of germline mutation of VHL gene located at short arm of chromosome 3 (3p25-26). In VHL, 80% of patients are inherited while only 20% arise *de novo*.[4] Ninety percent of patients develop one or other benign or malignant neoplasm by 65 years of age with reported mean age of initial tumor presentation at 26 years of age.

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History

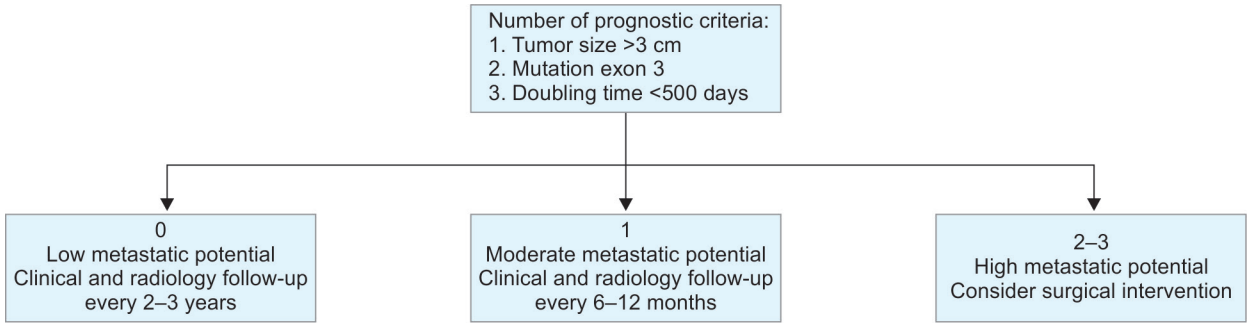
Familial retinal hemangioblastoma was first described by Treacher Collins in 1984 in pathological specimen from two siblings.[5,6] At the same time, clinical appearance and sequence of the retinal lesion were first studied by Eugene Von Hippel, which are now described as hemangioblastoma.[7]

The term central nervous system angiomatosis was first proposed by Arvid Vilhelm Lindau based on an analysis of clinical and pathological features of his 16 patients and 24 patients from literature.[8] After his publications, in acknowledgment of two authors who described retinal hemangioblastoma (Eugene Von Hippel) and cerebellar hemangioblastoma (Arvid Vilhelm Lindau), authors have shortened the descriptive term to the eponymous named the disease as *Von Hippel Lindau disease*.[9]

Epidemiology

VHL is a rare disease affecting 1 in 35,000–50,000 worldwide with a prevalence rate of 1 in 38,000 to 1 in 91,000.[1–3,10–12] Fifty percent of patients are present with one or the other symptoms by the second or third decade of life.[13] The most common presenting manifestation in VHL is the cerebellar hemangioblastomas.[11] Almost all the patients express VHL phenotype by 70 years of age.[13]

Flowchart 1: Modification to the 1998 recommendation by Libutti et al. as set out by Blansfield et al.



Among all the commonly inherited syndrome, VHL has the lowest life expectancy. Life expectancy of males is reported to be significantly higher than females (59.4 and 48.4 years, respectively).[6] Main cause of mortality in patients with VHL is due to central nervous system hemangioblastoma or renal cell carcinoma (RCC).[11,14]

Molecular Genetics

VHL Gene

VHL gene is a tumor suppressor gene located on chromosome 3p25-26. VHL gene consists of three exons that encode for a VHL protein, which is a glycan-anchored membrane protein responsible for signal transduction.[15] VHL conforms to the Knudson *two-hit* mutation, an initial germline mutation resulting in defective alleles (first hit) followed by somatic mutation (second hit). Missense mutation is the most common germline mutation (27–38%) in VHL. Other mutations consist of nonsense mutation[13–27] frame-shift mutation, large (9–20%) or microdeletion (10%) mutation, and gene rearrangement (25%).[16] In pheochromocytoma, the second hit most often consists of loss of heterozygosity (>90%).[17]

VHL Protein

VHL encodes for two proteins, a smaller one ($pVHL_{19}$), which results from an internal translation initiation from an in-frame ATG at codon 54 and produces 160 amino acids, and a larger one ($pVHL_{30}$) of 213 amino acids. Inactivating mutation between codon 54 and the carboxy terminal is responsible for VHL.

Under normoxic condition, VHL gene is responsible for degradation of hypoxia-inducible factor α (HIF α). However, mutation in VHL gene leads to hyperaccumulation of HIF α, which causes increased activation of various growth factors like vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF) glucose transporter 1, and phosphofructokinase-1. This leads to excessive angiogenesis and cellular proliferation. The pVHL also involves in the inactivation of p53 and increases NF-κB activity leading to increase in apoptosis, stabilization of microtubules, and regulation of extracellular matrix.[18]

Table 1: Genotype–phenotype of VHL

Types	*Clinical manifestations*	*Most common VHL variants*
IA	Retinal angioma CNS hemangioblastoma RCC Pancreatic neuroendocrine tumors (pNETS)	Truncating variants, exon deletions
IB	Retinal angioma CNS hemangioblastoma Low risk for RCC Pancreatic neuroendocrine tumors (pNETS)	Gene deletions encompassing VHL
IIA	Pheochromocytoma Retinal angioma CNS hemangioblastoma Low risk for RCC Endolymphatic sac tumor Epididymal cystadenomas Broad ligament cystadenomas	Missense variants (p.Y98H, p.Y112H, p.V116F)
IIB	Pheochromocytoma Retinal angioma CNS hemangioblastoma Pancreatic cyst Pancreatic NETs RCC Endolymphatic sac tumor Epididymal cystadenomas Broad ligament cystadenomas	Missense variants (p.R167Q, p.R167W)
IIC	Pheochromocytoma	Missense variants (p.V84L, p.L188V)

Types of VHL

Various types of VHL have been described, including type IA, IB, IIA, IIB, and IIC (Table 1), which are based on clinical phenotypical manifestations. Such phenotypic classification has been shown to correlate with genotypic expression.[19–21] Patients with type I VHL develop all the other tumors associated with the disease except pheochromocytoma and patients with type II develop pheochromocytoma with or without RCC.

Mutations causing disruption of protein activity including deletions, nonsense mutations, missense mutation, and other microdeletions/insertion are responsible for type I VHL.[22–24] Missense mutation resulting in substitution of amino acids is responsible for 78–96% of type II disease and may also predict a lifetime risk of pheochromocytoma (Table 2).[22,24] VHL type IIB is caused by missense mutation of codon 167 with increased risk of pheochromocytoma (82% by 50 years) as well as RCC (60% by 60 years of age).[25,26] Missense mutations at codon 238 and 259 were found in those families with only pheochromocytoma.[23,27]

Diagnostic Criteria for VHL

Clinical criteria for diagnosis of VHL were first proposed by Melmon and Rosen.[9] Lindau's disease was defined as association of cerebellar hemangioblastoma with one of the following: retinal hemangioblastoma, pancreatic cyst, renal, or epididymal abnormalities. The definition for clinical diagnosis was later refined by Lamiell et al. and Lonser et al.[5,28]

Table 2: Lifetime risk of VHL-associated tumors

Tumor (reference)	*Risk*	*Mean age of onset (range) years*
CNS hemangioblastoma	60–80%	8–61
Cerebellar[13,14,24]	35–79%	29–30 (13–61)
Brainstem[13,30]	4–22%	25–38 (16–60)
Spinal[13,14,24]	7–53%	33–34 (8–60)
Retinal angioma/ hemangioblastoma[24,31]	15–73%	25–37 (9–84)
Supratentorial hemangioblastoma[11,13]	1–7%	20–29 (14–48)
Endolymphatic sac tumor[32,33]	3–16%	22–40 (11–63)
Visceral		
Renal cell carcinoma[14,24]	30–70%	40–45 (20–69)
Renal cyst[11,13]	60%	34–39 (12–64)
Pheochromocytoma[5,34]	10–30%	20–29 (5–62)
Pancreatic neuroendocrine tumor[35–37]	15–56%	32–38 (16–68)
Pancreatic cyst[35–37]	21–72%	29–37 (12–63)
Epididymal cyst[32,33]	25%	24 (10–37)

Clinical diagnostic criteria for VHL include the following manifestations:

- CNS hemangioblastoma (including retinal hemangioblastoma)
- Renal cell carcinoma
- Pheochromocytoma or paraganglioma,
- Endolymphatic sac tumor
- Pancreatic neuroendocrine tumor or pancreatic cyst

An individual is said to have VHL if he/she has the following combination of manifestations:

- Presence of at least two CNS hemangioblastomas.
- One CNS hemangioblastoma with one of the manifestations described above.
- One of the manifestations described above with presence of mutation in VHL gene or patients with a first-degree relative with VHL.

Advanced genetic testings such as DNA sequencing and semiquantitative Southern blotting were used to identify VHL mutation in almost 100% of patients.[29]

Central Nervous System Hemangioblastoma (CNS HB)

CNS hemangioblastomas are common manifestation in patients with VHL with reported incidence of 60–70%. It may occur in the cerebellum (35–79%), brainstem,[4–22] spinal (7–53%), supratentorial (1–7%), and cauda equina (11%).[11,13,14,21,24] They are usually multifocal with mean age of onset at the second and third decade of life. Although benign, hemangioblastoma may usually cause significant morbidity and mortality as a result of mass effect of the tumor.[38] Mass effect may be due to growth of the tumor, surrounding edema, or formation of cyst (associated cyst occurs with 30–80% of hemangioblastoma).

Clinical Features

Clinical presentation of patients with CNS hemangioblastoma usually depends on the tumor size and site involved. Even a smaller lesion in the brainstem and spinal cord can produce significant symptoms as compared to those located in the cerebellum. Patients with cerebellar hemangioblastoma may present with headache (12%), vertigo (8%), diplopia (8%), gait ataxia (64%), vomiting (8%), and dysmetria (64%).[38,39] Rarely patients may present with spontaneous intracranial bleed. Patients with brainstem HB are usually present with hyperaesthesia (55%), gait ataxia (22%), dysphagia (22%), hyperreflexia (22%), headache (11%), and dysmetria (11%). Patients with spinal cord HB may present with hyperaesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), pain (17%), and incontinence (14%).[30]

Localization Study

Gold standard imagining modality for detecting and monitoring CNS HB is contrast-enhanced magnetic resonance imaging (MRI). Tumors as small as 2 mm can be visualized on T1W image. T2W image and fluid-attenuated inversion recovery (FLAIR) are used to detect cyst or edema. On injecting gadolinium contrast, nodules show hypervascular enhancement with no enhancement in the cyst wall. Arteriography is used to assess the drainage of large tumor and their vascular supply. On computed tomography (CT), cerebellar HB appears as well-defined homogenous mass with avidly enhancing mural nodule on unenhanced image. Spinal HB is visualized on CT an avidly enhancing mass, flow voids may be seen, and cyst may be seen in 50–100% of cases.

Grossly, CNS HB appears yellow solid well-circumscribed mass or distinct, red, vascular mass with thin layer of capsules. Histologically, the tumor consists of polygonal stromal cells with lipid-rich cytoplasm surrounding a vascular capillary network lined with hyperplastic endothelial cells.

Treatment

Surgery is the mainstay of treatment in patients with CNS HB.[5,40,41] Patients with symptomatic lesions require early surgery whereas those with asymptomatic lesions can be either managed with surgical resection or can be followed up with annual imaging studies. Preoperative embolization to reduce the tumor vascularity has been done at some centers but it is not routinely used as it has been found to be associated with additional risk.[5] Surgical intervention of spinal cord cyst/syrinx is recommended.

Stereotactic surgery is increasingly becoming popular. It may be useful in those patients with multiple CNS lesions or those with small tumors.[42,43] Pan et al. in their study in 2017 including 19 patients revealed that 94% of tumors were stable or showed sign of regression with 92% local control at 5 years. Symptomatic improvement was seen in 13 of 16 tumors.[44]

Endolymphatic SAC Tumor

Endolymphatic sac tumor is a benign tumor of vestibular aqueduct seen in 3–16% of VHL patients.[5,32,33] They usually present during the second to third decade of life but can involve any age-group. Bilateral involvement is seen in 30% of the patients.[32]

Clinical Features

Patients with these tumors may present with either partial or complete hearing loss, tinnitus, vertigo or facial paresis.[32,45]

Localization Study

Imaging modalities include CT of temporal bone and MRI with contrast of the auditory canal. CT changes include moth-eaten appearance of the petrous temporal bone, presence of calcific spiculation at the center, and presence of posterior rim calcification.[46,47] On MRI, they may appear hyperintense on T1W, secondary to hemorrhagic and proteinaceous contents. They may be either homogenous or heterogeneous intensity after pre-and post-contrast T1W images with variable patchy enhancement on post-contrast MRI.

Histopathology analysis shows highly vascular tumor with papillary cystic lesion lined with cuboidal epithelium, filled with proteinaceous contents with infiltrating surrounding connective tissues and bones.

Treatment

Surgery is the mainstay of treatment for these tumors and curative for completely excised tumors. Presence of progressive sensorineural hearing loss, vestibular symptoms, facial nerve compression, and local mass effect are various indications for surgery. After surgery, improvement in hearing has been reported in 97% of patients and complete resection of tumor can be achieved in 91% of patients with 3% risk of recurrence. Complete excision of tumor is associated with only minimal risk of recurrence (3%).[48]

Renal Cell Carcinoma and Cyst

RCC is the major malignant lesion in VHL patients affecting up to 30–70% of patients, occurring most commonly in the third or fourth decade of life but can present in any age-group with around 70% of patients developing RCC by 60 years of age. Cystic lesions in VHL can either be simple cyst, complex cyst, or cystic RCC. Transformation of renal cyst to RCC is rare.[27] Up to 1,100 cysts and 600 RCC foci can be found in a single kidney.[49] Patient of age <50 years is suspected to have VHL is he/she present with bilateral or multifocal RCC.

Clinical Features

They usually remain asymptomatic for long duration. When symptoms are present, large RCC may present with flank pain, abdominal mass, and/or hematuria. Renal function may remain normal even in patients with multiple cysts. As they are rarely symptomatic, early detection and diagnosis during screening have great impact on overall outcome.

Imaging

Ultrasound can differentiate solid from cystic lesion but its role is limited in complex cyst. Contrast-enhanced computed tomography (CECT) with renal protocol is the gold standard imaging modality for assessment as well as for characterization of renal lesion in patients with VHL. On CT, solid RCC is usually heterogeneous and shows early avid enhancement followed by delayed washout. On MRI, solid RCC appears hypointense on T1W image and hyperintense on T2W image. Those with presence of hemorrhagic foci may appear hyperintense on T1W image. Simple renal cyst appears hypointense on T1W and hyperintense on T2W.

Histology

Grossly, solid RCC appears well-defined encapsulated mass with areas of cystic degeneration or hemorrhage in between. Microscopically, both RCC and renal cyst are of clear cell type with presence of nest of epithelial cells having clear cytoplasm and well-defined cell membrane, separated by highly vascular stroma.

Treatment

Recommendation for treatment of VHL patients with renal lesion depends on type and size of the tumor. Currently, a 3 cm cutoff is often recommended for surgical excision. Previously, radical nephrectomy was the treatment of choice for VHL patients with RCC but now various newer studies have demonstrated that patients can be managed with either partial or nephron-sparing nephrectomies with better 5 and 10 years survival as compared to radical nephrectomies. Furthermore, the need for dialysis is comparatively lower even after multiple partial nephrectomies.[50,51]

RCC shows slow growth rate with reported growth rate of 0.2–2.2 cm/year with a mean doubling time of 24 months.[52,53]

Image-guided ablative surgeries including cryoablation and radiofrequency ablation are being increasingly used for smaller lesion or those who might require multiple surgical procedures. These modalities of treatment are contraindicated in tumor adherent to major abdominal structures.[54] In patients with metastatic RCC, various types of tyrosine kinase inhibitors like sunitinib, sorafenib, axitinib, or pazopanib have been tried with limited success.[55,56]

Pancreatic Neuroendocrine Tumors and Cyst

Pancreatic lesions are rare manifestations in patients with VHL and are being diagnosed as a result of better understanding of the disease added with improved imaging techniques. Various pancreatic manifestations in patients with VHL include pancreatic cyst, serous cystadenomas, and pancreatic neuroendocrine tumors. Pancreatic cysts are usually asymptomatic (94%), multiple (84%) and may be the only manifestation in 12% of patients with VHL.[35] Serous cystadenomas occur in 11% (range, 9–17%) and are usually asymptomatic or may present with some nonspecific abdominal pain, pancreatic insufficiency, or diabetes mellitus. They are usually well-demarcated and multiloculated, separated by thin fibrous septa. The wall of these cystic lesions is lined by cuboidal epithelium rich in glycogen.[57]

Pancreatic neuroendocrine tumors (pNETs) are found in 15–56% of patients with VHL.[35] They are usually seen in the third to fourth decade of life but can present at a very early age, much younger than that of patients with sporadic pNETs. Pancreatic lesions in VHL are usually nonfunctional, multiple, and can be located throughout the pancreases but are commonly found in the head and uncinate process. They are usually asymptomatic but can rarely present with abdominal pain due to pancreatitis, jaundice, or gastrointestinal bleeding.[58,59] Reported incidence of malignancy in patients of VHL with pNETs varies from 8 to 13%.[37] Patients with malignant pNETs presenting with metastasis have average survival of only 1–3 years.[60] Certain indicators of malignant potential are size of tumor >3 cm, tumor doubling time of 500 days, and mutation in exon 3 which is found in 80% of patients with metastatic pNETs as compared to 46% of those without metastasis.[35,60,61]

Imaging

Abdominal CT and MRI have been found to play an important role in evaluating pancreatic lesion in VHL patients. For surveillance of patients with simple and complex pancreatic lesion, CT is preferred over MRI.[60] On CT, pancreatic cysts are hypoattenuating without any enhancement at the early arterial phase. CT features of serous cystadenomas include multiloculated lesion giving a bunch of grape appearance with an enhancing central scar with stellate calcification, which is usually seen in 20% of cases. On MRI, they are usually hypointense on T1 and hyperintense on T2-weighted images.

On unenhanced CT, pancreatic neuroendocrine tumors demonstrate as hypoattenuating or isodense lesion but show avid enhancement on early arterial phase. Smaller lesion of <3 cm is usually homogenous and solid while tumor of size >3 cm may be heterogeneous. On MRI, pNETS are T1 hypointense and T2 hyperintense. The use of fluorine 18 (18F) fluorodeoxyglucose (FDG) PET/CT has been reported to be more sensitive than CT in detecting primary as well as metastatic lesions. Another advantage of FDG PET/CT is that it can provide potential prognostic information.[63] Recently, studies evaluating the use of ^{68}Ga-DOTA—conjugate peptides (^{68}Ga-DOTA-NOC,^{68}Ga-DOTA-TOC,^{68}Ga-DOTA-TATE) have shown promising results.[64,65]

Histology

Grossly, pNETs grossly appears as red-brown, yellow-tan, or grey well-circumscribed lesion. Histologically, the tumors are arranged in solid trabecular pattern and composed of clear cell and lipid-rich multivacuolated cells.[66] On immunohistochemical analysis, the

lesion stains positive for chromogranin A, synaptophysin, neuron-specific enolase, inhibin, and S 100 and demonstrates focal positivity for somatostatin, insulin, pancreatic polypeptide, and/or glucagon. Signs of local aggressiveness or malignancy include the presence of peritumoral fat infiltration, vascular invasion, and perineural invasion.[66]

Treatment

Treatment depends on the size, symptoms, and location of the pancreatic mass. As malignancy has been reported in only 20% of NET, those having tumor size <3 cm and are asymptomatic can be managed conservatively with follow-up at specific time interval. Some studies have shown that as many as 40% may remain stable or even decrease in size. Criteria for resection of tumor as recommended by Libutti et al. include the absence of metastatic disease, size of tumor >3 cm or >2 cm if located in the head of pancreases, and patients undergoing abdominal surgery for other pathologies. For patients with tumor less than 1 cm, they can be followed up with annual CT and MRI, and for those with tumor size of 1–3 cm, treatment depends on case-to-case assessment.[61]

Blansfield and coworkers suggested that lesions greater than 3 cm were more likely to behave in malignant fashion, those with presence of exon 3 germline mutation have high potential of metastasis and also suggested that the mean doubling time of metastatic lesion (377 days) was significantly smaller than that of nonmetastatic lesion (2,630 days). They modified the recommendation given by Libutti et al. (Fig. 1).[62]

Surgical resection includes enucleation for small tumors located away from the pancreatic duct, pylorus-preserving pancreaticoduodenectomy (Whipple's procedure) for tumor located at the head of pancreas, and partial or total pancreatectomy with replacement for multiple pancreatic lesions. In patients with hepatic metastasis, local therapies including ablative therapy or chemoembolization have been associated with long-term control of the tumor.

Epididymal Cystadenomas

Epididymal papillary cystadenomas are tumors of the mesonephric duct seen in 25–65% of men with VHL.[5] They can have unilateral or bilateral involvement. Bilateral involvement is seen in 60% of patients with VHL. They are usually seen in younger age-group of 20–30 years of age. They are small in size (1–4 cm), usually asymptomatic, or present with scrotal mass. Grossly, they are solid tumors with cystic filled space with colloid material. Histologically, tumors demonstrate small papilla that is lined by glycogen-rich cells.[67]

Imaging

They are usually diagnosed by high-resolution ultrasound. Diagnostic criteria of epididymal papillary cystadenomas include the presence of solid hypodense lesion of size more than 1 × 1.4 cm on ultrasound, slow growth, and occurrence in males with VHL.

Being benign lesions, they rarely need surgical intervention and are followed up by palpation and ultrasonography. Surgery is rarely indicated in those with local discomfort.[5]

Retinal Hemangioblastoma

Retinal hemangioblastoma is seen in around 49–62% of patients with VHL.[13,24] It is one of the most common tumors in VHL and may sometimes be the sole manifestation in VHL. The mean age of onset is 25 years (6–84 years) but in around 5% of patients, they are present in younger than 10 years. They are often multifocal and bilateral (50%).[68] Most common site of involvement is peripheral retina in 85% of cases followed by on or near the optic disk.

Clinical Features

Most retinal hemangioblastomas (61%) are usually symptomatic at presentation. Patients can present with complications of retinal hemangioblastoma such as exudative or tractional detachment, macular exudation, vitreous hemorrhage, glaucoma, and vision loss. Factors that have been found to be associated with poor vision outcomes include young age of onset, juxtapupillary lesion, extending peripheral retinal lesion, and presence of missense mutation or protein truncation.[68]

Diagnostic methods include thorough ophthalmological examination including dilated fundoscopy and slit-lamp examination. On ophthalmoscopic examination, tumors demonstrate vascular growth with dilated tortuous feeding vessel. Macular function as well as presence of any peripheral and optic nerve lesion can also be assessed by fluorescein angiography. Fluorescein angiography has also been used to confirm the presence of newly diagnosed lesions. MRI has a limited role in detecting retinal lesion.

Treatment

Early diagnosis and treatment are the cornerstone for prevention of blindness in patients of VHL with retinal lesion. Mainstay of

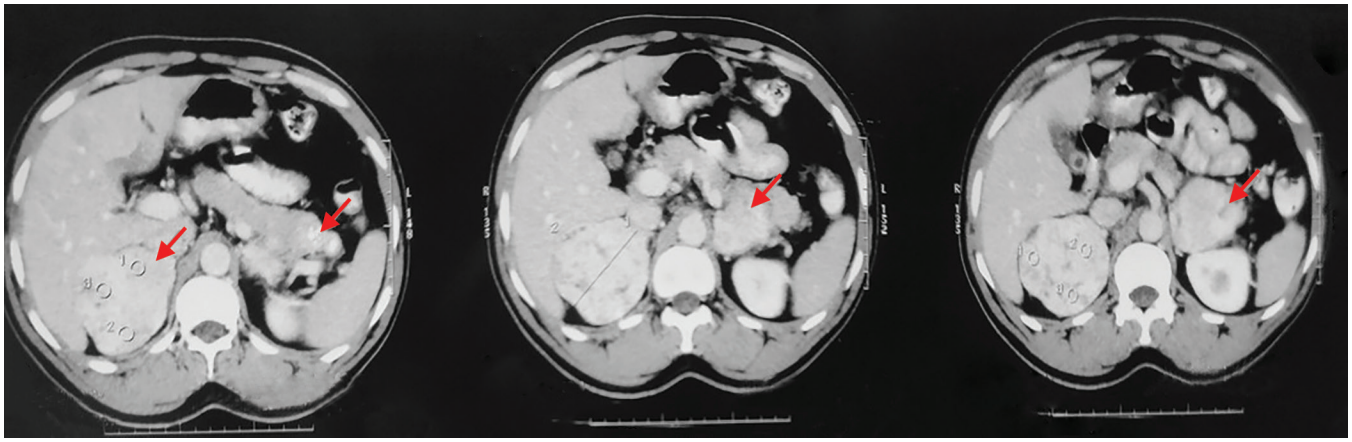


Fig. 1: Bilateral pheochromocytoma with distal pancreatic lesion in a 32-year-old man with VHL. CECT image of abdomen shows heterogenous enhancing lesion in bilateral suprarenal region (arrow) with hyperdense lesion in the pancreas (arrow)

surgical management of retinal hemangioblastoma includes laser cryotherapy and photocoagulation.[69] Vitrectomy is considered in patients with substantial tractional detachment of the retina with large fibrovascular component. For lesion close to optic nerve, they can be either monitored without any treatment or intravitreal anti-VEGF therapy may be used in smaller tumors that have been found to arrest progression, reverse exudate, and decrease edema in some cases.[68] For those not responding to usual methods, various radiotherapy treatments have been applied but their role in the management of retinal hemangioblastoma has not been defined.

Pheochromocytoma

Incidence of pheochromocytoma in patients with VHL syndrome is highly variable and mainly depends on the mutation in the VHL gene: some kindreds do not have pheochromocytoma, while others have a very high incidence of pheochromocytoma/paraganglioma. Presence of pheochromocytoma is reported in 25–30% of patients with VHL with a mean age of onset at 27 years (5–62 years).[5,34] Pheochromocytoma in VHL manifest more commonly in boys and around 20–50% maybe bilateral.[70,71] VHL pheochromocytoma have younger age of onset and are more likely to present with synchronous paraganglioma and they may be less symptomatic. In pediatrics population, pheochromocytoma may be the first manifestation of VHL. Walther et al. in their studies observed that VHL pheochromocytoma patients were associated with younger age at presentation, extra-adrenal location, smaller tumor size, and lower rates of symptoms, and normetanephrine-secreting tumors with more likely to have normal plasma/urinary metanephrine levels.[34] Risk of second tumor after initial diagnosis is around 50% and usually seen after 30 years. The reported malignancy rate is 1–5%.[68] Extra-adrenal pheochromocytoma/paraganglioma may be present in 15–20% of VHL cases mainly in abdominal region followed by the thorax and head and neck. Screening guidelines for adult patients with VHL have been established; however, screening guidelines for pediatric patients are less clear.

Clinical Features

Onset of pheochromocytoma in VHL can occur before the age of 10 years and can present with hypertensive crisis in young age. Patients can present with signs and symptoms of pheochromocytoma including intermittent or sustained hypertension, headache, palpitations, diaphoresis, pallor, nausea, vomiting, and abdominal pain. Because of the early onset of tumor compared to sporadic pheochromocytoma, screening for catecholamines usually starts at 2 years of age, especially in those with family history of pheochromocytoma.

Diagnosis

The diagnosis of pheochromocytoma is based on biochemical and imaging studies. Biochemical studies include traditional test urinary and plasma catecholamine which has now been replaced by 24-hour urinary metanephrine and normetanephrine with creatinine due to its low sensitivity and specificity. The reported sensitivity and specificity of 24-hour urinary metanephrine and normetanephrine are 98 and 98%, respectively. The diagnostic cutoff is based on normal ranges derived from normotensive volunteer reference groups.[72] Recently plasma free has been used to detect pheochromocytoma with higher sensitivity (96–100%) but lesser specificity (85–89%) than 24-hour urinary metanephrine and normetanephrine.[73,74]

Once there is biochemical evidence of pheochromocytoma, imaging test is done to localize the tumor. CECT is considered to be the most widely available and cost-effective mode of imaging for localization of pheochromocytoma. On CT, they demonstrate as heterogeneous lesion with avid enhancement with higher enhancement on the portal phase than on the arterial phase. Contrast MRI has similar sensitivity (90–100%) and specificity (70–80%) to CT for detecting abdominal pheochromocytoma.[75,76]

Radionuclide imaging using iodine 123 (^{123}I) or ^{131}I-metaiodobenzylguanidine (MIBG) scans is used for detecting bilateral or extra-adrenal tumors with a reported sensitivity of

Table 3: VHL family alliance surveillance guidelines

Age	*Surveillance recommendation*
At birth	• Clinical evaluation for neurological disturbance, ophthalmic examination, and newborn hearing test
1–4 years	• Annual comprehensive ophthalmic examination • Annual clinical evaluation for neurological disturbances and abnormalities in blood pressure, vision, and hearing
5–15 years	• All of the surveillance recommendation at birth and at ages 1–4 years • Annual biochemical tests, including plasma metanephrine or 24-hour urinary metanephrine levels • Annual abdominal ultrasound from 8 years or earlier if indicated; MR imaging of the abdomen or functional imaging with MIBG scintigraphy to be performed if only biochemical abnormalities are found • Audiology assessment every 2–3 years (annually if any audiovestibular symptoms) • MR imaging with contrast enhancement of the internal auditory canal every 2–3 years
≥16 years	• Annual comprehensive ophthalmic examination • Annual clinical evaluation for neurological disturbances and abnormalities in blood pressure, vision, and hearing • Annual biochemical tests, including plasma metanephrine or 24-hour urinary metanephrine levels • Annual abdominal ultrasound and abdominal MR imaging with or without contrast every 1–2 years • Annual MR imaging with or without contrast enhancement of the brain, petrous temporal bone, and whole spine every 2–3 years
Pregnancy	• Regular eye examination (risk of rapid progression of retinal HB) • MR imaging of the brain and whole spine without contrast • Plasma metanephrine levels in the early, mid-, and late pregnancy to test for active pheochromocytoma • Consider cesarean delivery if the patient has known retinal or CNS tumors

around 90–100% and specificity of 70–90%.[77] For detection of metastatic lesion, PET/CT, especially ^{68}Ga DOTATATE PET/CT, has been found to be more sensitive than ^{131}I MIBG.[78,79]

Treatment

Surgery via open or laparoscopic approach is the mainstay of treatment. If operable, all patients should be managed by surgical resection. Choice of surgical approach depends on size of the tumor surgeon's preference and expertise.[80] Elective surgeries in VHL patients with pheochromocytoma may need alpha adrenergic blockade. Blockade can be achieved using nonselective alpha blockade phenoxybenzamine or alpha-1 selective prazosin, doxazosin for 10–14 days before surgery. Beta-blockers may be added in patients with reflex tachycardia. In patients with hereditary pheochromocytoma, adrenal sparing surgery can be considered. Volkin et al. performed 18 successful cortical sparing surgeries in 10 pediatrics patients. Recurrence in ipsilateral gland developed in only two patients after a median follow-up of 7.2 years.[81]

Surveillance of Patients with VHL

Early identification and testing of at-risk individuals is the key to prevention of morbidity and mortality in VHL. Families with history of VHL should be counseled regarding the importance of identification of at-risk children, genetic testing to identify mutation carriers, and initiating periodic surveillance. Lifelong surveillance is mandatory given the ongoing risks of tumor development and increased risk of malignant growth with increasing age.

Various recommendations for surveillance of patients and carrier include the US National Institutes of Health[3] recommendation, the Danish VHL Co-ordination Group,[13] and the VHL Family Alliance recommendation (Table 3).[82]

Conclusion

VHL is a rare autosomal inherited disorder caused by a mutation in VHL gene located in the long arm of chromosome 3p25 comprising various benign and malignant tumors involving multiple organs. Understanding the underlying mechanism of tumor formation, natural history of various lesions associated with VHL, more precise detection using laboratory and imaging, and early detection via screening and surveillance are the keys for better outcomes.

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