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Von Hippel-Lindau Disease : A Comprehensive Review of Diagnosis, Genetics, Clinical Challenges, and Surveillance

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von Hippel-Lindau (VHL) disease is a genetic condition predisposing individuals to the development of benign and malignant tumors across various organs. This review explores the intricate genetic underpinnings of VHL disease, its clinical manifestations, and the associated malignancy risks. The latest diagnostic criteria, surveillance guidelines, and advancements in therapeutic strategies, including the Food and Drug Administration-approved hypoxia-inducible factor-2α inhibitor, belzutifan, are focused on. Through a multidisciplinary approach, tailored surveillance programs aim to improve patient outcomes while balancing intervention risks. Emerging technologies such as whole-body magnetic resonance imaging and liquid biopsies hold promises for enhancing non-invasive surveillance. This review underscores the significance of ongoing research and interdisciplinary care in managing this complex syndrome.

Key Words : von Hippel-Lindau disease · Genetics · Hemangioblastoma · Renal cell carcinoma · Pheochromocytoma.

INTRODUCTION

von Hippel-Lindau (VHL) disease, also known as VHL syndrome, is a hereditary neoplastic syndrome characterized by a predisposition to develop benign and malignant tumors across multiple organs. The disease was first described by Eugen Von Hippel in 1904 when he reported cases of retinal hemangioblastoma (HB), leading to the eponym in his name[110]. In 1926, Arvid Lindau extended the eponym after identifying the association between central nervous system (CNS) HBs and the systemic manifestations of the disease[42,64].

VHL disease is an autosomal dominant disorder that presents in early adulthood. The condition is rare, owing to the genetic predisposition it confers for developing various tumors and cysts in multiple organs, including the CNS, retina, kidneys, pancreas, and adrenal glands[73,97].

The estimated prevalence of VHL disease is approximately 1 in 36000–50000 live births worldwide[16,32,70]. The disease is associated with a reduction in life expectancy, with reported mean ages of death ranging from 40–60 years[10,81,109]. Given its potentially disastrous effects, VHL disease underscores the significance of early diagnosis and rigorous surveillance to reduce morbidity and mortality.

DIAGNOSIS

The diagnosis of VHL disease hinges on clinical features and/

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or genetic confirmation of a pathogenic mutation in the *VHL* gene. The clinical hallmark lesions of VHL disease include the CNS and retinal HBs, renal cysts and clear cell renal cell carcinomas (RCCs), pancreatic cysts and neuroendocrine tumors (NETs), pheochromocytomas (PHEOs)/paragangliomas, epididymal cysts, broad ligament cysts, and endolymphatic sac tumors (ELSTs)[16,32,71]. Although the specific composition of VHL-related manifestations may vary slightly depending on the diagnostic criteria[8,38,77], the overarching diagnostic framework includes the following : 1) the presence of a single CNS or retinal HB or a visceral tumor in a patient with a positive family history of VHL disease and 2) the presence of at least two or more VHL-related manifestations, one of which should be a HB, in a patient without a family history of the disease.

A conclusive diagnosis involves identifying pathogenic variants in *VHL*. Genetic testing for *VHL* mutations should be performed in patients suspected to be probands of VHL disease. Examples include individuals presenting with a HB or PHEO at age <50 years, RCC when aged <40 years, or multiple retinal HBs or ELSTs at any age[121]. If no germline mutation is identified in a patient meeting the clinical criteria for VHL disease, somatic mosaicism should be investigated using additional tissues (e.g., tumor or skin samples)[20]. Even in the absence of definitive genetic evidence, a diagnosis can be established based on clinical findings alone[121].

To ensure accurate diagnosis and management, patients suspected of VHL disease should undergo comprehensive evaluations, including magnetic resonance imaging (MRI) of the brain and spinal cord, ophthalmoscopy, abdominal computed tomography (CT) or MRI, biochemical assessments, and genetic testing, including family history and mutation analysis[75]. MRI with contrast enhancement is the modality of choice for detecting CNS HBs along the whole craniospinal axis, including the internal auditory canal[19]. For abdominal lesions, MRI or CT effectively reveals renal and pancreatic abnormalities. PHEOs are diagnosed based on clinical signs such as hypertension, biochemical markers, and radiographic findings of adrenal/extra-adrenal mass[5,80]. The diagnostic approaches tailored to specific lesions are summarized in Table 1.

GENETICS

VHL disease results from mutations in the *VHL* tumor suppressor gene, where structural defects or inactivation predispose individuals to tumor formation in various body parts. In 1988, *VHL* gene was mapped to the short arm of Chromosome 3 at 3p25-p26, a region also implicated in RCCs[61,98-100,107]. Since the gene's initial mapping, numerous studies have attempted to refine the genetic diagnosis of VHL disease. *VHL* isolation in 1993 significantly enhanced the accuracy of molecular diagnosis through direct gene analysis[61]. Advances in combined techniques, including Southern blotting, fluorescence *in situ* hybridization, and gene sequencing, enable the identification of all carriers of *VHL* mutations[15,21,105].

The disease follows an autosomal dominant inheritance pattern[73]. Approximately 80% of patients have an affected parent, whereas 20% of cases arise from de novo mutations[68,69,85]. The genetic mutations vary, ranging from large germline deletions to small intragenic changes, including deletions, insertions, and nonsense or missense substitutions[15,21,115]. The absence or abnormal function of the VHL protein, encoded by the *VHL* gene, leads to the accumulation of hypoxia-inducible factor (HIF). This accumulation dysregulates the expression of angio-

Table 1. Diagnostic tests and clinical findings for von Hippel-Lindau disease

Involved organ	Test	Additional finding
Central nervous system	MRI (brain and spinal cord)	Neurologic examination
Retina	Ophthalmoscopy, fluorescein angiography	Tonometry
Kidney	Ultrasound, MRI or CT scan	Urinalysis
Pancreas	MRI or CT scan	Endocrine/exocrine test
Adrenal gland	CT scan, 24-hour urinary catecholamines/metanephrine, serum catecholamines/metanephrine	Hypertension, thyroid gland enlargement, hypercalcemia
Endolymphatic sac tumor	Temporal MRI	Audiogram
Testicle, broad ligament	Ultrasound	Palpable mass, infertility

MRI : magnetic resonance imaging, CT : computed tomography

genic and mitogenic factors, driving tumor development[48,76]. In addition, a possible association between the molecular characteristics of gene mutations and clinical phenotypes has been identified[21]. Nielsen et al.[86] proposed five subtypes of VHL disease, classified based on the tumor spectrum and mutation type (Table 2). For example, missense mutations are strongly associated with PHEO, highlighting the need for intensive surveillance in carriers of these mutations[21]. In some genotype subtypes, the risk of RCC or PHEO is notably increased or decreased[86].

These genetic insights have facilitated advancements in therapeutic strategies. For example, the HIF 2-alpha (HIF-2α) inhibitor, Belzutifan, has been approved by the US Food and Drug Administration in 2021 for treating CNS HB, retinal HB, and RCC associated with VHL disease, particularly in patients who do not require immediate surgical intervention[18,25,28,47,125]. A meta-analysis reported disease stability in 31% of patients and a low progression rate of 2%[88]. Recent studies have demonstrated its efficacy and safety, with mild adverse effects such as fatigue or anemia, further reinforcing its therapeutic potential[88]. While other therapeutic agents targeting genetic and pathophysiological mechanisms are under development, most remain in the research stage. Long-term follow-up studies and further research are required to optimize treatment options, including the development of new chemotherapeutic agents.

Additionally, genetic counseling is crucial in helping families understand their risks and surveillance options. Genetic screening also enhances the cost-effectiveness of surveillance for inherited cancer syndromes by leveraging knowledge of molecular pathogenesis[69].

CLINICAL CHALLENGES

VHL disease manifests across multiple systems with a wide lesion spectrum[39,73]. Clinical symptoms depend on the location and size of the affected lesions. The most common manifestations and their lifetime risks are summarized in Table 3. Retinal and CNS HBs present earlier in the disease course than do visceral lesions, such as RCC[39].

CNS HBs

CNS HBs are one of the most significant lesions in VHL disease, frequently contributing to clinical symptoms. They occur in 60–80% of patients with VHL disease during their lifetime and are symptomatic in approximately 40% of cases at initial diagnosis[29,41,65,73,80]. The typical age of clinical presentation ranges 25–40 years, with men more commonly affected than women[29,59,86]. CNS HBs are benign vascular tumors comprising

Table 3. Common clinical manifestations associated with von Hippel-Lindau disease and their lifetime risks

Tumor	Lifetime risk (%)
Central nervous system hemangioblastoma	60–80
Cerebellar	44–72
Brainstem	10–25
Spinal	13–50
Retinal hemangioblastoma	25–60
Renal mass	25–75
Cyst	42
Renal cell carcinoma	17–75
Pancreatic mass	35–75
Cyst	75–85
Neuroendocrine tumor	10–17
Pheochromocytoma and paraganglioma	10–25
Cystadenoma	
Epididymis	25–60
Broad ligament	10
Endolymphatic sac tumors	4–16

Table 2. von Hippel-Lindau subtypes according to clinical phenotypes and gene mutation types

	Mutation variants	High risk manifestation	Low risk manifestation
Type 1	Deletions, insertions, truncations, and missense	CNS HB, retinal HB, RCC, and pancreatic NET	PHEO
Type 1B	Gene deletions encompassing *VHL*	CNS HB, retinal HB, and pancreatic NETs	RCC and PHEO
Type 2A	Missense (e.g., p.Y98H, p.Y112H, and p.V116F)	CNS HB, retinal HB, and PHEO	RCC
Type 2B	Missense (e.g., p.R167Q and p.R167W)	CNS HB, retinal HB, RCC, PHEO, and pancreatic NET	
Type 2C	Missense (e.g., p.V84L and p.L188V)	PHEO	CNS HB, retinal HB, and RCC

CNS : central nervous system, HB : hemangioblastoma, RCC : renal cell carcinoma, NET : neuroendocrine tumor, PHEO : pheochromocytoma

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endothelial and stromal cells[2]. Despite their benign histology, their rich vascularity causes hemorrhage in critical CNS structures, potentially causing life-threatening complications[39,54,80].

The cerebellum is the most commonly affected site, followed by the spinal cord, brainstem, cauda equina, and cerebral hemispheres[11,30,65]. Multiple lesions and early symptom onset are characteristics of VHL-associated HBs compared with the features of sporadic cases[65,93].

Clinical symptoms depend on the tumor's location, size, and the presence of peritumoral cysts[43,44]. Cerebellar HBs present with headaches, nausea, vomiting, hiccups, speech difficulties, or motor symptoms such as gait ataxia and dysmetria (Fig. 1)[44,65]. Spinal cord HBs may cause motor weakness, ataxia, sensory deficits, or pain, while brainstem lesions manifest as hiccups, dysphagia, sensory disturbances, or ataxia[65-67,114,117]. Symptomatic HBs, particularly those associated with peritumoral cysts, usually exhibit pronounced rapid progression[65].

Although VHL-associated HBs were traditionally believed to grow faster than do sporadic cases, recent studies indicated that most grow in a saltatory pattern, alternating between periods of growth and quiescence[65]. Median recurrence times range 16–19 years, indicating a slow growth rate[23,87]. However, approximately 20% of tumors demonstrate exponential growth and may recur late, posing challenges for detection and management, particularly in cases with extensive craniospinal involvement[2,65]. These findings underscore the significance of regular, long-term surveillance.

In the past, early surgical resection was considered for tumors with radiographic progression to prevent complications such as sudden intracranial pressure increases or spinal cord compression. However, recent treatment paradigms prioritize surgical intervention only for symptomatic cases, minimizing nonessential procedures and preserving neurological function[31,46,66,67,116]. For operable symptomatic HBs, surgical resection focuses on the solid portion, leaving the peritumoral cyst wall intact[26,106]. For inoperable or multiple lesions, or when repeated surgeries pose risks, stereotactic irradiation, such as radiosurgery or radiotherapy, is a viable alternative[4,14,89]. Radiosurgery has demonstrated effective tumor control in VHL-associated HBs, particularly for lesions located in surgically challenging areas. Compared to sporadic cases, relatively higher marginal doses are typically prescribed, with reported 5-year tumor control rates ranging from 91.9% to 93%[50,91]. Given the nature of VHL disease, which predisposes patients to frequent new tumor development[50,63], radiosurgery remains a valuable treatment option for inoperable lesions. Additionally, the HIF-2α inhibitor belzutifan has shown promising anti-tumor activity, including stabilizing disease and reducing progression rates[18,47,88]. Recently, belzutifan has demonstrated sustained anti-tumor activity in CNS HBs associated with VHL disease for over 3 years[45]. The results of the LITESPARK-004 trial further support its long-term efficacy and safety, highlighting its potential to reduce the need for surgical interventions in these patients[45]. However, further long-term studies are needed to fully assess the durability of response and long-term safety of these emerging treatments.

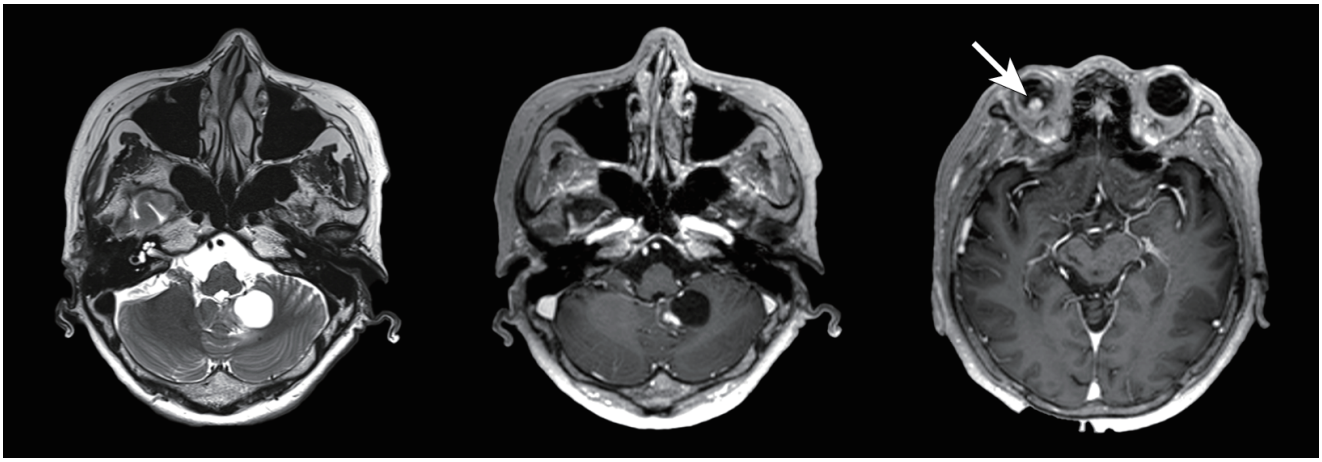

Fig. 1. Brain magnetic resonance images of cerebellar hemangioblastoma. T2-weighted images (left) and T1-weighted images with contrast enhancement (middle) show a cystic mass with a small enhancing nodule at the left cerebellar hemisphere. A small enhancing mass (right, arrow) is identified in the right eye, possibly retinal hemangioblastoma. These findings suggest the possibility of von Hippel-Lindau disease.

Ophthalmological cases

Visual challenges associated with retinal HBs are common in VHL disease, occurring in 25–60% of patients[33,75]. Retinal HBs are histologically identical to CNS HBs and usually present earlier, with a peak incidence between the ages of 10 and 30[34,39,102,119]. Bilateral retinal involvement is observed in approximately one-third of cases[59]. Although these tumors are histologically benign, they cause significant visual complications, including retinal hemorrhage, retinal detachment, and macular edema. These complications may manifest as decreased visual acuity, floaters, or blurred vision[122]. These symptoms progress without prompt treatment, potentially resulting in irreversible blindness.

Diagnosis relies on detailed ophthalmologic examinations, including ophthalmoscopy, fluorescein angiography, and tonometry. Management primarily involves laser photocoagulation or cryotherapy, which are effective in treating vascular lesions with minimal complications[36,94,118]. Early detection is crucial to prevent visual deterioration, emphasizing the significance of regular ophthalmologic examinations for early diagnosis and intervention during the presymptomatic stage[56,57].

Renal cysts and RCC and their malignancy risks

Renal manifestations in VHL disease primarily include simple cysts and clear cell RCC. Renal cysts are bilateral and multiple[84]. While they may carry a premalignant potential, malignant transformation is rare[55,113].

RCC occurs in approximately 75% of VHL cases and is the most common cause of mortality in patients with VHL disease[10,16,71,73]. The mean age of RCC diagnosis in individuals with VHL disease is approximately 37 years; however, diagnosis sometimes can be delayed owing to the absence of symptoms[3,16]. VHL-associated RCC is associated with a better prognosis than sporadic RCC[82]; however, it remains a leading cause of mortality in VHL disease owing to metastasis or uremic complications.

Regular monitoring of renal masses is critical for early identification and timely intervention in high-risk individuals. For clear cell RCCs smaller than 2 cm in diameter, active surveillance with serial imaging is generally recommended[13,96]. Surgical intervention is advised based on the risk/benefit analysis for treatment, typically for cases with growth of the tumor or with renal masses more than 3 cm[35,60,96]. For operable cases, nephron-sparing nephrectomy is the treatment of choice, where kidney function is adequately preserved[13,35]. Although surgical treatment improves survival rates, nephrectomy could cause renal failure and negatively impact quality of life[104]. Patients may need hemodialysis or kidney transplantation, which carries risks of tumor recurrence or secondary malignancies owing to immunosuppression[55,90]. Therefore, treatment plans should balance disease management with the preservation of kidney function and the patient's well-being.

Recent advances in targeted therapies have improved management options for VHL-associated RCCs. Belzutifan has shown promising results, with partial and complete responses in stabilizing the RCC reported in a phase II clinical trial[47]. Additionally, vascular endothelial growth factor receptor tyrosine kinase inhibitors have demonstrated favorable clinical responses[79]. These therapies represent significant progress in the treatment of VHL-associated RCCs; however, further studies are required to assess long-term results.

Pancreatic cysts and NETs

In VHL disease, various pancreatic masses can develop, including serous cystadenomas and NETs. The mean age at diagnosis of pancreatic lesions is 41 years[51,62]. Pancreatic cysts are common, occurring in 70–85% of VHL disease, although they are rarely symptomatic[7,101]. Most pancreatic NETs in patients with VHL disease are low-grade and nonfunctional[58]. Surgical intervention is generally reserved for symptomatic lesions or hormonally active NETs[58,83]. Although pancreatic NETs are less common in VHL disease, they carry the potential for malignancy and metastasis[51]. Early identification and appropriate management are crucial to prevent potential disease progression.

PHEOs and paragangliomas

Approximately 10–25% of patients with VHL disease develop PHEOs, which secrete catecholamines and cause symptoms such as hypertension, palpitations, and sweating[51,75]. Most PHEOs (approximately 90%) originate in the chromaffin cells of the adrenal glands, while the remaining cases develop in extra-adrenal tissues and are referred to as paragangliomas[124]. These lesions usually present in childhood, with a typical age of diagnosis between 11 and 13 years[24,27]; however, cases have been reported as early as the ages of 2 years[103]. In patients with VHL disease, PHEOs frequently manifest bilaterally, and adrenalectomy is indicated for growing lesions[112]. A comprehensive preoperative evaluation is essential to manage the risks associ-

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ated with catecholamine secretion, particularly to prevent perioperative complications such as severe hypertension or arrhythmias[40]. The overall risk of malignancy in VHL-associated PHEOs is considered to be <5%, which is lower than the malignancy rate of PHEOs unrelated to VHL disease (approximately 10%)[71].

Epididymal cystadenoma and broad ligament cyst

In male individuals with VHL disease, 25–60% develop cystic lesions in the scrotum, such as epididymal cystadenomas or cysts[16,75]. These lesions are identified through physical examination or ultrasound. However, the presence of epididymal lesions is not considered a definitive diagnostic criterion for VHL disease, as epididymal cysts are also common in the general population[1,120]. Bilateral epididymal cystadenomas in VHL disease may lead to infertility[120]; however, treatment is nonessential in most cases.

In female patients with VHL disease, cystadenomas of the mesosalpinx or broad ligament are rare[86]. These lesions are benign and are managed conservatively owing to their asymptomatic and non-progressive nature[66].

ELSTs

ELSTs are rare tumors associated with VHL disease, presenting in 4–16% of patients[6,17,74]. Common symptoms include hearing loss, tinnitus, vertigo, and facial weakness[6,66]. Genetic studies have indicated *VHL* germline mutations in 39% of ELST cases[6]. ELSTs are the initial clinical manifestation of VHL disease in 3.6–15% of patients, and bilateral ELSTs are considered pathognomonic for the disease[6,66,74].

Although ELSTs are histologically benign, they are highly vascular and invasive, usually leading to significant and irreversible audiovestibular morbidity[74]. Owing to their aggressive nature, preventive resection is recommended for symptomatic and asymptomatic patients with radiological evidence of tumors, intralabyrinthine hemorrhage, or hydrops on MRI[52,53,95]. In contrast to other CNS HBs, early intervention is critical to prevent further morbidity. Irradiation is not used as a primary treatment modality but may serve as an adjuvant therapy for residual tumors encasing major vessels[53].

SURVEILLANCE PROGRAMS

When an individual presents clinical indicators suggestive of VHL disease, a comprehensive diagnostic evaluation should be initiated. The current management strategy for VHL disease prioritizes minimizing mortality and morbidity throughout the patient's lifetime. This approach focuses on stabilizing lesions rather than pursuing radical obliteration, which may carry higher risks or nonessential interventions[26]. Active, lifelong surveillance programs are crucial in improving clinical outcomes in patients with VHL disease. These programs aim to detect emerging lesions early, monitor disease progression, and tailor interventions to optimize patient health and quality of life[8,92].

In 2022, the International VHL Surveillance Guidelines Consortium introduced updated, evidence-based recommendations for screening and treating VHL disease[22]. These guidelines emphasize a standardized, multidisciplinary approach to care. Patients should ideally be managed by clinicians with extensive experience in rare diseases. Multidisciplinary care teams are essential to provide comprehensive management of VHL-related complications. Genetic testing is recommended for patients with VHL disease and their at-risk relatives. Early detection of mutations facilitates targeted surveillance while avoiding nonessential screening in individuals who are not carriers. In addition, regular psychosocial screening and support are crucial, as VHL carriers usually experience significant psychological stress related to their diagnosis and ongoing care. The guidelines by this committee were summarized by organ system and patient age at the beginning of surveillance (Table 4). Even in specific conditions such as pregnancy, scheduled MRI surveillance should be combined with non-contrast imaging to ensure the safety of the mother and fetus[9,78]. Routine screening of the genitourinary system is not recommended unless clinically indicated.

The penetrance of VHL disease is nearly complete by the age of 65 years[70,72,84]. Beyond this age, patients develop few, if any, new lesions or symptomatic manifestations[49,123]. Thus, affected individuals and at-risk relatives should remain under regular surveillance until their seventh decade of life, when the disease is considered fully penetrated[10,70,72,73]. This approach ensures early detection and management of lesions during the active phase of the disease while minimizing unnecessary interventions in later years.

Table 4. Protocol of the surveillance by the tnternational von Hippel-Lindau surveillance guidelines consortium

	<5 years old	Beginning at the age of 5 years	Beginning at the age of 11 years	Beginning at the age of 15 years	Beginning at the age of 30 years	Beginning at the age of 65 years
History assessment and physical examination	Annually from 1	Annually	Annually	Annually	Annually	Annually
Blood pressure and pulse rate	Annually from 2	Annually	Annually	Annually	Annually	Annually
Ophthalmologic examination	Every 6–12 months	Every 6–12 months	Every 6–12 months	Every 6–12 months	Annually	Annually
Catecholamines/metanephrines		Annually	Annually	Annually	Annually	If indicated
Craniospinal axis MRI with/without contrast			Biennially	Biennially	Biennially	If indicated
Audiogram			Biennially	Biennially	Biennially	If indicated
Abdomen MRI/CT with/without contrast				Biennially	Biennially	If indicated
MRI of the internal auditory canal				Once		

MRI : magnetic resonance imaging, CT : computed tomography

CNS MRI : early detection of HBs

Studies have shown that most initial CNS HBs are detected during the ages of 11–65 years[12,65]. Therefore, the starting age for CNS imaging has been adjusted to 11 years, balancing the benefits of early detection with the burden and risks of repeated imaging[22]. For asymptomatic individuals, comprehensive annual history assessment and regular neurological examinations may serve as a reasonable alternative to frequent CNS imaging. This approach helps to reduce unnecessary imaging while maintaining vigilance for the development of symptomatic lesions.

Ophthalmologic exams : regular retinal screenings to identify HBs

Recent guidelines suggest beginning binocular funduscopy within the first year of life to identify retinal HBs early[22]. For asymptomatic patients, routine eye examinations can be performed annually after the age of 30 years[22].

Abdominal imaging : monitoring renal and pancreatic lesions

Recent recommendations have adjusted the starting age to 15 years, with routine imaging performed every 2 years[22]. If a tumor is detected during imaging, short-term follow-up or immediate treatment should be decided based on tumor size and other clinical factors[22].

Biochemical screening for PHEOs

Annual biochemical screening is recommended to begin at age 5 years, particularly for patients with *VHL* missense mutations[22]. For children with genetically confirmed *VHL* mutations, routine biochemical testing can begin as early as age 2 years[22].

Audiogram : screening for ELSTs

The recommended screening audiograms should begin at age 11 years and be repeated every 2 years to monitor audiovestibular symptoms[22]. MRI for ELST detection is not performed routinely but is recommended once between ages 15 and 20 years. Subsequent ELST surveillance can frequently be incorporated into routine CNS imaging for HBs, reducing the need for additional scans[22].

Emerging technologies

Emerging technologies such as whole-body MRI and liquid biopsies offer promising advancements for non-invasive and efficient surveillance of VHL disease. International surveillance guidelines recommend regular imaging for patients with VHL disease, which usually requires multiple expensive examinations for different body regions and repeated exposure to contrast agents. Whole-body MRI is being explored as a one-step approach to quickly and simultaneously scan the brain, spine, and abdomen using a single dose of contrast. This method has shown potential to enhance convenience and safety for patients with VHL disease[37,108]. Liquid biopsy, which involves analyzing urinary exosome-derived microRNA, is under investigation as a diagnostic tool for clear cell RCC in patients with VHL disease[111]. This non-invasive method could provide a new avenue for early detection and monitoring of malignancies in VHL disease.

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Ethical considerations

Screening for asymptomatic family members with VHL disease presents significant ethical challenges. It evokes various emotions, including anxiety and stress, and the confirmation of VHL disease or gene carrier status profoundly affects the physical and emotional well-being of affected individuals and their families. To address these concerns, providing accurate, clear, and empathetic communication about the disease is essential. Emphasis should be placed on the necessity of screening and the critical role of early detection in improving clinical outcomes. Supportive counseling and resources should also be available to help individuals and families navigate the psychological and social implications of screening and diagnosis.

CONCLUSIONS

VHL disease exemplifies a complex hereditary cancer syndrome that demands meticulous and lifelong care. Advances in genetic testing and imaging have significantly transformed the diagnosis and management of the disease, leading to improved patient outcomes. However, VHL carriers require continuous surveillance owing to the risk of recurrent and multiple tumor formation during their lifetime. Given the heterogeneity and complexity of VHL disease, a multidisciplinary approach is essential, with coordinated care provided by medical and surgical specialists across various fields. Furthermore, ongoing research into targeted therapies and gene editing holds significant promise, with the potential to revolutionize treatment paradigms. These advancements offer hope for improved medical care and quality of life for affected individuals and their families.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : NYJ, JBP; Data curation : NYJ, JBP; Formal analysis : NYK; Methodology : JBP; Project administration : JBP; Visualization : NYJ; Writing - original draft : NYJ; Writing - review & editing : NYJ, JBP

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