"VON HIPPEL LINDAU SYNDROME: AN OVERVIEW"

Sachin B. Somwanshi*, Mohini Landge1, Kiran B. Kotade2, Kiran B. Dhamak3

1Department of Pharmaceutics, P.R.E.S.’s, College of Pharmacy (For Women), Chincholi, Nashik, Maharashtra, India-422 102.
2Department of Pharmacology, P.R.E.S.’s, College of Pharmacy (For Women), Chincholi, Nashik, Maharashtra, India-422 102.
3Department of Pharmaceutical Chemistry, P.R.E.S.’s, College of Pharmacy (For Women), Chincholi, Nashik, Maharashtra, India-422 102.

ABSTRACT

Von Hippel Lindau (VHL) syndrome, or von Hippel Lindau disease is a hereditary rare genetic disorder associated with hemangioblastomas, which are blood vessel tumors of the brain, spinal cord, and eye. Von Hippel Lindau are originally described in 1911. The most recent developments have followed the identification of the VHL gene, first located on chromosome 3p25–26. The VHL gene (VHL) codes for a protein (pVHL) that is being widely investigated because of its apparent role in oxygen sensing and its link to stimulation of tumor angiogenesis through interaction with hypoxia-inducible factors and other proteins. This condition causes development of benign and malignant tumors in the central nervous system and the internal organs; tumors caused by VHL mutation include hemangioblastomas in the cerebellum, spinal cord, brain stem and retina, renal cell carcinoma (RCC), pheochromocytoma, and pancreatic carcinoma, positional vertigo, slurred Speech, nystagmus, intellectual disability. The treatment for CNS hemangioblastoma is basically by surgery, but occasionally by radiation, mainly stereotaxic irradiation. The degree of difficulty of treatment for this CNS tumor depends on its location. Almost everyone who inherits one VHL mutation will eventually acquire a mutation in the second copy of gene in some cells leading to the feature of Von Hippel Lindau syndrome. In this review, we summarize the recent literatures on the pathogenesis, clinical characteristics, diagnosis and treatment of VHL disease.

INTRODUCTION
Von Hippel-Lindau syndrome (VHL) is a hereditary condition associated with hemangioblastomas, which are blood vessel tumors of the brain, spinal cord, and eye. The eye tumors are also called retinal angiomas. People with VHL also have an increased risk of developing clear cell renal cell carcinoma, which is a specific type of kidney cancer; and pheochromocytoma, which is a tumor of the adrenal gland. Kidney cysts, which are closed sacs usually filled with fluid; pancreatic cysts, epididymal cystadenomas, which are tumors near a man’s testicles; and endolymphatic sac tumors, which are tumors of the ear that may cause hearing loss; are also features of VHL.\(^1\)(Figure 1).

![Figure No. 1: Major tumors and cysts in Von Hippel–Lindau (VHL) disease.\(^2\)](image)

HISTORICAL ASPECTS
The syndrome is eponymically derived from the name of the two physicians who described cardinal features of the disorder-The German Ophthalmologist Eugen von Hippel (1904), who credited initial description of familial retinal angiomas, and the Swedish pathologist Arvind Lindau, who provided a detailed description of cellular hemangioblastomas (1962).\(^3\)

Many others were also played an important part in the description of clinical manifestations of VHP syndrome. In 1872, Jackson first described a cerebellar haemangioblastoma, and retinal haemangioblastoma was described by Panas and Remy in 1879.\(^4\)
The first recorded case of a probable patient with von Hippel-Lindau disease was a 35-year-old woman who died in 1864 with eye and brain tumours. In 1895 von Hippel described the fundoscopic findings in the eye of a 23-year-old man, Otto Mayer, who had presented 2 years earlier with visual loss. Both the superior temporal artery and vein were dilated and supplied a prominent rounded mass located at the periphery of retina. In 1904, von Hippel presented further details of the same patient, who had developed three similar lesions, as well as another similar case, of a 28-year-old man. Von Hippel studied the histological characteristics of the right eye of Otto Mayer and concluded in 1911 that the retinal lesion was a congenital cystic capillary angiomatosis, which he named angiomatosis retinae.

However, it was Arvid Lindau who linked the retinal, cerebral, and visceral components of the disease into a single coherent entity in 1926. In his dissertation, he added 16 of his own patients to 24 previously reported patients with cystic cerebellar tumours. He noted that cerebellar tumours were frequently associated with retinal lesions but also with renal cysts, hypernephroma (renal cell carcinoma), and pancreatic and epididymal cysts. The term von Hippel-Lindau disease was first used by Davison and colleagues in 1936 and has been in common use since the 1970s. In 1964, Melmon and Rosen summarized these data and coined the term “von Hippel-Lindau disease”.

The most recent developments have followed the identification of the VHL gene, first located on chromosome 3p25–26, responsible for this disease in 1988 by Seizinger and colleagues, and fully described in 1993 by Latif and coworkers.[5-6]

**ETIOLOGY**

VHL is a genetic condition. This means that the cancer risk and other features of VHL can be passed from generation to generation in a family. The gene associated with VHL is also called VHL. A mutation, meaning alteration in the VHL gene gives a person an increased risk of developing kidney cancer and other symptoms of VHL. Nearly everyone who has VHL syndrome has an identifiable VHL mutation.[7]

**EPIDEMIOLOGY**

The incidence of von Hippel-Lindau syndrome is estimated to be 1 in 36,000 individuals. The inheritance is autosomal with high penetrance. Most people with VHL syndrome inherit an altered copy of the gene from an affected parent. However, in 20% of the cases, the altered gene is the result of a new mutation that occurred during the formation of reproductive cells.
(eggs or sperms) or very early in development. Males and females are equally affected. Unlike most autosomal dominant conditions, in which one altered copy of a gene is sufficient to cause the disorder, two copies of VHL gene must be altered to trigger tumor and cyst formation in Von Hippel-Lindau syndrome. A mutation in the second copy of the VHL gene occurs during a person’s lifetime in certain cells within organs such as the brain, retina and kidneys. Almost everyone who inherits one VHL mutation will eventually acquire a mutation in the second copy of the gene in some cells, leading to the features of Von Hippel-Lindau syndrome.\textsuperscript{8-9}

![Autosomal dominant](image)

Figure No. 2: Von Hippel–Lindau disease is inherited in an Autosomal Dominant pattern.

**VHL PROTEIN REGULATION**

![VHL Protein Regulation](image)

Figure No. 3: VHL Protein Regulation.
The regulation of HIF1α by pVHL. Under normal oxygen levels, HIF1α binds pVHL through 2 hydroxylated proline residues and is polyubiquitinated by pVHL. This leads to its degradation via the proteasome. During hypoxia, the proline residues are not hydroxylated and pVHL cannot bind. HIF1α causes the transcription of genes that contain the hypoxia response element. In VHL disease, genetic mutations cause alterations to the pVHL protein, usually to the HIF1α binding site. The VHL protein (pVHL) is involved in the regulation of a protein known as hypoxia inducible factor 1α (HIF1α). This is a subunit of a heterodimeric transcription factor that at normal cellular oxygen levels is highly regulated. In normal physiological conditions, pVHL recognises and binds to HIF1α only when oxygen is present due to the post translational hydroxylation of 2 proline residues within the HIF1α protein. pVHL is an E3 ligase that ubiquitinates HIF1α and causes its degradation by the proteasome. In low oxygen conditions or in cases of VHL disease where the VHL gene is mutated, pVHL does not bind to HIF1α. This allows the subunit to dimerise with HIF1β and activate the transcription of a number of genes, including vascular endothelial growth factor, platelet-derived growth factor B, erythropoietin and genes involved in glucose uptake and metabolism.[10-11]

PATHOGENESIS
It has been demonstrated that VHL disease originates from mutations of the von Hippel-Lindau (VHL) gene. This familial autosomal-dominant syndrome can lead to the development of a number of benign and malignant tumors. Those tumors include; CNS and retinal hemangioblastomas, pheochromocytomas, and clear cell renal carcinomas. At least 30% of the disease-causing mutations in the VHL gene need to be involved in order to cause clinical manifestations.[12] Identification of these mutations is not possible using PCR-based mutational scanning methods. Traditionally, quantitative Southern blot analysis has been utilized for the detection of complete or partial deletions and further alterations.[13]

CLASSIFICATION
Based on clinical manifestations, patients with VHL are classified into two different types.[14-15]

Type1 (without pheochromosytoma)

- Type 1A (only without pheochromocytoma).
- Type 1B (without pheochromocytoma and protection from renal cell carcinoma).
Type 2 (with pheochromocytoma)
- Type 2A (with pheochromocytoma and hemangioblastoma).
- Type 2B (with pheochromocytoma and renal cell carcinoma).
- Type 2C (with isolated pheochromocytoma, without hemangioblastoma or renal cell carcinoma).

SIGNs AND SYMPTOMS
Sometimes von Hippel Lindau disease has no symptoms. When it does have signs, they vary from person to person and depend on the problems caused by the disease.

Cerebellar Hemangioblastoma Symptoms
- Increased intracranial pressure and limb ataxia
- Headache
- Slurred speech
- Nystagmus
- Positional vertigo
- Labile hypertension (without pheochromocytoma)
- Vomiting
- Wide-based gait

Patients with spinal cord lesions most frequently present with pain, followed by signs of segmental and long track dysfunction due to progressive compression of the spinal cord. Patients with hemangioblastoma of the brain stem present with a long history of minor neurological symptoms that, in most cases, are followed by sudden exacerbation, which may necessitate immediate neurological intervention. In some patients of VHL disease, CNS hemangioblastomas may produce erythropoietin-like substances, resulting in polycythemia (usually clinically asymptomatic) at the time of diagnosis.

Pheochromocytoma Symptoms
Pheochromocytomas may cause symptoms that are like what you feel in an emergency (“fight or flight”) situation. These include
- High blood pressure, either all the time or just sometimes
- Sweating
- Headache
- Rapid or irregular heartbeats
- Feelings of anxiety, panic and fear
- Pale skin
- Dizziness or lightheadedness when you stand
- Tremor
- Weight loss

**Other symptoms**
- Abdominal pain and swelling,
- Back pain,
- Blood in the urine,
- Swelling of the veins around a testicle,
- Flank pain and
- Weight loss.

Other symptoms may include excessive hair growth in females, pale skin, vision problems, anaemia (resulting from depression of erythropoietin), hypertension, hypocalcaemia, sleep disturbances and recurrent fevers. RCC is difficult to treat and rarely cured once it has spread beyond the kidney and current therapies have limited efficacy.¹⁸

**EARLY DETECTION**
Because VHL varies so widely, there is no consistent set of symptoms in each person. Each possible feature of the disease is detected in a different way. If you have a family history of VHL, it is important to inform your doctor, or your child’s pediatrician, and begin screening early, before any symptoms occur. Most VHL lesions are much easier to treat when they are small. Confer with your doctor about the best time to begin screening and the right schedule for return visits. We recommend informing the pediatrician of the family’s history of VHL and beginning eye examinations for children at risk by age 1–3 years. You and your doctor Nearly all of us at one time or another have wondered if it is better not to know perhaps if we just don’t go through the testing, we’ll be okay. For a while, that may seem to be true. But a number of possible complications of VHL are sneaky you may not even have symptoms until the problem has developed to a critical level. It is a little like not taking care of your house or car. You may get away with it for awhile, and then it all catches up with you and it costs you a great deal all at once. There is clear, documented evidence that you will stay healthier longer if you use medical diagnostic techniques wisely and are watchful.
DNA testing can be used to determine which members of the family need to be followed closely. It can also determine which members may be reassured that they do not carry the altered VHL gene. If family members do not have the altered VHL gene, they will not need further testing. They also cannot pass the altered gene to their children.\textsuperscript{[19]}

**DIAGNOSIS**

The detection of tumors specific to VHL disease is important in the disease's diagnosis. In individuals with a family history of VHL disease, one hemangioblastoma, pheochromocytoma or renal cell carcinoma may be sufficient to make a diagnosis. As all the tumors associated with VHL disease can be found sporadically, at least two tumors must be identified to diagnose VHL disease in a person without a family history. Genetic diagnosis is also useful in VHL disease diagnosis. In hereditary VHL, disease techniques such as Southern blotting and gene sequencing can be used to analyse DNA and identify mutations. These tests can be used to screen family members of those afflicted with VHL disease; \textit{de novo} cases that produce genetic mosaicism are more difficult to detect because mutations are not found in the white blood cells that are used for genetic analysis.\textsuperscript{[20]}

**Benefits of diagnostic and predictive VHL testing**

Providing equity of access to VHL genetic testing across the country avoids local variations in funding arrangements for genetic testing provided by the states. Patients will no longer be affected by limited annual genetic testing budgets. Medicare listing will permit more patients with suspected VHL syndrome to be identified, with attendant benefits to themselves and their asymptomatic family members, through cascade testing.

Patients desire clarity in their diagnosis and the VHL genetic test would allow this. For a patient or family member that tests positive, it will provide confirmation of a VHL syndrome clinical diagnosis. It may also facilitate patient compliance with the intense surveillance that is necessary with the condition. For a patient or family member that tests negative, it would provide confidence that they do not have undiagnosed VHL syndrome. In patients with clinical symptoms, this exclusion of VHL would allow a differential diagnosis to be undertaken. A negative test result would also exclude the necessity for intense long-term surveillance for neoplasms, reduce the associated stress on the individual/family, and limit any possible impact on reproductive choice.\textsuperscript{[21]}
Disadvantages of diagnostic and predictive VHL testing
Testing must be done in the setting of a clinical genetics unit for adequate management of expectations regarding sensitivity/specificity of testing and implications of results. There may be family pressure to be tested; hence, genetic counselling is essential. For a patient with a clinical diagnosis of VHL and a positive genetic test result, there would be little change to circumstances as it is simply a confirmation or genetic explanation for a condition already known to be present. For asymptomatic family members with a positive genetic test result, certain knowledge of a known predisposition to VHL syndrome could be overwhelming, causing psychological harm—although, with pre-test counselling from a clinical genetics unit or similar service, there are seldom major long-term problems. The genetic defects of these subgroups are also distinct. Whereas type 2 disease is caused almost exclusively by missense mutations, type 1 disease can result from deletions and truncations in addition to missense mutations. Knowing the type of VHL disease could aid medical practitioners in targeting screening towards the most likely manifestations of the syndrome in that patient. Predictive VHL genetic testing would allow triaging of first- and second-degree family members of patients with confirmed mutations in the VHL gene, providing a mechanism for identifying the individuals that require lifelong routine screening.[21]

CLINICAL NEED
VHL syndrome affects approximately 1 in 91,000 people worldwide. It is characterised by both benign and malignant tumours in specific organs of the body, including the central nervous system (CNS), eye, inner ear, kidney, pancreas, adrenal gland, and epididymis in the male and broad ligament in the female. The mean age of onset of VHL disease is 26 years, and 90% of affected individuals will show signs of the disease by age 65 years. Before routine comprehensive screening, the median survival of patients with VHL syndrome was less than 50 years. Today, the life expectancy is similar to the norm due to improved screening guidelines (Nordstrom-O'Brien et al 2010). Mortality is mostly due to metastases of renal cell carcinoma (clear-cell) and complications of haemangioblastomas of the CNS. There are an association between genotype and phenotype that forms the basis of the clinical classification of VHL syndrome.[21]

TREATMENT
Von Hippel-Lindau syndrome is a complex disorder. Its management is associated with the treatment of the various clinical aspects associated with it.
For CNS hemangioblastomas, stereotactic radiotherapy may be an alternative to conventional neurosurgery for non-cystic small hemangioblastomas though adverse reactions may occur.

Most retinal angiomas respond well to laser photocoagulation or cryotherapy. External beam radiotherapy (EBRT) and vitreoretinal surgery are also a useful option in the treatment of retinal angiomas.

For renal cell carcinoma, nephrectomy (surgery to remove all or a part of the affected kidney) is recommended. Other useful options are chemotherapy, immunotherapy and radiation therapy.

Treatment of pheochromocytoma is with surgical removal but it is a high-risk procedure because intraoperative manipulation of the tumor may induce excessive catecholamine excretion, resulting in a life threatening hypertensive crisis.

Laparoscopic adrenalectomy has been shown to be a useful technique, alternative to surgery, for treating pheochromocytoma, in patients with tumors smaller than 7 cm.

Pancreatic neuroendocrine tumors are managed by surgical resection, depending on size and location of tumor.

For endolymphatic sac tumors, surgery is curative; can relieve vertigo and may prevent progression of hearing loss.

Since Von Hippel-Lindau is a hereditary disease and is transmitted in an autosomal dominant manner, family members of patients with these syndromes should be educated about familial multiple-cancer syndrome, and genetic counseling should be offered to the patients and family members.\[22\]

**DIET**

Dietary guidelines for patients with von Hippel-Lindau disease have been recommended by the VHL Family Alliance. These guidelines rely more on expert opinion and common sense rather than on randomized trials. The VHL Family Alliance encourages patients with von Hippel-Lindau disease and at-risk family members to make the following dietary changes.\[19\]

- Limit alcohol intake.
Increase consumption of phytochemicals, such as grains, cruciferous and other vegetables, fruits, and spices.

Decrease consumption of protein from fish, poultry, and meat.

**VON HIPPEL LINDAU DISEASE SCREENING**

Screening exams are important medical tests done when at risk but don’t have symptoms. They help find disease at its earliest stage. In von Hippel Lindau disease, early diagnosis increases your chance for successful treatment and better quality of life.\(^{[17]}\)

**Screening Guidelines**

**10 Years Old and Under**

- Complete general history and physical exam, including blood pressure measurement and neurological exam, every year.
- Thorough eye exam at diagnosis and every year.
- Ultrasound (link to definition) of the abdomen at diagnosis and every two years
- CT (computed axial tomography) scan (link) or MRI (magnetic resonance imaging) (link) if a problem is found on the ultrasound or if laboratory tests for pheochromocytoma are abnormal.
- MRI of the brain and spine if you have neurologic symptoms.
- Tests for pheochromocytoma at diagnosis and every year if you have a family history of VHL 2 or mutations associated with VHL 2. If you have a family history of VHL 1 or a mutation not associated with pheochromocytoma, you may want to be tested every two years.
- Tests for pheochromocytoma before any surgery.
- Hearing exam at diagnosis and every two years or as needed. This should include an MRI or CT scan of ear canals if you have hearing loss, ringing in the ears, dizziness or problems with balance.

**10 to 15 Years Old**

- Complete general history and physical exam, including blood pressure measurement and neurological exam, every year.
- Eye exam at diagnosis and every year; every six months during puberty.
- Ultrasound of the abdomen at diagnosis and every two years.
CT (computed axial tomography) scan or MRI (magnetic resonance imaging) if a problem is found on the ultrasound or if laboratory tests for pheochromocytoma are abnormal.

MRI of the brain and spine at diagnosis and every year.

Tests for pheochromocytoma at diagnosis and every year in patients with a family history of VHL type 2 or mutations associated with VHL 2. If you have a family history of VHL1 or in patients with mutations not associated with pheochromocytoma, you may want to be tested every two years.

Tests for pheochromocytoma before any surgery.

Hearing exam at diagnosis and every two years or as needed. This should include an MRI or CT scan of ear canals if you have hearing loss, ringing in the ears, dizziness or problems with balance.

15 Years Old and Older

Complete general history and physical exam, including blood pressure measurement and neurological exam, every year.

Thorough eye exam at diagnosis and every year.

Ultrasound of the abdomen at diagnosis and every year from ages 15 to 20.

MRI of the brain and spine at diagnosis and then every year. If your doctor says you are at low risk, you may need an MRI every two years.

CT or MRI scan of the abdomen at 20 or at diagnosis, then every two years. Alternate with ultrasound of every other year.

Tests for pheochromocytoma at diagnosis and every year in patients with a family history of VHL type 2 or mutations associated with VHL 2. If you have a family history of VHL1 or gene mutations not associated with pheochromocytoma, you may want to be tested every two years.

Tests for pheochromocytoma before any surgery and during pregnancy.

Hearing exam at diagnosis and every two years or as needed. This should include an MRI or CT scan of ear canals if you have hearing loss, ringing in the ears, dizziness or problems with balance.

FUTURE PROSPECTS AND NEED FOR GOVERNMENT SUPPORT

1. Supportive Activity by the VHL Family Alliance in the world: There is a growing trend to organize familial support groups for VHL disease. They constantly maintain mutual
cooperation for both the VHL patients and their families. Familial support groups were small in number at the beginning. For example, the VHL Alliance in USA was composed of only a few families at the 1st VHL symposium held in 1994. This increased to more than 2000 members consisting of patients and their families at the time of the 4th VHL symposium in the Mayo Clinic, Rochester, USA, in 2000. The organization is now worldwide. VHL family alliances act in the US, Canada, England, France, Germany, Italy and Japan. They have homepages to show their activity for VHL disease. They provide a reference handbook for VHL patients. They also maintain a database of information about doctors in the world who understand the specific features of VHL disease. They also donate some of their surgically removed tumors for research designed to improve understanding of VHL disease. Other families with VHL are there to listen and to share their own experiences, which may help you gain a different perspective on the problem. Listen and learn, or join in the conversation. Participate in local support group meetings. Think of it as an old-fashioned barn-raising.\(^{[19, 23]}\) (Figure No. 4)

![Figure No.4: “Self-help is barn rising revisited.”](image)

2. Need for Governmental Support

VHL is a lifetime disease. Patients need to be constantly checked for the tumors and cysts that develop at various sites in the CNS and visceral organs throughout his/her lifetime. Some patients even receive up to 20 surgical operations in their lifetime to remove tumors. The number of VHL patients in Japan is less than 1000, and the number of their families is less than 200. Each patient constantly suffers from problems caused by multiple tumors or cysts from various organs. Older patients who have received multiple operations have the serious problem of postoperative morbidity in the CNS and visceral organs. A hopeful prospect for this disease is the appearance of molecular targeting antiangiogenic drugs in the near future. They seemed to have shown considerable efficacy in the initial clinical trials. It is also highly
recommended that this disease be included as one of the intractable disease (‘Nanbyo’) by the Welfare and Labor Ministry in Japan. Although this process may take a long time, inclusion will encourage VHL patients in Japan. Patients with this disease must be cared for by well-trained specialists and genetic counselors throughout their life to improve the prognosis and their psychological conditions caused by the above-mentioned conditions.[2,24]

REFERENCES


