Cancer Association of South Africa (CANSA)

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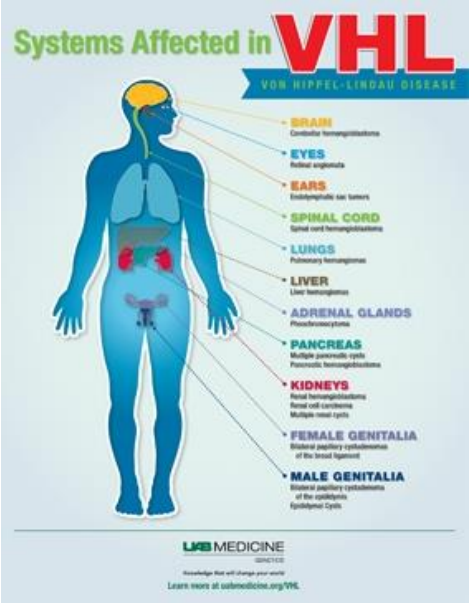
Fact Sheet on Von Hippel-Lindau Disease



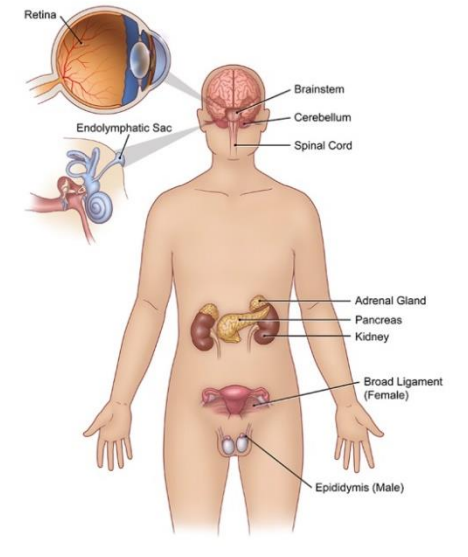
[Picture Credit: VHL]

Introduction

Von Hippel-Lindau (VHL) disease is an inherited disorder causing multiple tumours, both benign and malignant, in the central nervous system (CNS) and viscera (the internal organs in the main cavities of the body, especially those in the abdomen, e.g. the intestines). The most common tumours are retinal and CNS haemangioblastomas, renal cell carcinoma (RCC), and phaeochromocytoma.

Tumours also arise in the pancreas, epididymis or broad ligament of the uterus, and the inner ear (endolymphatic sac). The age at which the tumours present ranges from early childhood to the seventh decade of life. Early diagnosis, screening of family members and lifelong surveillance of VHL patients for tumours is recommended.

Tumours called haemangioblastomas are characteristic of VHL. These growths are made of newly formed blood vessels. Although they are typically noncancerous, they can cause serious or life-threatening complications. Haemangioblastomas that develop in the brain and spinal cord can cause headaches, vomiting, weakness, and a loss of muscle coordination (ataxia). Haemangioblastomas can also occur in the light-sensitive tissue that lines the back of the eye (the retina). These tumours, which are also called retinal angiomas, may cause vision loss.



[Picture Credit: VHL Disease]

People with VHL commonly develop cysts in the kidneys, pancreas, and genital tract. They are also at an increased risk of developing a type of kidney cancer called Clear-cell Renal Cell Carcinoma and a type of pancreatic cancer called a Pancreatic Neuroendocrine Tumour.

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VHL is associated with a type of tumour called a pheochromocytoma, which most commonly occurs in the adrenal glands (small hormone-producing glands located on top of each kidney). Pheochromocytomas are usually noncancerous. They may cause no symptoms, but in some cases they are associated with headaches, panic attacks, excess sweating, or dangerously high blood pressure that may not respond to medication. Pheochromocytomas are particularly dangerous if they develop during pregnancy.

Gläsker, S., Vergauwen, E., Koch, C.A., Kutikov, A. & Vortmeyer, A.O. 2020.
"Understanding of molecular mechanisms of tumor growth has an increasing impact on the development of diagnostics and targeted therapy of human neoplasia. In this review, we summarize the current knowledge on molecular mechanisms and their clinical implications in von Hippel-Lindau (VHL) disease. This autosomal dominant tumor syndrome usually manifests in young adulthood and predisposes affected patients to the development of benign and malignant tumors of different organ systems mainly including the nervous system and internal organs. A consequent screening and timely preventive treatment of lesions are crucial for patients affected by VHL disease. Surgical indications and treatment have been evaluated and optimized over many years. In the last decade, pharmacological therapies have been evolving, but are largely still at an experimental stage. Effective pharmacological therapy as well as detection of biomarkers is based on the understanding of the molecular basis of disease. The molecular basis of von Hippel-Lindau disease is the loss of function of the VHL protein and subsequent accumulation of hypoxia-inducible factor with downstream effects on cellular metabolism and differentiation. Organs affected by VHL disease may develop frank tumors. More characteristically, however, they reveal multiple separate microscopic foci of neoplastic cell proliferation. The exact mechanisms of tumorigenesis in VHL disease are, however, still not entirely understood and knowledge on biomarkers and targeted therapy is scarce."

The VHL Gene

VHL gene location. The VHL gene is located on the short arm of chromosome 3 at a site called 3p25-p26. An international team of scientists identified the precise structure of this gene in 1993. Alterations in the normal structure of this gene are known to result in the condition called VHL.

[Picture Credit: V H: Gene]

The VHL gene encodes the formula for a protein whose function seems extremely important in the fundamental process called 'transcription' which permits DNA to be transformed into a more simple molecule, RNA, which is used to create the protein.

Neoplastic Risks of Von Hippel-Lindau Disease (VHL)

The neoplastic risks (risk of being able to form new growths) of VHL include:

- Central nervous system (CNS) haemangioblastomas may cause life-threatening complications in spite of their benign nature and classic slow-growing course and remain a major cause of morbidity and mortality in VHL disease
- Retinal haemangioblastomas may cause retinal detachment, haemorrhage, glaucoma and cataract, leading to blindness, in absence of early detection and treatment
- Renal cell carcinomas is becoming the main cause of death in the disease, because of secondary dissemination mainly due to delay in diagnosis
- Pheochromocytomas are malignant in about 5-10% of cases
- Neuroendocrine pancreatic tumours tend to be slow growing but have the potential of a truly malignant course with locoregional dissemination
- Endolymphatic sac tumours is a low grade papillary adenocarcinoma resulting in progressive hearing loss. It can grow to the pontocerebelline angle and/or the middle ear, then destroying the temporal bone
- Epididymal cysts and cystadenomas of the broad ligament are benign tumours

Schuhmacher, P., Kim, E., Hagn, F., Sekula, P., Jilg, C.A., Leiber, C., Neumann, J.P., Schultze-Seemann, W., Walz, G. & Zschiedrich, S. 2019.
Background: Von Hippel-Lindau (VHL) disease is a multi-systemic hereditary disease associated with several benign and malignant tumor entities, including clear cell renal cell carcinoma (ccRCC). Since ccRCCs grow slowly, nephron sparing surgery is typically performed at a tumor diameter of 3-4 cm before the tumor metastasizes. However, in the case of recurrent disease, repeated surgical intervention can impair renal function. Therefore, it is crucial to optimize the timing for surgical interventions through a better understanding of the growth kinetics of ccRCCs in VHL. We investigated tumor growth kinetics and modern volumetric assessment to guide future therapeutic decisions.
Results: The prevalence of ccRCC was 28% in a cohort of 510 VHL patients. Of 144 patients with ccRCC, 41 were followed with serial imaging which identified 102 renal tumors, which exhibited heterogeneous growth kinetics. ccRCCs grew at an average absolute growth rate of 0.287 cm/year, an average relative growth rate $[(\ln V_1-\ln V_0)/(t_1-t_0)]$ of 0.42% and an average volume doubling time of 27.15 months. Women had a faster relative growth rate than men. Age and specific mutations did not influence tumor growth. Because of the tumor heterogeneity, we developed an additional cut-off volume of 40 cm^3 for surgical intervention.
Conclusions: Tumor heterogeneity and differences in growth kinetics is suggestive of a state of transient tumor dormancy in ccRCCs of VHL patients. The relative growth rate has not been previously described in other studies. Volumetric assessment as an additional parameter for surgical intervention could be a useful clinical tool and needs further investigation.

Incidence and Survival Rate for Von Hippel-Lindau Disease (VHL)
Because VHL itself is not a type of cancer, the National Cancer Registry (2017) does not provide information on the incidence of VHL.

Signs & Symptoms of Von Hippel-Lindau Disease (VHL)
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. These symptoms usually do

not mean one has VHL. However, it is important to discuss any symptoms with a doctor, since they may signal other health problems.

Pheochromocytoma Symptoms - pheochromocytomas may cause symptoms that are like what one feels 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 upon standing
- Tremor
- Weight loss

Diagnosis of Von Hippel-Lindau Disease (VHL)

The doctor will ask about symptoms and medical history. A physical examination will be done. If the patient has any VHL symptoms, he/she should consider being tested for the VHL gene. This is advised even if the patient has no known family history of the disease. This could be the first person in the family to have VHL. Or could be the first one to have it properly diagnosed since many people are not aware they have it.

A blood test that analyses DNA may be done to determine if the patient has the VHL gene.

Aronow, M.E., Wiley, H.E., Gaudric, A., Krisvosic, V., Gorin, M.B., Shields, C.L., Shields, J.A., Jonasch, E., Singh, A.D. & Chew, E.Y. 2019.

Purpose: To provide an update summarizing the biologic pathways governing von Hippel-Lindau (VHL) disease pathogenesis and to provide an overview of systemic manifestations as well as screening recommendations.

Methods: A PubMed search of the English language literature was reviewed using the following search terms: von Hippel-Lindau, von Hippel-Lindau disease, and VHL. Of 6,696 publications, the most current and pertinent information related to the pathogenesis and systemic aspects of VHL disease were included in this review.

Results: von Hippel-Lindau disease is one of the most frequently occurring multisystem familial cancer syndromes. The disease results from germline mutation in the VHL tumor suppressor gene on the short arm of chromosome 3. Mutation in the VHL gene affects multiple cellular processes including transcriptional regulation, extracellular matrix formation, apoptosis, and, in particular, the cellular adaptive response to hypoxia. As a result, there is widespread development of vascular tumors affecting the retina, brain, and spine, as well as a spectrum of benign and malignant tumors and/or cysts in visceral organs.

Conclusion: The ophthalmologist plays a key role in VHL disease diagnosis, as retinal hemangioblastoma is frequently the first disease manifestation. Screening guidelines for individuals with known VHL disease, and those at risk of VHL disease, help to ensure early detection of potentially vision-threatening and life-threatening disease.

Vanbinsti, A-M., Brussaard, C., Vergauwen, E., van Velthoven, V., Kuijpers, R., Michel, O., Foulon, I., Jansen, A.C. Lefevere, B., Bohler, S., Keymolen, K., de Mey, J., Michelsen, D. Andreescu, C.E. & Gläsker, S. 2019.

Background: Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumor syndrome. Affected patients develop central nervous system hemangioblastomas and abdominal tumors, among other lesions. Patients undergo an annual clinical screening program including separate magnetic resonance imaging (MRI) of the brain, whole spine and abdomen. Consequently, patients are repeatedly subjected to time-consuming and expensive MRI scans, performed with cumulative Gadolinium injections. We report our experience with a 35-min whole body MRI screening protocol, specifically designed for detection of VHL-associated lesions.

Methods: We designed an MRI protocol dedicated to the typical characteristics of VHL-associated lesions in different imaging sequences, within the time frame of 35 min. Blank imaging of the abdomen is carried out first, followed by abdominal sequences with Gadolinium contrast. Next, the full spine is examined, followed by imaging of the brain. A single dose of contrast used for abdominal imaging is sufficient for further highlighting of spine- and brain lesions, thus limiting the Gadolinium dosage. We used 1.5 Tesla equipment, dealing with fewer artifacts compared to a 3 Tesla system for spine- and abdominal imaging, while preserving acceptable quality for central nervous system images. In addition, imaging on a 1.5 Tesla scanner is slightly faster.

Results: From January 2016 to November 2018, we performed 38 whole body screening MRIs in 18 VHL patients; looking for the most common types of VHL lesions in the abdomen, spine, and brain, both for new lesions and follow-up. The one-step approach MRI examinations lead to 6 surgical interventions for clinically significant or symptomatic hemangioblastomas in the brain and spine. One renal cell carcinoma was treated with radiofrequency ablation. In comparison with previous conventional MRI scans of the same patients, all lesions were visible with the focused protocol.

Conclusions: Annual screening in VHL disease can be done in a rapid, safe and sensitive way by using a dedicated whole body MRI protocol; saving MRI examination time and limiting Gadolinium dose.

Zhao, R.N., Zhang, B. & Jiang, Y.X. 2019.

“Objective To analyze the clinical features of Von-Hippel-Lindau(VHL)syndrome and explore the diagnostic value of abdominal ultrasound for this disease.Methods The clinical features including age at first diagnosis,symptoms,signs,affected organs,number of operations,and diagnostic examinations of 35 patients with VHL syndrome admitted to our center from January 1994 to December 2017 were retrospectively analyzed.The diagnostic value of abdominal ultrasound for VHL syndrome was analyzed.Results Pheochromocytoma(*n*=14)and nervous system hemangioblastoma(*n*=13)were the common firstly-identified tumors.Nervous system hemangioblastoma(*n*=21),pheochromocytoma(*n*=19),renal carcinoma(*n*=17),and pancreatic mass(*n*=15)were common tumors.The main surgical reasons were nervous system hemangioblastoma(*n*=22),pheochromocytoma(*n*=23)and renal carcinoma(*n*=13).Abdominal organ involvements were found in 33 patients,which were first detected by abdominal ultrasound in 20 patients and were found accidently during routine health checkups in 6 patients.The ultrasound results were accurate in 27 of 33 adrenal gland scans,13 of 16 pancreas scans,and 8 of 19 kidney scans.Conclusions When multiple tumors are detected in the kidney,adrenal gland,and pancreas by ultrasound,the possibility of VHL syndrome should be considered.When the clinical findings suggest the possibility of VHL syndrome,ultrasound can discover and diagnose the abdominal tumors and can also be used for the long-term follow-up of the tumors.Therefore,ultrasound is an important method in the screening and follow-up of patients with VHL syndrome.”

Treatment of Von Hippel-Lindau Disease (VHL)

Von Hippel-Lindau disease (VHL) is usually a progressive disease. Surgical treatment may consist of argon laser photocoagulation, cryotherapy, fluid drainage, scleral buckling, penetrating diathermy, vitreous surgery, or endodiathermy. VHL varies according to the location and size of the tumour and its associated cyst. In general, the objective of treatment is to treat the growths when they are causing symptoms, but while they are still small so that they do not cause permanent problems by putting pressure on the brain or spine, blocking the flow of cerebrospinal fluid in the nervous system, or impairing vision.

Support Services for Von Hippel-Lindau Disease Survivors

Genetic Alliance SOUTH AFRICA

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About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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VHL
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VHL Alliance
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VHL Disease
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VHL Gene
https://www.google.co.za/search?q=VHL+gene+3p25-26&rlz=1C1GGRV_enZA751ZA751&source=lnms&tbm=isch&sa=X&ved=0ahUKEwjJxe-RvOndAhVJecAKHarwBI0Q_AUIDigB&biw=1094&bih=504#imgrc=x63R9uQe6MUbgM:

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