

von Hippel-Lindau syndrome

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von Hippel-Lindau syndrome (VHL) is a multisystem, neoplastic heritable disorder of high penetrance in affected individuals who carry the autosomal dominantly inherited trait. The disorder is also called a cancer syndrome because it includes malignant neoplasms or carcinomas that may arise in the kidneys and pancreas and, more rarely, in association with adrenal pheochromocytomas. Clinical manifestations mainly include hemangioblastomas of the brain and spinal cord, retinal angiomas, endolymphatic sac tumors, clear-cell renal carcinomas, pancreatic neuroendocrine tumors and cysts, and pheochromocytomas. Periodic surveillance for VHL tumors is guided by site-specific screening protocols, often leading to pre-symptomatic and early detection of occult neoplasms. Treatment is multidisciplinary, and although surgery remains the main treatment for VHL tumors, nonsurgical treatment modalities are emerging. VHL arises in individuals with a VHL gene mutation that is found most often in the germline. In 1993, the VHL gene was localized to chromosome region 3p26→p25 and was shown to be a tumor suppressor gene. In later years, improved methods were developed for genetic testing to increase detection rates of the various types of mutations among kindreds and to determine which members within these kindreds carry the trait. 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.

In recent years, because of increased awareness of von Hippel-Lindau syndrome (VHL; OMIM 193300), use of periodic pre-symptomatic surveillance testing, early detection, and increased treatment options, many individuals affected by VHL have a greatly improved quality of life. By contrast, this case was presented more than 12 years ago with examples of the natural history of many VHL tumor types in their untreated state.

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Case history

A 31-YEAR-OLD MALE with long-standing severe vision problems, including blindness in the right eye, presented for ocular screening by an ophthalmologist and a retina specialist in a hospital-based eye institute clinic in the early 1990s. The patient's ocular history, dating back to childhood, was notable for strabismus and a mature cataract with total retinal detachment in the right eye.

Aside from eye problems, the patient's history was unremarkable: no medical problems, no medications, no known allergies, and no history of having had imaging examinations for extraocular VHL tumors.

A family history was given of VHL syndrome in the patient's sister, who

died at age 38, 3 months post-partum, during a cholecystectomy. The patient's 42-year-old brother had a history of left-eye enucleation for a tumor at 15 years of age; a 10-year history of left-sided, sudden hearing loss, with a long-standing tumor at the cerebellopontine angle related to the left internal auditory canal; bilateral epididymal masses; pancreatic cysts; and polycystic kidney disease. The patient's mother died of a brain tumor at age 33, and two maternal uncles also died of cancer (not further described) before age 40.

Dilated funduscopic examination of the patient's left eye revealed multiple retinal angiomas of various sizes,

for which the patient later underwent argon laser treatment to the tumors and feeding vessels. Ultrasonography of the right eye showed a closed funnel total retinal detachment. Corrected visual acuity was NLP (no light perception) in the right eye and 20/40 in the left. Because of the high risk of extraocular tumors associated with VHL, the patient was referred for systemic screening.

Imaging and clinical assessment

At the referral center, comprehensive systemic screening of the patient was preceded by education about VHL, genetic counseling, and a review of the screening protocol prior to the patient's giving informed consent. Imaging studies included enhanced magnetic resonance imaging (MRI) of the head and spine, computed tomography (CT) of the abdomen (both pre- and post-contrast), and ultrasonography of the abdomen and testes. Laboratory tests included a complete blood count, chemistry 20 panel (including serum creatinine level), urinalysis, and 24-hour urinary catecholamine and metanephrine concentrations.

Imaging studies demonstrated tumors in the kidneys, liver, left adrenal gland, pancreas, brain, and spine that were compatible with a diagnosis of VHL.

Kidney lesions included one right-sided midpolar tumor and four left-sided solid masses, the largest being 1.5 cm. Complex cysts were present bilaterally. The urologic oncology surgeon at the center recommended monitoring the small VHL tumors with eventual treatment by partial nephrectomy once the largest solid mass approached 3 cm in diameter.

A CT scan of the *adrenal glands* revealed a 2.5-cm enhancing mass on the left gland consistent with a pheochromocytoma.

The patient's 24-hour urinary catecholamine levels were abnormally

elevated, with a norepinephrine level of 112 $\mu\text{g}/24$ h (normal range, 11–86 $\mu\text{g}/24$ h) and total metanephrine concentration of 1.1 mg/24 hr (normal range, 0–0.9 mg/24 h). Blood pressure was 110/70 mm Hg in the left arm and 120/80 mm Hg on the right, with the patient sitting, and 130/80 mm Hg with the patient supine.

The urologic oncology surgeon examined the patient and provided recommendations for further evaluation and management of the adrenal gland tumor. Arrangements were made for functional tests for pheochromocytoma, including MIBG (meta-iodobenzylguanidine) scintigraphy. It was explained to the patient that a pheochromocytoma must be treated before any other surgery is performed to avoid possible precipitation of a hypertensive crisis from the stress of surgery. It was further explained that following removal of the pheochromocytoma, the visceral and central nervous system (CNS) tumors could then be considered for either monitoring or treatment depending on the type, size, and location of each tumor and whether it was causing any signs or symptoms.

Imaging of the *pancreas* revealed a 3 cm \times 4 cm enhancing mass. Because its size was greater than 3 cm, surgical treatment was recommended after removal of the pheochromocytoma.

The *liver* had multiple enhancing lesions for which the differential diagnosis included benign hemangiomas and metastasis of islet cell carcinoma, now most often referred to as pancreatic neuroendocrine tumor. Further evaluation of the liver lesions was planned by red cell tag test, a nuclear medicine study, used to identify benign hemangiomas.

Brain and spine imaging showed a 1.5 cm \times 1 cm enhanced nodule and associated cyst at the outlet of the fourth ventricle. In the spine, at least two enhancing lesions were at the level of C7-T1 with an associated syrinx extending from C5 through T5. The

lesions were compatible with hemangioblastomas, and a neurosurgical consultation was completed during this initial visit.

Given the patient's stable neurological condition, together with the sizes and locations of these histologically benign CNS lesions, the plan was to perform another spinal MRI scan in 6 months, when the patient would meet with the neurosurgeons for a repeat neurologic examination and update of the surgeons' recommendations. The patient was instructed to contact the nurse coordinator for neurosurgery patients if symptoms developed before his scheduled return.

Follow-up

After the initial visit, the patient did not return for the recommended further evaluations and treatment. We were informed that he had made plans to see only his personal physician at the medical care center where he usually receives his care. Results and recommendations, along with reports of the studies, were provided to the patient and his physician.

Other family members were offered screening for VHL. Comprehensive screening and genetic counseling for VHL were completed for the patient's three brothers, two of whom were negative clinically.

Following the screening, the third brother, who had previously been diagnosed with VHL (see above), resumed treatment with his urologist at the medical care facility where he had received care for many years.

VHL surveillance and treatment guidelines for the screened individuals and their blood relatives were discussed, and copies of the guidelines were given to them for their managing physicians. In an arranged meeting, recommendations and guidelines were also given to the personal physician leading the team of caregivers for this family.

The proband had no children.

von Hippel-Lindau syndrome

About this rare disorder

VH_L is a heritable, autosomal dominant, neoplastic disorder that predisposes to development of specific types of benign and malignant tumors. The estimated prevalence of VHL disease is 1 in 35,000 to 1 in 40,000.¹

Reports of the syndrome began in the 1860s, with ophthalmologists describing retinal angiomas that caused blindness and were sometimes associated with identical lesions in the cerebellum. In 1894, Treacher Collins was the first to recognize the angiomatous nature of the retinal tumors in a family.² By 1904, Eugen von Hippel, a German ophthalmologist, published descriptions of retinal angiomas in members of a small number of families spanning several generations.³ In 1926, Arvid Lindau, a Swedish pathologist, published a report recognizing that retinal angiomas, cerebellar hemangioblastomas, and renal and pancreatic cysts were part of a familial syndrome.⁴ Melmon and Rosen's study of a large kindred and literature review in 1964 established the first diagnostic criteria of VHL including renal cancer.⁵ Linkage of the VHL gene (*VHL*) to the short arm of chromosome 3 was reported in 1988.⁶ Finally, Latif and colleagues at the National Cancer Institute identified the VHL tumor suppressor gene by positional cloning in 1993.⁷

Clinical manifestations

Individuals with VHL syndrome may be at risk for development of CNS hemangioblastomas, retinal angiomas, endolymphatic sac tumors, clear-cell renal carcinomas, pheochromocytomas, pancreatic neuroendocrine tumors, epididymal cystadenomas in men, and cystadenomas on the broad ligament in women.

CNS hemangioblastomas

Hemangioblastomas of the brain and spinal cord are the most common type of tumor in VHL syndrome, occurring in 40%–80% of all patients.⁸ The average age of presentation for CNS hemangioblastomas is 30 years. However, the age at onset can vary widely; for example, a diagnosis of VHL syndrome was reported in an 11-year-old, and an initial diagnosis was made in a 78-year-old.⁹

Hemangioblastomas in VHL are histopathologically benign but can cause major morbidity and, in some

cases, even death. They generally occur in the spinal cord and cerebellum but can arise anywhere along the craniospinal axis. Hemangioblastomas are often associated with edema and cysts. The detection rate of new lesions is high until individuals enter their 50s, when the new lesion formation rate usually slows.

Symptoms related to CNS hemangioblastomas depend on tumor location and size and the presence of edema or cysts. Hemangioblastomas of the CNS, regardless of location, have similar histologic characteristics, as originally described by Arvid Lindau. These tumors are well defined, thinly encapsulated lesions that appear bright red upon visualization at neurosurgery. Histologically, they consist of a rich vascular plexus surrounded by polygonal stromal cells. Mast cells that are also present may be responsible for production of erythro-



FIGURE 1 Enhanced magnetic resonance imaging of the brain and spine showing central nervous system tumors and cysts characteristic of von Hippel-Lindau syndrome (VHL). **Left:** T1 post-contrast hemangioblastoma (arrow) with associated cyst in the cerebellum. A second hemangioblastoma is present in the cerebellopontine angle cistern (arrowhead). **Right:** Sagittal T1 post-contrast enhancing hemangioblastoma in the dorsal cord at the T10 level (arrow). A spinal cord cyst is also present, and there is cord edema extending into a syrinx. Enhancement of draining veins is pronounced (arrowheads). Images courtesy of Dr. John Butman.

poietin, which can cause erythrocytosis. Pure, solid hemangioblastomas occur in about 20%–30% of cases and reportedly recur more frequently than cystic lesions.^{8,9}

CNS hemangioblastomas are best assessed by contrast-enhanced T1-weighted MRI. These tumors are easily identified and quantified by MRI (Figure 1). T2-weighted or FLAIR (fluid-attenuated inversion recovery) MRI is used to quantify tumor-associated edema and cysts. Arteriography typically shows intense, persistent staining of the hemangioblastoma, as well as arteriovenous shunting, and early draining of veins.¹⁰

Retinal hemangioblastomas

Retinal hemangioblastomas (retinal angiomas), also one of the most common tumors in VHL syndrome, are seen in as many as 60% of patients.¹¹ These tumors are often multifocal and may arise in the periphery or on or near the optic disc, or both. About 50% of affected individuals have bilateral lesions. Although the mean age of patients presenting with retinal hemangioblastomas is 25 years, 5% of these tumors are detected in patients younger than 10 years of age.

Retinal hemangioblastomas produce no symptoms in the initial stages and may be detectable only by examination of the dilated eye. Despite a lack of symptoms early on, they can progress to partial or, in some cases, total loss of vision. As the tumors grow, they cause visual symptoms, increased vascular permeability, accumulation of subretinal fluid, development of a hard exudate at the macula, and retinal detachment. Retinal hemangioblastomas appear grossly and histologically identical to CNS hemangioblastomas.¹²

Ophthalmoscopy with pharmacological dilation of the iris permits detection of most retinal tumors. Fluorescein angiography is used to assess macular function associated with peripheral and optic nerve lesions in VHL.¹⁰

Endolymphatic sac tumors

The endolymphatic sac is located at the end of the endolymphatic duct of the inner ear and lies within the dura of the posterior fossa. The function of the endolymphatic sac is poorly understood, but it may be involved in endolymph production and resorption. Endolymphatic sac tumors (ELSTs) are rare in the general population but are seen in 11% of patients with VHL. The mean age of onset of hearing loss is 22 years and ranges from 12 to 50 years.¹³

VHL syndrome is the only known condition associated with bilateral endolymphatic sac tumors.¹³ When these tumors erode the vestibular aqueduct to involve the inner ear structures, hearing and other functions become impaired. They can also grow outward into the cerebellopontine angle or cerebellum and thus mimic other types of tumors commonly found in these locations. Affected individuals usually present with partial or complete hearing loss, tinnitus, and equilibrium dysfunction; in some cases, facial paresis may also develop.

These highly vascular endolymphatic sac tumors often erode or expand into the surrounding temporal bone. Histologically, they form papillary cystic regions filled with proteinaceous substances. The tumors are not known to metastasize but are locally aggressive.

Radiological examination of endolymphatic sac tumors includes pre- and post-contrast MRI and CT of the internal auditory canals. In CT images, the tumors are generally isodense with brain parenchyma but also can have focal areas of low or high attenuation. CT of the temporal bones with large tumors shows a destructive or expansive lesion that is centered in the sigmoid sinus and internal auditory canal. T1-weighted MRI may show either homogeneous or heterogeneous intensity in pre-contrast images. Likewise, post-contrast T1-weighted MRI

also shows homogeneous or variable patterns of patchy enhancement. Audiograms are used to document hearing loss or its progression.

Renal cell carcinomas

Renal cell carcinomas (RCCs) are the major malignant neoplasm in VHL syndrome and a primary cause of inherited renal cancer. These tumors are seen in 24%–45% of patients; if renal cysts are included, the finding of renal lesions increases to 60%.¹⁴ The mean age at presentation is 39 years, with renal tumors being reported in individuals with VHL as young as 15 years of age.

Small renal tumors associated with VHL syndrome tend to be low grade and minimally invasive. However, their rate of growth varies widely. Renal lesions are often multiple and bilateral. Walther and colleagues estimated that as many as 600 microscopic tumors and 1,100 microscopic clear-cell-lined cysts might be present in the kidneys of some 37-year-old patients with VHL, as extrapolated from their study.¹⁵ Data from an investigation of 228 renal lesions in 28 patients who were followed for at least 1 year showed that the transition from a pure cyst to a solid lesion was rare.¹⁶ But complex cysts and solid lesions can contain neoplastic tissue that frequently enlarges.

Renal cell carcinomas often remain asymptomatic for long periods of time during their early growth phase. Serial imaging of the kidneys is useful for early detection and monitoring for signs of growth to determine when treatment is needed. Occasionally, the more advanced cases with large tumors can present with one or more of the classic triad of symptoms of kidney tumors: hematuria, flank pain, and/or a flank mass. Pure renal cysts in VHL are typically asymptomatic and rarely need treatment. However, mixed solid and cystic lesions—so-called complex cysts—need monitoring, as they often harbor solid compo-

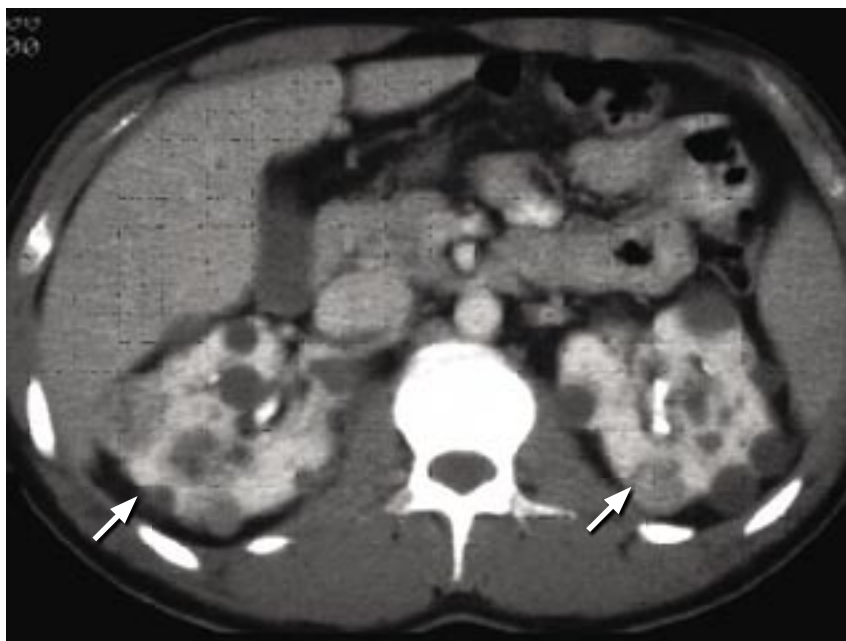


FIGURE 2 Contrast-enhanced computerized tomography of the abdomen demonstrates multiple bilateral kidney tumors and cysts, as commonly seen in von Hippel-Lindau syndrome (VHL). Following renal tumor resections in patients with VHL, the histopathology is shown to be clear-cell renal carcinoma.

nents of RCCs.¹⁶

Renal tumors in VHL disease appear grossly as yellow or orange encapsulated lesions. They can be solid or a mixture of solid and cystic tissue. Histologically, all renal tumors in VHL are clear-cell carcinomas,¹⁷ and small carcinomas tend to be low grade.¹⁵ Larger RCCs, especially those greater than 3 cm in diameter, have become metastatic to organs outside the kidneys.

Because small RCCs usually are not symptomatic and there is benefit from early detection and treatment, pre-symptomatic screening has the potential to improve overall outcome. Contrast-enhanced abdominal CT (Figure 2) is the diagnostic tool of choice for renal involvement in VHL.¹⁴ CT allows detection, quantification, and serial follow-up of the lesions by size and number of renal masses and cysts during the pre-treatment period. Imaging is usually recommended in 3–5 mm sections (both pre- and post-contrast). Pre- and post-contrast MRI is an alterna-

tive method of detection of renal and other VHL-related visceral tumors for patients who have reduced renal function or a history of severe reaction to contrast media.

Pheochromocytomas

Pheochromocytomas arise in 10%–20% of patients with VHL syndrome but may occur in a higher percentage of affected members of certain families.¹⁸ The mean age at presentation is about 30 years; however, children as young as 5 years of age have been diagnosed with these tumors. Pheochromocytomas in VHL syndrome can be multiple and bilateral, with the second or third tumor often being diagnosed after the patient has been tumor free for years. Rarely, these tumors might be the only manifestation of the disorder. They can also arise in extra-adrenal chromaffin tissue and present as paragangliomas in the glomus jugulare, carotid body, and peri-aortic tissue. About 5% of pheochromocytomas are malignant.¹⁸

The onset of pheochromocytomas

can occur before 10 years of age. They can present as hypertensive crisis in young children with VHL syndrome. The signs or symptoms of pheochromocytomas include intermittent or sustained hypertension, anxiety attacks, palpitations, tachycardia, headache, and episodic sweating. In one study, however, 13 of 37 newly diagnosed patients with pheochromocytomas had no symptoms and were identified by screening family members in affected kindreds.¹⁸

Owing to the young age of onset in some individuals and the possible absence of signs and symptoms, screening for elevated catecholamine levels is advisable starting as early as 2 years of age, especially in families with a history of pheochromocytomas.

Pheochromocytomas usually appear as red or orange encapsulated masses with foci of hemorrhage and necrosis. Histologically, the neoplastic cells arise from chromaffin cells of the adrenal gland and extra-adrenal ganglion tissues. These cells have a polyhedral to fusiform morphology with vesicular nuclei and granular, amphiphilic, or basophilic cytoplasm.

The diagnosis of pheochromocytoma is based on laboratory and imaging studies. Functional tests for these tumors are essential because they may show activity when imaging studies do not detect an adrenal or extra-adrenal lesion. In addition to 24-hour urinary measurements of catecholamines, measurement of free metanephrines in plasma, with reference ranges adjusted for age, is a sensitive method for detection of pheochromocytomas.¹⁹ If indicated, further assessment may include glucagon stimulation, a clonidine suppression test, or both. Pre-contrast and post-contrast CT or MRI can detect adrenal masses but have limitations for identification of extra-adrenal involvement. MIBG scintigraphy is useful for detecting extra-adrenal pheochromocytomas and can confirm their catecholamine production.

Pancreatic neuroendocrine tumors, cysts, and cystadenomas

Pancreatic neuroendocrine tumors are seen in 8%–17% of individuals with VHL syndrome. Pancreatic cysts and serous cystadenomas occur with a prevalence of 17%–56% of patients. Overall, 35%–70% of patients with VHL have pancreatic involvement.²⁰ The mean age at presentation for pancreatic cysts is 37 years and for neuroendocrine tumors is 35 years. Among 17 patients studied with surgically removed pancreatic neuroendocrine tumors, patients' ages ranged from 18 to 48 years.²⁰

Pancreatic cysts may be extensive in this disease, but they are benign, are generally asymptomatic, and do not need treatment. In contrast, the pancreatic neuroendocrine tumors arise separately from the cysts, and these tumors do require treatment. Characteristically, in VHL these tumors are non-functional and clinically silent. The pancreatic neuroendocrine tumors are generally encapsulated and well circumscribed. Histologically, they are formed from pancreatic islets and have been historically termed islet cell tumors. Although they are clinically nonfunctional, they stain positive for pancreatic and gastrointestinal hormones by immunohistochemistry.²¹

Routine periodic imaging of asymptomatic individuals is important in VHL syndrome. Occasionally, it may be difficult to distinguish between a benign multicystic cystadenoma and a pancreatic neuroendocrine tumor with malignant potential. A pancreatic neuroendocrine tumor can be seen as an enhancing mass in post-contrast CT imaging done during the arterial phase. Once this tumor is identified with CT, MRI of the pancreas can be used to confirm the diagnosis. Additional studies, including endoscopic ultrasonography in conjunction with somatostatin receptor scintigraphy, also may be useful.

Epididymal cystadenomas

Epididymal papillary cystadenomas are seen in 25%–60% of men with VHL syndrome.²² These cystadenomas arise from the epididymal duct. The tumors are benign but can be multiple and bilateral. They typically appear in the teenage years.

These cystadenomas are characteristically asymptomatic. The diagnosis is made by palpation and confirmed by ultrasonography.²² Epididymal cystadenomas appear to be solid but in reality consist of multiple cysts filled with a colloidal material and papillary structures with fibrovascular cores. Histologically, the epithelium has clear-cell features similar to other neoplasms in VHL.

Broad ligament cystadenomas

Papillary cystadenomas on the broad ligament have only rarely been reported and usually go unrecognized in women with VHL syndrome.²³ The mean age of women at presentation and the true frequency of cystadenomas of the broad ligament in VHL are unknown. The tumors are believed to arise from the remnant of the embryonic mesonephric duct, similar to the epididymal duct in men. The earliest age at which this tumor was diagnosed is 16 years.²⁴

These lesions can be diagnosed by CT imaging or ultrasonography. The tumors are grossly and histologically similar to epididymal cystadenomas.

Screening and diagnosis

When VHL syndrome is diagnosed in a patient (Table 1), a geneticist and a physician informed about VHL manifestations should be consulted to coordinate the various tests (Table 2) needed to completely evaluate the proband. Next, a plan should be initiated to work with the proband and offer contact information for counseling and screening of at-risk family members who choose informed testing for VHL. The aim is to diagnose symptomatic and asymptomatic affected individuals among at-risk family members, allowing earlier detection and opportunities for improved treatment outcomes.

TABLE 1

Diagnostic approaches to von Hippel-Lindau syndrome (VHL)

With a family history of VHL

Genetic testing: test for same VHL gene mutation as in affected biologic relative(s).

Clinical diagnosis (when genetic testing marker/VHL mutation is unavailable):

- One or more of the following:
 - CNS hemangioblastoma
 - Renal cell carcinoma, clear-cell, multifocal
 - Pheochromocytoma
 - Retinal angiomas
 - Pancreatic neuroendocrine tumor
 - Pancreatic cysts and/or cystadenomas
 - Endolymphatic sac tumor
 - Epididymal or broad ligament cystadenomas

Without a family history of VHL

Genetic testing: may be negative if VHL mutation occurred post zygotic (eg, VHL mosaicism)

Clinical diagnosis (when genetic testing marker/VHL mutation is unavailable):

- Either or both of the following:
 - CNS hemangioblastoma
 - Retinal angiomas
- If only one of the above is present, then also one of the following:
 - Renal cell carcinoma, clear-cell
 - Pheochromocytoma
 - Pancreatic cysts and/or neuroendocrine tumor
 - Endolymphatic sac tumor
 - Epididymal or broad ligament cystadenomas

Adapted and updated from Glenn et al⁴⁴

For patients known to carry the disorder or for at-risk family members, a number of clinical screening regimens have been proposed, ranging from ophthalmologic examination to laboratory tests and various imaging techniques (Table 2). Screening tests are

TABLE 2

Suggested screening guidelines for manifestations of von Hippel-Lindau syndrome (VHL)

Exam/test	Age and frequency ^a
Ophthalmoscopy	From infancy; every 6–12 months
Fluorescein angiography	If needed (not routine)
Catecholamines and metanephrine levels	From 2 years; annually and if symptoms
Enhanced MRI of brain/spine ^b	From 11 years; every 1–2 years and if symptoms
Abdominal CT with and without contrast	From 18 years, earlier if indicated; every 1–2 years
Abdominal ultrasonography	Annually from 8 to 18 years, earlier if indicated
MRI and CT/IACs, ^b audiology, neurology	Any age when hearing loss, tinnitus, or vertigo

CT = computed tomography; IACs = internal auditory canals; MRI = magnetic resonance imaging.

^a Frequencies of exams or tests may be increased at organ sites of VHL lesions being monitored.

^b Brain MRIs may be examined in areas of internal auditory canals (IACs) for signs of endolymphatic sac tumors (ELSTs). If signs or symptoms of ELSTs are present, examine by CT and MRI of IACs.

Adapted from Choyke et al⁹ and Lonser et al¹⁰

advised periodically throughout the lifetime of individuals affected by or at risk for VHL. Any new symptoms should be investigated immediately.

The international support group for patients with VHL syndrome, VHL Family Alliance, has been a source of information and physician referral for patients and healthcare professionals for about a decade and continues to promote the concept of regional VHL clinical care centers. For information on reaching the VHL Family Alliance, see page 243.

Genetic testing

Individuals in at-risk families should be informed that genetic testing for VHL is now available. The voluntary decision for testing is obtained within the process of genetic counseling that precedes informed consent. The genetic test result may exclude the diagnosis and thus eliminate unnecessary clinical testing among family members who are not carriers of their family's VHL trait.

Advances in techniques of molecular genetic testing for VHL, including Southern blotting and DNA sequence analysis, have increased the detection rate of VHL mutations to

nearly 100%.²⁵ There are more than 200 mutations reported in affected families worldwide. Mutation types include missense, nonsense, insertion, deletion, frameshift, splice-site mutation, and partial or complete deletion of one allele of the VHL gene.

Genetic testing should occur within the context of genetic counseling as recommended by the American Society of Human Genetics, American Society of Clinical Oncology, and other medical societies. Patients should make the decision whether to be tested or not after discussing the medical, economic, and psychosocial implications for themselves and their families. The decision to be tested must be entirely voluntary after informed consent is given and signed. Both pre-test and post-test genetic counseling continue through the process of the testing decision and result disclosure, as well as in the follow-up period as needed.

Discovery of a germline mutation in the VHL gene is an indication for a lifetime of periodic screening for susceptible tumors. Early detection and management of VHL-related neoplasms may result in decreased morbidity and mortality and improved

quality of life. At-risk family members also need genetic counseling, clinical screening, and/or genetic testing to clarify their individual risks.

De novo or spontaneous mutations present a challenge in genetic counseling and diagnostic testing for VHL syndrome. The actual frequency of new *VHL* mutations is not known. One report from a registry of 181 families found 42 individuals (23%) had VHL as the first affected member in their family.²⁶ The initial mutation in a de novo case might result in mosaicism (ie, some, but not all, tissues carry the new mutation). Two such patients were reported after being confirmed by additional molecular investigations.²⁶ Such patients might have clinical signs of VHL but test negative genetically because the *VHL* mutation is not found in peripheral blood leukocytes. Mosaicism can occur as a result of a mutated gene present only in somatic cells, or only in germ cells, or finally in some portion of both somatic cells and germ cells. The tissues affected by the mutation depend upon the stage of embryogenesis in which the new mutation arose. Therefore, the risks of tumor development in the carrier of a new mutation, compared with those in their offspring, may be very different in cases of VHL mosaicism.

Treatment

Surgical resection remains the treatment of choice for most VHL tumors. Depending on the type or types of VHL tumor(s) present, different specialists will be required. In addition to the tumor being evaluated for treatment, the treating specialist arranges screening for other types of VHL tumors that might be present. This is critical with regard to possible pheochromocytomas, which must be ruled out before any type of surgical procedure is performed. When there is more than one type of tumor requiring treatment, the specialists confer with each other and decide on the order of treatment, and in some cases

visceral tumors in more than one organ may each be resected by a different surgeon during a single surgery.

Nonsurgical treatment modalities for VHL tumors may increase in the future, but currently they are used much less often than surgery, and their use is limited to carefully selected cases or patients enrolled in investigative protocols.

Brain and spinal cord

Most CNS hemangioblastomas can be safely and completely excised by neurosurgery.^{27,28} However, they commonly grow at several sites simultaneously, new tumors arise with time, and tumor growth patterns can be unpredictable. Therefore, to avoid unnecessary surgery, resection is usually deferred until the onset of symptoms. At some centers, preoperative embolization is used to reduce tumor vascularity before resection.

Stereotactic radiation therapy of VHL-related CNS hemangioblastomas has also been used, due to the potential morbidity associated with surgical resection of multiple intracranial lesions.²⁹ Small hemangioblastomas and those not associated with cysts might respond safely to such focused radiation therapy. Nevertheless, larger studies over longer periods are needed to determine the true effectiveness and the potential for long-term effects of this treatment.

Kidneys

For RCCs, most urologic surgeons recommend nephron-sparing surgery for VHL-related renal tumors that have a maximum diameter of 3 cm. Nephron- or renal-sparing surgery of tumors approaching or equal to 3 cm in diameter is designed to reduce the risk of metastasis while preserving kidney function. Walther and colleagues reported a 10-year investigation of renal-sparing surgery on patients whose tumors had a maximum diameter of 3 cm. In 52 patients who received such surgical treatment,

there was no evidence of metastasis and no need for dialysis or kidney transplantation during a median follow up of 60 months.³⁰

Radiofrequency ablation and cryoablation of RCCs (ie, less than 3 cm in diameter) are percutaneous treatments that are experimental, but they hold promise as less invasive therapies. Pavlovich and colleagues reported the initial results of radiofrequency ablation of 24 renal tumors of 3 cm or less in 19 patients who had RCCs associated with VHL syndrome. After 2 months of follow up, CT showed that 19 of the 24 lesions were ablated.³¹ Other researchers have reported success using percutaneous cryoablation guided by MRI in the treatment of four patients with a total of five renal tumors ranging in size from 2.8 cm to 5 cm.³²

Larger carcinomas—those greater than 3 cm in diameter—with bulky multifocal disease carry an increased risk for metastases. Surgeons might advise tumor enucleation or partial nephrectomy for these patients. In rare cases, the kidneys cannot be preserved, and total nephrectomy might be the only option. When unilateral total nephrectomy is required, renal function provided by the remaining kidney is often adequate.

Historically, metastatic clear-cell renal carcinoma has remained resistant to standard chemotherapy and hormonal therapy; however, immunotherapy has shown some promise in these cases. Investigational protocols for patients with larger RCCs that have metastasized continue to emerge, as well as research into molecular targeting for systemic therapy when needed.

Endolymphatic sac tumors

Surgery is a curative treatment for completely excised endolymphatic sac tumors in which the pre-operative level of hearing is usually preserved.³³ Decisions about the timing of surgery

depend upon a number of variables, including the growth pattern of the tumors, pre-operative hearing level, severity of vestibular symptoms, possibility of hearing loss or facial nerve injury as a result of surgery, and the possibility of bilateral tumors. The role of radiation therapy is unclear in the treatment of endolymphatic sac tumors.

Pheochromocytomas

Treatment of pheochromocytomas is by surgical resection and is preferably laparoscopic when the tumor is in the adrenal gland. The surgery is increasingly done as partial adrenalectomy or enucleation to preserve adrenal function. Preoperative pharmacological control should be adequate with a combination of adrenergic blocking agents that may be continued during and even after surgery. Indications for surgery may include clinically functional tumors, tumors with MIBG uptake, or tumors greater than 3.5 cm.¹⁸ Early intervention with cortical-sparing adrenal surgery results in low recurrence rates and long-term corticosteroid independence when used in the treatment of pheochromocytomas in patients with VHL syndrome.

Pancreas

For treatment of pancreatic neuroendocrine tumors, surgical resection and the specific approach to be used are determined by the location and size of the tumor. Tumors detected by imaging during asymptomatic periods and resected on the basis of size have been successfully managed with no development of metastasis. Libutti and colleagues recommend resection of these lesions on the basis of the following criteria: no evidence of metastatic focus, tumor size greater than 3 cm in the body or tail of the pancreas or greater than 2 cm in the head of the pancreas, or the patient is undergoing laparotomy for other lesions.²⁰ Surgical resections can be done by

enucleation; pylorus-preserving pancreaticoduodenectomy (Whipple procedure); or partial or, very rarely, total pancreatectomy with replacement therapy. Tumors in the body and tail of the pancreas have been successfully managed via laparoscopic surgery.

Preservation of a functional pancreas should be the aim while keeping in mind the malignant potential of the tumor cells. The most common site of metastasis is the liver. Long-term control of hepatic metastases has been achieved by combinations of ablative therapy and isolated hepatic chemotherapeutic perfusion.

Ocular VHL tumors

Early detection and treatment of retinal hemangioblastomas can prevent failing or lost vision. Most peripheral retinal lesions respond to treatment by laser photocoagulation or cryotherapy.³⁴ Vitrectomy may be considered for patients with substantial tractional retinal detachment with a large fibrovascular component. Tumors on the optic disc should be monitored without treatment because of the potential for damage that may be caused by treatment. Enucleation may be necessary for irreversible glaucoma as a consequence of end-stage ocular disease.

Various types of radiation therapies have been applied to cases of severely affected retinas that did not respond to usual methods, but the benefit of these approaches and their role in the management of retinal hemangioblastomas need to be defined. Pharmacologic treatment targeting the vascular endothelial growth factor (VEGF) receptor has been reported to restore visual function in a patient with a tumor in the optic nerve head, and this treatment might provide hope in other cases that are not amenable to current treatments.³⁵

Epididymal and broad ligament papillary cystadenomas

When present, these tumors are

benign and typically asymptomatic and, therefore, are managed conservatively. Treatment is reserved for the rare patient who presents with symptoms associated with these tumors. Ultrasonography can be used to follow their size over time. If clinically indicated, imaging of broad ligament cystadenomas may be accomplished with either CT or ultrasonography. It is important to recognize these benign VHL tumors to avoid a mistaken diagnosis and overtreatment.

Molecular genetics and biology

The VHL gene is located on the short arm of chromosome 3 in the region 3p26→p25.⁷ This gene is highly conserved among species, from *Drosophila* to mammals, suggesting that its functions are fundamental to life. The VHL gene acts as a tumor suppressor gene. Therefore, when both *VHL* alleles (alternative forms of *VHL*, one from each parent) within a cell are inactivated, cellular transformation occurs and results in unregulated cell divisions and replications to form a tumor. The affected individual inherits a germline mutation of the *VHL* allele from the affected parent, and a normal (wild-type) gene allele from the unaffected parent. Tumors in susceptible target organs develop when cells in those organs undergo deletion or mutation of the remaining normal allele, resulting in no remaining normal *VHL* allele. In studies of non-inherited, sporadically occurring CNS hemangioblastomas³⁶ and RCCs,³⁷ investigations have shown somatic inactivation of both *VHL* alleles in the tumor cells.

The VHL gene consists of three exons that encode the protein pVHL, which is found in both the nucleus and cytoplasm. The protein complexes with elongin B, elongin C, and Cullin 2 (Cul2), interacts with Ring box protein 1 (Rbx1), and forms the VCB ubiquitin ligase complex.^{38,39} In the presence of oxygen, the VCB

complex binds to alpha subunits of hypoxia inducible factors (HIF) and targets them for degradation. As a result, the alpha subunits of HIF are rapidly degraded under normal conditions but are stabilized under hypoxic conditions.⁴⁰

Abnormal or absent pVHL function, as occurs in VHL syndrome, may indirectly interfere with tumor suppression through HIF-mediated effects or directly through VHL-mediated mechanisms, or both. Many tumor-suppressive effects may result from degradation of HIF. HIF is a transcriptional activator of a number of genes, including those involved in angiogenesis and vascular regulation, erythropoiesis and iron metabolism, glucose transport and glycolysis, collagen matrix formation, proliferation, differentiation, apoptosis, catecholamine biosynthesis, and extracellular pH regulation.⁴¹ Many of these mechanisms are shown by increased expressions of several angiogenic and growth factors, eg, VEGF, platelet-derived growth factor beta (PDGFβ), transforming growth factor alpha (TGFα), and erythropoietin. If pVHL functions were absent or abnormal, then HIF could persistently stimulate angiogenesis, which is critical for VHL tumors to grow. HIF-mediated angiogenesis could result from increases in levels of VEGF and PDGFβ, which are known to be important for proliferation of endothelial cells and pericytes, respectively. This might explain the highly vascular nature of many tumors, especially hemangioblastomas and RCCs, in VHL syndrome.

Another potential mechanism of HIF-mediated carcinogenesis is TGFα overproduction. In addition to being a potent mitogenic factor, particularly for renal epithelium, elevated TGFα can stimulate cellular overexpression of epidermal growth factor receptors, such as receptors for TGFα, creating an autocrine loop.

There are other possible mecha-

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A patient's perspective

Altheada L. Johnson, RD | Brooklyn, NY

WHEN I WAS FINALLY DIAGNOSED with VHL, I had already had an EMG, 8 weeks of chiropractic treatments, countless CTs, MRIs, a myelogram, an angiogram, and extensive spinal cord surgery. A heman-gioblastoma and the associated cyst (a jelly-like substance causing a "sausage" in my spinal column, according to the neurosurgeon) had been surgically removed and sent to pathology.

The doctor told me, "Ms. Johnson, you have a genetic disease called von Hippel-Lindau. You will need to have your eyes and kidneys looked at as well." All the time I'm wondering what he is talking about. Where could this have come from? While I felt devastated by the news then, I have since realized how very lucky I was: My surgeon knew enough about VHL to look beyond my spinal cord. I had a retinal examination, and a small angioma was found and treated. Eventually I had a craniotomy to remove a heman-gioblastoma from my cerebellum.

Family tree

So many people with VHL go for decades without knowing what is wrong with them. I have talked with many who have had a number of different manifestations of VHL throughout their lives, never knowing that all these things were related to one disease.

My grandfather suffered with severe headaches. One day he came home from work, laid down, and never got up again. My father had several brain surgeries. My siblings and I watched him taken away by ambulance for a surgery from which he never recovered. Three years later, my 19-year-old brother died in the hospital after his second brain surgery.

Three generations, undiagnosed. At the time of my brother's death, doctors told my mother there was a tumor condition in our family, found only in males. Not knowing anything about genetics, my three sisters and I felt there was no need to worry.

It was nearly 20 years before there were any other VHL manifestations. During my sister KJ's first pregnancy, she had vision problems. Her doctor told her she had a bleed as a result of high blood pressure. The only treatment she received was blood pressure medication. I know now that it is unusual for an ophthalmologist not to recognize VHL when he sees it. I have talked to many VHL patients, newly diagnosed by their eye doctor.

When my back pain started, it got so severe I had difficulty walking. When the VHL diagnosis came, we were finally able to make the pieces fit. We had an answer.

We have since learned that, among the sisters, only KJ and I have VHL. She has had two kidney surgeries and a craniotomy and is blind in her eye that did not receive any treatment. She has two children, both of whom have VHL. Her son has had a craniotomy, but so far her daughter is symptom-free. I have had four spinal cord surgeries. My sister's first kidney surgery resulted in removal of her kidney. There is obviously lots more research needed to figure out just what role your environment, lifestyle, and actual genetic mutation play in which manifestations you will have. Right now, we just work on the assumption that if you have VHL, you are at risk for any or all possible manifestations.

A way of life

VHL is a familial cancer, an autosomal dominant genetic condition. A par-

ent has a 50% chance of passing the VHL mutation on to his or her children. VHL is family-related in that it is passed on to you by one of your parents. But it is family-related in another sense: your family can pull you through those crises that are bound to pop up from time to time. My husband, mother, sisters, other family members, and friends were there for me. I could not have made it through without them. I spent about 3 months in the hospital with my first hospitalization. I had visitors every day. I had home-cooked food on a regular basis, and my room was filled with reminders of home. All this went extraordinarily far to ensure my survival.

Now, routine screening is a way of life for me: annual MRIs, CT scans, and eye exams. It is so important to find the tumors early so that treatment, if necessary, is provided early. I believe that had I had early diagnosis and treatment, I would not be a wheelchair user right now.

Because VHL is such an unusual disorder, patients have to be their own advocates. At the VHL Family Alliance, we encourage people to join a support/education group. Patients can offer each other invaluable information that can help them avoid repeating the same mistakes all over again. When I first learned I had VHL, I felt very alone. Now, I've met others with my condition. I know what to look and listen for. I'm active in the support group for VHL, and I have met many other health-care professionals who have the interest of VHL patients at heart.

While VHL is a serious disease, it does not mean your life is over. You learn how to deal with the bumps in the road VHL is likely to cause; you get over them and go on with your life until the next bump.

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nisms of absent or abnormal pVHL causing tumorigenesis, independent of HIF. They include disruption of the normal cell cycle, matrix metalloproteinase (MMP)-induced angiogenesis, and dysregulation of extracellular fibronectin matrix.⁴² Mutations of the protein itself could increase VEGF expression through errors in transcriptional and post-translational regulation. These mutations might add to the angiogenic effects mediated by HIF and further increase permeability of tumor blood vessels. Finally, although cells without pVHL can secrete fibronectin, they cannot properly assemble the extracellular matrix of fibronectin, which may contribute to carcinogenesis.⁴³ Overall, HIF-mediated, direct pVHL-mediated, and unknown effects of abnormal or absent pVHL probably interact to induce formation of the various VHL tumors.

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von Hippel-Lindau syndrome

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