

Diagnosis and Treatment of Von Hippel–Lindau Syndrome

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Von Hippel–Lindau (VHL) is an uncommon autosomal dominant syndrome caused by a germline mutation in the VHL gene that has been mapped to chromosome 3p25. This is the only gene currently known to cause VHL.¹ The product of this gene, pVHL, functions as a tumor suppressor protein much like the product of the retinoblastoma gene. Therefore, the Knudson two-hit model has been proposed for VHL syndrome: A germline mutation inactivates one copy of the VHL gene in all cells and later a somatic mutation causes the disease to manifest. Cells lacking pVHL do not degrade hypoxia-inducible factors (HIF) in the presence of oxygen, and they also overproduce other hypoxia-induced mRNAs such as erythropoietin, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Many tumors have high levels of HIF genes just in the hypoxic regions of the tumor, but tumors resulting from VHL have high levels of HIF genes in all of their tumor cells. VHL-associated tumors, therefore, are often highly vascular because of the overproduction of these angiogenic products.¹

Incidence. The incidence of VHL is about one in 36,000 births, and most patients present between the ages of 10 and 40, with the average age being about 26.¹ There is no race or gender predilection. Since VHL is autosomal dominant, children of affected parents have a 50 percent risk of developing

it, but de novo mutations do occur in about 20 percent of patients. Almost 100 percent of those with the mutation will manifest symptoms at some point. Retinal capillary hemangioblastomas (RCH) are some of the most common lesions, found in up to 85 percent of patients with the VHL mutation. The RCH lesions are considered benign hamartomas and may be the earliest manifestation of VHL (see image.)

Signs and Symptoms

Symptomatic VHL can include vision loss. Retinal capillary hemangioblastomas are usually located in the peripheral retina or in the juxtapapillary region. Multiple lesions can be present in both eyes, but often there is asymmetry between the two eyes. These lesions are red-orange, well-circumscribed vascular tumors with a large feeder vessel and a large draining vessel. They can grow on the surface of the retina (endophytic) or within the retina (exophytic). Vision loss results either from exudation of fluid into the macula or from glial proliferation. Exudation can cause an exudative retinal detachment, whereas glial proliferation can cause tractional retinal detachment or macular pucker. Vitreous hemorrhage, iris neovascularization with glaucoma or cataracts may also be seen. Extraocular signs and symptoms include headache, vomiting and ataxia seen with cerebellar hemangioblastomas; constant or transient hypertension seen with pheochromocytomas; and hearing loss seen with endolymphatic sac tumors.



SIGN OF VHL. Color fundus photo of the right eye showing a large retinal capillary hemangioblastoma superiorly with a large feeder vessel causing exudation and macular edema. There is also a small RCH in the inferior arcade.

Differential Diagnosis

The differential diagnosis for RCH includes Coats disease, Wyburn-Mason syndrome, vasoproliferative tumors of the retina, retinal cavernous hemangioma and racemose hemangioma. With these other entities, the main distinguishing characteristic is the lack of a large feeder vessel leading to the lesion. With juxtapapillary and endophytic RCH, other entities to be considered are disc edema, ischemic optic

neuropathy and choroidal neovascularization. In the past, the diagnosis of VHL was based on two criteria: a positive family history with one or more typical lesions, or no family history but two or more retinal lesions or one retinal and one other visceral lesion.

Definite diagnosis of VHL now is mainly done by gene analysis. Given our current genetic testing, those with only one VHL-like lesion and a negative gene analysis are effectively ruled out from having VHL disease, although in some cases somatic mosaicism for the gene mutation is still a possibility; these patients should be monitored. In general, a younger person with one or more VHL-like lesions is more likely to have VHL than an older person with only one lesion.

Screening

The VHL gene is the only gene known to be associated with VHL disease, and current molecular testing detects the mutation in nearly 100 percent of those with the disease. This allows physicians to direct the extensive screening process only to those who actually manifest the germline mutation.

The criteria to refer someone for genetic testing are threefold: those who are blood relatives of someone diagnosed with VHL by a positive gene analysis; those who have a VHL-like lesion and a positive family history of someone with VHL syndrome (not necessarily diagnosed by gene analysis); and those with two or more VHL-like lesions.² Such VHL-like lesions include central nervous system or retinal capillary hemangioblastomas, clear-cell renal cell carcinomas (RCC), pheochromocytomas, serous cystadenomas or neuroendocrine tumors of the pancreas, endolymphatic sac tumors and epididymal tumors. Simple cysts of the kidney, pancreas or liver are not considered VHL-like lesions.

Surveillance has focused primarily on hemangioblastomas (including retinal angiomas), renal cell carcinomas and pheochromocytomas, the three manifestations most often resulting in severe disability or death. For ophthalmologists, the accepted screening

guidelines are for an annual dilated exam starting at the age of one year. Screening guidelines for systemic disease include complete blood count to look for polycythemia vera; measurement of urinary catecholamine metabolites (vanillylmandelic acid, metanephrines and total catecholamines) to detect pheochromocytomas; urinalysis for hematuria; and urine cytology to detect RCC. Annual abdominal ultrasounds are also indicated to evaluate the kidneys, adrenal glands and pancreas. A CT scan or MRI is then used to clarify suspicious findings on ultrasound. Brain or spinal cord imaging is often not recommended as long as there are no neurological symptoms.¹

Treatment

The two main treatment options are photocoagulation on smaller lesions and cryotherapy for larger ones. Multiple treatments with photocoagulation or cryotherapy are needed to fully obliterate the tumor. Observing smaller lesions may be an option, as some have been known to remain stable for years or even to regress.

It is now known that RCHs cause an upregulation of, or are sensitive to, many growth factors, including VEGF and PDGF. Antiangiogenic agents, such as bevacizumab (Avastin) or ranibizumab (Lucentis), have therefore been used both intravenously and intravitreally.² So far, limited studies, including our own institutional experience, have found that anti-VEGF therapy reduces the amount of exudation and may improve vision but does not change the size of the lesion. Of note, both systemic anti-VEGF therapy and photodynamic therapy combined with intravitreal anti-VEGF therapy for cerebellar hemangioblastoma have been tried with some success.

Last, there are case series looking at pars plana vitrectomy with excision of the RCH.² However, none of these methods has been studied in a randomized controlled study.

Small lesions are best managed with early photocoagulation. Large lesions respond better to cryotherapy, but usually carry a poor prognosis.

Prognosis

Patients with VHL have a life expectancy of 50 years. Systemic morbidity is mainly due to RCC and pheochromocytoma. For ophthalmologists, a study looking at the visual effect of VHL found that the prevalence of severe bilateral vision loss is about one in 18. The risk of vision loss is greater with older patients, with juxtapapillary lesions and with a larger number of RCHs. About one-fourth of those with RCH will have visual acuity worse than 20/160, and about one-fifth will have profound vision loss and phthisis bulbi, eventually requiring enucleation.¹

Recently, genetic testing has allowed us to diagnose these patients at a younger age. In some cases we can also predict what tumors they may be more likely to develop. The biggest consideration is how likely such patients are to develop pheochromocytomas because these carry significant morbidity and mortality. Recently, a study looked at ocular RCH and different VHL gene mutations and found that different mutations had an effect on both the risk of developing ocular VHL and the location of the RCH.² These findings may help with future screening guidelines and counseling of patients and may ultimately improve the prognosis.

Patient Resources

There are multiple online resources for patients, including the VHL Family Alliance at www.vhl.org and the National Cancer Institute at www.cancer.gov, which contain general information for VHL patients and their families. Other organizations are the Kidney Cancer Association at www.curekidneycancer.org and the National Eye Institute at www.nei.nih.gov.

1 Wong, W. T. and E. Y. Chew. *Curr Opin Ophthalmol* 2008;19:213–217.

2 Magee, M. A. et al. *Semin Ophthalmol* 2006;21(3):143–150.

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