Ocular Findings in von Hippel–Lindau Disease

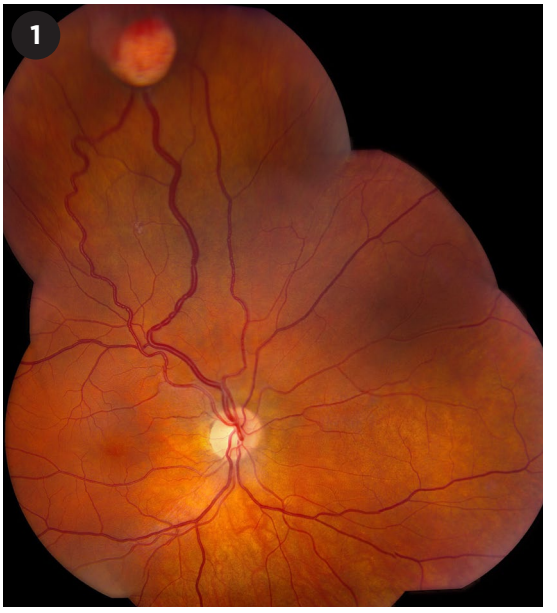
Von Hippel–Lindau (VHL) disease is a tumor syndrome that affects the central nervous system (CNS), retina, and visceral organs. Inherited in an autosomal dominant manner, it arises from germline mutations in the *VHL* gene.[1] The syndrome is rare, with an incidence of approximately 1 in 40,000 people; an estimated 7,000 people with VHL disease live in the United States.[2]

In the early 1900s, Eugen von Hippel, a German ophthalmologist, described retinal hemangioblastomas that were passed down through several generations. In 1926, Arvid Lindau, a Swedish pathologist, recognized the association between retinal lesions and cerebellar hemangioblastomas in addition to findings in other organs, as part of a familial syndrome. In subsequent years, clinical diagnostic criteria for VHL disease were established (See "Clinical Criteria" page 37), and the *VHL* tumor suppressor gene on the short arm of chromosome 3 was identified.[3]

Although multiple benign or malignant tumors and cysts may develop in the tissues of the CNS and in visceral organs including the kidney, adrenal gland, pancreas, epididymis, and broad ligament, the ophthalmic manifestations of the syndrome are both characteristic and diagnostic of VHL disease.[4] Retinal hemangioblastoma is a common, early manifestation of VHL disease.[2] Thus, ophthalmologists are instrumental in the diagnosis and care of affected patients.

Pathophysiology

Carriers of a *VHL* germline mutation are especially at risk for developing VHL disease. The *VHL* gene is a tumor suppressor gene and, consistent with Knudson's two-hit hypothesis, requires mutation of both copies of the *VHL* gene for tumors to develop. When a germline mutation is present, a second "hit" in the other *VHL* gene allele at the somatic level transforms the cell into a tumor cell. Also, VHL disease can occur in the absence of a germline mutation. In this case, both *VHL* gene alleles would have to be affected by independent hits at the somatic level. Patients who have *VHL* germline mutations tend to develop tumors multicentrically and bilaterally in the CNS and viscera, and the disease manifests at a younger age than patients without a *VHL* germline mutation.[5]



VIEW OF A TUMOR. *Fundus photograph of a VHL patient with retinal hemangioblastoma.*

Mechanism. In healthy people, the VHL protein helps to target specific transcription factors for degradation. These hypoxia-inducible factors (HIFs) are produced in the presence of low tissue oxygen tension, upregulating proteins that enable a cell to survive in a hypoxic state. These proteins include erythropoietin (EPO), platelet-derived growth factor, and vascular endothelial growth factor (VEGF).

A mutation in the *VHL* gene leads to disruption of VHL protein function, which results in unregulated levels of HIFs and, subsequently, increased levels of downstream gene products. Elevated levels of VEGF and EPO stimulate cell growth and angiogenesis, which contribute to tumor formation.[4]

Signs and Symptoms

Retinal hemangioblastomas. Typically, this is the earliest lesion identified in VHL patients, often presenting in the first three decades of life. Although

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most patients with this finding are asymptomatic and detected by surveillance ophthalmoscopy or fluorescein angiography (FA), some may present with vision loss.[6,7]

CNS hemangioblastomas. These also occur earlier in life and most commonly develop in the spinal cord and cerebellum. Presenting symptoms vary depending on tumor location and may include pain, headaches, paresthesia, and limb weakness due to the tumor's compressive effects.

Renal cysts and renal cell carcinoma. These normally develop in middle age and may manifest as flank pain, hematuria, and a palpable abdominal mass.

Pheochromocytoma. This may present with hypertension and other signs of catecholamine excess.

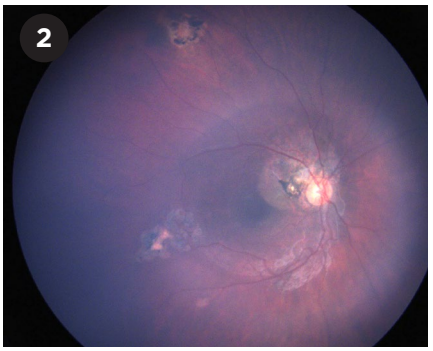
Other VHL-associated lesions. Patients may develop pancreatic tumors and endolymphatic sac tumors of the inner ear. Due to the autosomal dominant inheritance pattern of VHL disease, tumors in patients with a family history of the syndrome are often identified via routine surveillance at an early age before they become symptomatic.[7]

Ophthalmic Manifestations

The principal ophthalmic finding in VHL disease is retinal hemangioblastoma. Its prevalence is between 45% and 65%.[8] The probability of developing retinal hemangioblastoma increases with age, with the median age of onset being 21 years.

Retinal hemangioblastomas usually develop as solitary tumors, but up to 50% of patients have multiple and bilateral lesions.[1] These circumscribed, rounded, vascular tumors appear orange-red in color and are supplied by enlarged, tortuous feeder vessels. Most commonly, hemangioblastomas are found in the temporal peripheral retina but may also be present in the juxtapapillary region in up to 15% of patients.[4]

Although small lesions may remain stable for years, most hemangiomas tend to increase in size over time, leading to retinal changes. Blindness or significant visual loss from ocular VHL occurs in less than 10% of patients. This is often caused by secondary tumor



POST TREATMENT. *(2) Appearance of multiple retinal hemangioblastomas on funduscopy after treatment with laser photocoagulation.*

effects including intraretinal and subretinal exudation,[9] with exudation usually localized to the area surrounding the tumor.[2] In later stages, the tumors may cause massive exudation and retinal detachment (RD), macular edema, uveitis, cataracts, and glaucoma.[9]

Diagnosis

Appearance on imaging. Retinal hemangioblastomas may be diagnosed with indirect ophthalmoscopy, fundus photography, and FA. Specifically, fluorescein hyperfluorescence in the dilated feeder arteriole is seen in the arterial phase. The tumor then displays homogeneous capillary filling, followed by increased fluorescence of a prominent draining vein in the venous phase. FA is particularly helpful in identifying juxtapapillary retinal hemangioblastomas and in detecting occult lesions. Indocyanine green angiography is used to help differentiate choroidal lesions, and ultrasonography is used to assess tumor thickness. Patients undergo magnetic resonance imaging and/or computed axial tomography to detect concurrent CNS and visceral tumors.[9]

DDx. The differential diagnosis for retinal hemangioblastoma includes other ocular conditions in which vascular tumors may be found (e.g., Coat's disease, retinal cavernous hemangioma, racemose hemangioma, and vasoproliferative tumors of the retina).

Genetic testing. The ability to test for *VHL* gene mutations has allowed researchers to study possible associations between mutational genotype and ocular phenotype. After the diagnosis of VHL disease has been confirmed, genotypic analysis may be used to assess the likelihood of particular disease manifestations, including probable organ involvement, age of onset, and type and severity of characteristic features. For example, a recent study found that deletion of the *VHL* germline gene leads to less severe eye disease compared with missense or truncating mutations in the gene. This finding suggests that abnormal VHL protein function may be more pathogenic in retinal tissue than complete absence of the protein.[4]

Treatment

Management of patients with VHL disease often requires a multidisciplinary approach given the complexities associated with multiple tumors in various organs. Treatment of the ocular manifestations of VHL disease can be particularly challenging because of the possibility of bilateral, multiple tumors and new tumor formation. Current treatment modalities include laser photocoagulation, cryotherapy, plaque radiotherapy, and vitreoretinal surgery.[1]

Photocoagulation. In eyes with clear media, laser photocoagulation is indicated for treatment of small tumors located in the peripheral retina. In general, the feeder artery is occluded first, and, if necessary, the tumor's surface can also be treated. This treatment modality has a response rate of 91% to 100%, and complications, including RD or retinal/vitreal hemorrhages, are uncommon.[10]

Cryotherapy. Cryotherapy is preferred for lesions found in the periphery of the retina with subretinal fluid.[11] A double freeze-thaw technique is used under indirect ophthalmoscopy. This method is particularly successful in treating larger hemangioblastomas.[12]

Radiation. Plaque radiotherapy may be useful in treating ocular VHL disease in cases that respond poorly to conventional laser or cryotherapy.[12]

Surgery. Vitreoretinal surgery is reserved for patients who have complications secondary to their eye disease. For example, vitreous hemorrhage may occur in the presence of large tumors, or tractional RD may result from con-

traction of the fibrovascular tissue that often accompanies retinal hemangioblastomas. These complications may be treated with vitrectomy.[12]

Possible role for antiangiogenics? The discovery that upregulation of downstream genes, such as *VEGF*, may play a role in tumor development has prompted the study of antiangiogenic drugs as a therapeutic option for ocular VHL disease.[4] Although antiangiogenic therapy has often been used for extraocular manifestations of VHL disease, there have been conflicting reports on its usefulness in treating retinal hemangioblastomas. Several case reports have found that although anti-VEGF therapy did not reduce tumor size, it did decrease exudation, which led to a subsequent improvement in visual acuity and visual field. Prospective trials are needed to further evaluate the efficacy of this approach.[4]

Other considerations. Ocular tumor location has been found to play a role in treatment success. Peripheral tumors may be treated successfully with laser photocoagulation, photodynamic therapy, cryotherapy, and plaque radiotherapy. Generally, small peripheral tumors respond best to photocoagulation while larger peripheral lesions are better managed, initially, with cryotherapy.[13]

Clinical Criteria

If family history is:	Feature
Positive	One retinal or CNS hemangioblastoma *or* Pheochromocytoma *or* Renal cell carcinoma
Negative	Two or more retinal or CNS hemangioblastomas *or* One retinal or CNS hemangioblastoma plus a visceral tumor*

*Visceral lesions include renal cysts, renal carcinoma, pheochromocytoma, pancreatic cysts, islet cell tumors, epididymal cystadenoma, and endolymphatic sac tumor.

SOURCE: Binderup M et al. *Eur J Hum Genet.* 2017;25(3):301-307.

However, juxtapapillary tumors are more difficult to treat. Treatment of tumors near the optic nerve and major retinal vessels involve higher risk of visual loss. Because tumor progression in this location may lead to adverse visual effects, treatment considerations must be based the patient's visual symptoms and tumor progression.

Summary

Retinal hemangioblastoma is a common, early sign of VHL disease. The typical fundus findings, appearance on FA, and other diagnostic tools allow ophthalmologists to play a key role in diagnosing the disease as well as managing the ocular manifestations. Although treatments such as laser photocoagulation and cryotherapy may help mitigate visual loss, further development of therapies targeting the pathophysiology of the syndrome is promising for patients living with VHL disease.

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