Von Hippel-Lindau Disease

A review of the physiopathlology, epidemiology, diagnosis, and treatment for this rare condition.

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Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited multisystem cancer syndrome with a predilection for the central nervous system (CNS) and the retina. Retinal capillary hemangioma is one of the most common and often the earliest manifestations of VHL disease[1] and, therefore, ophthalmologists are frequently involved in the care of patients with this disease. The incidence of VHL disease is approximately one in 40,000 live births,[2] and it is estimated that there are approximately 7,000 patients with VHL disease in the United States.[3]

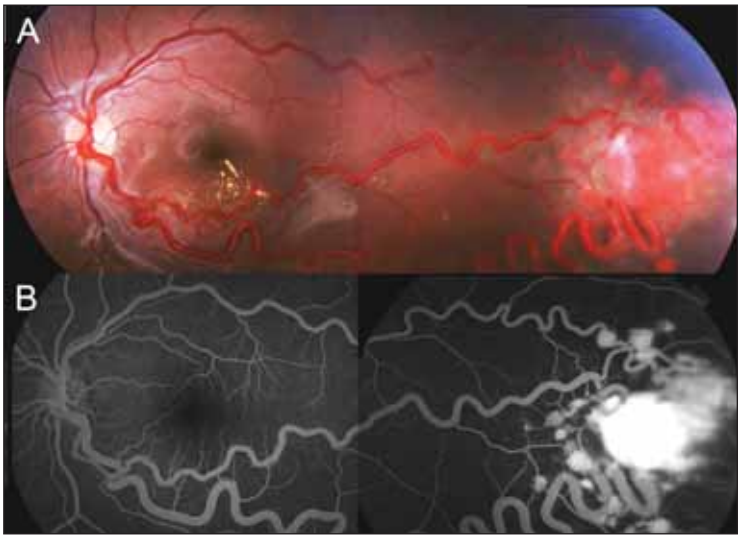

Figure 1. Retinal capillary hemangioma (A). Note the macular exudates, with multiple hemangiomas and feeder vessels in the temporal periphery. Fluorescein angiography (mosaic) demonstrating hyperfluorescent and dilated retinal arteries and veins leading to and coming from multiple leaking angiomas (B).

OPHTHALMIC MANIFESTATIONS AND NATURAL HISTORY

The main ophthalmic finding in VHL is retinal capillary hemangioma, which is a benign hamartoma. The anterior segment is only rarely secondarily involved due to complications such as neovascular glaucoma and cataract formation.[4] A large cohort study found only 2% of eyes had neovascularization of the iris.[5]

RETINAL FINDINGS

Retinal capillary hemangiomas are usually orange-red, circumscribed, round, vascular tumors supplied by a pair of dilated and tortuous feeder vessels. They are most commonly located in the temporal peripheral retina. Juxtapapillary retinal capillary hemangiomas are less common, representing about 11% to 15% of cases, and their appearance can vary depending on whether the lesion is endophytic, exophytic, or sessile. The endophytic form protrudes from the optic disc and adjacent retina into the vitreous, while the exophytic form presents as a nodular orange lesion that grows in the outer layers of the retina and might stimulate chronic optic disc edema. The sessile variant is subtle and might be difficult to diagnose.[4,6] Retinal capillary hemangioma usually manifests as a solitary tumor, but approximately one-third of patients have multiple retinal hemangiomas, and up to half of patients have bilateral involvement.

Secondary effects leading to visual loss, such as intraretinal and subretinal exudation, are often limited to the vicinity of the hemangioma but can be remote, often producing a macular star exudate. Glial proliferation can lead to tractional retinal detachment and macular pucker. Retinal or vitreal hemorrhages are rarely observed, occurring in fewer than 3% of cases.[5]

EPIDEMIOLOGY AND NATURAL COURSE

The frequency of occurrence of retinal capillary hemangiomas in VHL disease has been reported to vary from 49% to 85%. The mean age at diagnosis of retinal capillary hemangiomas in VHL disease is approximately 25 years, and most patients present between the ages of 10 and 40 years.[6] The probability of developing a retinal capillary hemangioma increases progressively with age. Recent publications indicate that the hemangioma is usually manifest by age 30, and the prevalence rate is stable thereafter. Therefore adults with a normal retina at age 30 years may have a low risk of developing a retinal capillary hemangioma during the remainder of their lives.[4]

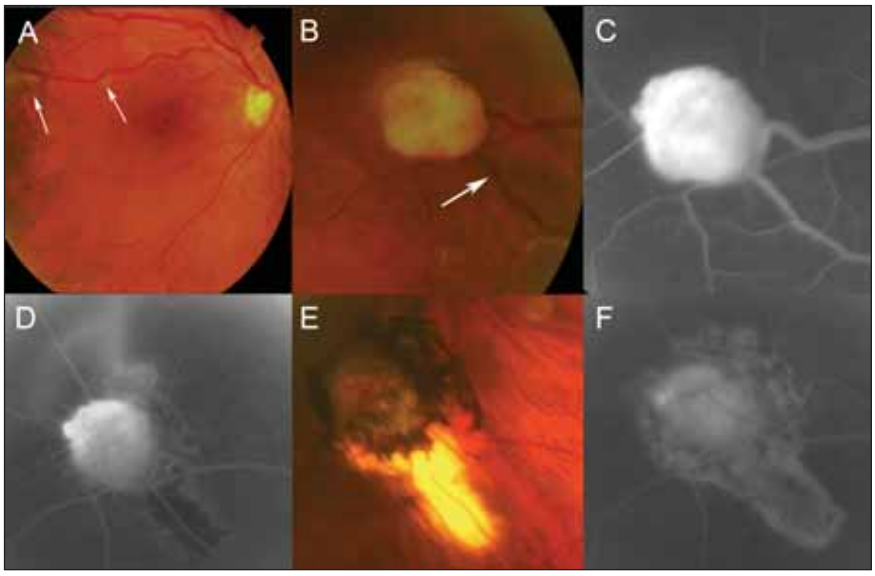

Figure 2. Upper row: Retinal capillary hemangioma before treatment: Arrows pointing to exudates superotemporal to macula (A). Hemangioma located at the temporal periphery of the retina. Arrow pointing to feeder arteriole (B). Fluorescein angiography demonstrating intense hyperfluorescence of the lesion (C).
Bottom row: Retinal capillary hemangioma after laser treatments: Fluorescein angiography after first laser treatment, demonstrating persistent leakage from the superior part of the lesion (D). Lesion after last laser treatment (E). Fluorescein angiography of lesion after last laser treatment, demonstrating minimal leakage (F).

The natural course of retinal capillary hemangiomas is variable (progression, stability or spontaneous regression). Small lesions may remain stable for years or may show evidence of gliosis without leakage, but some have been documented to enlarge. Most hemangiomas, however, tend to enlarge progressively and lead to retinal changes. In late stages they may cause massive exudation and retinal detachment, uveitis, glaucoma and phthisis.[6] Classification systems to aid in staging the clinical progression have been developed.[7,8]

DIFFERENTIAL DIAGNOSIS

The fundus findings of retinal capillary hemangioma are usually typical, and diagnosis can be made based on ophthalmoscopic examination. The diagnosis might be confused with retinal macroaneurysm or adult Coats disease when severe exudation exists, as peripheral capillary hemangiomas might be overlooked.[6] The vascular abnormality, however, in Coats disease is diffuse rather then localized. Wyburn-Mason disease (congenital retinal arteriovenous malformation, racemose hemangioma) is characterized by dilation and tortuosity of retinal arteries and veins; however, these vessels do not have an intervening hemangioma, and they do not leak or cause exudation. In retinal cavernous hemangioma there is a cluster of small vascular dilations around a central vein, but there are no prominent feeder vessels or exudation.[4]

Vasoproliferative tumors of the retina are benign, vascular, pink-to-yellow lesions, occurring in healthy patients between ages 40 and 60 years.[9] They are often associated with exudation and intraretinal hemorrhages as retinal capillary hemangiomas but lack feeder vessels or stellate macular exudates. They are found in the extreme inferior retinal quadrants, while retinal capillary hemangiomas are mostly evident in the midperipheral temporal retina. Approximately one-quarter of these lesions are secondary to retinitis pigmentosa, uveitis, or long-standing retinal detachment.[10]

Juxtapapillary retinal capillary hemangioma can stimulate unilateral disc edema, juxtapapillary choroiditis, choroidal neovascularization, choroidal hemangioma, and amelanotic choroidal melanoma.[6]

DIAGNOSTIC METHODS

Indirect ophthalmoscopy, fundus photography, and fluorescein angiography are the most informative diagnostic tools. Fluorescein hyperfluorescence is evident in the arterial phase in the dilated feeder arteriole; the tumor displays fine capillary homogeneous filling, and the draining vein becomes prominent in the venous

phase. The tumor demonstrates progressive hyperfluorescence with late leakage of dye into the surrounding structures and vitreous. Fluorescein angiography is helpful in establishing the diagnosis for juxtapapillary retinal capillary hemangioma and may detect occult lesions. Photography with angiography is used as an adjunct to treatment planning; differentiating the feeder arteriole from the draining vein and can help assess the therapeutic response.[6] Indocyanine green can help differentiate choroidal lesions,[10] while ultrasonography (US) can help measure the tumor thickness. The A-scan demonstrates high internal reflectivity, and B-scan shows a well-demarcated retinal lesion without choroidal invasion. Magnetic resonance imaging or computed axial tomography should be employed to detect synchronous central nervous system and visceral tumors.[4]

TREATMENT

The treatment of retinal capillary hemangiomas can be a challenge to the ophthalmologist due to the presence of bilateral multiple tumors and the likelihood of new tumor formation. Despite treatment, up to 25% of cases can have permanent loss of visual acuity to less than 20/40 in one or both eyes. Various treatment modalities, including observation, cryotherapy, plaque radiotherapy, and vitreoretinal surgery, have been utilized.[4] Recent advances in the understanding of VHL protein function and tumorigenesis have led to new treatments targeting the biology of the disease, as opposed to ablative or surgical approaches. Molecules upregulated in the context of VHL mutation, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), have been targeted in investigational anti-angiogenic therapies, both in systemic manifestations of the disease and in ocular disease.[11]

OBSERVATION AS TREATMENT

Observation is rarely employed due to the tendency of retinal capillary hemangiomas to progress. Observation only might be chosen in small (<500 µm) nasal hemangiomas lacking exudation that do not threaten vision, and in hemangiomas that have undergone spontaneous regression with gliosis, sheathing and lack of feeder vessels.

Juxtapapillary hemangiomas are initially managed with observation, because they can remain stable for years. Treatment should only be undertaken in case of tumor progression or a threat to visual acuity due to the adverse effect of treatment on the optic nerve and major vessels.[4,6]

LASER PHOTOCOAGULATION

Laser photocoagulation is currently used to treat small retinal capillary hemangiomas located in the posterior retina in eyes with clear media. When possible, we first occlude the feeder artery, then (if necessary) treat the tumor's surface. A response rate of 91% to 100% has been shown with direct tumor treatment. Multiple treatment sessions might be required. Complications, such as transient retinal detachment or retinal and vitreal hemorrhages, are uncommon

CRYOTHERAPY

Indications for cryotherapy are anterior location of the hemangioma and subretinal fluid, which can reduce the laser energy uptake and diameter greater than 3 mm (up to 4.5 mm). Double freeze-thaw technique is employed under indirect ophthalmoscopy.[4,6] A 15-year review found that all hemangiomas under 3.75 mm in diameter successfully responded to cryotherapy.[12]

ANTI-VEGF STRATEGIES

Recent studies have indicated that anti-VEGF strategies can be effective in the treatment of tumors associated with loss of VHL function, especially renal cell carcinoma. For retinal capillary hemangiomas, recent case reports involving anti-VEGF agents, delivered systemically or via intravitreal injection, show conflicting results.[13] SU5416, a systemic intravenously administered inhibitor of VEGF-receptor-2, was studied in a case series of six patients. Of these, only two were reported to achieve stability or improvement in retinal lesions.[14] A prospective study of intravitreal pegaptanib, an aptamer that inhibits VEGF isoform 165, found that pegaptanib did not have an effect on lesion regression but can minimally decrease exudation in some cases.[15] Recently, a prospective study regarding five patients with retinal capillary hemangiomas related to von Hippel-Lindau disease using monthly injections of ranibizumab also did not show broadly positive anatomical or functional results.[13]

Other therapy modalities described for retinal capillary hemangiomas include transpupillary thermotherapy (TTT), photodynamic therapy, proton beam radiation, plaque radiotherapy, and, finally, pars plana vitrectomy and enucleation for complex complications.[4]

SYSTEMIC DISEASE AND GENETICS

The systemic manifestations of VHL are multiple and include CNS hemangiomas of the brain and spinal cord, renal cell carcinomas, renal cysts, pheochromocytomas, pancreatic cysts, islet cell tumors, epididymal cystadenomas, endolymphatic sac tumors of the inner

ear, and adnexal papillary cystadenomas of the broad ligament. After retinal capillary hemangioma, the most frequently affected organ systems are the CNS, kidneys and adrenal glands, many of them occurring years after the initial presentation with retinal capillary hemangiomas.[4]

The diagnosis of VHL disease is based on three elements, which include retinal capillary hemangioma or CNS hemangioma, visceral lesions, and a family history of similar lesions.[4,6] After diagnosis is made, screening protocols should be followed, including urinary catecholamines and ophthalmoscopy on a periodic basis with MRI of the brain and spinal cord at least every 2 years, and yearly abdominal US with an additional abdominal CT scan every 2 to 3 years.[4]

GENETIC TESTING

VHL disease is an autosomal dominant disease whose gene is located on chromosome 3p 25-26. The gene functions as a tumor suppressor gene that promotes tumorigenesis when its function is lost. The normal protein product of the VHL gene forms a complex with other proteins that targets hypoxia inducible factors (HIFs) for degradation.[6] Mutations in the VHL gene result in stabilization of the HIFs, which bind to specific enhancer elements in the VEGF gene and stimulate angiogenesis.[16] With a near-complete penetrance of the disease and only rare instances of mosaicism, genetic testing has been proved helpful in early diagnosis and clinical screening for disease manifestations.[11]

SUMMARY

VHL disease is an autosomal dominantly inherited multisystem cancer syndrome with a predilection for the CNS and the retina. Retinal capillary hemangioma is one of the most common and earliest manifestations of VHL disease. Fundus findings are usually typical, and the diagnosis can be made based on ophthalmoscopic examination; however, fluorescein angiography is an additional and informative diagnostic tool. Various treatment modalities exist, although the mainstays of therapy are laser photocoagulation and cryotherapy. VHL disease, however, is associated with significant mortality secondary to either CNS hemangioma or renal cell carcinoma. Life expectancy of affected individuals can be improved by early detection, genetic testing and systemic treatment. ■

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