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Ocular Von Hippel-Lindau Disease: Clinical Update and Emerging Treatments

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Abstract

Purpose of review—von Hippel-Lindau (VHL) disease is an inherited, multi-systemic cancer syndrome often involving the retina. This review will provide an update for the clinical characterization and treatment of ocular VHL disease.

Recent findings—A comprehensive and quantitative clinical characterization of ocular VHL disease has been limited by small patient numbers and non-representative sampling. Recently, a large population of patients with clinically and genetically defined VHL disease has systemically characterized in a single center, enabling a quantitative evaluation of the ocular involvement of this syndrome. Correlations between the nature of VHL gene mutations and the ocular phenotype were also examined, providing clues as to how disruptions in VHL protein function may result in eye disease. This understanding may be relevant to the development of new therapies targeting the molecular biology of VHL disease, some of which are presently being investigated.

Summary—Quantitative studies enable a full characterization of the impact of VHL disease on eye health and visual function. Establishing correlations between the genotype of the VHL mutation and the phenotype of eye disease may inform us as to how ocular VHL disease arises, and help guide molecular interventions in ocular VHL disease.

Keywords

von Hippel-Lindau disease; genotype-phenotype correlations; anti-angiogenic therapy

Introduction

Von Hippel-Lindau (VHL) disease is an uncommon, autosomal-dominant, inherited cancer syndrome arising from germline mutations in the VHL gene. Its manifestations are multi-systemic, affecting the retina and central nervous system, as well as visceral organs, including the kidney, pancreas, liver, adrenal glands, and the broad ligament at varying frequencies [1]. The hallmark tumor lesion in the eye is the retinal capillary hemangioblastoma (RCH), which appears as a round, circumscribed, orange-red vascular lesion, found in either the peripheral retina or the juxtapapillary retina [2]. Although not present in every VHL patient, the RCH constitutes one of the diagnostic criteria of clinically defined VHL disease [3]. Despite being slow growing and sometimes quiescent, the RCHs

are capable, over time, of causing significant visual morbidity through either exudative or tractional effects on the surrounding retina [4*].

The discovery of the VHL gene in 1993 [5] was a seminal step in the molecular study of VHL disease. As techniques for molecular testing for VHL mutations improved [6], genetic diagnosis in members of affected families became increasingly available. With a near-complete penetrance of the disease, and only rare instances of mosaicism [7], genetic testing has proven helpful in early diagnosis and clinical screening for disease manifestations [8]. The isolation of the gene for VHL disease has also led to significant advances in understanding how the VHL protein functions and how its inactivation may result in tumorigenesis. The VHL protein is ubiquitously expressed and acts to degrade particular transcription factors called hypoxia inducible factors (HIFs) [9]. HIFs are produced in response to low tissue oxygen levels, or hypoxia, and serve to up-regulate proteins that can help reverse hypoxia, such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [10]. Loss of VHL function by mutation of the VHL gene results in unregulated high levels of HIF, which in turn produces high levels of downstream gene products. It is thought that constitutively elevated levels of proteins such as VEGF and PDGF stimulate angiogenesis, growth, and cell division, contributing to tumor formation [11].

The mutations in the VHL gene that result in VHL disease are highly varied, and may range from the substitution of a single amino acid to the complete deletion of the entire gene [12,13]. Although many of these mutations are thought to impair the ability of VHL to regulate HIF, the diversity in the manifestations of VHL disease suggests that different mutations may actually affect VHL protein function in different ways, and possibly even confer novel functions [14]. Correlating the nature of a patient's VHL mutation (i.e. the genotype) to how VHL disease manifests (i.e. the phenotype) can help discern how different types of VHL mutations result in disease. These correlations, applied to ocular VHL, may help uncover the mechanisms by which VHL mutations affect the eye.

The understanding that the upregulation of downstream genes, such as VEGF, may lead to the formation of vascular tumors has prompted the investigation of anti-angiogenic therapies as a possible treatment for ocular VHL. The use of anti-angiogenic therapies for the treatment of neovascular diseases in the retina such as choroidal neovascularization associated with age-related macular degeneration has been beneficial. How similar strategies may be adapted for use in the treatment of vascular tumors such as in ocular VHL is a topic of present investigation [15*].

Ocular involvement and visual impact of VHL disease

Ocular VHL disease typically occurs as retinal capillary hemangioblastomas (RCHs) found either in the peripheral retina and/or the juxtapapillary region. Visual loss from RCHs is generally caused by exudation from the tumor, causing retinal edema, or by tractional effects, in which glial proliferation on the surface of the tumor induces retinal striae and distortion [2]. Treatment traditionally involves physical tumor disruption by modalities such as laser photocoagulation, cryotherapy, photodynamic therapy and radiation, or by surgical excision [16]. The efficacy and applicability of treatment are very much influenced by location of the RCH; treatments that can be successfully directed at RCHs in the peripheral retina cannot be safely applied to juxtapapillary RCHs without damage to the optic nerve, with ensuing vision loss [17,18].

Definitive treatment and counseling of individual patients with ocular VHL benefit from the understanding of a well-characterized natural history of VHL-associated RCHs for a

balanced prognosis for visual function. Quantitative clinical characterizations of ocular VHL have been challenged by the small size of available case series and non-representative sampling from ophthalmic practices. In a collaborative study with the National Cancer Institute [19*], we have recently assembled a large collection of 890 patients that have undergone detailed multi-specialty evaluations in a single clinical center and confirmed to have clinically definite VHL disease according to the criteria of Melmon and Rosen [3]. These patients were recruited throughout the US and Canada and are referred because of systemic findings, rather than presenting with ocular symptoms. Almost all (98.1%) of these patients were also confirmed to have a germline mutation in the VHL gene.

In this cross-sectional study, we found that about 37% of patients with definite VHL disease have ocular involvement in the form of RCH, an estimate lower than found in previous series [2]. About 58% of patients with ocular VHL had bilateral involvement. Of eyes with visible RCHs, about 5 out of 6 eyes had RCHs only in the peripheral retina; 1 out of 12 had RCHs in only the juxtapapillary region, while the remainder had RCHs in both locations. Interestingly, while tumor number did not increase significantly as a function of age, the risk of vision loss was found to increase with age, as was found in another cross-sectional series [20]. The risk of severe vision loss also increased with the presence of juxtapapillary lesions and increasing peripheral tumor number and extent.

The results of our quantitative clinical characterization provide the following counseling guidelines for patients with ocular VHL disease: (1) the overall prevalence of legal blindness from ocular VHL is low; only 1 out of 18 patients with ocular VHL disease have severe bilateral visual acuity impairment ($Va < 20/160$); (2) the impact of RCH on the individual eye is however real; this negative impact increases with age, juxtapapillary tumors, and large tumor numbers; (3) on the whole, about 1 in 4 eyes affected with RCH have acuities $< 20/160$ and about 1 in 5 affected patients have ocular involvement severe enough to cause phthisis or enucleation in at least one eye. In summary, because of the considerable rate of unilateral disease and asymmetric disease severity in bilateral disease, the rate of bilateral visual impairment is low but the risk of severe unilateral ocular disability remains significant. These characterizations are obtained in the context of standard therapy - the challenge of newer therapies is to improve this overall morbidity of ocular VHL disease.

Genotype-phenotype correlations in ocular VHL disease

The advent of genetic testing for mutations in the VHL gene has proven to be a real advance in affected families. Instead of screening all family members for disease manifestations, attention can be focused on family members who have inherited the disease gene. Comparing the present clinical situation to previous periods when genetic testing was unavailable, it has been shown that overt disease can be detected at a higher rate and at a younger age [21*]. Having confirmed the diagnosis, the further application of genotypic analysis is in prognosing the likelihood of VHL disease manifestation in particular organ systems, the likely age of onset, and the nature and severity of the manifestation should it occur. Information of this nature will be very useful in developing screening strategies and for the counseling of patients.

Information of this nature derives from statistical analyses of how likely VHL disease is to present in a certain form, given particular VHL mutations, (i.e genotype-phenotype correlations). Previous analyses have found that mutations that delete VHL or lead to the loss of protein structure confer a low risk of pheochromocytoma (type 1 disease) while missense mutations in which a single amino acid is altered confer a higher risk of pheochromocytoma (type 2 disease) [22,23,24]. Analogously, correlations found between mutational genotype and ocular phenotype will be useful in the prognosis and screening of

VHL-related eye disease. This represents part of an ongoing effort in genetic ophthalmology in which genotype data in inherited eye disease is being collected, analyzed, and used to drive medical vision care [25,26].

Do different mutations in the VHL gene result in different ocular manifestations of ocular VHL disease? We have analyzed the prevalence of RCHs in a population of 873 patients with clinical and genotypic evidence of definite VHL disease [27*]. We divided our study population into one of 3 genotypic classes: (1) Missense mutations, in which only one amino acid is substituted, (2) Truncating mutations, resulting from nonsense and missense mutations, and (3) Deletions, in which the entire VHL gene is deleted. Interestingly, after adjusting for age, gender, and familial relationships, we found that the prevalence of RCHs in VHL patients with complete deletions is significantly *lower* (14.5%) than for either missense mutations (38.0%) or truncating mutations (40.1%). Also, even among patients with RCHs, patients with deletion mutations had a better visual acuity score than the other mutation classes (84.7 letters, compared with 54.9 and 51.7 letters, in the worse seeing eye, $p = 0.01$). Previous smaller studies however did not uncover a relationship between genotype [28] and ocular disease prevalence or visual morbidity [29], but these studies may have been limited by the smaller number of patients analyzed. The finding that a complete absence of the VHL germline gene actually results in less and milder eye disease suggests that aberrant VHL function may be more pathogenic in the retina than a simple absence of VHL function.

We are currently analyzing genotype-phenotype correlations in the subset of patients with missense mutations in which only one amino acid in the entire protein sequence is mutated. The VHL protein contains 2 structural domains, α and β , which are known to interact with different molecular partners and are likely to carry out different cellular functions [30]. The contribution of these functional domains to ocular disease in VHL is unknown, and indications of their relative roles may be obtained by comparing the ocular phenotype in patients with point mutations in the α versus the β domain. Our preliminary analysis in 412 VHL patients with missense mutations indicate that patients with point mutations in domain α are significantly more likely to have ocular VHL disease than patients with point mutations in domain β . Among patients with ocular VHL disease, patients with domain α mutations have a greater tendency to have RCHs in the juxtapapillary region while patients with domain β mutations have a greater tendency to have tumors in the peripheral retina (Wong et al., unpublished observations).

In summary, our analyses show that the nature of a patient's germline mutation in the VHL gene has an effect on how likely ocular VHL disease will occur, the location of the VHL lesions, and their resulting visual impact. These relationships will aid in future screening and counselling of VHL patients, and may help discover pathogenetic mechanisms underlying VHL tumorigenesis in the eye.

Treatment of ocular VHL disease

Recent advances in the understanding of VHL protein function and tumorigenesis in VHL disease have led to treatments targeting the biology of the disease, as opposed to ablative or surgical approaches. Molecules upregulated in the context of VHL mutation, such as VEGF and PDGF, have been targeted in investigational therapies, especially in the treatment of renal cell carcinoma [31,32,33]. For ocular VHL disease, the use of systemically administered anti-angiogenic therapy has also been recently described. The use of SU5416, an intravenously administered inhibitor of VEGF receptor-2, has been described in a few case reports. Aiello et al., [34] reported a single case of a juxtapapillary RCH in which treatment did not result in a decrease in tumor size but effected an improvement in visual

acuity and visual field. Girmens et al., [35] reported a case of a treated peripheral tumor that similarly did not shrink in size but however decreased in exudation. Madhusudan et al., [36] found in a series of 6 similarly treated patients in which only 2 achieved stability or improvement in their ocular lesions. In a case report, another agent, bevacizumab, a humanized anti-VEGF antibody, was also used systemically (6mg/kg body weight); treatment decreased tumor exudation transiently but did not improve eventual visual outcome [37]. A prospective, pilot study of systemic sunitinib, targeting multiple receptor tyrosine kinase receptors, including PDGF receptor and VEGF receptor is presently being planned at the National Eye Institute.

Local therapy of VHL-related RCH using anti-angiogenic agents has also been reported. Ziemssen et al., [38] reported a case where a single intravitreal bevacizumab, combined with one session of photodynamic therapy, resulted in a durable decrease in exudation, tumor regression, and improved visual acuity. However, in a prospective, pilot study of 5 patients treated with pegaptanib, an aptamer that inhibits VEGF isoform 165, given every 6 weeks, there was no vision improvement and only minimal anatomical improvement [39]. Preliminary analysis of another recently concluded, prospective, pilot, 5-patient study at the NEI using monthly injections of ranibizumab also did not show positive anatomical or functional results (Wong et al., unpublished observations).

These data suggest that the general efficacy of anti-angiogenic agents in this disease is uncertain. While case reports may be illustrative, prospective clinical trials are important in evaluating the efficacy of this approach. The relative merits of systemic versus local therapy are still unclear. Systemic therapy has the potential to deliver treatment to tumor in multiple organs, however local therapy may have fewer systemic side effects. There is also concern that in intravitreal injections, drug access to target cells in large mature tumors may be limited.

It also remains uncertain what the optimal molecular targets in ocular VHL disease are. Pegaptanib, bevacizumab, and ranibizumab, have been used extensively for ocular disease, and have a relatively good safety profile, but it is unclear if VEGF is the ideal target in the inhibition of VHL-related tumor growth and behavior. An improved genetic and molecular understanding of how VHL dysfunction results in ocular disease and the development of an animal model for ocular VHL disease will be the next substantive steps forward in the generation of new therapies.

Conclusions

The advances in the study of the genetic and molecular bases of VHL disease have not only provided a better understanding of its pathophysiology but also advanced in a general way our understanding of how tissue respond to oxygen levels. For ophthalmologists, the diagnosis and treatment of VHL disease also continues to evolve from these developments. With improved clinical characterizations of the disease, we can better put into context the impact of VHL disease on eye health and understand the functional implication of tumor phenotypes. In recent years, genetic diagnosis have provided a higher yield for our screening programs, and minimized unnecessary screening. In the future, genetic information may allow us to prognosticate the course of ocular disease and help guide screening, treatment, and counselling. Future advances in molecular understanding of the disease may also yield therapeutic agents that target the biology of the disease, delivering treatment with greater effectiveness and less collateral visual morbidity and tissue damage.

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