

Journal of Translational Medicine & Epidemiology

Special Issue on von Hippel Lindau Disease

Edited by:

Hiroshi Kanno

Professor, Department of Neurosurgery, Yokohama City University School of Medicine, Japan

Review Article

Retinal Capillary Hemangioma in von Hippel-Lindau Disease: Current Concept, Diagnosis and Managements

Satoru Kase* and Susumu Ishida

Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Japan

Abstract

von Hippel-Lindau (VHL) disease is caused by a mutation in the VHL gene, resulting in the functional disorder in VHL-encoded protein (pVHL). Recent advances in experimental and clinical studies on VHL gene/protein and VHL disease have provided novel concepts in molecular pathology and clinical managements. pVHL plays a critical role in the regulation of hypoxia inducible factor (HIF)-dependent as well as HIF-independent signaling pathways. These mechanisms should underlie the pathogenesis of VHL-related retinal vascular tumors. It is still controversial whether the histological term "hemangioma" vs "hemangioblastoma" should be appropriate in calling retinal vascular tumors of VHL disease. Recent clinical studies have proved efficacy of various therapeutic options depending on the location of retinal tumors between peripheral and optic disc/juxtapapillary hemangioma. Long-term follow-up observation can be achieved in VHL disease patients, showing favorable outcomes of conventional standard treatments. However, there still exists a population suffering from irreversible severe visual disturbance even though the conventional treatments had been performed enough. Further challenging of molecular targeting therapy as well as development of vitreoretinal surgeries and gene/protein transfer technique may contribute to preservation of the patients' vision in the future.

*Corresponding author

Satoru Kase, Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Nishi 7, Kita 15, Kita-ku, Sapporo 060-8638, Japan, Tel: +81-11-706-5944; Fax: +81-11-706-5948; E-mail: kaseron@med.hokudai.ac.jp

Submitted: 10 October 2013

Accepted: 26 December 2013

Published: 28 December 2013

Copyright

© 2013 Kase et al.

OPEN ACCESS

Keywords

- Retinal capillary hemangioma
- von Hippel-Lindau disease
- Histopathology
- Management

INTRODUCTION

von Hippel-Lindau (VHL) disease is a rare hereditary (1/36,000 live births) autosomal dominant syndrome [1]. VHL disease is manifested by a range of different benign and

malignant tumors, including hemangioma/hemangioblastoma of the retina and central nervous system, renal cell carcinoma, pheochromocytomas, pancreatic carcinoma, and cysts in the kidneys, liver, and pancreas [2]. There are two different clinical patterns for diagnosis of the disease: 1) patients with a positive

history of developing retinal hemangioma as well as systemic tumors such as renal cell carcinoma, pheochromocytoma, pancreatic tumors or cysts, epididymal cystadenoma associated with VHL, and 2) patients without a family history of VHL who present with retinal hemangioma in combination with other various tumors [3]. VHL is an age-dependent and highly penetrant disease with the more common manifestations being retinal hemangiomas. VHL-associated retinal hemangioma occurs in over 60% of the patients [4], and is the first manifestation of the disease in 43% of patients [5]. On the other hand, about half of retinal hemangiomas are related to VHL [6]. However, it remains unclear whether retinal capillary hemangioma that occurs without a family history is most commonly sporadic or most commonly represents an initial manifestation of VHL [7,8].

It is indisputable that biotechnology and molecular science have developed dramatically during a couple of decades. Indeed, long-term follow-up cases have been accumulated according to recent literatures. These backgrounds certainly provide an opportunity to reconsider the previous concept and clinical aspects of the disease. In this review, the current development of molecular pathological studies, clinical characteristics, histopathology, differential diagnosis and managements are included and discussed.

Recent advances in molecular pathology of VHL

VHL disease is caused by a mutation in the *VHL* gene [2], resulting in the functional disorder in VHL-encoded protein (pVHL). Originally identified as a tumor suppressor, the pVHL is now known to repress expression of mRNAs that are normally induced under hypoxic conditions [9]. The hypoxia-inducible factor (HIF) is a key transcription factor responsible for up-regulation of various hypoxia-inducible genes' expression. When mutated, the *VHL* gene produces a protein that is unable to regulate HIF, permitting accumulation of HIF and subsequent activation of vascular endothelial growth factor (VEGF) and other hypoxia-inducible genes [10]. This can result in growth of retinal hemangiomas and other tumors associated with VHL disease. pVHL is a substrate recognition component of an E3-ubiquitin ligase that rapidly destabilizes HIF- α under normoxic, but not hypoxic, conditions. Thus, pVHL is known to be regulating angiogenic factors through HIF- α depending on tissue oxygen concentration. Chemokines are a group of structurally related secretory and transmembrane proteins whose major tasks are to coordinately recruit various leukocyte populations into target tissue sites via specific receptors. Chemokine receptor CXCR4 is reported to be down-regulated by the pVHL and upregulated by HIF [11].

Apart from HIF dysregulation, further conditions that favor tumorigenesis may be related to both non-functional or absent pVHL in the cell. VHL-deficient cells lose the ability to exit the cell cycle, making it the initial step in VHL tumorigenesis. Ultimately, cells lacking pVHL are deficient in assembly of an extracellular fibronectin matrix or in regulating growth arrest mediated by cell-extracellular matrix signaling [12,13]. To clarify how the HIF-independent mechanisms by pVHL underlie pathogenesis of retinal hemangioma is a future issue.

Recent *in vivo* studies have shown that VHL gene is essential

for normal development of the retinal tissue and vitreoretinal vasculature. Kurihara et al. generated retina-specific conditional-knockout mice for VHL (Vhl(α)(-CreKO) mice. These mice exhibit arrested transition from the fetal to the adult circulatory system, persistence of hyaloid vessels and poorly formed retinal vessels. These defects are suppressed by intraocular injection of FLT1-Fc protein [a VEGF receptor-1 (FLT1)/Fc chimeric protein that can bind VEGF and inhibit its activity], or by inactivating the HIF-1 α gene. These suggest that not only macrophages mediating programmed cell death, but also tissue oxygen-sensing mechanisms regulate the transition from the fetal to the adult circulatory system in the retina [14]. VHL also plays a crucial role in the tissue maintenance of the neural retina as well as retinal pigment epithelium (RPE). Lange et al. demonstrated that VHL-dependent regulation of HIF-1 α in the RPE is essential for normal RPE and iris development, ocular growth and vascular development in the anterior chamber, whereas VHL-dependent regulation of other downstream pathways is crucial for normal development and maintenance of the retinal vasculature [15].

Clinical features of retinal capillary hemangioma

Ocular VHL disease typically occurs as retinal capillary hemangioma found either in the peripheral retina and/or the optic disc/juxtapapillary region (Figure 1). Retinal hemangioma originates from the inner, midperipheral retina and usually grows, causing visual impairment due to leakage leading to various secondary changes in the eye [16]. Approximately one-third of patients have multiple retinal capillary hemangiomas, while two-third have isolated tumor [4]. The most common clinical finding of these retinal hemangiomas is a highly vascularized tumor in the superotemporal region of the retina [17]. The coloration of the vascularized tumors is commonly found as reddish, while orange-yellow tumors can be seen [18]. These tumors are often endophytic and peripheral spherical masses classically associated with a dilated tortuous feeding artery and a draining vein. Usually, two or three tortuous feeding vessels with dilatation are accompanied with the peripheral tumors. Even in case of peripheral retinal hemangiomas, coloration of the optic disc can be reddish, and the optic disc margin may be unclear (Figure 1) in the same eye. Alternatively, retinal hemangioma may

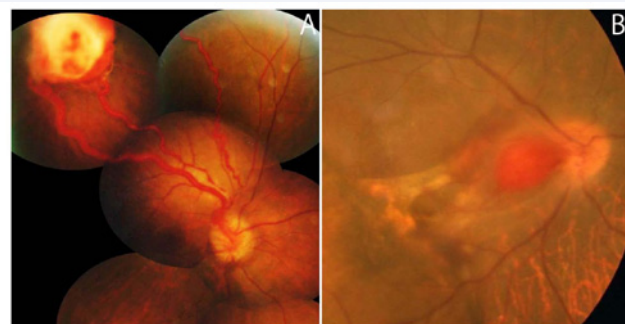


Figure 1 Fundus photograph of two von Hippel Lindau Disease patients with retinal capillary hemangioma in the temporal periphery (A), and juxtapapillary hemangioma (B) of the right eye. Two dilated vessels emanate from the tumor (A). In contrast, no dilated feeder vessels are noted in juxtapapillary hemangioma (B). (B: Case courtesy of Dr Hiroshi Yoshikawa).

be exophytic, and arise from the outer retinal layers. Exophytic tumors are not usually associated with arteriovenous shunting. They tend to develop in the juxtapapillary region (Figure 1), and are frequently misdiagnosed as papilledema, choroidal neovascularization or tumors of RPE or choroid.

Approximately one quarter (22%) of eyes demonstrated de novo ocular involvement, with 18% demonstrating new retinal hemangiomas in a peripheral retinal location only, 2% demonstrating new tumors in a juxtapapillary location only, and 2% demonstrating new tumors in both juxtapapillary and peripheral locations [19]. These anatomical features between peripheral and optic disc/juxtapapillary tumors may reflect on different clinical course and therapeutic approach. In a recent cross sectional study, vision loss in 335 patients with VHL-associated retinal hemangiomas more likely occurred when the lesions were in the juxtapapillary region [20]. Severe vision loss in the affected eyes was also related to the patients' age, the number and size of tumors located in the periphery [20]. The study also showed that although bilateral involvements are common, the rate of bilateral visual impairment is less common due to the asymmetric disease burden. However, the tumor can still lead to blindness and the rate of significant morbidity in one eye remains high. Among eyes with ocular VHL disease at baseline, 88% did not demonstrate retinal hemangiomas in a new retinal location, 70% remained stable in the number of retinal hemangioma, and 79% remained stable in the extent of the tumor involvement. Mean visual acuity for all study eyes decreased by 5.1 ± 0.6 letters across follow-up, with 16.1% of the eyes decreasing by more than 10 letters in visual acuity. Among eyes affected at baseline, greater vision loss was associated with the presence of juxtapapillary hemangioma, development of retinal hemangioma in a new location, and increase in peripheral hemangioma number and extent [19].

Secondary changes of the disease usually entail exudative or tractional effects surrounding the tumor [21]. Exudation occurs in 25% of cases, of which 10% is intraretinal exudation and a further 16% can cause retina detachment. Fibrovascular proliferation secondary to peritumoral ischemia in the 9% of cases produces tractional retinal detachment, macular ectopia, epimacular proliferation and traction leading to rhegmatogenous retinal detachment [22].

Of all the ancillary tests available to detect retinal capillary hemangioma, fluorescein angiography (FA) is the most informative diagnostic tool because of the vascular nature of the tumor. The retinal tumor has fine capillary filling, which rapidly becomes homogeneous. The draining vein becomes prominent in the venous phase, while the tumor demonstrates progressive hyperfluorescence with late leakage of dye into the surrounding structures [4]. Optical coherence tomography (OCT) is useful in diagnosis of the exophytic retinal hemangioma [23] despite the presence of the juxtapapillary or peripheral region [24], in detecting subretinal fluid, and in monitoring the response to treatments [25].

Histopathology of surgically excised retinal tissues

Whether we should use terms "hemangioma" or "hemangioblastoma" in calling retinal vascular tumors has yet to be determined. Hemangioblasts are the multipotent precursor

cells that can differentiate into both hemopoietic and endothelial cells [26]. Principally, the term "hemangioblastoma" should be used in tumorigenesis of the hemangioblasts. Recently, isolated erythropoietin-positive cells, indicative of developmentally arrested hemangioblasts, were detected in retinal vascular tumor associated with VHL [27,28], suggesting that the retinal tumor may be closely associated with the term "hemangioblastoma". On the other hand, when the term "hemangioblastoma" is used, the tumor cells morphologically should have nuclear atypia and dense cell proliferation with some undifferentiated changes, malignancy and/or malignant potential rather than "hemangioma". For example, these tendencies are clearly seen in histology of retinoblastoma, which is totally different from that of retinoma [29]. As described below, the tumor cells do not present with nuclear atypia, mitotic figure, or high cellularity in case of retinal vascular tumor in VHL disease. These findings are marginally different from cerebellar hemangioblastoma in VHL. In order to prove this, comparative studies on histopathology will be needed between the retinal and cerebellar vascular tumors of VHL disease. Although traditionally the vascular tumor in VHL disease has been recognized as hemangioblastoma, various authors have recommended that capillary hemangioma rather than hemangioblastoma be used to describe vascular tumors in VHL disease [4], based on histological findings. Therefore, in this review, the term "hemangioma" has been used in retinal vascular tumor observed in VHL disease.

Histologically, the basic lesion is a capillary hemangioma, but not cavernous hemangioma, in vascular tumors of the retina in patients with VHL. The tumor, a capillary hemangioma, is composed of endothelial cells, pericytes, and stromal cells. It is likely that the hemangioma replaces full-thickness of the retina. Retinal hemangioma reveals a variety of vacuolated "foamy" stromal cells reside among the thin capillary-like channels [30]. Morphologically, the stromal cells can present with characteristic pale, polygonal cells (Figure 2). The stromal cells appear foamy due to the presence of phagocytosed lipids produced by leaking capillary endothelium. The lipid is plasma-derived cholesterol stearate [31]. In addition to these typical histological findings, Chan and associates have identified sporadic tumorlet-like cells characterized by small cellular clusters, which form angiomesenchymal islands in optic disc hemangioma of VHL disease [28,32]. Immunohistochemical studies show that the

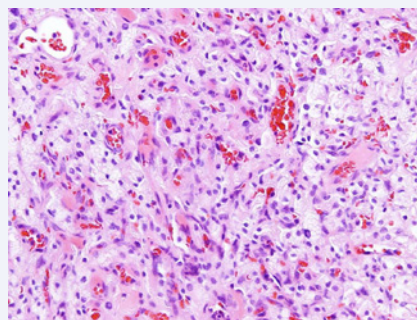


Figure 2 Histological finding of retinal hemangioma in a patient with von Hippel Lindau Disease (Case courtesy of Professor Akito Hirakata). Note collection of marked microvessels without nuclear atypia admixed with foamy stromal cells.

foamy stromal cells reveal positive reaction for glial fibrillary acidic protein, which appear to be of glial origin. However, the stromal cells also showed positive for neuron-specific enolase (NSE), indicating that the stromal cells are not originated from glial cells only. Some of the stromal cells stained positively for inhibin alpha [27]. These results suggest that stromal cells in retinal hemangiomas are neuroectodermal in origin with immunohistochemical features. Miyazawa et al. recently demonstrated that the NSE-positive stromal cells expressed VEGF protein in retinal hemangioma. Chan CC et al. showed expression of VEGF, and HIF, as well as several stem cell markers including erythropoietin, erythropoietin receptor, and CD133, in human retinal and juxtapapillary hemangioma in VHL disease [28,33,34]. In contrast, CD117, the stem cell factor receptor, was not expressed in retinal tumor cells of VHL disease, suggesting that the tumor may not have myeloid/neural crest lineage [28]. Recently, Liang et al. demonstrated CXCR4 immunoreactivity in the cytoplasm and nuclei of the stromal and vascular cells in retinal hemangiomas of VHL cases, whilst CXCL12 was negative in the retina [35]. They also showed that gene expression of VEGF and CXCR4 was highly detected in retinal hemangioma tissues. The VHL gene deletion may be restricted to the stromal cells, suggesting that the stromal cells are the neoplastic component in retinal hemangiomas, and induce the associated neovascularization [36]. Further pathological examinations will definitely characterize the morphology and biological features in hemangioma/hemangioblastoma.

Differential diagnosis

Primitive retinal vascular abnormalities are benign conditions of the retinal circulation that comprise vascular tumors and telangiectasias. Retinal vascular tumors include not only retinal capillary hemangioma, but also vasoproliferative retinal tumors (VPRTs), cavernous hemangioma of the retina, and racemose hemangiomatosis of the retina or Wyburn-Mason syndrome [25]. Of particular importance, many of the vascular tumors of the retina have significant associations with systemic disease. As ocular symptoms are often the most common presenting disease manifestation, the ophthalmologist plays an important role in accurate and early diagnosis [37]. Especially, recent several researchers have conducted pathological and immunohistological analyses in patients with VPRT. Therefore, clinical and molecular differences in VPRT from retinal hemangioma are discussed in this review; otherwise, please refer to recent and previous review articles regarding differential diagnosis of other important retinal vascular tumors [4,25].

VPRTs are benign glial and vascularized tumors of the sensory retina (Figure 3), located at the temporal periphery. VPRT causes retinal neovascularization or exudative retinal changes. The tumors are associated with no large retinal feeder vessels, as observed in retinal hemangiomas associated with VHL disease. Approximately 75% of cases are idiopathic and the rest is secondary to retinitis pigmentosa, chronic retinal detachment, and Coats disease. Patients with VPRTs have no systemic tumors such as VHL disease. Laser photocoagulation or cryotherapy is commonly performed for these tumors [38]. Plaque radiotherapy, photodynamic therapy (PDT), or pars plana vitrectomy might be performed when the tumors do not respond to these procedures [39]. The histology of the tumor

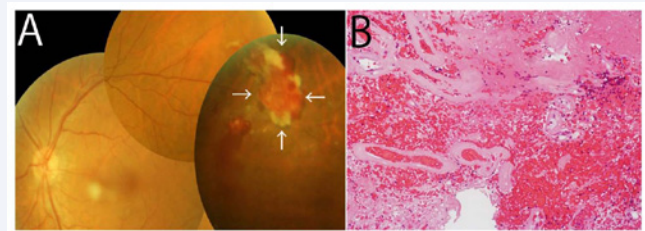


Figure 3 Fundus photographs (A), and histological findings (B) of the surgically excised vasoproliferative retinal tumor tissue.

Fundus photograph shows elevated reddish retinal tumor at the temporal mid-periphery (arrow), involving neovascularization on the surface (A). Light micrograph demonstrates a correction of small vessels with thickened vessel walls and marked hyalinization. Spindle-shaped stromal cells are intermingled in the tumor. (hematoxylin-eosin, original magnification x200).

demonstrated a correlation between small vessels with a thickened vessel wall and marked hyalinization, where glial cells are intermingled (Figure 3). The pathological findings in the abnormal vessels are different from those in retinal hemangioma of VHL disease. Liang et al. demonstrated that there was no immunoreactivity against VEGF or CXCR4 in VPRT [35], whereas we have shown immunoreactivity for VEGF in tumor tissues of VPRT [40]. Although the immunohistochemical results are still controversial, anti-VEGF antibody therapy is basically effective for patients with VPRT [40]. Loss of heterozygosity of VHL genes is detected with microsatellite marker D3S1110 in retinal tumor tissues coming from VHL disease but not in VPRT [35].

Managements of peripheral retinal hemangioma

The universal goal in the treatment of retinal hemangioma is preservation of visual acuity and the visual field without destruction of the function of the retina around the tumor. In order to achieve the therapeutic goal, it may be a significant process to reduce tumor volume via sclerosis of dilated feeder vessels. A study showed that patients with smaller lesions (less than 1.5 mm) were more likely to remain stable. Those that progressed in this group were well controlled with standard therapies including cryotherapy and/or photocoagulation [41]. Hence, retinal hemangiomas are generally treated with cryotherapy or laser photocoagulation, and patients receive a 72% and 74% success rate, respectively [41]. Laser treatment is sufficient in small peripheral tumors and cryotherapy could be carried out in patients with large retinal tumors. We herein demonstrate a VHL case of peripheral retinal hemangioma treated with laser photocoagulation (Figure 4). A twenty-year-old female complained of blurred vision in both eyes. She had a medical history of cerebellar and spinal cord hemangioblastomas. Her father had been diagnosed with VHL disease. At the age of 23, visual acuity became no light perception in her right eye due to retinal detachment although she received several times of laser photocoagulation. In contrast, she also received laser photocoagulation to the small retinal tumors for 21 times in total, which has been keeping favorable vision over 20 years (Figure 4). In addition to those therapies, Kreusel et al. conducted retrospective study including 25 retinal capillary hemangiomas of 24 patients treated with brachytherapy using 106-ruthenium/106-rhodium plaques. Of 25 tumors, 23

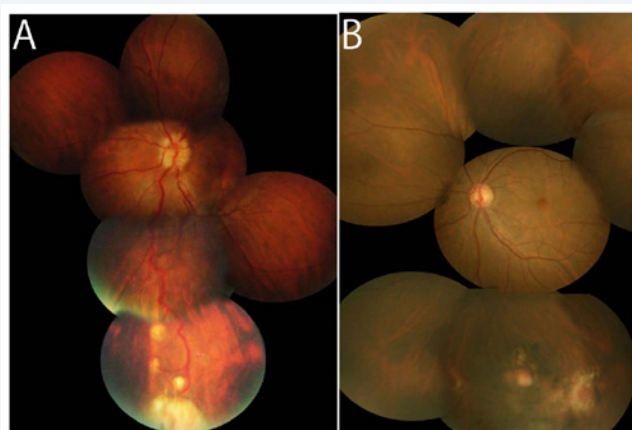


Figure 4 Fundus photograph before and after laser photocoagulation in a patient with VHL disease.

A 21-year-old female shows retinal capillary hemangioma at the inferior periphery (A) before treatments. She eventually has received laser photocoagulation 21 times at outpatient ward. At the age of 44, fundus delimits the tumor lesion with regression of the feeding vessels (B).

hemangiomas could be destroyed by single brachytherapy. They also concluded that a favorable outcome could be expected if a hemangioma's diameter is 5.0 mm or smaller and if there is no preoperative exudative retinal detachment [42]. External beam radiotherapy has been also shown to be useful when standard therapy has not prevented progression [43]. Palmer et al. have found proton-beam irradiation to be an efficacious and safe treatment for large retinal hemangiomas, measuring more than 3 mm, and for cases complicated by exudative retinal detachments or for tumors involving the optic nerve [44]. However, there may exist a problem if the tumor recurs. In such cases, it may be hard to conduct additional radiotherapy to the eye. Combination therapies including ruthenium plaque radiotherapy, cryotherapy, and PDT can be required to induce complete tumor regression and sclerosis of the dilated vessels [18] in selected cases.

Anti-VEGF agents are also candidates for retinal hemangiomas in VHL patients. There are two ways for administration of anti-VEGF agents to the human body: systemically and intravitreally. Intravitreal injections of anti-VEGF therapy (pegaptanib) may decrease retinal thickening minimally and reduce retinal hard exudates in some patients with advanced hemangiomas in patients with VHL [45]. However, the efficacy of agents in this class such as VEGF receptor inhibitor SU5416, and anti-VEGF agents including bevacizumab, ranibizumab and pegaptanib are uncertain [46-50].

Interferon (IFN)- α has an established role in cancer therapy in some cancer types such as hairy cell leukemia and melanoma. Niemela et al. reported that recombinant human IFN- α -2a (Roceron-A; Roche) was injected subcutaneously into VHL patients at a dose of 3×10^6 IU, 3 times/week for 12 months. There was a transient decrease in size and fluorescein leakage from the retinal hemangioma during the therapy. They concluded that IFN- α -2a might decrease blood flow in hemangiomas as suggested by shrinkage and diminished leakage of retinal hemangiomas [51].

On the other hand, larger tumors may have been shown to

be non-responsive to medical treatments. A retrospective study of patients showed that for lesions between 7–9 mm, surgical resection of retinal tumors improved visual acuity or kept it the same [35,52]. Therefore, surgical resection of the tumor should be considered for patients with large retinal hemangiomas. The surgery should consist of pars plana vitrectomy, argon endolasing of the feeder vessels, endodiathermy of the vascular lesion, artificial posterior vitreous detachment formation, and filling of the vitreous cavity with silicone oil [35]. Expected intraoperative or postoperative complications include cataract, hemorrhage during resection, epiretinal membrane, and intraoperative retinal breaks, and recurrent retinal detachments [52]. Bimanual technique is useful to reduce intraoperative bleeding and to resect tumor tissues safely during vitrectomy [27].

Managements of optic disc/juxtapapillary hemangioma

Ophthalmologists may choose observation unless the associated visual impairments happen in patients with optic disc/juxtapapillary hemangioma, because overtreatments may lead to an irreversible optic nerve disorder. Instead, the treatments should be considered if the optic disc tumors complicate serous retinal detachment and retinal exudation formation in the macula, and subsequent visual disturbance. Laser photocoagulation may be applied if the optic disc is completely covered with the tumor, which should be confirmed using FA. Even though the tumor partially involves the optic disc, laser may be possible in case of cooperative patients to the treatments, and favorable vision fixation during laser irradiation. Otherwise, the laser photocoagulation should be avoided.

PDT can be effective in reducing macular edema associated with retinal hemangioma; however, this does not always correspond with an improvement in visual acuities especially for juxtapapillary tumors, which is more characteristic for VHL-positive patients [53]. Reynolds et al. reported that VHL patients with juxtapapillary hemangioma could experience treatment complications, including a vitreous hemorrhage and rhegmatogenous retinal detachment. At that time, scleral buckling procedure, vitreoretinal surgery, and endo-laser photocoagulation may be required [54].

Anti-VEGF agents are also candidate treatments for optic disc hemangioma. von Below et al. demonstrated that 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 [50]. Aiello et al. reported the treatment involving the systemic administration of a VEGF receptor inhibitor SU5416. The juxtapapillary hemangioma did not result in a decrease in tumor size but effected an improvement in visual acuity and visual field [46]. As mentioned above in the peripheral retinal hemangioma, effects of anti-VEGF treatments on suppression of tumor growth vary in each case [55]. The reasons may be related to a reduction in vasopermeability, because there was no apparent effect of treatment on the size of the primary retinal hemangiomas [45].

Matsuo et al. reported an 18-year-old woman with optic disc hemangioma in the background of VHL disease [56]. The patient underwent low-dose external beam radiation (20 Gy) to the eye

using a lens-sparing single lateral technique, which led to the inhibition of visual disturbance associated with serous retinal detachment. Therefore, the authors recommended low-dose external beam radiation as the initial treatment option for optic disc hemangioma [56]. In contrast to such destructive therapies, infrared diode laser transpupillary thermotherapy provides a useful modality in the treatment of retinal capillary hemangiomas, and may be particularly favorable for juxtapapillary lesions because of its relatively nondestructive characteristics [57] in selected cases.

Corticosteroids have a significant anti-angiostatic capacity. The primary mechanism of action of angiostatic steroids appears to be in aiding breakdown and blockage of the formation of capillary endothelial basement membranes [58]. Toyokawa et al. reported a case of juxtapapillary hemangioma successfully treated with intravitreal injection of bevacizumab combined with posterior subtenon injection of triamcinolone acetonide (TA) (1.25 mg bevacizumab and 20 mg TA) [59]. Suh et al. showed that verteporfin PDT combined with intravitreal TA appeared to cause involution of the hemangioma with reduction in macular edema and improvement in visual acuity [60]. Therefore, it is likely that TA should be considered one of therapeutic options for patients with retinal and juxtapapillary hemangiomas.

Future prospects on therapeutic approach

Propanolol is a β -blocker commonly used in cardiology that may induce endothelium vasoconstriction and inhibit endothelial proliferation. It has been shown to be effective in infantile facial hemangiomas, and proved safe and effective for the choroidal hemangioma [61]. However, β -blocker has yet to be challenged for patients with retinal capillary hemangioma. Although β -blocker affects systemic circulation of human body including blood pressure, it may be initially tried especially for patients showing refractory to other treatments, after approving the ethical issues in the future.

Recently, adenovirus-mediated VHL intraocular gene transfer has been attempted, and VHL expression in adenovirus-mediated VHL-transduced cells was confirmed at the transcript and protein levels. Adenovirus expressing VHL led to a significant reduction in VEGF expression *in vitro* under normoxic or hypoxic conditions. Akiyama et al. demonstrated that adenovirus-mediated VHL effectively inhibited pathological angiogenesis in the monkey retina [62]. More recently, Sufan et al. analyzed adenovirus-mediated delivery of the bioengineered VHL protein, which contributed to the dramatic inhibition of angiogenesis and growth regression of human renal cell carcinoma xenografts in a dorsal skin-fold window chamber model [63]. Therefore, targeted VHL gene and protein transfer into the eye may open a novel therapeutic approach for retinal hemangioma of VHL disease in the future.

CONCLUSIONS

Recent advances in basic and clinical studies on VHL gene/protein and VHL disease have provided novel concepts in molecular pathology and clinical managements. pVHL plays a critical role in the regulation of HIF-dependent as well as HIF-independent signaling pathways. These mechanisms should

underlie the pathogenesis of VHL-related retinal vascular tumors. It is still controversial whether the histological term "hemangioma" vs "hemangioblastoma" should be appropriate in calling retinal vascular tumors of VHL disease. Further morphological and histochemical analyses will be required to resolve the issue. Recent clinical studies have proved application of various therapeutic options depending on the location of retinal tumors between peripheral and optic disc/juxtapapillary hemangioma during a couple of decades. Indeed, long-term follow-up observation can be achieved in VHL disease patients, showing effectiveness of conventional standard treatments. However, there still exists a population suffering from irreversible severe visual disturbance even though the conventional treatments had been performed enough. Further challenging of molecular targeting therapy as well as development of vitreoretinal surgeries and gene/protein transfer technique may contribute to preservation of the patients' vision in the future.

ACKNOWLEDGEMENTS

This study was supported in part by a Grant-in-aid for Research on von Hippel-Lindau (VHL) Diseases, the Ministry of Health, Labour and Welfare of Japan (Grant no. H24-Nanchi-Shitei-004 to T Shuin).

REFERENCES

1. Fearon ER. Human cancer syndromes: Clues to the origin and nature of cancer. *Science*. 1997; 278: 1043-1050.
2. Tootee A, Hasani-Ranjbar S. Von hippel-lindau disease: a new approach to an old problem. *Int J Endocrinol Metab*. 2012; 10: 619-624.
3. Shuin T, Yamasaki I, Tamura K, Okuda H, Furihata M, Ashida S. Von Hippel-Lindau disease: molecular pathological basis, clinical criteria, genetic testing, clinical features of tumors and treatment. *Jpn J Clin Oncol*. 2006; 36: 337-343.
4. Singh AD, Shields CL, Shields JA. von Hippel-Lindau disease. *Surv Ophthalmol*. 2001; 46: 117-142.
5. Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, Ferguson-Smith MA. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med*. 1990; 77: 1151-1163.
6. Niemela M, Lemeta S, Sainio M, Rauma S, Pukkala E, Kere J, et al. Hemangioblastomas of the retina: impact of von Hippel-Lindau disease. *Invest Ophthalmol Vis Sci*. 2000; 41: 1909-1915.
7. Ridley M, Green J, Johnson G. Retinal angiomas: the ocular manifestations of von Hippel-Lindau disease. *Can J Ophthalmol*. 1986; 21: 276-283.
8. McDonald HR, Schatz H, Johnson RN, Abrams GW, Brown GC, Brucker AJ, et al. Vitrectomy in eyes with peripheral retinal angioma associated with traction macular detachment. *Ophthalmology*. 1996; 103: 329-335.
9. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*. 1999; 399: 271-275.
10. Semenza GL. Regulation of mammalian O₂ homeostasis by hypoxia-inducible factor 1. *Annu Rev Cell Dev Biol*. 1999; 15: 551-578.
11. Staller P, Sulitkova J, Lisztwan J, Moch H, Oakeley EJ, Krek W. Chemokine receptor CXCR4 downregulated by von Hippel-Lindau tumour suppressor pVHL. *Nature*. 2003; 425: 307-311.

12. Thoma CR, Toso A, Meraldi P, Krek W. Double-trouble in mitosis caused by von Hippel-Lindau tumor-suppressor protein inactivation. *Cell Cycle*. 2009; 8: 3619-3620.
13. Turturro F. Beyond the Knudson's hypothesis in von Hippel-Lindau (VHL) disease-proposing vitronectin as a "gene modifier". *J Mol Med (Berl)*. 2009; 87: 591-593.
14. Kurihara T, Kubota Y, Ozawa Y, Takubo K, Noda K, Simon MC, et al. von Hippel-Lindau protein regulates transition from the fetal to the adult circulatory system in retina. *Development*. 2010; 137: 1563-1571.
15. Lange CA, Luhmann UF, Mowat FM, Georgiadis A, West EL, Abrahams S, et al. Von Hippel-Lindau protein in the RPE is essential for normal ocular growth and vascular development. *Development*. 2012; 139: 2340-2350.
16. Wittebol-Post D, Hes FJ, Lips CJ. The eye in von Hippel-Lindau disease. Long-term follow-up of screening and treatment: recommendations. *J Intern Med*. 1998; 243: 555-561.
17. Dollfus H, Massin P, Taupin P, Nemeth C, Amara S, Giraud S, et al. Retinal hemangioblastoma in von Hippel-Lindau disease: a clinical and molecular study. *Invest Ophthalmol Vis Sci*. 2002; 43: 3067-3074.
18. Bastos-Carvalho A, Damato B. Images in clinical medicine. Retinal hemangioblastoma in von Hippel-Lindau disease. *N Engl J Med*. 2010; 363: 663.
19. Toy BC, Agron E, Nigam D, Chew EY, Wong WT. Longitudinal analysis of retinal hemangioblastomatosis and visual function in ocular von Hippel-Lindau disease. *Ophthalmology*. 2012; 119: 2622-2630.
20. Wong WT, Agron E, Coleman HR, Tran T, Reed GF, Csaky K, et al. Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel-Lindau disease. *Ophthalmology*. 2008; 115: 181-188.
21. Kreusel KM, Bechrakis NE, Krause L, Neumann HP, Foerster MH. Retinal angiomas in von Hippel-Lindau disease: a longitudinal ophthalmologic study. *Ophthalmology*. 2006; 113: 1418-1424.
22. Gonzalez Escobar AB, Morillo Sanchez MJ, Garcia-Campos JM. Von Hippel-Lindau disease: family study. *Arch Soc Esp Oftalmol*. 2012; 87: 368-372.
23. Chin EK, Trikha R, Morse LS, Zawadzki RJ, Werner JS, Park SS. Optical Coherence Tomography Findings of Exophytic Retinal Capillary Hemangiomas of the Posterior Pole. *Ophthalmic Surg Lasers Imaging*. 2010; 9: 1-5.
24. Yavas GF, Okur N, Kusbeci T, Norman E, Inan U. A case of von Hippel-Lindau disease with juxtapapillary retinal capillary hemangioma and nutcracker phenomenon. *Int Ophthalmol*. 2013; 33: 309-314.
25. Knutsson KA, De Benedetto U, Querques G, Del Turco C, Bandello F, Lattanzio R. Primitive retinal vascular abnormalities: tumors and telangiectasias. *Ophthalmologica*. 2012; 228: 67-77.
26. Eichmann A, Corbel C, Le Douarin NM. Segregation of the embryonic vascular and hemopoietic systems. *Biochem Cell Biol*. 1998; 76: 939-946.
27. Miyazawa A, Inoue M, Hirakata A, Okada AA, Iihara K, Fujioka Y. Expression of inhibin alpha by stromal cells of retinal angiomas excised from a patient with von Hippel-Lindau disease. *Jpn J Ophthalmol*. 2009; 53: 501-505.
28. Chan CC, Chew EY, Shen D, Hackett J, Zhuang Z. Expression of stem cells markers in ocular hemangioblastoma associated with von Hippel-Lindau (VHL) disease. *Mol Vis*. 2005; 11: 697-704.
29. Kase S, Parikh JG, Rao NA. Expression of alpha-crystallin in retinoblastoma. *Arch Ophthalmol*. 2009; 127: 187-192.
30. Park S, Chan CC. Von Hippel-Lindau disease (VHL): a need for a murine model with retinal hemangioblastoma. *Histol Histopathol*. 2012; 27: 975-984.
31. Jakobiec FA, Font RL, Johnson FB. Angiomatosis retinae. An ultrastructural study and lipid analysis. *Cancer*. 1976; 38: 2042-2056.
32. Chan CC, Collins AB, Chew EY. Molecular pathology of eyes with von Hippel-Lindau (VHL) Disease: a review. *Retina*. 2007; 27: 1-7.
33. Chan CC, Lee YS, Zhuang Z, Hackett J, Chew EY. Von Hippel-Lindau gene deletion and expression of hypoxia-inducible factor and ubiquitin in optic nerve hemangioma. *Trans Am Ophthalmol Soc*. 2004; 102: 75-79.
34. Chan CC, Vortmeyer AO, Chew EY, Green WR, Matteson DM, Shen DF, et al. VHL gene deletion and enhanced VEGF gene expression detected in the stromal cells of retinal angioma. *Arch Ophthalmol*. 1999; 117: 625-630.
35. Liang X, Shen D, Huang Y, Yin C, Bojanowski CM, Zhuang Z, et al. Molecular pathology and CXCR4 expression in surgically excised retinal hemangioblastomas associated with von Hippel-Lindau disease. *Ophthalmology*. 2007; 114: 147-156.
36. Yanoff M, Fine BS. *Ocular Pathology*, Mosby 2002: 5; 29-30.
37. Turell ME, Singh AD. Vascular tumors of the retina and choroid: diagnosis and treatment. *Middle East Afr J Ophthalmol*. 2010; 17: 191-200.
38. Smith J, Steel D. The surgical management of vasoproliferative tumours. *Ophthalmologica*. 2011; 226: 42-45.
39. Cohen VM, Shields CL, Demirci H, Shields JA. Iodine I 125 plaque radiotherapy for vasoproliferative tumors of the retina in 30 eyes. *Arch Ophthalmol*. 2008; 126: 1245-1251.
40. Saito W, Kase S, Fujiya A, Dong Z, Noda K, Ishida S. Expression of vascular endothelial growth factor and intravitreal anti-VEGF therapy with bevacizumab in vasoproliferative retinal tumors. *Retina*. 2013; 33: 1959-1967.
41. Singh AD, Nouri M, Shields CL, Shields JA, Perez N. Treatment of retinal capillary hemangioma. *Ophthalmology*. 2002; 109: 1799-1806.
42. Kreusel KM, Bornfeld N, Lommatzsch A, Wessing A, Foerster MH. Ruthenium-106 brachytherapy for peripheral retinal capillary hemangioma. *Ophthalmology*. 1998; 105: 1386-1392.
43. Raja D, Benz MS, Murray TG, Escalona-Benz EM, Markoe A. Salvage external beam radiotherapy of retinal capillary hemangiomas secondary to von Hippel-Lindau disease: visual and anatomic outcomes. *Ophthalmology*. 2004; 111: 150-153.
44. Palmer JD, Gragoudas ES. Advances in treatment of retinal angiomas. *Int Ophthalmol Clin*. 1997; 37: 159-170.
45. Dahr SS, Cusick M, Rodriguez-Coleman H, Srivastava SK, Thompson DJ, Linehan WM, et al. Intravitreal anti-vascular endothelial growth factor therapy with pegaptanib for advanced von Hippel-Lindau disease of the retina. *Retina*. 2007; 27: 150-158.
46. Aiello LP, George DJ, Cahill MT, Wong JS, Cavallerano J, Hannah AL, et al. Rapid and durable recovery of visual function in a patient with von hippel-lindau syndrome after systemic therapy with vascular endothelial growth factor receptor inhibitor su5416. *Ophthalmology*. 2002; 109: 1745-1751.
47. Girmens JF, Erginay A, Massin P, Scigalla P, Gaudric A, Richard S. Treatment of von Hippel-Lindau retinal hemangioblastoma by the vascular endothelial growth factor receptor inhibitor SU5416 is more effective for associated macular edema than for hemangioblastomas. *Am J Ophthalmol*. 2003; 136: 194-196.

48. Madhusudan S, Deplanque G, Braybrooke JP, Cattell E, Taylor M, Price P, et al. Antiangiogenic therapy for von Hippel-Lindau disease. *JAMA*. 2004; 291: 943-944.
49. Rosenblatt MI, Azar DT: Anti-angiogenic therapy. Prospects for treatment of ocular tumors. *Semin Ophthalmol*. 2006; 21: 151-160.
50. von Buelow M, Pape S, Hoerauf H. Systemic bevacizumab treatment of a juxtapapillary retinal haemangioma. *Acta Ophthalmol. Scand*. 2007; 85: 114-116.
51. Niemela M, Maenpaa H, Salven P, Summanen P, Poussa K, Laatikainen L, et al. Interferon alpha-2a therapy in 18 hemangioblastomas. *Clin Cancer Res*. 2001; 7: 510-516.
52. Schlesinger T, Appukuttan B, Hwang T, Atchaneeyakasul LO, Chan CC, Zhuang Z, et al. Internal en bloc resection and genetic analysis of retinal capillary hemangioblastoma. *Arch Ophthalmol*. 2007; 125: 1189-1193.
53. Papastefanou VP, Pili S, Stinghe A, Lotery AJ, Cohen VM. Photodynamic therapy for retinal capillary hemangioma. *Eye (Lond)*. 2013; 27: 438-442.
54. Reynolds SA, Shechtman D, Falco L. Complex juxtapapillary capillary hemangioma: a case report. *Optometry*. 2008; 79: 512-517.
55. Wong WT, Chew EY. Ocular von Hippel-Lindau disease: clinical update and emerging treatments. *Curr Opin Ophthalmol*. 2008; 19: 213-217.
56. Matsuo T, Himeki K, Ichimura K, Yanai H, Nose S, Mimura T, et al. Long-term effect of external beam radiotherapy of optic disc hemangioma in a patient with von Hippel-Lindau disease. *Acta Med Okayama*. 2011; 65: 135-141.
57. Parmar DN, Mireskandari K, McHugh D. Transpupillary thermotherapy for retinal capillary hemangioma in von Hippel-Lindau disease. *Ophthalmic Surg Lasers*. 2000; 31: 334-336.
58. Ryan SJ. Capillary hemangioma of the retina and von Hippel-Lindau disease. In: Hinz BJ, Schachar AP, editors. *Retina*. 4th ed. Mosby. Elsevier Inc. 55; 2006.
59. Toyokawa N, Kimura H, Kuroda S. Juxtapapillary capillary hemangioma treated by intravitreal injection of bevacizumab combined with posterior subtenon injection of triamcinolone acetonide. *Jpn J Ophthalmol*. 2010; 54: 168-170.
60. Suh SC, Jin SY, Bae SH, Kim CG, Kim JW. Retinal capillary hemangioma treated with verteporfin photodynamic therapy and intravitreal triamcinolone acetonide. *Korean J Ophthalmol*. 2007; 21: 178-184.
61. Arevalo JF, Arias JD, Serrano MA. Oral propranolol for exudative retinal detachment in diffuse choroidal hemangioma. *Arch Ophthalmol*. 2011; 129: 1373-1375.
62. Akiyama H, Tanaka T, Itakura H, Kanai H, Maeno T, Doi H, et al. Inhibition of ocular angiogenesis by an adenovirus carrying the human von Hippel-Lindau tumor-suppressor gene in vivo. *Invest Ophthalmol. Vis Sci*. 2004; 45: 1289-1296.
63. Sufan RI, Moriyama EH, Mariampillai A, Roche O, Evans AJ, Alajez NM, et al. Oxygen-independent degradation of HIF-alpha via bioengineered VHL tumour suppressor complex. *EMBO Mol Med*. 2009; 1: 66-78.

Cite this article

Kase S, Ishida S (2013) Retinal Capillary Hemangioma in von Hippel-Lindau Disease: Current Concept, Diagnosis and Managements. *J Transl Med Epidemiol* 1(2): 1010.