Hemangioblastomas of the Retina: Impact of von Hippel–Lindau Disease

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PURPOSE. To assess the prevalence of von Hippel–Lindau (VHL) disease and prognosis of vision in patients with retinal hemangioblastomas (HBs).

METHODS. Thirty-six consecutive patients with retinal HBs were treated at Helsinki University Hospital between 1974 and 1998. Detailed neurologic, ophthalmologic, and radiologic examinations; pedigree; mutation analyses; and collection of all relevant clinical, imaging, operative, and autopsy data were performed to identify VHL.

RESULTS. The median follow-up time was 10 years. No patient was lost to follow-up. There were three patient groups: 1) 11 patients with clinically definite VHL; 2) 10 patients with clinically suspected VHL with more than one retinal HB (5/10) or visceral cysts (5/10), but with no family history, no detected germ-line mutations, and no VHL-related neoplasms; and 3) 15 patients without VHL with a single retinal HB but no other data suggestive of VHL. In the 11 patients with definite VHL, retinal HBs were detected at a median age of 27 years versus 40 years in the 15 non-VHL patients, and 21 of the 22 eyes were affected. Two VHL patients were totally blind at the end of follow-up compared with one legally blind patient with suspected VHL, but none of the non-VHL patients was blind. The clinical appearance of HBs did not differ among the patient groups.

CONCLUSIONS. The prevalence of VHL among patients with retinal HBs was 30% to 58% (11–21 of 36). Visual prognosis was more favorable in non-VHL than VHL patients. All patients with retinal HB should undergo thorough VHL exclusion. (Invest Ophthalmol Vis Sci. 2000;41:1909–1915)

The von Hippel–Lindau (VHL) syndrome is a rare (1/36,000 live births) dominantly inherited disease predisposing to hemangioblastoma (HB) of the central nervous system (CNS) and the retina, renal cell carcinoma (RCC), pancreatic carcinoma, pheochromocytoma, and visceral cyst.1–7 It is caused by a defect in the VHL tumor-suppressor gene on chromosome 3p25-p26.8 Individuals with a gene defect almost always have clinical manifestations, and their children have a 50% risk of having the disease.9 Half of cases are familial, and half are caused by new mutations.4 The mean age at death is 40 to 50 years,10 and RCC is the leading cause of death, followed by HB of the CNS.10

The HB is a highly vascular, benign, and well-circumscribed, slowly growing neoplasm composed of stromal cells, endothelial cells, pericytes, and mast cells.6,11 The origin of the stromal cells, believed to be the true neoplastic cells of HB tissue, is still undefined.11 HB of the CNS is sporadic in 60% to 90% of cases,12–16 and when it occurs, it is typically a single, cystic lesion of the cerebellum, appearing at the average age of more than 40 years.13 In VHL, HBs of the CNS tend to be multiple and occur approximately 10 years earlier.10,17 HB of the retina (sometimes called capillary angioma or hemangioma) originates from the inner, midperipheral retina and is histologically identical with HB of the CNS.18–20 Although atypical incipient HBs without draining vessels exist,21 retinal HBs are distinctive enough to permit ophthalmoscopic diagnosis.19,20,22 They can be asymptomatic for years22 and may even regress spontaneously.23 Usually, however, they grow and cause visual impairment due to leakage, leading to secondary changes in the vitreous and retina. With early treatment, however, the visual prognosis is good.22 Retinal HB is the first manifestation in approximately half of VHL patients and is usually bilateral and multifocal or becomes so over the years.5,10 The mean age at initial manifestation is 25 years.5,10,22 There is no general influence of germ-line mutation on the severity of retinal HB(s).20

There can be sporadic retinal HBs without VHL,24 but the prevalence of VHL among patients with retinal HBs still remains undefined. The purposes of the present study were to assess the prevalence of VHL in 36 consecutive patients with retinal HB treated at a single center and to study the long-term prognosis of vision in patients with VHL and those without.
METHODS

Patients

As judged from the hospital files, 36 consecutive patients with retinal HB were treated at the Department of Ophthalmology, Helsinki University Hospital, a unit with population responsibility (the hospital must treat the people living in the assigned surrounding area), between January 1, 1974, and June 30, 1998, and were included in the study (Figs. 1A through 1I).

**FIGURE 1.** Retinal HBs in patients with VHL, those with suspected VHL, and those without VHL. (A) A small incipient HB of the retina in a 66-year-old VHL patient 1 month after laser coagulation. A typical mature HB with draining arteriole and venule in a 40-year-old non-VHL patient: ophthalmoscopic view (B), and fluorescein angiogram; (C) before treatment; ophthalmoscopic view (D) and fluorescein angiogram; (E) at 2 months after cryocoagulation showing narrowing of the feeders. (F) Ophthalmoscopic view at 6 months showing shrinkage of the HB. (G) A large HB with draining vessels and lipid exudates in a 65-year-old VHL patient. (H) A juxtapapillary HB in a 25-year-old patient with suspected VHL. (I) Local exudative and tractional retinal detachment caused by an HB in a 26-year-old non-VHL patient.
Follow-up Data and Clinical Examination

The files of the Department of Ophthalmology, and all other hospitals involved were surveyed for clinical, imaging, operative, and autopsy evidence of VHL in the 36 patients. The addresses and the death certificates of the patients were obtained from the Population Registration Center and the Bureau of Statistics in Finland. The follow-up time started at the detection of retinal HB and ended at death (6/36), emigration (1/36), or on December 31, 1998. No patient was lost to follow-up.

All living patients were invited to a multidisciplinary follow-up evaluation between 1991 and 1998. Of the 36 patients, 31 (86%) could attend the detailed clinical examinations conducted to detect signs of VHL, including family history for VHL, neurologic examination, enhanced magnetic resonance image (MRI) scan (1.0 T) of the head and the spine, and enhanced computed tomographic (CT) scan of the upper abdomen (kidneys, adrenals, liver, and pancreas). Ophthalmologic examination included indirect ophthalmoscopy and Goldmann 3-mirror contact lens fundus examination. In the remaining five patients (one had emigrated, three had died, and one refused to participate), all available ophthalmologic and other relevant data from other centers were reviewed.

Family Pedigrees and Finnish Cancer Registry

Detailed pedigrees including first- and second-degree relatives were constructed for all 36 patients by interviewing the patients and using the files of the Population Registration Center and parish records. These 36 patients and their 995 relatives were linked with the files of the Finnish Cancer Registry (FCR) to find VHL-related neoplasms (HB of the CNS, RCC, pancreatic carcinoma, and pheochromocytoma). The population-based nationwide FCR has functioned since 1953. All hospitals, health care centers, pathology laboratories, and physicians are requested to notify FCR of all cancer cases (benign and malignant CNS tumors included) that come to their attention, and FCR is also informed of all death certificates with a cancer diagnosis: over 99% of the 63,722 solid tumors diagnosed in Finland from 1985 through 1988 were recorded at FCR.25 Everybody living in Finland has had a unique 11-digit personal identification code since 1967 that allows complete follow-up of every person until death or emigration and also links files between different registries.

Mutation Analysis

Germ-line mutations of the VHL gene were studied by direct sequencing in 29 of the 36 patients in whom peripheral blood samples were available. High-molecular-weight DNA was extracted from peripheral blood leukocytes (QiA Amp Blood kit; Qiagen, Cambridge, UK). The three exons of the VHL gene (coding region of 852 nucleotides) were sequenced, including the exon splice sites. The primers and the polymerase chain reaction (PCR) conditions (with slight modification) were as
described elsewhere. We also used a reverse primer for the exon 1, SS1, 5’-GCCTAGAGGGCTTGAGCGTG-3’. PCR products were purified (QiA Quick PCR Purification kit; Qiagen, Hilden, Germany), and the sequencing reactions were performed (Prism Dye Terminator sequencing kit; Perkin-Elmer/ Applied Biosystems, Foster City, CA), and were analyzed on a sequencer (model 373A; Perkin-Elmer). Sequencing of both strands of genomic DNA was performed.

**VHL Criteria in Patients with Retinal HB**

Diagnosis of VHL is based on mutation analysis, clinical manifestations, and long-term follow-up. In our study, a patient with HB(s) of the retina was classified as having definite VHL if the patient had a germ-line mutation or family history of VHL or other VHL-related neoplasms (HBs of the CNS, RCC, or pheochromocytoma). A patient with no family history and no other VHL-related neoplasms had suspected VHL if the patient had either one retinal HB and visceral cysts or more than one retinal HB.

**Statistical Methods**

Median and range were used to describe distributions. Fisher’s exact test (two-tailed) and Yates corrected \( \chi^2 \) test were used to assess differences in frequencies in different patient groups.

**RESULTS**

**Distinction of VHL among Patients with Retinal HB**

All previous clinical data and the present data obtained by a detailed clinical and radiologic examination (31/36 patients), pedigree analysis (36/36 patients), germ-line mutation analysis (29/36 patients), and linkage of the 36 patients and their 995 first- and second-degree relatives (a median of 28 relatives per patient) to the files of the FCR led to the distinction of three patient groups: 1) 11 (30%) patients with definite VHL; 2) 10 (28%) patients with suspected VHL with multiple retinal HBs or with a single retinal HB and visceral cysts but no other VHL-related neoplasms and no family history; and 3) 15 (42%) patients without VHL with a single retinal HB but no other VHL manifestations and no family history of VHL. The link up to the FCR files to find out VHL-related tumors did not disclose any VHL patients or families not known before. Germ-line mutation analysis was possible in 8 of the 11 patients with clinically definite VHL. VHL gene sequencing disclosed a mutation in six (75%) of them: three in exon 1 (277 G to C causing amino acid missense substitution Arg to Pro, 278 G to C causing substitution Gly to Ala, and 293 A to G causing substitution Tyr to Cys) and three (two patients from the same family) in exon 3 (all three 501 C to G causing substitution Pro to Arg). The sequencing of the VHL gene was performed in 9 of the 10 patients with suspected VHL and in 12 of the 15 patients regarded clinically to be free of VHL, and no mutations were found. There was a female predominance (2:6:1) among the 36 patients with retinal HBs (Fisher’s exact 2-tailed test and Yates corrected \( \chi^2 \) test \( P = 0.09 \)).

**Patients with Definite VHL**

In the 11 patients with definite VHL (four men, seven women), HBs of the retina were detected at a median age of 27 years (range, 11–65 years). Eight VHL patients (73%) had familial disease (seven unrelated pedigrees), and three had an apparently new mutation. At detection, three patients (27%) had one unilateral retinal HB, six (55%) had bilateral HBs, and one had two HBs in one eye. During a median follow-up time of 12 years (range, 1.5–30 years) six patients had new retinal HBs that developed outside the already treated areas. Eventually, 21 eyes became affected, and the number of HBs varied from one to seven per eye (Fig. 1G).

As in other manifestations of VHL, HBs of the CNS were detected in 9 (82%) of the 11 VHL patients at the median age of 32 years (range, 18–59 years), RCC in 7 at the median age of 40 years (range 28 to 57 years), and pheochromocytoma in 1. Cysts of internal organs were detected in nine (82%) patients. So far, four patients have died during the follow-up at the median age of 50 years (range, 27–66 years), all due to VHL (two of RCC, and two of HBs of the CNS).

**Patients with Suspected VHL**

At the end of the median follow-up time of five years (range, 0.2–21 years) five female patients had either bilateral HBs or more than one unilateral HB without other VHL-related neoplasms. At detection, two of them had bilateral HBs, one had two, and one had four unilateral HBs. Two patients (one with bilateral HBs at detection) had new lesions that developed outside the already treated areas. The median age of 40 years (range, 14–45 years) at primary detection, negative family history, the absence of other VHL manifestations (one patient with a single renal cyst), and the absence of germ-line mutations (4/5 patients studied) were findings resembling those in non-VHL patients. One patient died of a nonrelated cause at the age of 35 years.

Another five female patients with a single retinal HB, detected at the median age of 37 years (range, 25–61 years), had visceral cysts. However, negative family history, the absence of other VHL manifestations, and absence of germ-line mutations (all patients studied) suggest that the retinal HB(s) in these five patients were not related to VHL. Furthermore, the number of cysts per organ and per patient was less than in the patients with definite VHL.

**Non-VHL Patients**

Fifteen of the 36 patients (nine women, six men) had only a single HB of the retina (Figs. 1B, I) detected at the median age of 40 years (range, 17–58 years), and no de novo HBs appeared during the median follow-up of 2 years (range, 0.2–17 years). The absence of other VHL manifestations, negative family history, and the absence of germ-line mutations of the VHL gene (12/15 patients studied) suggest that the retinal HB was not VHL related.

**Visual Outcome in Patients with Retinal HB**

Six of the 11 definite VHL patients (55%) were asymptomatic at detection of retinal HBs (median age, 31 years; range, 23–65 years), and five had visual impairment with one blind eye (median age, 27 years; range, 11–57 years). One VHL patient had incipient HBs without draining vessels in both eyes (Fig. 1A), and all others had typical mature HBs of varying sizes with dilated and tortuous draining vessels (Fig. 1G). Two of the 10
patients with suspected VHL (1/5 and 1/5, respectively) and 6 of the 15 non-VHL patients (40%) were asymptomatic at detection of retinal HB(s). One patient with suspected VHL and one non-VHL patient had incipient HBs. All others had mature HBs in varying sizes with dilated draining vessels. One patient with suspected VHL with visceral cysts had a single juxtapapillary HB (Fig. 1H).

During the follow-up, five more eyes in VHL patients lost light perception. At the end of follow-up there were six eyes (29%) without light perception, one of which was enucleated. Two VHL patients were totally blind due to retinal detachment and/or neovascular glaucoma. One eye in a patient with suspected VHL had lost light perception due to vitreous hemorrhage, total retinal detachment, and neovascular glaucoma caused by a large HB. At the end of follow-up, the patient was legally blind (vision <20/400 in the better eye). In two more eyes, vision remained impaired (<20/60) in spite of vitrectomy and surgery. However, none of the non-VHL patients had visual acuity of less than 20/60 in the affected eye.

**DISCUSSION**

**VHL in Patients with Retinal HB**

Our series is the first consecutive series of patients with retinal HB(s) treated at a single center with population responsibility. Our study, with meticulous multidisciplinary VHL exclusion, should reflect the true risk of VHL, patient characteristics, and outcome of vision in patients with retinal HB(s).

Our series of 36 patients suggests that approximately half of cases of retinal HBs are not related to VHL but are sporadic, non-VHL-related tumors. Earlier, without the possibility of germ-line mutation analysis and modern imaging to exclude VHL, it was postulated that retinal HB(s) are always VHL or, in most cases, are manifestations of VHL. Recently, Webster et al. were able to identify 17 non-VHL patients with retinal HBs collected from several ophthalmologic and genetic centers in the United Kingdom, using MRI and mutation analysis. In general, the presence of more than one retinal HB is suggestive of VHL. In our series, five patients had more than one HB of the retina but had no VHL in the pedigree, had no VHL germ-line mutations detected by direct sequencing, and so far had had no other VHL-related neoplasms. They may have a mild form of VHL. In these patients our detection method, direct sequencing, which picks up 60% to 70% of VHL gene mutations, excludes a typical germ-line mutation pattern of VHL. But because this method misses large deletions, they cannot be excluded. These multiple HBs may also represent germ-line mosaicism or segmental cell population with VHL gene defect or, although unlikely, a local spread of the same tumor. In any case, this patient group with a favorable overall prognosis should be followed up to define the natural history of this condition. Thus, multiple HBs without other VHL manifestations may represent a similar entity, such as schwannomatosis without neurofibromatosis (NF) type 2. NF2 is another dominantly inherited syndrome predisposing to multiple schwannomas and meningiomas, but the defective NF2 tumor-suppressor gene is also causative of sporadic schwannomas and meningiomas. Of cases of schwannoma, 95% are single and obviously sporadic, 3% are related to NF2, and 2% are multiple but obviously NF2.

In our series, there were five patients with a single retinal HB and visceral cysts without other VHL manifestations or family history. Visceral cysts are also a known manifestation of VHL but do not necessarily indicate VHL. Visceral cysts develop in most VHL patients but incidental cysts are rather common in otherwise healthy subjects, and occurrence increases with age. The occurrence of visceral cysts (in the kidneys in 10% of cases, and in the liver in 15%) corresponds to that of the incidental cysts in the general population.

Therefore, the five patients most probably represent non-VHL patients with sporadic visceral cysts. The prevalence of VHL in our series of patients with retinal HB(s) varied between 30% and 58% (11 of the 36 patients with definite VHL and 10 with suspected VHL). The missense mutations found in our series are known to be associated with pheochromocytomas, which were present in one VHL patient and in the family of another VHL patient.

**Patient Characteristics**

Females predominated, for unknown reasons, in our series of cases of VHL (1.8:1), suspected VHL (all females), and non-VHL (1.5:1). Webster et al. found a female predominance (2.4:1) in their non-VHL patients. There was also an excess of females among the VHL (1.4:1) and non-VHL (2.1) patients, with uncertain VHL exclusion, collected from the literature by Chang et al. In HBs of the CNS, there is a slight female predominance according to a literature review by Resche et al. In our series, retinal HBs were detected at younger age in patients with definite VHL than in those without VHL, probably because of awareness of the disease in the family and earlier screening, analogous to HBs of the CNS and tumors in other familial cancer syndromes, whereas Webster et al. found no age difference. Retinal HBs were incidental findings in 55% of our patients with definite VHL, corresponding to data in the literature, and in 40% of the non-VHL patients, less than the 63% reported by Webster et al. We confirm that the appearance of retinal HBs did not differ among patients with definite VHL, suspected VHL, and no VHL.

**Long-Term Prognosis of Vision in Patients with Retinal HB**

In our series, the prognosis of vision with retinal HB(s) was more favorable in patients without VHL than in those with definite VHL, whereas Webster et al. found equal outcome in both groups. In general, the patient with suspected VHL had a prognosis of vision resembling that of the non-VHL patients. However, in one patient with bilateral HBs and in another with unilateral multiple HBs, visual outcome resembled that of the patients with definite VHL. No enucleations were performed in our 15 non-VHL patients, whereas 2 of the 17 affected non-VHL eyes were removed in the series of Webster et al. In our 11 patients with definite VHL, all but one had bilateral disease, and at the end of the follow-up, six (29%) eyes had lost light perception (one of them was enucleated), and two patients were totally blind (bilateral no light perception), which points up the importance of ophthalmologic screening and early treatment of retinal HBs in patients with VHL.

The average life-expectancy of VHL patients is 40 to 50 years, 50 years in our series. Therefore, all patients with retinal HB(s) should be screened for VHL by MRI of the head.
and spine and an upper abdominal CT scan or MRI, a family history should be obtained, and germ-line mutation analysis should be performed. Patients with a single retinal HB but no other VHL manifestations, negative family history, and no germ-line mutations found should remain under ophthalmologic observation. Genetic counseling should be offered to all VHL patients, and annual lifelong follow-up visits should be arranged conjointly by an ophthalmologist, a neurosurgeon, and a urologist. Retinal screening of children at risk should start as soon as cooperation permits the detection of even incipient HBs.

CONCLUSIONS

The prevalence of VHL was 30% to 58% (11–21 of 36) in this unselected series of 36 patients with retinal HB(s). Internal organ cysts in patients with retinal HBs do not necessarily indicate VHL. The appearance of retinal HB(s) did not differ between patients with definite VHL and those without VHL. Visual outcome was less favorable in patients with definite VHL. Patients with retinal HB(s) are predominately female.

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