Solitary juxtapapillary capillary retinal angioma and von Hippel–Lindau disease

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ABSTRACT • RÉSUMÉ

Background: The aim of this study was to evaluate patients with solitary juxtapapillary capillary retinal angioma for the presence of von Hippel–Lindau disease (VHL).

Methods: A retrospective case series of 11 patients, each presenting with a solitary juxtapapillary capillary retinal angioma, was examined. Patients were evaluated for type of angioma, presence of other VHL lesions, and mutations of the VHL gene.

Results: Juxtapapillary angioma was exophytic in 7 patients and endophytic in 4 patients. VHL could be diagnosed in 7 patients (64%). Four patients were affected by VHL-related lesions as distinct from ocular angioma. A mutation of the VHL gene could be detected in 6 patients; in 1 of these patients, this mutation of the VHL gene was the only evidence of VHL. There was no difference in the age at manifestation or the type of juxtapapillary angioma in VHL patients compared with non-VHL patients.

Interpretation: A solitary juxtapapillary angioma may indicate the presence of VHL in a majority of patients, irrespective of the growth pattern of the tumour. Molecular genetic diagnostics is the most effective method of detecting VHL. Because of the high risk of the presence of other VHL lesions, thorough screening for VHL is mandatory for patients presenting with a solitary juxtapapillary angioma.

Contexte : Cette étude avait pour objet d'évaluer la présence du syndrome von Hippel–Lindau (VHL) chez des patients atteints d'un angiome capillaire juxtapapillaire solitaire de la rétine.

Méthodes : On a examiné en rétrospective une série de cas chez 11 patients qui s'étaient présentés avec un angiome capillaire juxtapapillaire de la rétine. On a évalué les patients quant au type d'angiome, à la présence d'autres lésions VHL et aux mutations du gène du VHL.

Résultats : L'angiome juxtapapillaire était exophytique chez 7 patients et endophytique chez les 4 autres. On a pu diagnostiquer le VHL chez 7 patients (64%). Quatre patients étaient affectés par les lésions liées au VHL contrairement à l'angiome oculaire. Une mutation du gène du VHL a pu être dépistée chez 6 patients; chez un de ces derniers, la mutation en question était le seul signe du VHL. Il n'y avait pas de différence d'âge au moment de la manifestation ni quant au type d'angiome juxtapapillaire chez les patients atteints du VHL comparativement aux autres patients.

Interprétation : Un angiome juxtapapillaire solitaire peut indiquer la présence du VHL chez une majorité de patients, quelles que soient les caractéristiques de croissance de la tumeur. Le diagnostic génétique moléculaire est la méthode la plus efficace de dépistage du VHL. À cause du risque élevé de présence des autres lésions VHL, il faut absolument procéder au dépistage méticuleux du VHL chez les patients qui se présentent avec un angiome juxtapapillaire solitaire.

Capillary retinal angioma is a benign vascular tumour that occurs in von Hippel–Lindau disease (VHL) but may also be sporadic.[1] VHL is a multitumour syndrome predisposed not only to retinal angiomas but also to different multiple tumours such as CNS (central nervous system) hemangioblastomas or renal carcinomas. Retinal angioma, however, is the most frequent initial manifestation of VHL and eventually develops in up to 70% of gene carriers.[2–5] The classic hallmark of VHL is peripheral capillary retinal angioma typically

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showing morphology of a spherical orange–red tumour with dilated feeder vessels.[6] Capillary retinal angioma may also be found at the optic disc. The juxtapapillary type, on the other hand, shows a less characteristic appearance compared with peripheral angioma[7] and it can either develop in an endophytic growth pattern that has been attributed to VHL,[8,9] or grow as an intraretinal or exophytic tumour. This latter variant is regarded as being a hamartoma not associated with VHL when occurring as a solitary tumour.[10] Diagnostic criteria for VHL have been refined in the past few decades,[11] and once the causative gene was identified,[12] molecular genetic diagnosis became the recommended standard procedure for suspected VHL.[13] In the present study, we evaluated patients presenting with solitary juxtapapillary capillary retinal angioma for the presence of VHL. In addition, we evaluated the possible relation between angioma growth pattern and the presence of VHL.

METHODS

The patients described in this paper all presented with an apparently solitary juxtapapillary capillary retinal angioma at the University Eye Clinic of Freiburg and the Eye Clinic of the Benjamin Franklin University Hospital of the Free University of Berlin between 1974 and 1998. Patients were unrelated and did not show evidence of any additional retinal angioma. Fluorescein angiography was performed to visualize both the capillary nature of each angioma and the relation of the tumour to the normal retinal vessels. Angiomas were classified as endophytic if protruding into the vitreous cavity or obscuring normal retinal vessels (Fig. 1). Angiomas were classified as intraretinal or exophytic if normal retinal vessels could be visualized over the angioma surface (Fig. 2). Evaluation of VHL comprised personal and family history for VHL-associated lesions, a medical screening programme according to the current recommendations,[2,6] and genetic screening for a mutation of the VHL gene.

Medical screening for other VHL lesions comprised magnetic resonance imaging (MRI) of the brain and spinal cord (gadolinium-enhanced), urine catecholamines, and abdominal sonography or computed tomography (CT). Complete screening was performed on 8 patients, incomplete screening performed on 1 patient, and 2 patients were not screened at all. VHL was diagnosed according to current criteria.[11]

Molecular genetic screening for a mutation of the VHL gene was performed in all patients. After the patients received genetic counselling, EGTA (ethylene glycol tetraacetic acid) blood samples were taken for molecular genetic analysis of the VHL gene. DNA was extracted by using standard methods and the exons amplified with polymerase chain reaction (PCR) by means of specific primers. Amplification products were separated by single-stranded conformation polymorphism (SSCP) for the detection of intragenic mutations.[14] Aberrant bands were sequenced to identify mutations. Southern blot was performed to detect large deletions if the SSCP failed to show a band shift.[15] To date, this procedure has been capable of detecting germline mutations in virtually all VHL families.[13]

Data were tested for significance by means of the unpaired *t* test for continuous variables and by the χ^2 test for dichotomous variables.

This study was undertaken within the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the clinic.

RESULTS

An overview of the basic data and the ocular findings of 11 patients with solitary juxtapapillary angioma are given in Table 1.

Mean (SD) age at presentation was 23.7 (17.3) years. VHL could be detected in 7 patients. There was no dif-

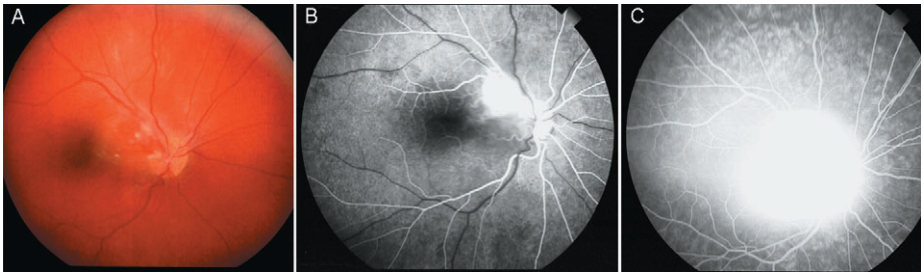

Fig. 1—Patient 1, 10-year-old girl. A. Endophytic juxtapapillary angioma in the right eye, protruding into the vitreous cavity and obscuring the retinal vessels. Visual acuity was 20/50. B. Early phase fluorescein angiogram, demonstrating rapid filling of the lesion, concomitant with the retinal arteries. C. Late phase fluorescein angiogram, demonstrating excessive leakage of dye into the vitreous cavity, thus obscuring the posterior pole of the eye.

ference in age at presentation between patients with or without VHL (22.5 [16.9] vs. 25.8 [20.3] years, $p = 0.9$). All patients had symptomatic loss of visual acuity. Median visual acuity at presentation was 20/60 with a range from 20/200 to 20/30. Seven angiomas were of the exophytic type and 4 angiomas of the endophytic type. Predominantly, the temporal (7 angiomas) and inferior (5 angiomas) disc margins were occupied by the angioma, whereas the superior (2 angiomas) or nasal (1 angioma) margins of the optic disc were less frequently involved. In the 7 VHL patients, 2 angiomas were endophytic and 5 were exophytic. In the 4 non-VHL patients, 1 angioma was endophytic and 3 were exophytic. There was no difference in angioma type between VHL and non-VHL patients (endophytic vs. exophytic, $p = 0.6$). Additional angiomas were detected in the fellow eye during follow-up in 2 patients. Data concerning the diagnosis of VHL are given in Table 2.

VHL was evident in 2 patients when we evaluated their personal medical history. VHL could be diagnosed in 4 patients when family history was also taken into consideration. Detection of VHL lesions that were different from retinal angioma provided evidence of VHL in 2 additional patients. Molecular genetic testing

Table 1—Solitary juxtapapillary capillary retinal angioma: patient characteristics and ocular findings

No.	Age, years	VA	Eye	Type	Location	Follow-up, years	VHL
1	10.8	20/50	OD	endo	temporal	10.4	–
2	19.5	20/64	OD	exo	temporal	1.5	–
3	17.1	20/100	OD	endo	temp/inf	3.0	–
4	55.8	20/50	OS	exo	nasal	0.6	–
5	14.3	20/200	OS	exo	inferior	1.5	+
6	24.6	20/200	OD	exo	temp/inf	7.1	+
7	12.0	20/50	OD	exo	temporal	3.9	+
8	5.6	20/125	OD	endo	temporal	3.7	+
9	54.3	20/100	OD	exo	superior	1.4	+
10	34.0	20/30	OS	endo	inf/temp	4.0	+
11	12.6	20/32	OS	endo	temp/inf/sup	5.0	+

Note: No. = patient number; age is age at first presentation; VA, visual acuity at first presentation; type, endophytic (endo) or exophytic (exo) growth pattern of angioma; location, margins of the optic disc occupied by the angioma: temporal, nasal, inferior, superior; "+" present, "–" absent.

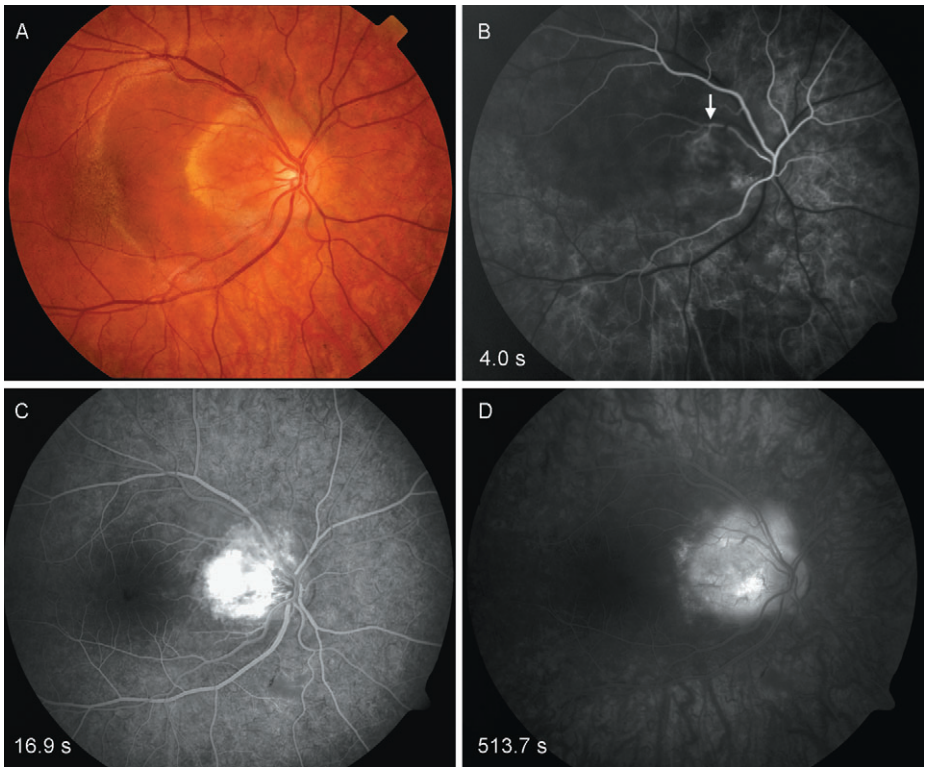

Fig. 2—Patient 2, 19-year-old male. A. Exophytic juxtapapillary capillary angioma occupying the temporal and inferior margin of the optic disc and causing a drop in visual acuity to 20/64 due to macular edema. Retinal vessels can be identified on top of the angioma, thus indicating exophytic growth of the lesion. B. Early phase fluorescein angiogram. Filling of the lesion from the upper temporal retinal artery (arrow) concomitant with filling of the retinal vessels is demonstrated. C. Mid phase fluorescein angiogram showing the extension of the angioma. D. Late phase fluorescein angiogram demonstrating excessive dye leakage from the lesion.

detected a mutation of the VHL gene in 6 patients. Thus in 7 of 11 patients, VHL could be detected. The only evidence for the disease in 1 patient was a mutation of the VHL gene. When comparing all the diagnostic tools utilised, molecular genetic testing was the most powerful in detecting VHL.

Interpretation

Retinal angiomatosis, or the presence of capillary retinal angioma, is the hallmark of VHL. The peripheral type of this vascular tumour is identified by its typical spherical appearance, orange–red colour, and tortuous feeder vessels. Occurrence of multiple retinal angioma has been shown to be indicative of VHL[2,16]; it may, however, also be sporadic if occurring as a solitary angioma.[1] The morphology of juxtapapillary angioma is less characteristic and may be misdiagnosed as papilledema, papillitis, granulomatous disease, or other juxtapapillary manifestation.[17,18] Fluorescein angiography has proven to be a valuable tool in characterizing the vascular nature of the angioma and in distinguishing it from other entities.[7,8,10]

Juxtapapillary angioma is less common than peripheral angioma in VHL. In a study on a large Newfoundland family with VHL, angiomas at the optic disc presented in 5 of 18 patients with retinal angiomatosis.[19] Moore et al reported a comparable number, namely 5 juxtapapillary angiomas in 17 patients.[20] Webster et al diagnosed juxtapapillary angiomas in 8%[21] of a series of 124 VHL patients with retinal angiomatosis. Details on the angioma type were not given for any of these studies.

Solitary juxtapapillary capillary angioma is regarded as not commonly associated with VHL. Schindler et al found only 5 of 41 patients (12%) with a single juxtapapillary angioma associated with VHL.[7] Gass et al, who confined their study to the exophytic type of this tumour, found no association to VHL in 6 cases evaluated. They concluded that a solitary exophytic capillary angioma should be considered as a hamartoma that is not associated with VHL.[10] In a series of 68 patients with juxtapapillary angioma, including patients with multiple angiomas, McCabe et al reported VHL in 34%.[9] In our series, we found 2 substantial differences from these studies concerning solitary juxtapapillary angioma. First, we did not find mutual exclusion of exophytic juxtapapillary angioma and VHL, and second, we detected VHL in higher proportion, namely, in 64% of patients. We are aware that the small number of patients may have biased our results. Nonetheless, our results compare well with the studies of Webster et al who, by means of molecular genetic testing, also found that a single juxtapapillary angioma more often occurs in VHL than it does sporadically. In a large series of 175 patients carrying the VHL gene, they found that a single optic disc angioma was the only ocular manifestation of VHL in 9 patients (5.1%).[21] In a parallel study on sporadic capillary angioma from the same group, only 4 patients with juxtapapillary angioma were included.[1] We are inclined to attribute the higher percentage of VHL detected, in comparison with older studies, to the increased expertise in the diagnosis of VHL. Screening for VHL is much improved by progress in molecular genetics, and the characterization of the VHL gene has enabled molecular genetic diagnostics of VHL in virtually all affected families.[12,13] In our series, VHL was most often diagnosed by molecular genetics, corroborating the superiority of molecular genetic analysis compared with clinical information in the diagnosis of VHL.[22]

The importance of a correct diagnosis of VHL is underlined by the number and severity of VHL lesions detected in our patients, namely, pheochromocytoma, renal cell carcinoma, and cerebellar hemangioblastoma. The probability of developing renal carcinoma or cerebellar hemangioblastoma in the course of VHL by the age of 60 has been calculated as being 69% and 84%, respectively.[2]

We conclude that presence of a single juxtapapillary capillary retinal angioma indicates VHL in the majority of patients, irrespective of the endophytic or exophytic type of the tumour and that molecular genetic testing for a mutation of the VHL gene is mandatory in these patients. Considering the number and severity of other possible VHL lesions, vigorous clinical screening of the patient and relatives of the patient who are at risk is highly recommended.

Table 2—Diagnosis of von Hippel–Lindau disease by medical history, presence of other VHL lesions, and results of molecular genetic testing

No.	VHL	Personal history	Family history	Other lesions*	Mutation†	Screening performed
1	–	–	–	–	–	+
2	–	–	–	–	–	+
3	–	–	–	–	–	(+)
4	–	–	–	–	–	+
5	+	–	–	–	705G/T	+
6	+	–	–	CNS	–	n.p.
7	+	–	+	–	407C/G	n.p.
8	+	ECA, CNS	+	RCC, PHEO, CNS	557 A/G	+
9	+	CNS	+	PHEO, CNS	746 T/A	+
10	+	–	+	–	505 T/C	+
11	+	–	–	PHEO	505 T/C	+

*Other lesions = von Hippel–Lindau (VHL) lesion different from retinal angioma present at first presentation or on follow-up.
†The description of the mutation refers to the nucleotide number, the nucleic acid of the wild-type gene, and the nucleic acid of the mutated gene. G = guanine, T = thymine, A = adenine, C = cytosine.
Note: "+" present, "–" absent, (+) incomplete, "n.p." not performed; ECA, epididymal cystadenoma; CNS, CNS hemangiblastoma; RCC, renal carcinoma; PHEO, pheochromocytoma.

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