

MINI REVIEW

Von Hippel-Lindau disease

Von Hippel-Lindau (VHL) disease is a dominantly inherited familial cancer syndrome with variable expression. The most frequent complications are retinal angiomas, cerebellar and spinal haemangioblastomas, and renal cell carcinoma.¹ Renal, pancreatic, and epididymal cysts are also common. Pheochromocytoma occurs in less than 10% of patients, but in some families this is the most frequent complication. Although VHL disease has been considered to be rare, it is frequently underdiagnosed, and a recent study in East Anglia has demonstrated a minimum birth incidence of 1 in 36 000.² Furthermore, for each affected individual there are likely to be another four or five relatives at significant risk (25% or more) of becoming affected so that the management of families with VHL disease is a common problem.³

The penetrance of VHL disease is age and tumour dependent. Most patients present in the second and third decades, but onset may be in infancy or in old age.^{1,4} Retinal angiomas is the most frequent initial complication of VHL disease and the ophthalmologist has a central role in the diagnosis and management of patients with this disorder. The proportion of patients with retinal angiomas who have VHL disease is not well defined (estimates vary between 25% and 80%), but all patients, and their first degree relatives, with solitary retinal angioma should be investigated for evidence of VHL disease. The mean age at diagnosis of retinal angioma in VHL disease is 25 years and the younger the age at onset the more likely is VHL disease. Among patients with retinal angioma the presence of multiple retinal angiomas is diagnostic of VHL disease, as is a single retinal angioma and a positive family history or another manifestation of the disorder (such as cerebellar haemangioblastoma, renal cell carcinoma, pheochromocytoma, or multiple pancreatic and renal cysts).

The central nervous system and ocular vascular tumours are similar in histological appearance and are best classified as haemangioblastomas.⁵ They are composed of vascular endothelial lined channels separated by masses of vacuolated foam cells. Three main cell types are recognised in the tumour: endothelial cells, pericytes, and lipid laden interstitial stromal ('foam') cells.⁵⁻¹¹ In contrast to normal retinal capillaries the tumour endothelial cells are fenestrated,^{8,11} which is in keeping with the clinical findings of retinal vascular exudation. Despite the many histological and electron microscopic studies the cellular origin of the retinal tumours and, in particular, the interstitial 'foam' cells remains controversial.⁵⁻¹¹ It has been suggested that these may derive from astrocytes,^{5,7} neuroendocrine cells,¹⁰ or primitive vascular stem cells.¹¹ Immunohistochemical studies of retinal tumours are also inconclusive.^{5,10,11}

The retinal and optic nerve haemangiomas seen in VHL disease are of two clinical types. Endophytic tumours arise from the superficial retina or anterior surface of the optic disc and grow inwards towards the vitreous where they are seen as elevated red vascular tumours. There is great variation in size and larger peripheral retinal tumours usually have a dilated feeding arteriole and draining vein. Early tumours, seen as tiny capillary dilatations, may be easily missed on ophthalmoscopy but are usually readily apparent on fluorescein angiography or angiography.^{1,12,13} Visual loss may occur secondary to exudative or tractional retinal detachment,

vitreous haemorrhage, macular oedema, or epiretinal membrane formation causing macular distortion. Less commonly, exophytic tumours may arise from the outer retinal layers; they tend to occur in the peripapillary retina and often lead to difficulties in diagnosis.^{14,15} The usual presentation is with central visual loss and fundus examination usually reveals retinal oedema and exudates but without any visible angioma. They may be mistakenly diagnosed as papilloedema, peripapillary disciform, or juxtapapillary choroiditis.¹⁴ The diagnosis is usually made on stereo fluorescein angiography which demonstrates a deep retinal angioma which fills early in the arterial phase. The angioma often shows a dual circulation from both the ciliary and superficial retinal vessels.^{14,15}

The lack of reliable information about the natural history of untreated retinal angiomas makes it difficult to recommend a rational treatment protocol. Furthermore with large angiomas the complications of treatment may be similar to those of the tumour itself and it may be difficult to assess the efficacy of the treatment. Although some tumours may show spontaneous regression¹⁶ most do not. Management depends mainly on the size and site of the tumour. Peripheral angiomas respond well to treatment especially if they are small but the results of treatment of optic disc and peripapillary exophytic tumours are still disappointing.^{14,15} Many different treatment modalities including cryotherapy,^{1,12,17} diathermy,¹⁷ xenon arc photocoagulation,^{12,17} laser photocoagulation,^{14,15,18-20} radiotherapy,^{21,22} and local resection²³ have been used. Small peripheral angiomas (<3 mm) are best treated with argon laser photocoagulation¹⁸⁻²⁰ which may be combined with intravenous fluorescein to increase laser uptake.²⁰ More than one treatment session may be necessary. Cryotherapy is used for larger peripheral tumours, those with extensive subretinal fluid, or those arising close to the ora serrata. In tumours not responding to cryotherapy, irradiation²² or local excision²³ may be used. Experience with these latter modalities is limited however. Large tumours, or their response to treatment, may cause vitreous haemorrhage, exudative retinal detachment (which may take months to resolve after treatment), and epiretinal fibrosis. These complications may require vitreoretinal surgery once the tumours have regressed. Treatment of optic disc and peripapillary exophytic lesions is not indicated unless there is already visual loss. Results of laser photocoagulation are disappointing^{14,15,24} and radiotherapy, using newer lens sparing techniques,²¹ may offer an alternative approach. However, some patients will show relentless progression of their tumour and visual loss despite treatment. Prognosis is best for small peripheral tumours and visual screening programmes should identify retinal angiomas at an early stage when treatment is effective.¹³

All affected patients require lifelong ophthalmic follow up and annual investigation for extraocular complications. The cumulative risk of a VHL disease patient developing a retinal angioma, cerebellar haemangioblastoma, and renal cell carcinoma at age 30 years are 44%, 38%, and 5% respectively, rising to 84%, 70%, and 69% respectively at age 60 years.¹ It follows that the majority of patients with VHL disease will develop a renal cell carcinoma if they live long enough, and renal cell carcinoma is now the most common cause of death

Table 1 Cambridge screening protocol for VHL disease in affected patients and at risk relatives. These guidelines are for asymptomatic individuals; symptomatic patients should be investigated urgently. The frequency of screening may be reduced in relatives in whom DNA linkage studies reduce their risk

Affected patient

- (1) Annual physical examination and urine testing.
- (2) Annual direct and indirect ophthalmoscopy with fluorescein angiography or angiography.
- (3) Magnetic resonance imaging (MRI) (or computed tomography (CT)) brain scan every 3 years to age 50 and every 5 years thereafter.
- (4) Annual renal ultrasound scan, with CT scan every 3 years (more frequently if multiple renal cysts present).
- (5) Annual 24 hour urine collection for VMAs (vanillyl mandelic acids).

At risk relative

- (1) Annual physical examination and urine testing.
- (2) Annual direct and indirect ophthalmoscopy from age 5. Annual fluorescein angiography or angiography from age 10 until age 60.
- (3) MRI (or CT) brain scan every 3 years to from age 15 to 40 years and then every 5 years until age 60 years.
- (4) Annual renal ultrasound scan, with abdominal CT scan every 3 years from age 20 to 65 years.
- (5) Annual 24 hour urine collection for VMAs.

For full details see Maher *et al.*¹

in VHL disease.¹ Patients with VHL disease are not only at greatly increased risk of tumour development, but, as with other inherited cancers such as retinoblastoma, are predisposed to develop multiple tumours and at a younger age than sporadic cases.²⁵ The majority of patients with central nervous system haemangioblastoma have, or will develop, multiple tumours and, similarly, 50% or more of patients with renal cell carcinoma have bilateral or multicentric cancers. Presymptomatic diagnosis of retinal angiomas and extraocular complications of VHL disease significantly reduces morbidity and mortality. The Cambridge screening protocol is shown in Table 1. Systematic ophthalmic and systemic screening of asymptomatic patients and relatives is important and worthwhile. We detected asymptomatic retinal angiomas in 60% of affected patients with no previous ophthalmic investigation and 30% of asymptomatic at risk relatives had subclinical evidence of VHL disease.¹³ While screening of relatives at risk of developing VHL disease is productive and cost effective, the efficiency of screening would be enhanced by the presymptomatic diagnosis of gene carriers. This would allow low risk individuals to be reassured and screened less frequently.

The mapping of the gene for VHL disease to the short arm of chromosome 3 opened the way for the development of presymptomatic diagnosis using linked DNA markers.²⁶ The VHL disease gene has now been mapped to a small region at the tip of the short arm of chromosome 3 and close flanking markers (that is, either side of the gene) identified.²⁷⁻²⁹ An important finding has been that although there are clear interfamilial differences in the clinical manifestations of VHL disease (for example, risk of pheochromocytoma) all available evidence points to there being only a single gene for VHL disease.²⁷⁻²⁹ This has enabled two groups to demonstrate that presymptomatic diagnosis of VHL disease using linked DNA markers is possible in the majority of families with suitable structure.³⁰⁻³¹ However this form of analysis is not possible for relatives of isolated cases. The isolation and characterisation of the gene for VHL disease would be a major breakthrough in understanding the pathogenesis of this disorder and increasing the availability of presymptomatic diagnosis. There is statistical, cytogenetic, and molecular genetic evidence that the VHL disease gene functions as a tumour suppressor gene of the retinoblastoma type.²⁵⁻³² Chromosome 3p allele loss is a frequent finding in many non-inherited human cancers including renal cell carcinoma. If the VHL disease gene does prove to be similar to the retinoblastoma gene then it is likely that it will be implicated in the pathogenesis of sporadic tumours in addition to VHL disease neoplasms.

Almost 100 years ago Treacher Collins³³ described familial retinal angioma. Since then more than 700 patients with what subsequently became known as VHL disease have been reported. In recent years, improved knowledge about the natural history has led to the recognition of the importance of ascertaining and screening patients and at risk relatives. In addition, advances in molecular genetics are now facilitating the management of families with VHL disease by enabling presymptomatic diagnosis in many cases. Research groups in the United Kingdom and United States are closing in towards isolating the gene and it is hoped that the VHL disease gene will have been analysed by the anniversary of Treacher Collins' description.

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Details of a national register for VHL disease families and of molecular genetic investigations are available from Dr E R Maher, Department of Clinical Genetics, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK.

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