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 angiomatosis, cerebellar and spinal haemangioblastomas, and renal cell carcinoma.\(^1\) Renal, pancreatic, and epididymal cysts are also common. Phaeochromocytoma 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.\(^4\) 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.\(^5\)

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.\(^4\) Retinal angiomatosis 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 angiomatosis 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, phaeochromocytoma, 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.\(^3\) 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.\(^6\) In contrast to normal retinal capillaries the tumour endothelial cells are fenestrated,\(^7\)\(^8\) 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.\(^9\)\(^10\) It has been suggested that these may derive from astrocytes,\(^7\) neuroendocrine cells,\(^10\) or primitive vascular stem cells.\(^11\) Immunohistochemical studies of retinal tumours are also inconclusive.\(^9\)\(^10\)\(^11\)

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.\(^4\)\(^12\)\(^13\) 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.\(^4\)\(^14\)\(^15\) 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.\(^11\) 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.\(^11\)\(^16\)

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 regression\(^4\) 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,\(^4\)\(^12\)\(^17\) diathermy,\(^17\) xenon arc photocoagulation,\(^17\)\(^18\) laser photocoagulation,\(^14\)\(^19\)\(^20\) radiotherapy,\(^10\)\(^12\) and local resection\(^23\) have been used. Small peripheral angiomas (<3 mm) are best treated with argon laser photocoagulation\(^20\) 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, irradiation\(^21\) or local excision\(^15\) 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\(^14\)\(^15\)\(^21\) and radiotherapy, using newer less 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.\(^15\)

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 50 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.
Almost 100 years ago Treacher Collins 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 2QZ, UK.

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33 Treacher Collins E. Two cases, brother and sister, with peculiar vascular new growth, probably primarily retinal, affecting both eyes. Trans Ophthalmol Soc UK 1894; 14: 141–9.