PostScript

LETTERS

Ophthalmic pathology of genotypically confirmed von Hippel Lindau disease type 1

Von Hippel Lindau disease (VHL) is a rare^{1,2} autosomal dominant disorder. Descriptions of the ophthalmic pathology predate identification of the underlying molecular genetic basis of the disease. We present a case where provisional diagnosis was made on the basis of clinical findings and histopathology, in whom classic clinical features and the genotypic subtype have now been demonstrated.

Case report

A 7 year old boy presented with a visual acuity of 6/60 in the left eye and 6/5 in the right. Examination revealed a left optic disc capillary haemangioblastoma associated with macula oedema (fig 1A and B). The right eye was healthy. No treatment was offered since the lesion involved the optic nerve. Family history was unremarkable and no systemic abnormalities were found. A provisional diagnosis of VHL was made.

Routine follow up appointments were missed. He returned 5 years later with corneal oedema, elevated intraocular pressure, and dense cataract in the left eye. The right eye was unremarkable. Extracapsular cataract extraction was performed. Following surgery, total retinal detachment was identified and

rubeotic glaucoma developed. The intraocular pressure remained high and the eye was subsequently enucleated. Histology supported the clinical diagnosis of VHL (fig 2).

Five years later a capillary haemangioblastoma (fig 1C and D) developed in the right eye, which was treated with focal argon laser. Blood was sent for DNA analysis and a known VHL gene mutation² was identified, coding for VHL 1.

The right eye remains stable, however, a recent magnetic resonance imaging scan revealed three cerebellar haemangioblastomas.

Comment

VHL is thought to result from deactivation of a tumour suppressor gene² found on the short arm of chromosome 3 (3p25-26).³ The first mutant gene was identified in 1993.⁴ Since then many other mutations have been identified.²

VHL is characterised by capillary haemangioblastomas of the eye and central nervous system, visceral lesions including renal cell carcinoma and pheochromocytoma, and visceral cysts.^{1,5-8} VHL can be classified phenotypically into VHL 1 (no association with pheochromocytoma) and VHL 2 (associated with pheochromocytoma).^{8,9} VHL 2 is further classified as VHL 2A, where there is high risk of pheochromocytoma and low risk of RCC; VHL 2B, where there is high risk of pheochromocytoma and RCC²; and VHL 2C, which is only associated with pheochromocytoma.⁹

VHL 1 is thought to result from structural aberrations of the gene. It results in complete or partial inactivation of the VHL proteins.^{2,10} In this case a missense gene was found identifying the subject as having VHL 1.

Classically, clinical diagnosis of VHL is made when two or more capillary haemangioblastomas are found, or when a single capillary haemangioblastoma occurs with a visceral manifestation. Where there is a positive family history, only one haemangioblastoma or visceral manifestation is required.^{1,5} In this case, only one capillary haemangioblastoma was found at presentation. According to the diagnostic guidelines, VHL could only be diagnosed 10 years after presentation. With genetic screening, the diagnosis could have been made earlier.

This case demonstrates that patients with VHL may present with isolated retinal haemangioblastomas. Genetic screening allows early identification of those at risk of developing sight and life threatening complications of VHL.

Acknowledgements

We are grateful to Professor W R Lee for his detailed pathological description of the enucleated specimen.

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doi: 10.1136/bjo.2005.079152

Accepted for publication 29 August 2005

Figure 1 (A) Capillary haemangioblastoma of the left optic disc with macular oedema and exudates. (B) Fluorescein angiogram showing diffuse leakage from the left optic disc capillary haemangioblastoma. (C) Exudates and oedema associated with a capillary haemangioblastoma. (D) Supratemporal capillary haemangioblastoma in the right eye.

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Figure 2 (A) Macroscopic specimen showing funnel shaped retinal detachment with prominent tortuous blood vessels on the outer surface and a mass at the optic disc (black arrows). The cataract surgery wound with iris prolapse is identified at the edge of the cornea (white arrow). (B) The mass at the optic disc shows a vascular proliferation in keeping with a capillary haemangioblastoma (arrows) (haematoxylin and eosin, $\times 25$). (C) Histological section of one of the smaller retinal capillary haemangioblastomas showing a vascular proliferation with intervening glial cells and foamy histiocytes (arrows). (periodic acid Schiff, $\times 400$). (D) The prominent abnormal vascular proliferation is highlighted by immunohistochemical staining for factor VIII (factor VIII, $\times 100$).

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Rapid development of severe toxic retinopathy associated with continuous intravenous deferoxamine infusion

Deferoxamine mesylate is a chelating agent used in the treatment of iron overload in patients requiring regular transfusions. Deferoxamine is most commonly administered as a slow subcutaneous infusion but continuous intravenous infusion may be required for treating life threatening cardiac complications due to iron overload.¹ Toxic retinopathy is one of the complications associated with deferoxamine, in which

different manifestations including pigmentary retinopathy, bull's eye maculopathy, and vitelliform maculopathy have been described.^{2–8} We report a patient who had rapid development of irreversible diffuse pigmentary retinopathy with severe visual loss while receiving continuous intravenous deferoxamine infusion.

Case report

A 17 year old β thalassaemic patient was referred for ophthalmic assessment with recent onset of colour vision impairment 4 months after commencement of continuous intravenous deferoxamine infusion. He had been on subcutaneous deferoxamine for 14 years but stopped self administration 6 months before presentation. As a consequence of the poor compliance, he developed iron overload with a serum ferritin level of 6370 $\mu\text{g/L}$, causing dilated cardiomyopathy and arrhythmia. Owing to the severity of the heart condition, he was treated with 44 mg/kg/day (therapeutic index = 0.007) continuous deferoxamine infusion via an indwelling intravenous catheter. On presentation, his visual acuity was 6/18 in both eyes with normal colour vision testing on Ishihara plates. Slit lamp and dilated fundus examinations revealed no abnormality. In view of the severe life threatening cardiac complications, deferoxamine was continued despite the visual symptoms. Three weeks later, his visual acuity deteriorated to counting fingers on reassessment. Fundus examination revealed diffuse pigmentary changes at both macula and peripheral retina (fig 1). Serum ferritin level was found to have decreased to 430 $\mu\text{g/L}$ (therapeutic index = 0.103). Since his heart condition had stabilised, the deferoxamine dosage was reduced to 11 mg/kg/day and later changed to subcutaneous infusion. One year after initial presentation, his visual acuity improved to 6/60 but the diffuse pigmentary retinopathy remained unchanged. Electro-oculogram showed severely reduced response with Arden ratio of 1.1 bilaterally and full field electroretinogram demonstrated reduced scotopic and photopic response amplitudes with normal implicit times in both eyes.

Comment

The use of subcutaneous deferoxamine is generally safe and the development of ocular toxicity is uncommon.^{3,9} However, compliance with subcutaneous therapy may be poor particularly in young patients, and intravenous infusion is sometimes required to treat life threatening complications.^{1,4} It has been suggested that monthly monitoring of serum ferritin to adjust the deferoxamine dosage below a therapeutic index of 0.025 (daily dose per body weight (mg/kg) divided by serum ferritin level ($\mu\text{g/L}$)) may prevent deferoxamine related complications.¹⁰ However, this was derived based on ototoxicity and it was unclear whether it applied to ocular toxicity. Our case illustrated the rapid development of severe pigmentary retinopathy over 3 weeks because of a sudden fall in serum ferritin level, which resulted in a therapeutic index four times above the limit. Despite prompt reduction of deferoxamine dosage, the severe pigmentary retinopathy persisted and resulted in irreversible retinal damage with profound visual loss. A previous study on the long term outcome of continuous 24 hour deferoxamine infusion has described a case of reversible retinal toxicity