Von Hippel Lindau disease: keep it in the family

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SUMMARY

We describe a case of von Hippel-Lindau disease (VHL) through three generations of the same family. First presentation was a young female with a 6-week history of headaches behind the eyes. On examination she was found to have bilateral retinal capillary haemangiomas (RCH). Preliminary diagnosis of VHL was suspected and further investigations confirmed the initial diagnosis. The patient was found to have pancreatic and kidney lesions and her mother had a cerebellar haemangioblastoma. Following genetic testing, the VHL gene appeared in the 9-year-old boy. On recent presymptomatic ophthalmic screening, the child was found to have RCH. Both patient and child's RCHs were successfully managed with a variety of treatments.

BACKGROUND

Von Hippel-Lindau disease is a multisystem hereditary disease that principally produces vascular, neoplastic and cystic lesions in mesoderm-derived structures. The management of this condition is complex and requires a multidisciplinary approach. This case highlights a three-generation history of VHL with multiple manifestations. Also, it demonstrates the need for presymptomatic screening of at-risk individuals.

CASE PRESENTATION

A 32-year-old woman presented with 6-week history of headaches. She had no visual concerns. She had no other significant ocular or medical history. On examination, her visual acuity was 6/12 in both eyes. Anterior segment examination as well as intraocular pressure was normal bilaterally. Dilated fundus examination of the right eye showed grossly enlarged feeder vessels (figure 1A) leading to angiomatous peripheral lesions (figure 1B) and localised exudative retinal detachment. Also, there were two smaller yet similar lesions in the left eye. The patient was accompanied by her mother who appeared to have an ataxic gait.

The unexpected finding of retinal angiomas prompted a search for other VHL disease-associated lesions in the patient and her mother.

INVESTIGATIONS

A systemic study was arranged for the patient and at-risk family members. The whole body scan of the patient showed a pancreatic cyst as well as polycystic kidney disease. Her mother had a cerebellar haemangioblastoma. All her first-degree relatives received genetic screening. The results of which showed the patient and the 9-year-old child carried the VHL gene. Patient's mother did not carry the VHL gene. Also, genetic testing and counselling

was offered for the at-risk group of her family. After the initial screening process, the Cambridge screening protocol for VHL continues to be followed.

DIFFERENTIAL DIAGNOSIS

The following should be included in the differential diagnosis of peripheral retinal haemangiomas:

- ▶ Coats' disease
- ▶ Retinal cavernous haemangioma
- ▶ Retinal artery macroaneurysm
- ▶ Retinoblastoma
- ▶ Sickle cell retinopathy
- ▶ Racemose haemangioma

TREATMENT

Treatment was initially in the form of argon laser ablation of the retinal haemangiomas to both eyes. The left eye's retinal lesion showed some regression post-treatment. Laser treatment for the right eye produced a vitreous haemorrhage and exudative retinal detachment which dropped the vision to hand movements. Therefore, right vitrectomy, cryotherapy with gas Tamponade was carried out.

OUTCOME AND FOLLOW-UP

At 6-month follow-up, the patient's vision was 6/9 bilaterally with complete involution of the retinal angiomatous lesions and flat retinae (figure 1C). The patient is reviewed on an annual basis. The patient's male baby who was noted to bear the VHL gene at screening has been reviewed annually for 3 years with no retinal lesions detected till recently, when he was found to have a right superior retinal haemangioma (figure 2A). He was treated successfully with cryo-ablation (figure 2B). On follow-up, further two small lesions were found that require no immediate intervention. His vision remains 6/6 bilaterally. The female baby is also reviewed annually with no obvious clinical signs of the condition. The whole family is being reviewed in a multidisciplinary setting.

DISCUSSION

VHL is an inherited disorder causing multiple tumours with a propensity for the central nervous system and the retina. The inheritance is autosomal dominant with high penetrance. It occurs in 1 of 36 000 births/year.¹ The diagnosis of VHL syndrome should be suspected in individuals with characteristic lesions including haemangioblastomas, renal cysts and renal cell carcinoma, pheochromocytoma and endolymphatic sac tumours. Renal pheochromocytoma and renal cell carcinomas are the main cause of death.

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Figure 1 (A) Fundus photograph of the right eye showing enlarged feeder vessels. (B) Three peripheral angiomatous lesions. (C) Complete involution of the peripheral angiomatous lesions following treatment.

Retinal capillary haemangioma is the earliest manifestation of VHL disease and it is present in 70% of patients. It may be present as a standalone condition or as a part of the VHL disease, where one third are multiple and half are bilateral.²

RCH is usually a circumscribed, round retinal lesion with an orange-red colour. There are various systems used to classify RCH depending on retinal distribution (peripheral and juxtapa-pillary), morphology (endophytic, exophytic and sessile), effects on the retina (exudative and tractional) and associated systemic features (with or without VHL disease).³

RCH if left untreated, or if treatment is delayed, the high-flow arteriovenous shunt and incompetent capillaries will lead to visual loss due to the following possible consequences; cystoid macular oedema, subretinal exudates, exudative or tractional retinal detachment, vitreous haemorrhage, or a macular traction due to epiretinal membrane.

Screening of affected patients and family members who are at risk is recommended at least during the most susceptible age (10–60 years). There is significant research to suggest that many at-risk individuals when investigated explicitly for manifestations of VHL disease show subclinical lesions. The visual outcome is significantly better than symptomatic patients with RCH.⁴

The Cambridge screening protocol includes annual physical examination for neurological signs and abdominal masses,

annual abdominal ultrasound, ophthalmic examination +/- fundus fluorescein angiogram, and 24 h urine collection for vanilylmandelic acid tests. MRI (or CT) brain scan is generally performed every 3 years from age 15 to 40 years and then every 5 years until the age of 60.

The treatment of RCH can be challenging because of the presence of bilateral multiple tumours with a potential for onset of new tumours. It is most frequently managed by observation, laser photocoagulation and cryotherapy. The factors that determine the selected treatment are the size, location and secondary effect of the RCH.⁵ The mainstay of treatment is laser photocoagulation with the blue-green argon laser. It is 100% effective in lesions smaller than one disc diameter (1.5 mm). If lesions are >3 mm are located in the extreme retinal periphery or have associated subretinal fluid, they are best managed with cryotherapy. Early diagnosis and treatment of RCH before severe visual loss are recommended.

In summary, VHL disease is an inherited and life-long disease. Family members of the patient should undergo clinical and/or molecular genetic screening. This case highlights the importance of presymptomatic screening of at-risk individuals, which allows early diagnosis and treatment of asymptomatic retinal capillary haemangioma that gives a favourable visual prognosis.

Figure 2 (A) Two small peripheral angiomatous lesions. (B) Involution of the lesions following cryo-ablation.

Learning points

- ▶ Von Hippel Lindau (VHL) disease is a multisystem disorder with a tendency for retinal and central nervous system lesions.
- ▶ The earliest and most common manifestation of VHL disease is retinal capillary haemangioma.
- ▶ In the investigative phase of VHL diagnosis, all physicians should refer patients for ophthalmic assessment.
- ▶ Patients with an isolated retinal capillary haemangioma should have a formal systemic workup.
- ▶ Presymptomatic screening of offspring of affected parents is crucial as clinical screening of children at risk of VHL disease can detect tumours with resultant reduction in morbidity.

Competing interests None.

Patient consent Obtained.

REFERENCES

- 1 Maher ER, Yates JR, Harries R, *et al.* Clinical features and natural history of von-Hippel-Lindau disease. *Q J Med* 1990;77:151–63.
- 2 Ridley M, Gree J, Johnson G. Retinal angiomas: the ocular manifestations of von Hippel-Lindau disease. *Can J Ophthalmol* 1986;21:276–83.
- 3 Singh AD, Shields CA, Shields JA. Von Hippel-Lindau disease—major review. *Surv Ophthalmol* 2001;46:117–42.
- 4 Webster AR, Maher ER, Bird AC, *et al.* Clinical characteristics of ocular angiomas in von Hippel-Lindau disease and correlation with germline mutation. *Arch Ophthalmol* 1999;117:371–8.
- 5 Singh AD, Nouri M, Shields CL, *et al.* Treatment of retinal capillary haemangioma. *Ophthalmology* 2002;109:1799–806.

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