CASE REPORT

Von Hippel–Lindau disease

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Abstract

Von Hippel–Lindau (VHL) disease is a rare autosomal dominantly inherited multisystem disorder characterised by the development of a variety of benign and malignant tumours. We report a case of VHL disease that was inherited by a daughter from her father, who both presented at a young age with progressive headache and were found to have a posterior fossa haemangioblastoma (HB) on magnetic resonance imaging (MRI). Multiple benign pancreatic and renal cysts were also noted in both patients.

Introduction

Von Hippel–Lindau (VHL) disease has a broad spectrum of clinical manifestation, in which about 40 different lesions in 14 different organs have been described.[1] These include retinal and central nervous system (CNS) HB, endolymphatic sac tumours, renal cysts and tumours, pancreatic cysts and tumours, pheochromocytomas and epididymal cystadenomas. It is a rare disease and the prevalence of VHL has been estimated to be between 1:35,000 and 1:40,000[2] with an autosomal dominant inheritance with high penetrance and variable expression. Males and females are equally affected.

Case report

A 22-year-old Malay girl presented with a history of worsening headache, which was associated with blurred double vision, nausea and vomiting for 1 year. She denied any history of seizure, prolonged fever, loss of weight or loss of appetite. There was no history of trauma. On examination, she was alert and conscious. Her blood pressure was normotensive. Eye examination showed diplopia in all directions with nystagmus but no papilloedema. Cerebellar signs were positive. The rest of the CNS examination revealed normal findings. Magnetic resonance imaging (MRI) of the brain revealed a well-defined extra-axial mass arising from the cisterna magna and extending superiorly until the floor of the 4th ventricle (**Figure 1**), suggestive of HB. Abdominal ultrasound was performed and showed multiple simple cortical cysts at the body of the pancreas and both kidneys (**Figure 2**). The liver, spleen and both adrenal glands were normal.

The patient later underwent a suboccipital craniectomy and excision of the tumour. The histopathology result (HPE) showed features of HB (WHO grade I). The diagnosis of VHL disease was made based on these findings.

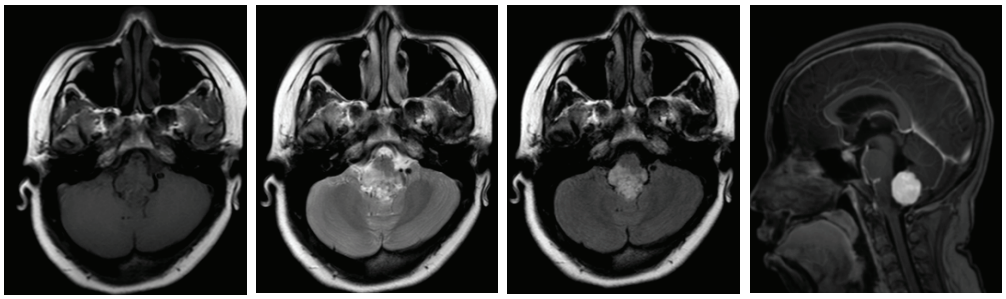

Figure 1A Figure 1B Figure 1C Figure 1D

Figure 1. Serial images of MRI brain in axial (A) T1, (B) T2, (C) FLAIR and (D) sagittal post-gadolinium showed a well-defined extra-axial mass, which appeared to be heterogeneously hypointense on T1WI, hyperintense on T2WI, not suppressed on FLAIR and avidly enhanced post-gadolinium, arising from the cisterna magna and extending superiorly until the floor of 4th ventricle

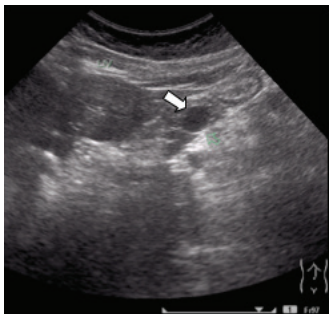

Figure 2A

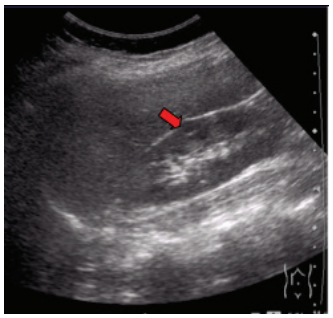

Figure 2B

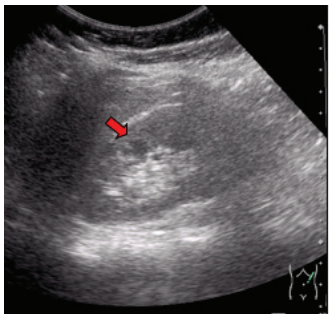

Figure 2C

Figure 2. Ultrasound examination showed multiple simple cysts at the body of pancreas (white arrow) and both kidneys (red arrow)

Our patient had a strong family history of brain tumour. Her father presented at the age of 29 years old with a history of progressive headache for 2 months. MRI of the brain showed multiple cerebellar masses. Occipital craniectomy with excision of tumour was performed and HPE showed features of HB. Computed tomography (CT) scan of the abdomen revealed multiple cystic lesions at the head, body and tail of the pancreas. However, there were no similar lesions within the liver, spleen, kidneys and adrenal glands. He had tumour recurrence and underwent another tumour removal.

Discussion

The clinical diagnostic criteria for VHL disease were proposed by Melmon and Rosen.[3] If a family history of retinal or CNS HB exists, only one HB or visceral lesion is required to make the diagnosis of VHL disease. For isolated cases without a clear family history, two or more HB or one HB and a visceral manifestation are required. The unique gene responsible for VHL disease has been located and identified on the short arm of chromosome 3 (3p25).[4] Our patient had a family history of VHL disease (father), which supports the evidence of inheritance. No history was available regarding the presence of this disease among her grandparents and ancestors. Approximately 20% of cases of VHL disease are found in individuals without a family history, known as *de novo mutations*.[5]

CNS HB is one of the most common manifestations of VHL disease. Typical sites are the cerebellum (44–72%), spinal cord (13–59%) and medulla (5%).[6] When associated with VHL disease, they occur at a younger age and have a worse prognosis.[7] In this case, both patient and her father presented at a young age – 22 and 29 years, respectively. HBs are highly vascular lesions and they may be solid, cystic, haemorrhagic or mixed. Primary treatment is surgical removal of symptomatic lesions.[7]

Renal involvement in VHL disease is multicentric and bilateral in at least 75% of patients, ranging from simple cysts to renal tumours. Renal cysts occur in 59% to 63% and renal cell carcinoma in 24% to 45% of VHL patients.[7] In our patient, multiple simple cortical cysts were seen in both kidneys. Early identification of renal cancers is critical because they account for 50% of deaths in patients with VHL disease.[8] Therefore, careful follow-up of cysts is essential.

The frequency of pancreatic involvement in VHL disease is 15% to 77%, with a spectrum of simple pancreatic cysts (91%), serous cystadenomas (12%), neuroendocrine tumours (7–12%) and combined lesions (11%).[9] Pancreatic cysts are extremely rare in the general population.[10] Therefore, the presence of a single cyst in an individual undergoing family screening for VHL disease would increase the likelihood of the diagnosis. Cystic pancreatic lesions in VHL disease are asymptomatic or associated with only mild symptoms.

Understanding the variable presentation of VHL disease is important when extracting the history. Therefore, in a primary care setting, when a patient presents with a history of chronic headache, a proper clinical history and thorough physical examination are crucial. Presence of associated symptoms such as blurred vision and vomiting warrants further evaluation. The patient should be referred for further imaging, such as a CT scan, if a space-occupying lesion is suspected. A proper family history should also be obtained to exclude hereditary disease.

When VHL disease is suspected, the family should be referred to genetic professionals for evaluation and testing. Patients with germline mutations can be identified and offered clinical and radiographic screening that can identify the major manifestations of VHL disease at a presymptomatic phase, thus allowing early monitoring and intervention to be undertaken.

Conclusion

A diagnosis of VHL disease could pose major implications for daily life due to its chronicity and unpredictable course. Therefore, early screening and identification are essential to prevent avoidable morbidity and mortality related to the disease. A multidisciplinary team approach is important in screening for VHL disease.

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