



Case Report

Illustrative Case Report of Von Hippel-Lindau Syndrome with Emphasis on Screening Guidelines

Pradeep H. N¹, Berton Monteiro², Vishwanth Joshi², C P Nanjaraj³, C N Pradeepkumar¹

¹Assistant Professor, ²Final Year Post Graduate, ³Professor and Head,
Department of Radiodiagnosis, MMCRI, Mysore, India.

Corresponding Author: Pradeep H. N

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ABSTRACT

Von Hippel–Lindau (VHL) disease is an autosomal dominant neuro-cutaneous dysplastic complex disease. Manifestations of the disease include predisposition to CNS hemangioblastomas (most common), retinal haemangioblastomas, renal cell carcinoma, pheochromocytoma, endolymphatic sac tumors, bilateral and multicentric renal angiomas and cysts of the kidney, pancreas and epididymis. Clinical symptomatology usually begins by the third to fourth decade. Blindness and permanent brain damage can occur in these patients if the offending retinal and CNS lesions are not treated prospectively. Hence, screening of pre symptomatic patients of VHL and at risk relatives of unknown genetic status for early detection and removal of tumours is of utmost importance.

Our objective is to emphasize the importance of screening of pre-symptomatic patients with VHL or at risk relatives of unknown genetic status with an illustrative case report.

Key Words: Von Hippel Lindau, Haemangioblastoma, Screening.

INTRODUCTION

Von Hippel–Lindau (VHL) disease is a rare, autosomal dominantly inherited multisystem disorder characterized by development of a variety of benign and malignant tumors. VHL is an autosomal dominant neuro-cutaneous dysplastic complex disease. Manifestations of the disease include predisposition to CNS hemangioblastomas (most common), retinal haemangioblastomas, renal cell carcinoma, pheochromocytoma, endolymphatic sac tumors, bilateral and multicentric renal angiomas and cysts of the kidney, pancreas and epididymis. [1,2] The various manifestations can be demonstrated with different imaging modalities such as

ultrasonography, computed tomography, magnetic resonance imaging, and nuclear medicine. Although genetic testing is available, the manifestations of the syndrome are protean; therefore, imaging plays a key role in identification of abnormalities and subsequent follow-up of lesions. It is also used for screening of asymptomatic gene carriers and their long-term surveillance. Screening is important because the lesions in VHL disease are treatable; thus, early detection allows use of more conservative therapy and may enhance the patient's length and quality of life. A

multidisciplinary team approach is important in screening for VHL disease. [3]

CASE REPORT

A 20 year old male patient presented with history of paresthesia and numbness of all 4 limbs since one and half years, weakness of all 4 limbs since one year, headache and vomiting with blurred vision since 3months. Patient had undergone an operation 4 years back to resect a

haemangioblastoma in the left cerebellar lobe.

On examination, tone was decreased in both the upper limbs and increased in both the lower limbs. Power in the upper limbs was - proximally grade 4, distally grade 2-3. Sensations were decreased from D2 level downwards with graded sensory loss from L2 to S2 and uniform sensory loss to fine touch and pain. Temperature sensation was lost between D2 to L3 on right side and D4 to L3 on left side.

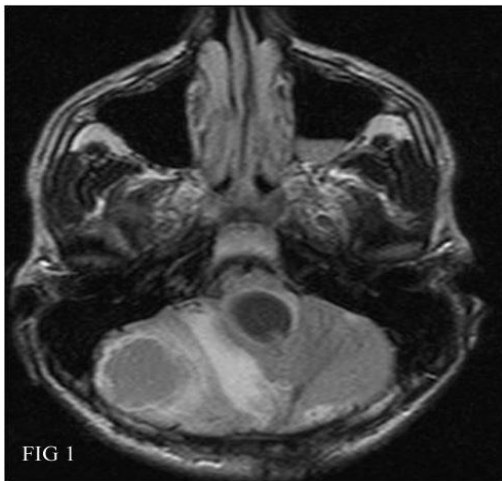


Figure 1: T1 weighted image showing hemangioblastoma involving right cerebellar lobe and brain stem.

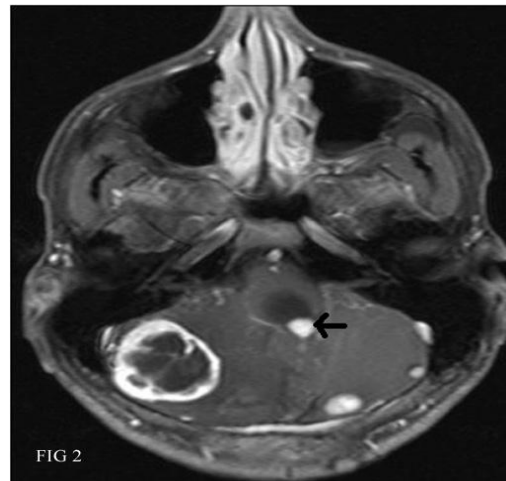


Figure 2- T1 contrast showing hemangioblastomas with enhancing mural nodule (arrow). The hemangioblastoma in the right cerebellum is a recurrence with previous operative history.

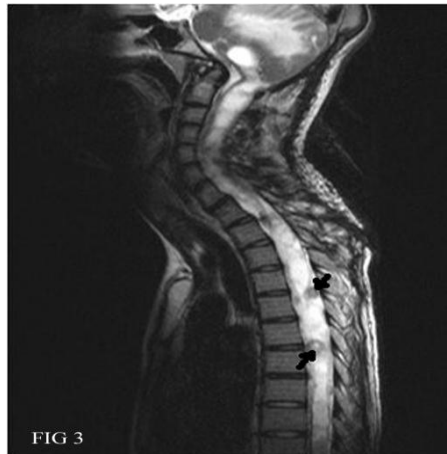


Figure 3:T2WI showing multiple spinal hemangioblastomas which are isointense (arrows) causing secondary syringohydromyelia.



Figure 4: T1 weighted post contrast image showing multiple enhancing mural nodules (arrows).

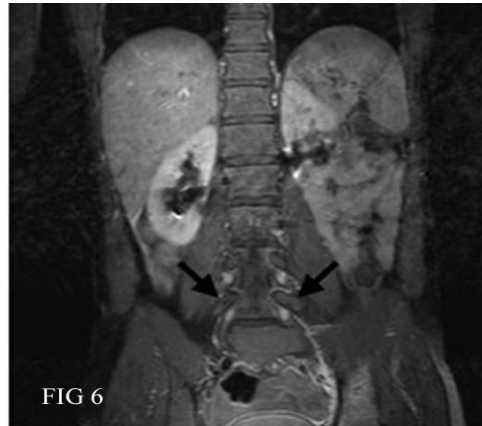
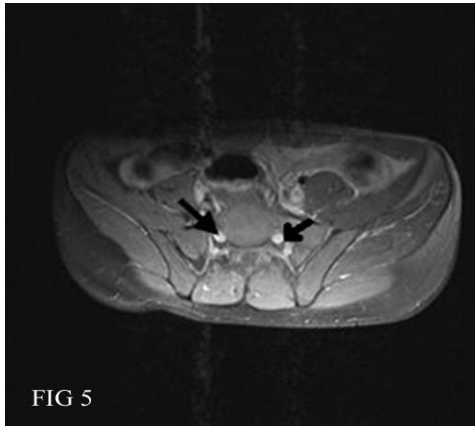
MRI scan of the brain and spine was performed which revealed multiple

intracranial hemangioblastomas (Figures 1 and 2) and spinal hemangioblastomas

(Figures 3 and 4) causing secondary syringo-hydromyelia. On contrast study the lesions show intense mural nodule enhancement (Figures 2 and 4). The sacral nerve roots also revealed hemangioblastomas (Figures 5 and 6). On USG scan of the abdomen a pancreatic cyst

was detected. Above features are diagnostic of VHL.

Family history revealed that his elder sister also had been diagnosed to have VHL. She had delivered a child recently which would also require screening to rule out VHL.



Figures 5-6: T1 weighted post contrast images shows spinal nerve hemangioblastomas in the lumbar region (arrows).

DISCUSSION

VHL is also known as retino-cerebellar angiomas. The VHL gene is located on the 3p chromosome. [3] The diagnosis of the disease is established by the following criteria:

- a) More than one hemangioblastoma in the CNS or
- b) One CNS hemangioblastoma and visceral manifestations of VHL or
- c) One manifestation and a known family history.

Hemangioblastomas of the CNS are demonstrated as cystic lesions with a 3- to 15-mm mural nodule in 75% of patients. They are demonstrated as an enhancing lesion with multiple cystic areas in 15% of patients and as an enhancing solid mass in 10% patients. The cerebellum is most commonly involved, followed by the medulla, the spinal cord, and even the spinal nerve roots. Supratentorial hemangioblastomas are rare, but they have been reported.

The preferred radiological imaging modalities are ultrasonography of the abdomen, MRI of the brain, spine and abdomen and angiography.

MRI appearances of a hemangioblastoma are those of a well-demarcated cystic lesion with a highly vascular mural nodule that always abuts the pia mater. Appearance of the cystic component varies depending on the protein concentration and/or presence of hemorrhage within the cyst. The cystic component may be isointense relative to cerebrospinal fluid (CSF) on images obtained with all pulse sequences, but more often it is slightly hyperintense relative to CSF on T1- and T2-weighted images. Mural nodules are slightly hypointense on T1-weighted images and hyperintense on T2-weighted images, and they enhance avidly after the administration of contrast material. Large feeding or draining vessels are often present at the periphery and within the solid component, and they may show tubular areas of flow void on spin-echo images. [4,5]

Spinal hemangioblastomas are intramedullary tumors in most patients (75%), but may be radicular (20%) or intradural extramedullary (5%). Most of these tumors are located in the cervicothoracic spine. They usually expand the cord and have an intratumoral cystic component. On MRI, they appear as a well-demarcated gadolinium-enhancing mass. Spinal hemangioblastomas are an unusual cause of cryptic subarachnoid hemorrhage. Large dorsally placed draining veins may appear as curvilinear areas of signal void. A syrinx is a frequently associated finding.

Endolymphatic sac tumors are heterogeneous on both T1- and T2-weighted images. They are associated with focal high signal intensity due to subacute hemorrhage and areas of low signal intensity due to calcification or hemosiderin. [6]

On MRI, choroidal capillary hemangiomas associated with VHL are minimally hyperintense on T1-weighted images. They may mimic ocular melanoma, but unlike pigmented melanoma they are usually hyperintense on T2-weighted images. As a result of the small size of retinal hemangiomas (1.5-2.0 mm) they are usually not identified on MRIs.

A pheochromocytoma associated with VHL has MRI appearances no different from that of the sporadic form. The tumor appears isointense or slightly hypointense relative to the liver on T1-weighted images and it is extremely hyperintense on T2-weighted images.

Ultrasonography is the modality of choice in screening the abdomen in patients with known VHL. This is a useful examination for imaging the retina also; sonograms may show small hypoechoic masses, most often in the temporal retina.

Angiography of hemangioblastoma reveals a hypervascular lesion with intense and prolonged early enhancement of the mural nodule associated with dilated feeding

vessels. Endolymphatic sac tumors are hypervascular on angiography, and the blood supply is derived from the external carotid artery. Large tumors have an additional blood supply from the internal carotid artery and posterior circulation.

M. D. Anderson Screening Guidelines for Pre-symptomatic VHL Disease. [7]

10 Years of Age & Under

- Complete general history and physical exam (particularly focusing on blood pressure measurement and neurological exam) yearly.
- Ophthalmologic exam at diagnosis and then yearly.
- Abdominal ultrasound at diagnosis and then every 2 years.
- CT abdomen (or MRI) using VHL-specific protocol only if abnormality detected on US or abnormal pheochromocytoma screening labs.
- MRI of the brain and spine only if neurologic symptoms.
- Screening for pheochromocytoma (typically with plasma metanephrines and plasma catecholamines) at diagnosis and then yearly in patients with a family history of VHL type 2 or mutations known to be associated with VHL 2; consider every 2-year testing in patients with a family history of VHL 1 or in patients with mutations not associated with pheochromocytoma; screening should always be done in patients going to surgery for any reason.
- Audiology examination at diagnosis and then every two years or sooner; obtain imaging (MRI and CT) of the internal auditory canals in patients with hearing loss, tinnitus, vertigo, or unexplained balance difficulties.

10-15 Years of Age

- Complete general history and physical exam (particularly focusing on blood pressure measurement and neurological exam) annually.
- Ophthalmologic exam at diagnosis and then every 6 months.
- Abdominal ultrasound at diagnosis and then every year.
- CT abdomen (or MRI) using VHL-specific protocol only if abnormality detected on US or abnormal pheochromocytoma screening labs.
- MRI of the brain and spine at diagnosis and then yearly.
- Screening for pheochromocytoma at diagnosis and then yearly in patients with a family history of VHL type 2 or mutations known to be associated with VHL2; consider every 2-year testing in patients with a family history of VHL 1 or in patients with mutations not associated with pheochromocytoma; screening should always be done in patients going to surgery for any reason
- Audiology examination at diagnosis and then every two years or so; obtain imaging (MRI and CT) of the internal auditory canals in patients with hearing loss, tinnitus, vertigo, or unexplained balance difficulties.

15 Years of Age & Older

- Complete general history and physical exam (particularly focusing on blood pressure measurement and neurological exam) annually.
- Ophthalmologic exam at diagnosis and yearly.
- Abdominal ultrasound (US) at diagnosis and then every year from ages 15 to 20.

- MRI of the brain and spine at diagnosis and then yearly (consider every 2 years in low risk patients).
- CT abdomen (or MRI) using VHL-specific protocol starting at age 20 (or at diagnosis, if older than 20 years of age) and then every 2 years, alternating with abdominal US every other year
- Screening for pheochromocytoma at diagnosis and then yearly in patients with a family history of VHL type 2 or mutations known to be associated with VHL2; consider every 2-year testing in patients with a family history of VHL 1 or in patients with mutations not associated with pheochromocytoma; screening should always be done in patients going to surgery for any reason and during pregnancy.

CONCLUSION

This case herein emphasizes that the manifestations of VHL disease are protean. Although genetic testing is available, imaging plays a key role in the identification of abnormalities and their subsequent follow-up, in the screening of asymptomatic gene carriers, and in their long-term surveillance. The importance of screening is emphasized because the lesions in VHL disease are treatable; thus, early detection enables more conservative therapy to be performed and may enhance the patient's length and quality of life.

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