 DOI: 10.18231/2455-8451.2016.0010

# Von Hippel–Lindau (VHL) disease: A case report

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## Abstract

Von Hippel–Lindau (VHL) disease is an autosomal dominant disorder which is associated with multiple tumors and cysts in the central nervous system (CNS) and other visceral organs. The most commonly seen tumors are hemangioblastoma in the CNS and retina, pheochromocytoma in the adrenal gland, renal cell carcinoma and pancreatic neuroendocrine tumors. Here we report a 38 year old lady who presented with headache, vomiting, vertigo and ataxia and non specific abdominal pain, who was diagnosed to have von Hippel–Lindau disease. The pathophysiology involves the inactivation of the VHL tumor suppressor gene present at 3p25-26 with results in loss of function of the VHL protein, and Elongin B, C complex resulting in a dysfunction of the ubquitination of hypoxia-inducible factor, which is a crucial step in the development of highly vascular tumors. There is no definitive treatment available till date. Management basically aims at early recognition and treatment of specific manifestations in order to decrease complications and improve the quality of life. Increasing knowledge about the molecular role of VHL proteins (pVHLs) has led to investigate the role of antiangiogenic drugs designed to reduce or prevent tumorogenesis in VHL disease.

**Keywords:** Von Hippel–Lindau (VHL) disease, hemangioblastoma

## Introduction

The VHL disease was described in von Hippel's literature in 1911 and Lindau's literature in 1926 (3,4) and the responsible gene was named as 'VHL tumor suppressor gene', which is located on the chromosome 3p25–26.[(1)] von Hippel–Lindau (VHL) disease is an autosomal dominant disorder, characterized by the development of various benign and malignant tumors and cysts. The major tumors and cysts are hemangioblastoma (HB) in the central nervous system (CNS), retinal hemangioblastoma (RA), pheochromocytoma (Pheo), renal cell carcinoma (RCC), renal cyst, pancreatic cystadenoma and pancreatic neuroendocrine tumors. Inactivation of the VHL tumor suppressor protein and subsequent loss of the function of the VHL protein, and Elongin B, C (VBC) complex results in the dysfunction of the ubiquitination of hypoxia-inducible factors (HIF) and other proteins for VBC complex. The failure in the degradation of HIFs is an important step in the development of highly vascular tumors.[(2)]

## Clinical criteria for the diagnosis of VHL Disease

The following criteria are used for the diagnosis of VHL disease:

1. Patients with a family history of developing HB in the CNS or RA, RCC, Pheochromocytoma or pancreatic tumors or cysts, epididymal cystadenoma.
2. Patients without a family history of VHL disease, but who develop HB or RA in combination with other tumors, such as RCC, Pheochromacytoma, pancreatic tumors or cysts, or epididymal cystadenoma.

After diagnosis, genetic testing should be done to identify the prevailing mutation in VHL gene, which can be beneficial for the family members. After identifying the proband's mutation its presence or absence in the family members who are at risk can define their status.

## Case Report

A 38 year female patient presented to the medicine OPD with the complains of off and on headache with vomiting associated with vertigo and difficulty in walking with swaying to either sides along with non specific diffused abdominal since the last one and a half month. There was no history of tingling or numbness, or loss of sensation. No associated history of trauma to the back region, backache or bowel and bladder involvement. No history of aural fullness, tinnitus, hearing loss or ear discharge was present. Patient did not had any complain in the upper limb. On examination signs of cerebellar involvement in the form of nystagmus, hypotonia, gait ataxia, and pendular knee jerk was present. The other findings of the neurological examination were within normal limits. Fundus examination of the patient was within normal limits. Magnetic Resonance Imaging (MRI) brain and spine was done which revealed a large cystic lesion with eccentric nodule showing avid contrast enhancement involving vermis and part of left cerebellar hemisphere which was suggestive of hemangioblastoma. MRI imaging of the spine showed syrinx and cystic lesions in the whole spine. Computer Tomography (CT) of the abdomen showed bilateral renal involvement in the form renal cyst and multiple cyst in the in pancreas including the head, body and tail region which were suggestive serous cystadenoma. In the context of

radiological findings a diagnosis of von- Hippel Lindau Disease was made. There was no history suggestive of familial involvement. Since in our case cerebellar hemangioblastoma was symptomatic patient was adviced surgical resection for the same. The size of the renal cyst was about 2 cm (<3 cm) and accordingly patient was adviced for follow up to watch for any increase in size of the cyst or malignant transformation at the earliest. The patient was also adviced for genetic testing to identify the mutation in VHL gene.

## Discussion

Von- Hippel Lindau is a rare disease which is inherited in autosomal dominant fashion and results in development of hemangioblastoma of central nervous system (CNS), retinal hemangioblastoma, renal cell carcinoma or renal cyst, neuroendocrine tumours and cyst of pancreatic gland, pheochromocytoma, epididymal cyst adenoma.

Hemangioblastoma of the CNS usually develop from childhood at an age of <10 years or early teen until the age of 30 years.[5] The mean age (and ranges) of diagnosis of retinal hemangioblastoma, cerebellar hemanfioblastoma, and renal cell carcinoma are 25 years (1-67), 30 years (11-78), 37 years (16-67) respectively.[6] The most common sites for hemangioblastoma development are cerebellum and spinal cord as evident in our patient. The symptoms of hemangioblastoma are usually caused by expansion of tumour in intracranial space and spinal cord. Asymptomatic small tumour are carefully watched until the onset of symptoms. The best treatment modality for this tumour is surgical resection, in cases of large tumour burden where surgical resection is not possible gamma knife surgery can substitute the treatment modality.

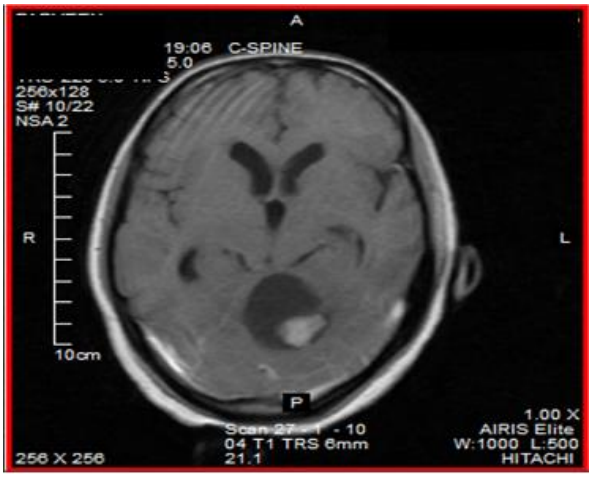


**Fig. 1: Large cystic lesion with eccentric nodule with avid contrast enhancement involving vermis and part of left cerebellar hemisphere suggestive of hemangioblastoma**

Spinal hemangioblastomas occur in 13-59% of the cases. In 80% of the cases spinal hemangioblastomas are associated with von- Hippel Lindau disease unlike cerebellar hemangioblastomas where the association is not so strong. Extensive replacement ("hemangioblastomatosis of the cord") of the spinal cord and brain have also been reported.[7]

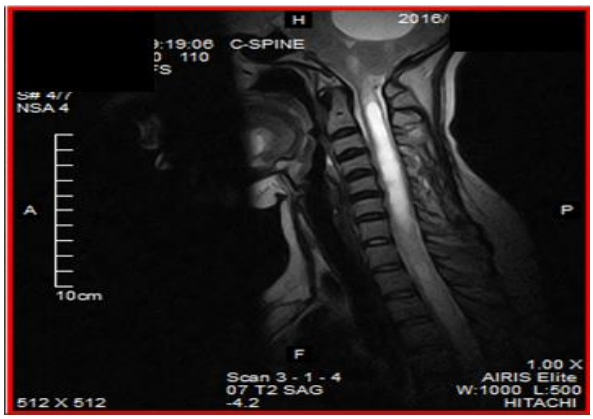


**Fig. 2: An altered signal intensity lesion which is hyperintense on T2 in the middle of the cord suggestive of syrinx with multiple cystic cavities**

Renal cyst are present in 59-63% of individual in VHL and Renal cell carcinoma dovelops in 24-45% of VHL patients.[6,8] Renal involvement in VHL is multicentric and bilateral in atleast 75% of the patients.[9] Tumours with a diameter <3 cm are carefully observed and those with diameter of >3cm should be removed with enucleation or partial nephrectomy. Recently percutaneous radiofrequency ablation or cryosurgery are also performed to remove the tumour.

Pancreatic cystadenomas or cysts are generally asymptomatic, characteristically seen as multiple cyst in the pancreas on imaging.

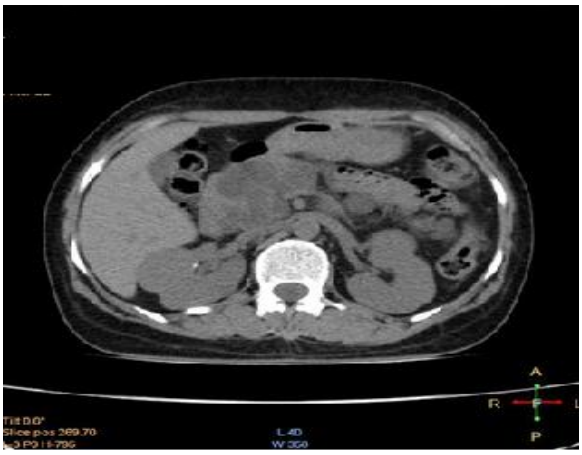

**Fig. 3: Multiple cystic lesions present in the pancreas along with cystic lesion in bilateral kidneys**

In recent times various clinical trials have been conducted with the use of anti-angiogenic therapies to stop both initiation and progression of these highly vascular tumours seen in VHL disease. Various drugs designed to inhibit VEGF – receptor kinase are under trail. These drugs are yielding very promising results in clinical studies showing >40% cases of partial response and upto 90% cases of partial response plus stable disease.[10,11] Various other specific inhibitors e.g. for HIFs may be developed in near future.

The prognosis of VHL disease initially was ascribed in accordance with the outcome of RCC treatment, but with the advent of nephron sparing surgery and other non- surgical techniques such as radiofrequency ablation, it is now becoming a curable condition.

**Conclusion**

VHL is a lifetime disease with no cure till date. Patients should be constantly checked for tumours and cysts that develop at various sites in his/her lifetime along with required intervention whenever needed at earliest. Patient with this disease constantly suffer from problems caused by multiple tumours and cyst from various organs including postoperative morbidity in the form of paraplegia, sensory and motor deficits. A hopeful prospect for this disease is invention of molecular targeting anti angiogenic drugs in near future. Patients must be offered care by well-trained specialist and genetic counselors throughout their life to improve prognosis and their psychological conditions caused by above mentioned conditions.

## Conflict of Interest

None Identified.

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