Case Report

A Rare Case of Von Hippel-Lindau Disease

J. Vasavi Reddy[1], K. Venkatram Reddy[2], G Ramakrishna Reddy[3]

[1]Junior Resident, Department of Radiodiagnosis, [2]Professor & HOD, Department of Radiodiagnosis, [3]Professor, Department of Radiodiagnosis, SVS Medical College and Hospital, Mahabubnagar, Telangana, India

Corresponding author: J. Vasavi Reddy, Junior Resident, Department of Radiodiagnosis, SVS Medical College and Hospital, Mahabubnagar, Telangana, India

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A B S T R A C T

Introduction: Von Hippel-Lindau syndrome (VHL) is a familial neoplastic condition seen in approximately 1 in 36,000 live births. It is caused by germline mutations of the tumor suppressor gene VHL, located on the short arm of chromosome 3. While the majority of the affected individuals have a positive family history, up to 20% of cases arise from de novo mutations. VHL syndrome is characterized by the presence of benign and malignant tumors affecting the central nervous system, kidneys, adrenals, pancreas, and reproductive organs. Common manifestations include hemangioblastomas of the brain, spinal cord, and retina; pheochromocytoma and paraganglioma; renal cell carcinoma; pancreatic cysts and neuroendocrine tumors; and endolymphatic sac tumors. Diagnosis of VHL is prompted by clinical suspicion and confirmed by imaging and molecular testing.

Case Report: A Female patient of age 30 years presented with giddiness since 6 months, MRI revealed cerebellar and spinal hemangioblastoma with multiloculated syrinx in cervical and dorsal spine associated with pancreatic cysts, Hemangioblastoma was confirmed by histopathology

Conclusion: VHL is a lifetime disease with no cure till date. Regular follow-up with imaging ultrasound, CT, MRI are also necessary to follow the previous lesions and detect any newlydeveloped VHL-associate tumors.

Keywords: Von Hippel-Lindau (VHL), Hemangioblastomas, Central Hemangioblastomas (CHbs)

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. The spectrum of clinical manifestations of the disease is broad and includes retinal and central nervous system hemangioblastomas, endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas. The most common causes of death in VHL disease patients are renal cell carcinoma and neurologic complications from cerebellar hemangioblastomas.[1,2]

CASE REPORT

A 30 year female patient came for the evaluation of giddiness for 6 months duration. Magnetic resonance imaging of brain and cervicodorsal spine was done which revealed a mass in the left cerebellum and in dorsal spine which is in the postero left lateral aspect of cord opposite to D3 –D4 intervertebral level and D9 vertebral body level which is cystic and nodular which are varied from 2 to 5 mm, these lesions were hypointense on T1 and hyperintense on T2 with intense contrast enhancement. The associated long segment multiloculated syrinx extending from C3 –C4 to D10 –D11 intervertebral disc, multiple pancreatic cysts (fig-1,2,3,4).
In view of known occurrence of multiple hemangioblastomas in VHL disease, patient was further investigated radiologically. An ultrasound of abdomen revealed multiple simple cysts in pancreas, the liver, spleen, kidney and adrenals were normal further MRI abdomen revealed multiple cysts in pancreas body and tail In view of the imaging findings, a diagnosis

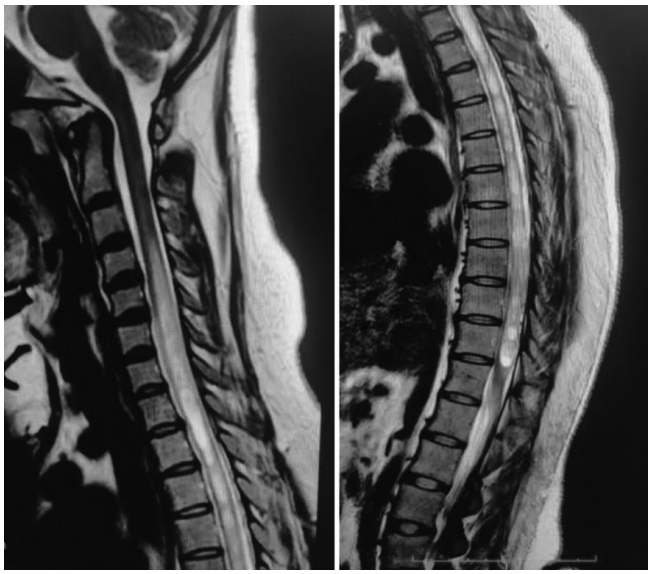

Figure-1: MRI T2W Cervical & Dorsal spine showing multilevel multiloculated syrinx.

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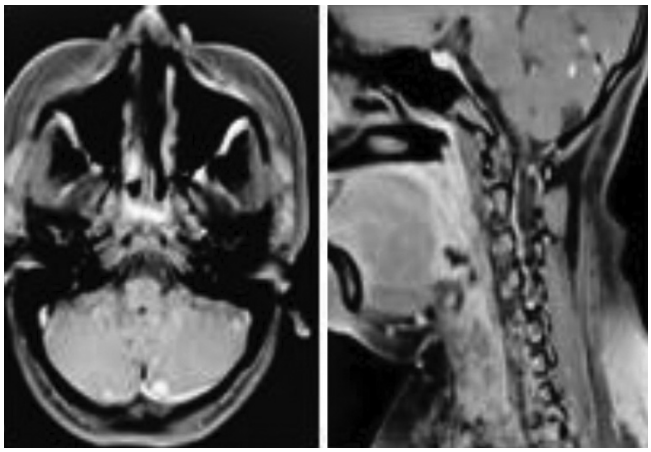

Figure-2: MRI Brain T1W contrast showing enhancing cerebellar hemangioblastomas.

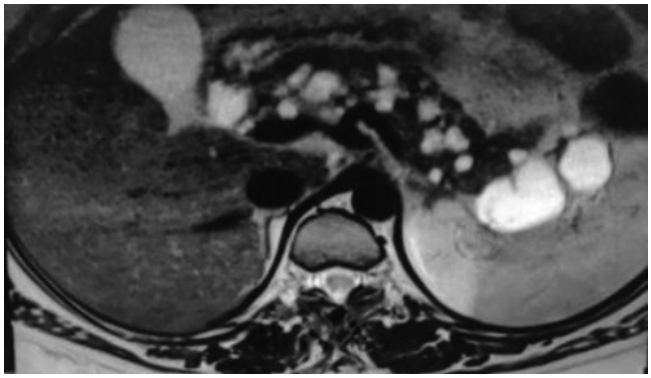

Figure-3: MRI axial T2W abdominal image showing multiple variable sized pancreatic cysts.

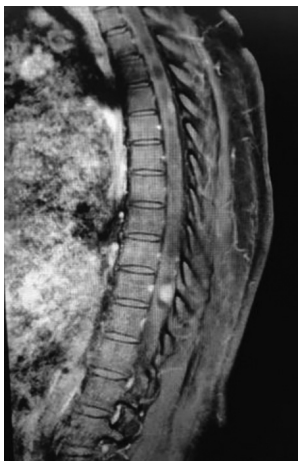

Figure-4: MRI T1W contrast showing intensely enhancing hemangioblastoma at lower dorsal level.

of VHL disease was established. The patient's father died of renal cell carcinoma.

Provisional diagnosis

Based on the above findings diagnosis of von hippel lindau disease were made

DISCUSSION

Von Hippel–Lindau syndrome (VHL) is an autosomal-dominant hereditary tumor disease that arises owing to germline mutations in the VHL gene, located on the short arm of chromosome 3. Patients with VHL may develop multiple benign and malignant tumors involving various organ systems, including retinal hemangioblastomas (HBs), central nervous system (CNS) HBs, endolymphatic sac tumors, pancreatic neuroendocrine tumors, pancreatic cystadenomas, pancreatic cysts, clear cell renal cell carcinomas, renal cysts, pheochromocytomas, paragangliomas, and epididymal and broad ligament cystadenomas.[3] This case shows that in a patient with central nervous system (CNS) hemangioblastoma, one should rule out VHL by suitable investigations. The cranio-spinal lesions in this patient were eccentric as well as centrally located and had intense homogeneous enhancement. Mild to moderate peritumoral oedema was also present. Pancreatic cysts were further evaluated by MRI which showed high signal intensity due to water content and background tissue was suppressed. This results in better delineation of cystic lesions and its internal contents. VHL disease has been recognized for almost 70 years and recent developments in the genetics and imaging of VHL have significantly improved our understanding of the disease and its natural history. The prevalence of VHL has been estimated to be between 1:35,000- 1:40,000.[1,2] The VHL gene was localized to the short arm of (3p25-26) chromosome in the late 80s and early 90s by researchers at the National Cancer Institute.[4] If a family history of retinal or central nervous system hemangioblastoma (Hb) exists, only one Hb or visceral lesion (renal tumours, pancreatic cysts or tumours, pheochromocytoma, papillary cystadenomas of the epididymis) is required to make the diagnosis of VHL. For isolated cases without a clear family history, two or more Hb or one Hb and a visceral manifestation is required. Central nervous system hemangioblastomas commonly involve cerebellum, spine and medulla. CHb associated with VHL occurs at a younger age, is often multiple and has a worse prognosis than sporadic CHb, which occurs in 44-72% of VHL patients, making it one of the most common manifestations of the disease. Medullary hemangioblastomas (MHb) occur in about 5% of VHL patients.[5] They are found in postrema of the medulla and may lead to syringobulbia. Unusual sites of hemangioblastomas in VHL include the anterior lobe of the pituitary, pituitary stalk, hypothalamus, optic nerve, corpus callosum, wall of the third ventricle, temporal horn of the lateral ventricles, frontal and temporal lobe and meninges.[6] Spinal hemangioblastomas (SHb) occur in 13-59% cases. Unlike CHb where only a minority are associated with VHL, SHb is associated with VHL in 80% of all cases. SHb can be intramedullary, partially intra and extramedullary or exclusively extramedullary. Extensive replacement ("hemangioblastomatosis of the cord") of the spinal cord and brainstem has also been reported in VHL.[7] The best imaging technique available for hemangioblastomas is contrast enhanced MRI employing a gadolinium chelate. Routine screening of the CNS in VHL should include, pre and post contrast T1 weighted images of the brain and spinal cord, with thin sections through the posterior fossa and spinal cord and surface coil images of the entire spinal cord. CHb commonly contain cystic areas with a solid mural nodule. Small (10 mm or less) hemangioblastomas are mostly isointense on T1-weighted images and

hyperintense on T2-weightedimages showing homogeneous post contrast enhancement. Small hemangioblastomas are located at the surface of the spinal cord while larger ones tend to be hypointense or show mixed signal intensity on T1 weighted images and appear heterogeneous on T2-weighted images. These lesions show heterogeneous post contrast enhancement. A hemangioblastoma larger than 24 mm is invariably accompanied by vascular flow voids.[8] The solid and contrast-enhancing portions give low signal on diffusion weighted imaging (DWI) with resultant increase in the apparent diffusion coefficient (ADC). These findings indicate rich vascular spaces of the hemangioblastomas which is not seen in the other tumours. DWI may be useful for distinguishing hemangioblastomas from other enhancing cerebellar tumours.[9] Renal cysts are found in 50–75% of patients with von Hippel-Lindau diseaseRenal cell carcinoma occurs in 28–45% of patients with von Hippel-Lindau disease and is a frequent cause of morbidity and mortallity.[10] Microscopic solid tumorlets have been identified within the renal parenchyma of patients with VHL. Some of these may develop into macroscopic tumours. Solid tumours have been observed to grow at a mean rate of 1.6cm/year which is somewhat faster than those observed in sporadic renal cell carcinoma. Retinal hemangioblastomas (RHb) is seen in 45-59% of patients with VHL. They have been called "retinal angiomas" and "retinal haemangiomas" but hemangioblastoma is the preferred term since they are histologically identical to lesions found in the CNS.[5]

CONCLUSION

VHL is a lifetime disease with no cure till date. Regular follow-up with imaging (ultrasound, CT, MRI) are also necessary to follow the previous lesions and detect any newly developed VHL-associate tumors. 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

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