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Von Hippel Lindau Disease with Retinal, Endolymphatic Sac, Renal and Pancreatic Involvement-A Case Report

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Abstract: The objective of this study is to report a rare case of Von Hippel Lindau syndrome with family history and multisystem involvement. It is an autosomal dominant condition caused by mutation of VHL tumour suppressor gene on chromosome 3p25-26. A 24 year old female presented to our OPD with presenting complaints of diminution of vision in both eyes since four years and photopsia since two years. She also complained of hearing loss, tinnitus and vertigo since one year. Ocular workup including visual acuity, fundus examination, Fundus Fluoroscein Angiography (FFA) ,B Scan ultrasonography, colour doppler ,MRI Brain ,abdominal CT scan and pure tone audiometry(PTA) were performed. Her four elder brothers and father had similar ocular complaint for which her two brothers underwent laser photocoagulation. Her visual acuity in both eyes was perception of light present and projection of rays inaccurate. Fundus examination revealed multiple tumour masses in both eyes with dilatation and tortousity of supplying artery and draining vein extending from optic disc, suggesting retinal capillary hemangioblastoma.FFA showed early hyperfluorescence, late leakage with rapid filling and exit of dye. B scan revealed vitreous hemorrhage, vitreous and retinal detachment. Doppler showed increased vascularity in feeder vessels. CT Abdomen revealed multiple renal and pancreatic cysts. MRI Brain revealed focal hyperintensity on right side on T1 image suggesting endolymphatic sac tumour. PTA showed sensorineural hearing loss. She was advised vitreoretinal surgery in both eyes and surgical resection of endolymphatic sac tumour.

Keywords: Tinnitus, vertigo, fluoroscein, audiometry, photocoagulation, hyperfluoroscence, hemangioblastoma, endolymphatic, vitreoretinal.

INTRODUCTION

VHL is an autosomal dominant, multisystem; familial syndrome caused by mutations in VHL tumor suppressor gene.It is one of the groups of conditions known as phakomatoses, which have cutaneous, ocular and neurological manifestations. The incidence of VHL is 1 in 36000 and penetrance is almost complete by age 65 [1]. VHL gene was mapped to chromosome 3p25-26 [2].VHL protein is thought to downregulate transcriptional elongation by binding to components of elongin complex [3,4].This complex targets hypoxia inducible factors for degradation. These factors are produced in response to hypoxia and regulate production of VEGF [5],which promote angiogenesis and uncontrolled cell proliferation. Somatic inactivation of the wild-type VHL allele is found in most VHL tumors, and is consistent with the "Knudson's two hit hypothesis" of tumorigenesis seen in retinoblastoma [6,7], where inactivation or loss of a tumor suppressor gene also appears to be involved. Retinal Capillary Hemangioblastomas (RCH), cerebellar or spinal cord hemangioblastomas, renal cell carcinoma (RCC) and pheochromocytoma are main causes of morbidity and mortality [8,9].

About 50% of VHL patients manifest only one feature of the disease and very few develop all manifestations.RCH are present in up to 70% of VHL patients and are frequently the first clinical manifestation [10,11], they can be asymptomatic for years and may even regress spontaneously, but usually grow and cause visual impairment [12-15].They are frequently the first clinical manifestation. Other manifestations of VHL that may come to an ophthalmologist attention include hypertensive retinopathy from pheochromocytoma, retinal vascular hamartomas [16], chiasmal syndrome [17], afferent pupillary defect from optic nerve hemangioblastomas [18] , and papilledema (due to CNS lesions, optic nerve lesions, or pseudo-papilledema with peripapillary RCH [19,20]. Patients and at risk family members may benefit from a screening protocol designed for presymptomatic detection and treatment of most common tumors.

Prognosis of VHL was once considered to be related to the outcome of RCC treatment. RCC is the most serious tumor, with high metastasizing potential and can cause uremia. However, with recent emergence of novel surgical techniques such as,partial adrenalectomy and nephron-sparing surgery,as well as radiofrequency ablation, VHL has become curable condition. A considerable risk of morbidity is reported to originate from postoperative complications caused by treatment of spinal cord hemangioblastoma. Such complications usually consist of wide range of neurologic damage including paraplegia and sensory and motor disturbances [21] Recently, new drugs have been developed and their therapeutic effects are being investigated. These medications include antiangiogenic agents used in treatment of RCC. Although thalidomide with interferon or SU5416 alone was demonstrated to halt tumor growth in RCC, it did not reduce its size. There are inhibitors of VEGF receptor kinase, which are in process of clinical trials. These drugs have been promising in terms of clinical effects. Moreover, some inhibitors designed specifically for HIFs(Hypoxia Inducible Factors) may prove to be effective in the future [22].

CASE REPORT

A 24 years old female presented to our OPD with presenting complaints of diminution of vision in both eyes since four years and photopsia since two years. She also complained of hearing loss, vertigo and tinnitus since one year. She had significant family history.Her four elder brothers and father had similar ocular complaint for which her two brothers underwent laser photocoagulation. Complete ophthalmological examination was performed including visual acuity, fundus examination, fundus fluorescein angiography(FFA), Optical coherence tomography(OCT), B scan ultrasonography and colour Doppler. It was executed after approval from ethical committee of Gajra Raja Medical College, Gwalior, Madhya Pradesh.

Her visual acuity in both eyes was perception of light present and projection of rays inaccurate.(Fig-1)

Fundus examination revealed multiple tumour masses in both eyes with dilatation and tortousity of supplying artery and draining vein extending from optic disc, suggesting retinal capillary hemangioblastoma(Fig-2).

FFA showed early hyperfluorescence, late leakage with rapid filling and exit of dye. B scan revealed vitreous hemorrhage, vitreous detachment and retinal detachment. Doppler showed increased vascularity in feeder vessels(Fig-3). OCT revealed retinal detachment (Fig-4).

MRI brain and abdominal CT scan were also performed. Axial CT images showing multiple and bilateral simple renal cysts along with pancreatic cysts (Fig-5).

MRI Brain revealed focal hyperintensity on right side on T1 image suggesting endolymphatic sac tumour for which she was referred to ENT department where tuning fork tests were performed which showed sensorineural hearing loss(Fig-6).

Pure tone audiometry (PTA) showed sensorineural hearing loss (Fig-7)

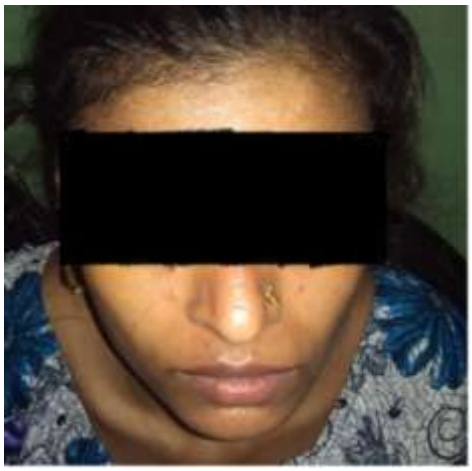

Fig-1: Clinical Photograph

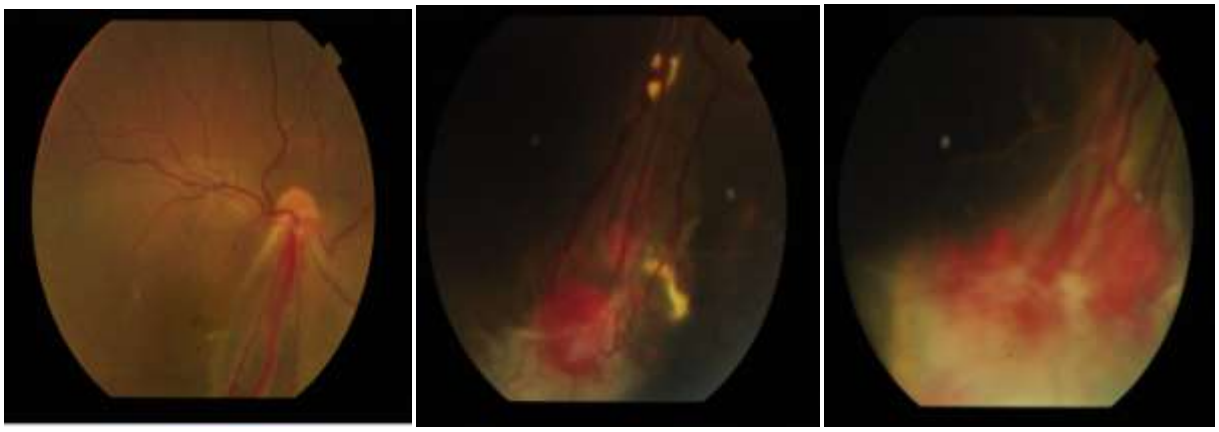

Fig-2: Fundus photographs

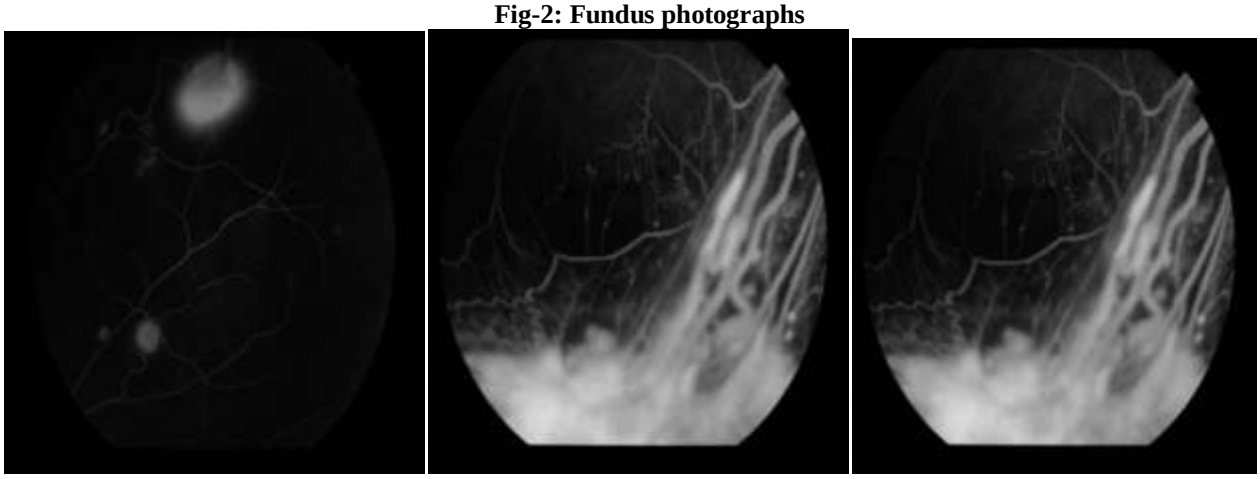

Fig-3: FFA Photographs

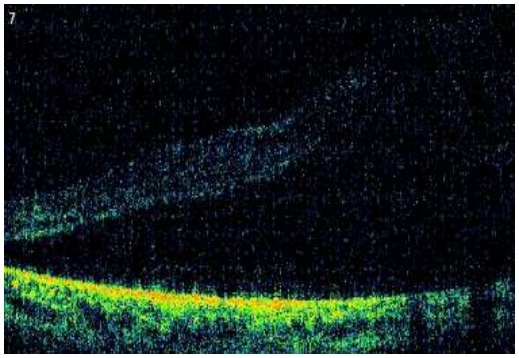

Fig-4: OCT Photograph

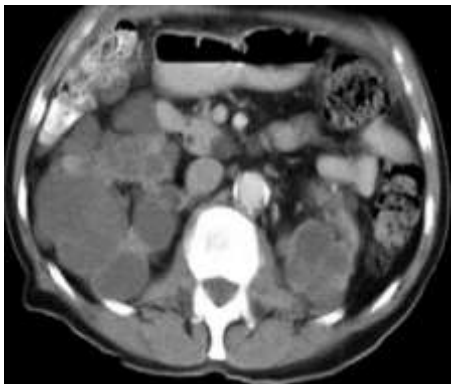

Fig-5: CT scan abdomen showing renal and pancreatic cysts

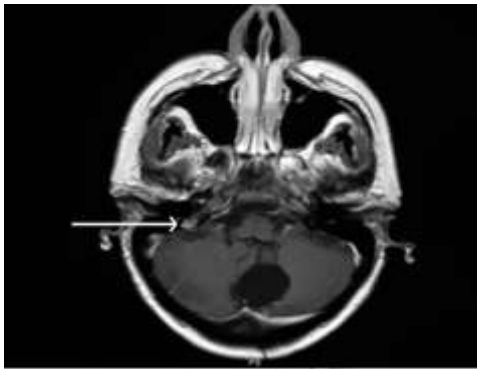

Fig-6: MRI brain including temporal bone showing endolymphatic sac tumour

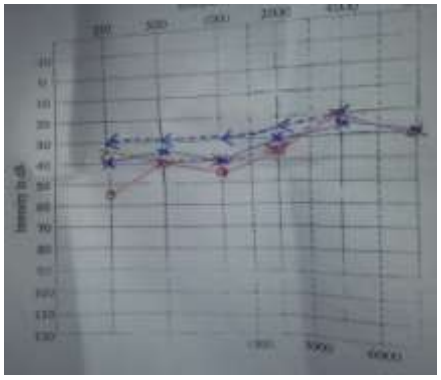

Fig-7: Pure tone audiometry

DISCUSSION

VHL syndrome is a disorder characterized by retinal capillary hemangioblastomas, CNS hemangioblastomas, various solid and cystic visceral hamartomas and malignant neoplasms, including renal cell carcinomas(RCC) and pheochromocytomas. Affected individuals are at substantial risk of early death due to intracranial hemangiomatous lesion or renal cell carcinoma, median age at detection of first clinical features of VHL is 20–25 years [23]. Capillary hemangiomas of retina are the earliest detected manifestation of VHL whereas CNS hemangioblastomas typically appear slightly later and renal cell carcinomas substantially later in life. Molecular biological studies have localized VHL gene to chromosome 3p25-26 [24].

The classical CNS lesions of VHL are solid and cystic cerebellar hemangioblastomas [25] which occur in about 40% of affected individuals by 30 years and in about 70% by 60years [23]. The component cells in these tumors appear benign by histopathological criteria. Similar vascular lesions also occur in medulla and spinal cord in 10–15% of patients. Renal cell carcinomas in VHL are bilateral in approximately 75% of cases [23]. This tumor can metastasise, so it must be recognized early and treated aggressively to avoid fatal outcome. Other visceral neoplasms that develop in VHL

include pheochromocytoma, islet cell carcinoma and cystadenomas of pancreas and epididymis [23]. They have strong tendency to develop multifocal cysts in kidneys, pancreas and ovaries [24]. Approximately 50–60% of patients with VHL develop retinal capillary hemangioma during their lifetime and about half of these individuals have multiple retinal capillary hemangiomas in both eyes. Tumor enlargement, intraretinal bleeding, exudation, gliosis and retinal detachment may occur. These complications can result in profound visual loss or even phthisis bulbi. If associated renal tumors and intracranial vascular tumors are not detected at early stage or are not controlled by aggressive intervention, they can be fatal [23,25] Consequently, life expectancy of patients with VHL is reduced considerably. Median age at death is 45–50 years.

RCC develops in 50% of patients with VHL and is distinctive for its early onset, in third, fourth or fifth decade of life and for its bilateral and multifocal involvement [26]. Sophisticated molecular genetic studies in patients with von Hippel-Lindau disease eventually led to identification of VHL tumor suppressor gene [27].

This syndrome should be considered in any patient with early-onset or multifocal RCC or RCC in combination with any of following: history of visual or neurologic symptoms, family history of blindness, central nervous system tumors, or renal cancer, coexistent pancreatic cysts, epididymal lesions or inner-ear tumors [28]. Patients suspected of having von Hippel Lindau disease or appropriate relatives of those with documented disease, should strongly consider genetic evaluation. Patients with germ line mutations can be identified and offered clinical and radiographic screening that can identify the major manifestations of von Hippel-Lindau disease at a presymptomatic phase, allowing potential amelioration of the considerable morbidity associated with this syndrome [29]. Investigators at the National Institutes of Health have recommended that such patients be evaluated with (1) an annual physical examination and ophthalmologic evaluation beginning in infancy; (2) estimation of urinary catecholamines at the age of 2 years and every 1 to 2 years thereafter; (3) an MRI of the central nervous system biannually beginning at the age of 11 years; (4) an ultrasound examination of the abdomen and pelvis annually beginning at the age of 11 years, followed by CT scanning every 6 months if cysts or tumors develop; and (5) periodic auditory examinations

Although there is no cure for VHL, the associated tumors can be treated. Early detection and treatment of tumors significantly improves patient's prognosis. Left untreated, VHL may result in blindness, permanent brain damage, or death. Depending on the location of the tumors, our neurosurgical specialists may also collaborate with urologists, ophthalmologists, endocrinologists, and other physicians.

Hemangioblastomas of the central nervous system

Frequently they are completely resectable as it is clearly demarcated from surrounding tissue. However recurrences after surgical excision are common.

Retinal capillary hemangioblastomas

Retinal angiomas can be effectively treated with cryotherapy or laser photocoagulation in 60% cases, particularly when lesions are still small. Multiple treatment sessions may be necessary to achieve complete success. Early diagnosis increase the likelihood of successful treatment, yet the ocular lesions of VHLare asymptomatic prior to retinal detachment. Therefore children known to be at risk for the disease undergo periodic ophthalmological examination beginning at age of 5 years

Renal cell carcinoma

Depending on the extent of disease, renal cell carcinoma may either be treated with nephron-sparing surgery (removing the tumor while sparing unaffected portion of kidney) or radical nephrectomy (removal of whole kidney).

The prognosis for patients with VHL depends on the location and complications of tumors. Untreated, VHL may result in blindness and permanent brain damage. With early detection and treatment the prognosis is significantly improved. Death is usually caused by complications of brain tumors or kidney cancer.

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