

## Von Hippel – Lindau Disease, Involvement of Multiple Members of the Same Families

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### ABSTRACT

*Von Hippel – Lindau disease is a heritable multisystem cancer syndrome that is associated with a germline mutation of the VHL tumour suppressor gene on the short arm of chromosome 3. This disorder is not rare (about one in 36 000 live births) and is inherited as a highly penetrant autosomal dominant trait (i.e. with a high individual risk of disease). Affected individuals are at risk of developing various benign and malignant tumours of the central nervous system, kidneys, adrenal glands, pancreas, and reproductive adnexal organs. Because of the complexities associated with management of the various types of tumours in this disease, treatment is multi-disciplinary.*

**Objectives:** *We present an overview of the clinical aspects, management, and treatment options for von Hippel-Lindau disease in three families, a total number of 7 patients.*

**Study Design:** *It was a descriptive observational study.*

**Material and Methods:** *In this study we included 7 patients belonging to 3 families. In the first family there was a father and a son, both of them had Von Hippel-Lindau disease. In the second family two sisters and one brother was involved, while in the third family one brother and one sister had this disease. This study was conducted in the Department of Neurosurgery, Lahore General Hospital, Lahore.*

**Results:** *In this study we observed that 1 out of 7 patients died, 1 is bed ridden with paraparesis. The rest 5 patients are passing their normal routine life. We observed that in all of our patients (100%) there was CNS involvement, the recurrence in our series is quite high. (70%), 3 of our patients required permanent V.P. Shunt while 1 patient required per operative EVD. In 2 of our patients eye surgery was required. 1 of our patient underwent the Gama Knife (Radio surgery).*

**Key words:** *Von Hippel-Lindau disease, germline mutation, tumour suppressor gene, penetrant autosomal dominant trait.*

### INTRODUCTION

Von Hippel – Lindau disease is an autosomal dominant neoplasia syndrome that results from a germline mutation in the *VHL* gene.<sup>1-3</sup> Germline mutations in the *VHL* gene lead to the development of several benign or malignant tumours, and cysts in many organ systems.

Affected individuals might develop CNS lesions including cerebellar, spinal cord, brainstem, nerve root, and supratentorial haemangioblastomas, as well

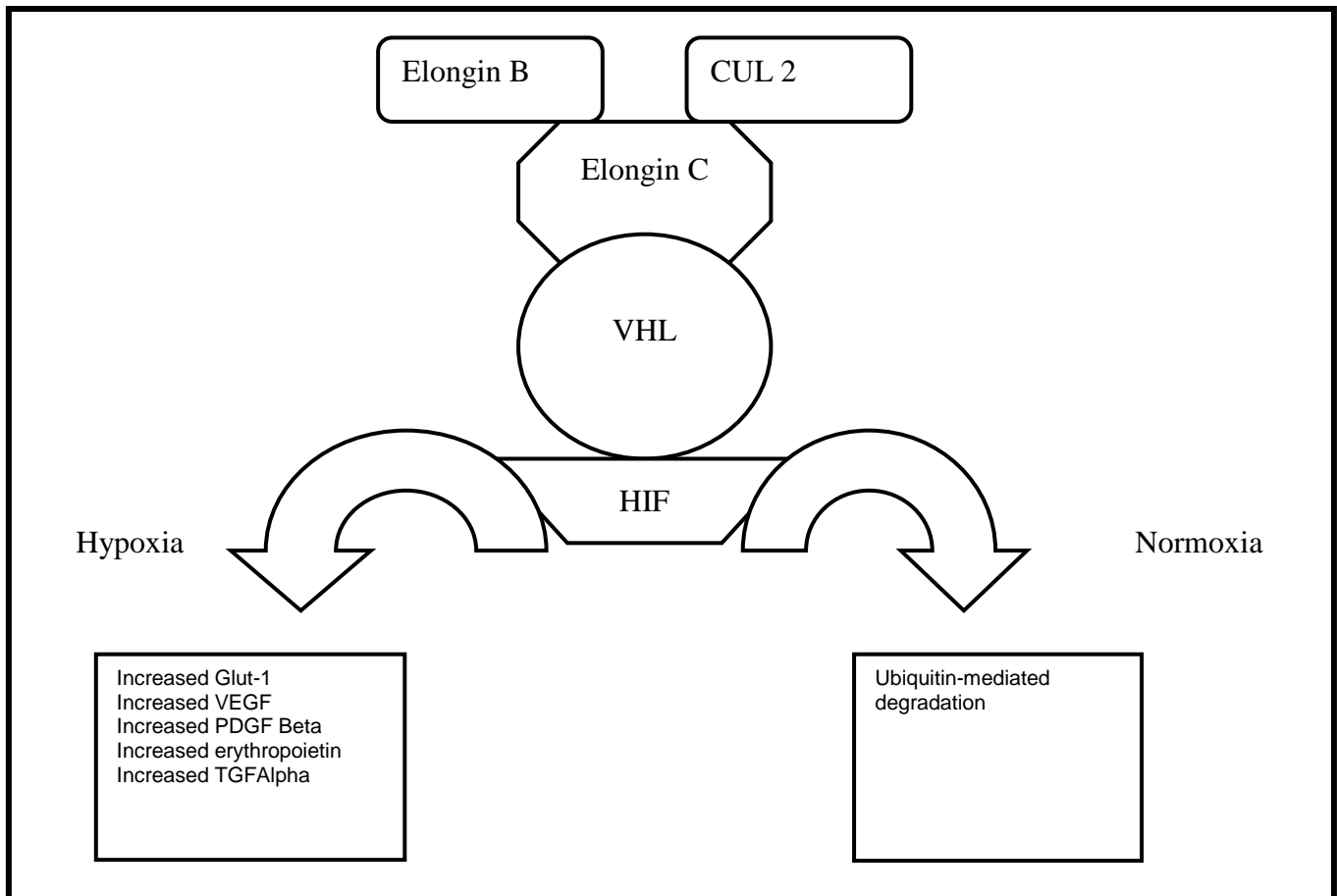
as retinal haemangioblastomas and endolymphatic sac tumours.<sup>2,4</sup> Visceral features of the disorder include renal cysts and carcinomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumours, as well as epididymal and broad ligament cystadenomas. Von Hippel-Lindau is not rare (incidence is roughly one in 36 000 live births),<sup>5,6</sup> and has over 90% penetrance by 65 years of age.<sup>5</sup> Before comprehensive screening surveys became routine, median survival of patients with the disease was less than 50 years of age.

The main causes of death were complications linked to renal cell carcinomas and CNS haemangioblastomas.<sup>7-10</sup> Improved surveillance, earlier diagnosis of lesions by modern imaging and laboratory studies (panel 1),<sup>11</sup> improvements in treatment, and increased knowledge of this disease have improved prognosis and reduced the complications related to these tumours. Because of the progressive, diverse nature, and high frequency of multiple neoplasms in various organ systems, the management of the tumour types is complicated by the presence of others. A multi specialty team is needed for the optimum assessment and treatment of these patients. Comprehensive serial screening and routine scheduled follow-up are essential for proper care.<sup>11</sup>

**Molecular Genetics**

VHL is a tumour suppressor gene on the short arm of chromosome 3 (3p25–26).<sup>23</sup> Most people with the

disorder inherit a germline mutation of the gene from the affected parent, and a normal (wild type) gene from the unaffected parent. According to Knudson’s two-hit hypothesis of tumorigenesis, initiation of tumour formation arises when both VHL alleles are inactivated.<sup>24,25</sup> Germline mutations of VHL are present in all the cells of affected individuals who inherit the genetic trait. However, only those cells that (1) undergo a deletion or mutation of the remaining wild type allele, and (2) are constituents of susceptible target organs. Subsequently, disruption of VHL – protein mediated degradation of HIF could contribute to tumour formation through multiple mechanisms (Figure 1). If VHL function were absent or abnormal, HIF could stimulate angiogenesis, which is critical for persistence of tumours associated with the disorder. HIF – mediated angiogenesis could result from increased levels of VEGF or PDGF Beta, or both, which are known to be important for proliferation of endothelial cells and pericytes, respectively (Figure 1). This link



**Fig. 1:** Interaction of VHL protein with other proteins including elongin B, elongin C and CUL<sub>2</sub>, to form the VCB – CUL<sub>2</sub> complex.

might explain the highly vascular nature of tumours associated with von Hippel – Lindau disease, especially haemangioblastomas and renal cell carcinomas.

Moreover, high vascular permeability of the tumour vessels, resulting from increased VEGF levels, might also underlie the peritumoural oedema and cysts generally present in this disorder.<sup>10</sup> Another potential mechanism of HIF – mediated carcinogenesis is overproduction of TGF Alpha. Besides being a potent mitogenic factor (especially for renal epithelium), raised TGF Alpha can stimulate cellular over expression of epidermal growth factor receptors (receptors for TGF Alpha), creating an autocrine loop.<sup>6,22,23–28</sup>

Other possible mechanisms of tumorigenesis caused by absent or abnormal VHL protein, independent of HIF, include disruption of normal cell cycle, increased angiogenesis, and abnormalities in the extracellular matrix. The inability to leave the cell cycle (ie, to enter Go) is seen in cells without VHL protein.<sup>24</sup> This event might take place early in tumorigenesis. Furthermore, mutations of the protein itself could increase VEGF expression through incorrect transcriptional and posttranslational regulation.<sup>27,28</sup> These mutations might augment the angiogenic effects mediated by HIF and further increase tumour vessel permeability. Finally, although cells without VHL protein can secrete fibronectin, they cannot properly assemble a fibronectin extracellular matrix, which could contribute to carcinogenesis.<sup>23</sup> Overall, HIF – mediated, direct VHL protein – mediated, and unknown effects of abnormal or absent VHL protein probably interact to induce formation of the various tumours in this disease.

## CLINICAL PRESENTATION

VHL is associated with tumors in a multitude of organs, including the kidney, adrenal gland, CNS, eye, inner ear, epididymis, and pancreas. With current imaging modalities and genetic testing, many individuals are diagnosed while still asymptomatic. The diagnosis continues to be based on clinical criteria. Individuals with a family history are considered positive for the disease if screening tests diagnose a CNS hemangioblastoma (including retinal), pheochromocytoma, or renal manifestations. Patients who are diagnosed de novo without a family history must have evidence of two or more CNS hemangioblastomas or one CNS manifestation with a visceral tumor to meet diagnostic criteria.<sup>13</sup>

## Central Nervous System Lesions

Hemangioblastomas are the most common tumor found in VHL patients, affecting up to 80% of patients. The average age of presentation is 33 years,<sup>14</sup> these lesions are always benign but may cause significant morbidity because of volume effect. These lesions may occur anywhere along the craniospinal axis and may cause swelling and symptoms based on their location along this axis.

## Retina

Retinal hemangioblastomas are very common in VHL patients, occurring in 60% of patients.<sup>13</sup> They may be multifocal or bilateral and occur early in life. The mean age of diagnosis of retinal hemangioblastomas is 25 years.<sup>13</sup> They are benign but symptomatic and may lead to vision loss.

## Inner Ear

Occurring in 11% of VHL patients, endolymphatic sac tumors are not as common as other CNS manifestations of VHL. They may lead to hearing loss and problems with equilibrium.<sup>15</sup>

## Visceral Lesions

### Kidneys

VHL patients are prone to both renal cystic disease and solid lesions of the kidneys. RCC, which may be malignant, occurs in 25% to 45% of VHL patients.<sup>13</sup> VHL may also be associated with renal cysts that do not have a malignant potential but may cause local effects. Sixty percent of VHL patients have some renal manifestation.<sup>13</sup> Because of its malignant potential, RCC is a significant cause of death in VHL patients, and when left untreated, it can lead to death from metastases in 13% to 42% of patients.<sup>16,17</sup> These renal manifestations may be multifocal and bilateral, including bilateral RCCs.

The mean age of presentation for renal manifestations is 39 years.

### Adrenal Glands

Pheochromocytomas occur in up to 20% of patients with VHL disease. These may be multiple as well as bilateral and may occur as extra-adrenal lesions as paragangliomas.<sup>13</sup> They occur at a mean age of 30 years.

**Pancreas**

Most of the pancreatic lesions associated with VHL are cystic and are classified histologically as serous cystadenomas. These cystic lesions may occur as a single lesion or as multiple lesions and occur in 17% to 56% of patients with VHL.<sup>18,19</sup> These lesions have no malignant potential but may replace enough of the pancreas to cause endocrine or exocrine insufficiency of the pancreas or compression of the intestine or the bile duct. Solid lesions are also linked to VHL. Pancreatic neuroendocrinetumors (PNETs), which are always nonfunctional, have a malignant potential. PNETs have been previously reported to be present in 12% to 17% of patients with VHL, and these tumors behave in a malignant fashion in up to 17% of patients. Despite their malignant potential, they remain an uncommon cause of death.<sup>20</sup> An association between PNETs and pheochromocytoma has been reported.<sup>21</sup>

**Epididymis and Broad Ligament**

**Cystadenomas**

Broad ligament cystadenomas have been reported in women with VHL.

Epididymal cystadenomas are benign and typically asymptomatic but may occur in up to 60% of patients with VHL.

**Clinical Diagnosis**

Diagnosis of von Hippel – Lindau disease is often based on clinical criteria. Patients with a family history, and a CNS haemangioblastoma (including retinal haemangioblastomas), pheochromocytoma, or clear cell renal carcinoma are diagnosed with the disease. Those with no relevant family history must have two or more CNS haemangioblastomas, or one CNS haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts, which are frequent in the general population) to meet the diagnostic criteria.<sup>9</sup> Specific correlations of genotype and phenotype have emerged in affected families. Several familial phenotypes of von Hippel-Lindau disease are now recognized, providing useful information to screen and counsel affected individuals (panel 2). Type 1 families have a greatly reduced risk of pheochromocytomas, but can develop all the other tumour types generally associated with the disease. Type 2 families have pheochromocytomas, but have either a low – risk (type 2A) or high-risk (type 2B) for renal cell carcinomas. Type 2C families have pheochromocytomas only, with no other neoplastic findings of VHL (panel 2).

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**Adapted from reference 11. Imaging techniques that are generally recommended before and after contrast infusion**

Type I	Retinal haemangioblastomas CNS haemangioblastomas Renal cell carcinoma Pancreatic neoplasms and cysts
Type II A	Phaeochromocytomas Retinal haemangioblastomas CNS haemangioblastomas
Type II B	Phaeochromocytomas Retinal haemangioblastomas CNS haemangioblastomas Renal cell carcinomas Pancreatic neoplasms and cysts
Type II C	Phaeochromocytoma only

**Panel 1: Recommended Intervals for Screening in At – Risk Individuals**

Test	Start age ( Frequency)
Ophthalmoscopy	Infancy (yearly)
Plasma or 24 h urinary catecholamines and metanephrines	2 years of age (yearly and when blood pressure is raised)
MRI of craniospinal axis CT and MRI of internal auditory canals	11 years of age (yearly) Onset of symptoms (hearing loss, tinnitus, vertigo, or unexplained difficulties of balance)
Ultrasound of abdomen	8 years of age (yearly; MRI as clinically indicated)
CT of abdomen	18 years of age or earlier If clinically indicated (yearly)
Audiological function tests	When clinically indicated

**MATERIAL AND METHODS**

This was a prospective study performed in the department of Neurosurgery Lahore General Hospital over a period of 6 years from January 2006 to January 2012.

**RESULTS**

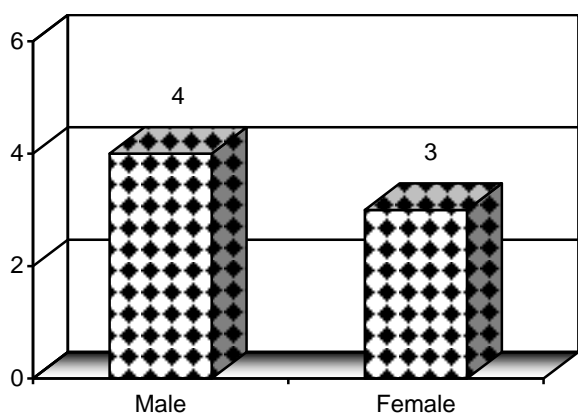
7 patients belonging to 3 families were included in this study. The first family had involvement of a father and his son, both of them had Von Hippel – Lindau disease. The second family had two sisters and one brother having VHL disease. In the third family a brother and a sister was the victim of this disease. At the first admission, we did all neurological imaging studies and visceral screening. Sporadic Hemangioblastomas were not included in our study. Ophthalmologist, nephrologists / urologist were consulted whenever required.

**Panel 2:** *Genotype – phenotype classifications in families with von Hippel – Lindau disease.*

Site	Percentage	Sign and Symptoms
Cerebellum	37	Gait ataxia (64%), Dysmetria (64%), Headaches (12%), Diplopia (8%), Vertigo (8%), Emesis (8%)
Brain stem	10	Hypaesthesia (55%), Gait ataxia (22%), Dysphagia (22%), Hyper-reflexia (22%), Headaches (11%), Dysmetria (11%)
Spinal cord	50	Hypaesthesia (83%), Weakness (65%), Gait ataxia (65%), Hyper-reflexia (52%), Pain (17%), Incontinence (14%)

**Frequency of signs and symptoms of patients who were undergoing resection.**<sup>12</sup>

**Gender Distribution Total No. of Patients = 7**



**Figure 2:** *Male to Female ratio.*

Sub occipital craniectomy was done in all cases.

In our study of 7 patients 1 of our patient expired, 1 of the patient is bed ridden with paraparesis. The remaining 5 patients are passing their normal routine life.

In our study we found that all the 7 patients (100%) there was central nervous system involvement. In 2 of the patients there was eye involvement, 2 of the

patients had renal involvement, 1 patient has involvement of the pancreas, one has involvement of the spinal cord and 1 has liver involvement as well. The recurrence in our series is quite high (70%).

In 3 of our patients we had to place permanent Ventriculo-peritoneal Shunt while 1 of the patient we had to put per-operative extra ventricular drain (EVD).

Two of the patients with eye involvement needed eye surgery and were referred to the ophthalmology department, while 1 patient was sent for Gama Knife (Radio surgery). Pre operative symptoms improved in all post neurosurgical procedures. There was no wound infection in any case. No new neurological deficit in any case except transient nasal regurgitation in one case which improved at the same hospital admission.

**DISCUSSION**

In VHL patients might develop CNS lesions including cerebellar, spinal cord, brainstem, nerve root, supratentorial haemangioblastomas and endolymphatic sac tumours. With the current imaging modalities and genetic testing, many individuals are diagnosed while still asymptomatic. The diagnosis continues to be based on clinical criteria. Individuals with a family history are considered positive for the disease if

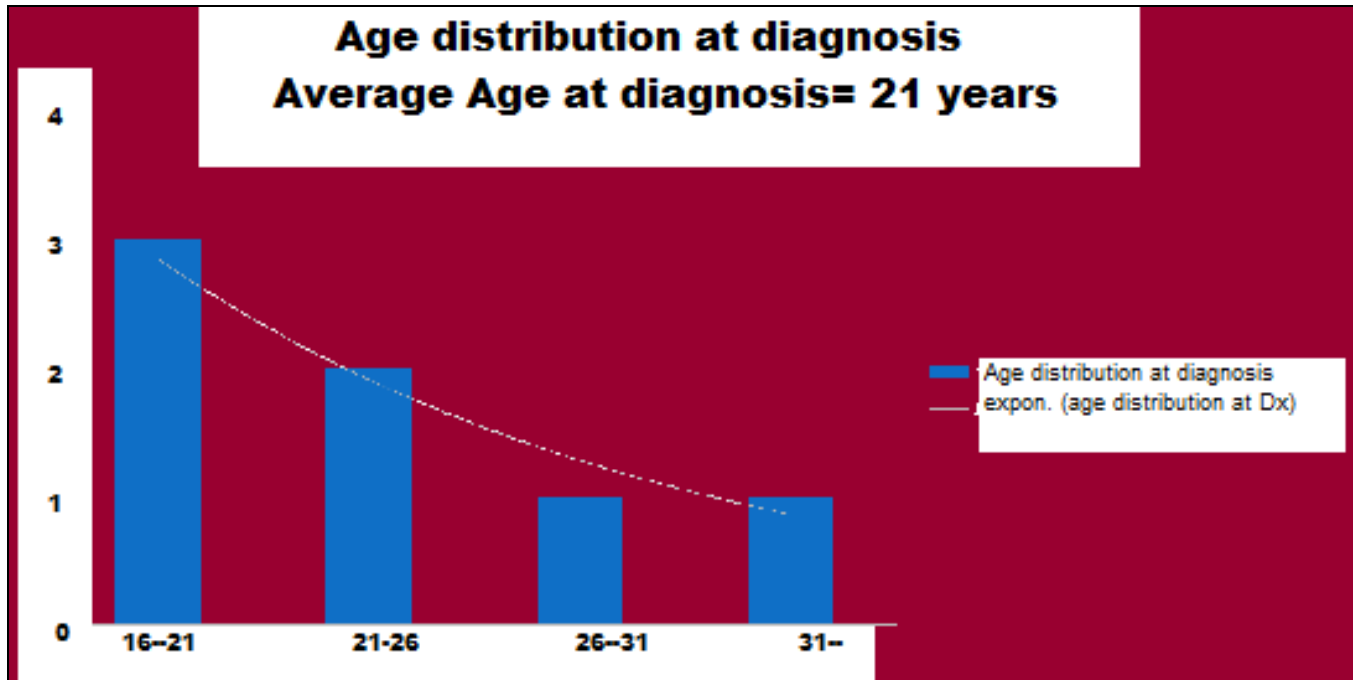


Figure 3: Age distribution at the time of diagnosis.

screening tests diagnose a CNS hemangioblastoma (including retinal), pheochromocytoma, or renal manifestations. Patients who are diagnosed de novo without a family history must have evidence of two or more CNS hemangioblastomas or one CNS manifestation with a visceral tumor to meet diagnostic criteria.

In our study one of our 14 years male patient whose father also had a VHL disease presented to us with headache, vomiting and ataxia for last 2 months. The patient also underwent indirect Argon Laser and

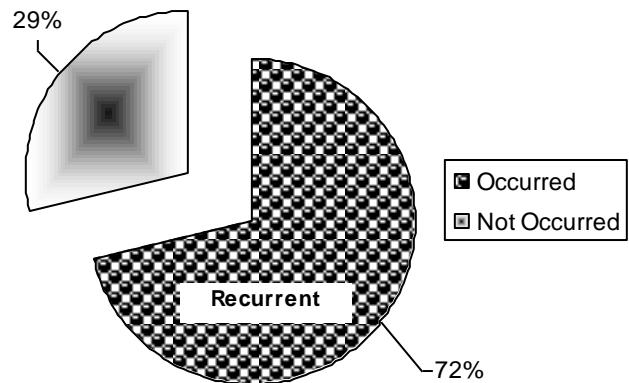


Figure 5: Recurrence of tumor.

**Hemisphere Cerebellar Involvement**

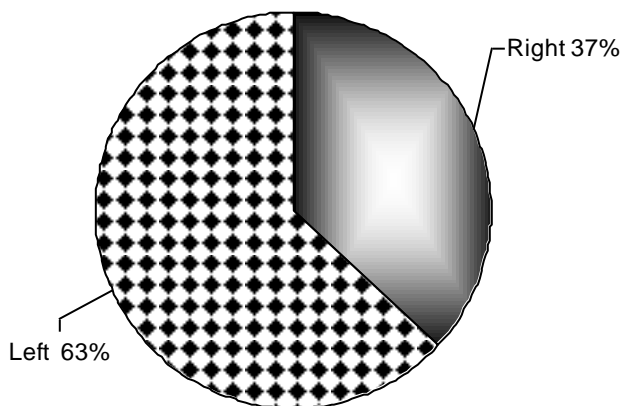


Figure 4: Cerebellar hemisphere involvement.

Cryo treatment to Lt. Eye 6 years earlier but the patient's vision did not improve. MRI showed cystic posterior medulla oblongata space occupying lesion. Midline sub occipital craniectomy and excision of brain stem lesion was performed. Brain stem biopsy was inconclusive; the symptoms of the patient improved and he was discharged from the hospital.

Meanwhile, the patient developed duodenal perforation and underwent laprotomy.

The same patient after a lapse of 3 years again presented to our department with spinal cord multiple lesions. D<sub>1</sub> – D<sub>4</sub> Laminectomy and excision of

intradural intramedullary tumour was done. Three dark grayish nodules with the cyst excised. Biopsy revealed

Hemangioblastoma.

After about 1 year the patient presented with

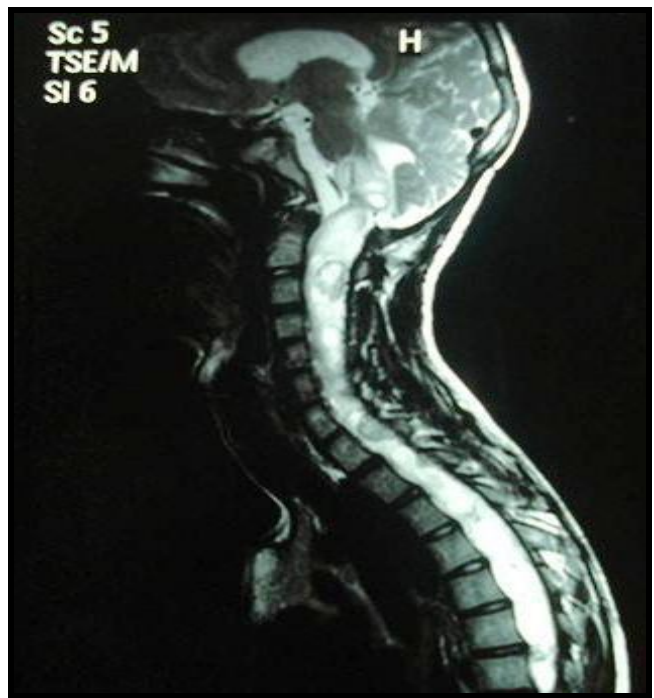


Figure 6: MRI Cervico Dorsal spine sagittal views.

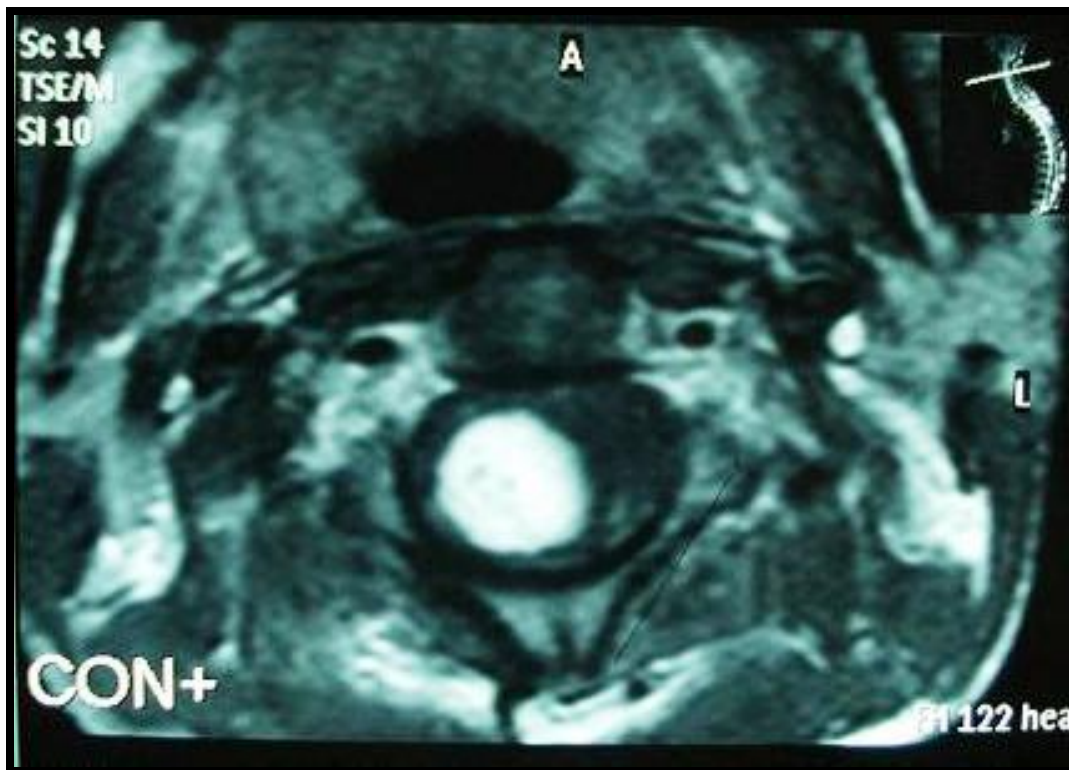


Figure 7: MRI Spine axial view with contrast.

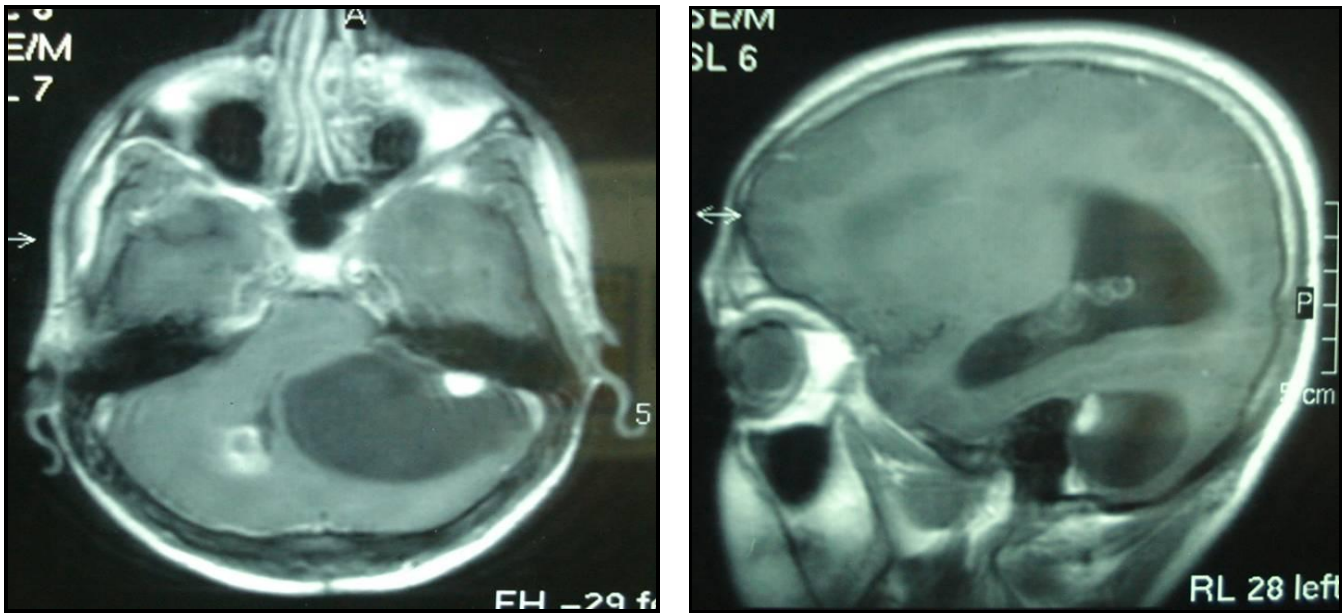


Figure 8: Pre-operative MRI Brain.

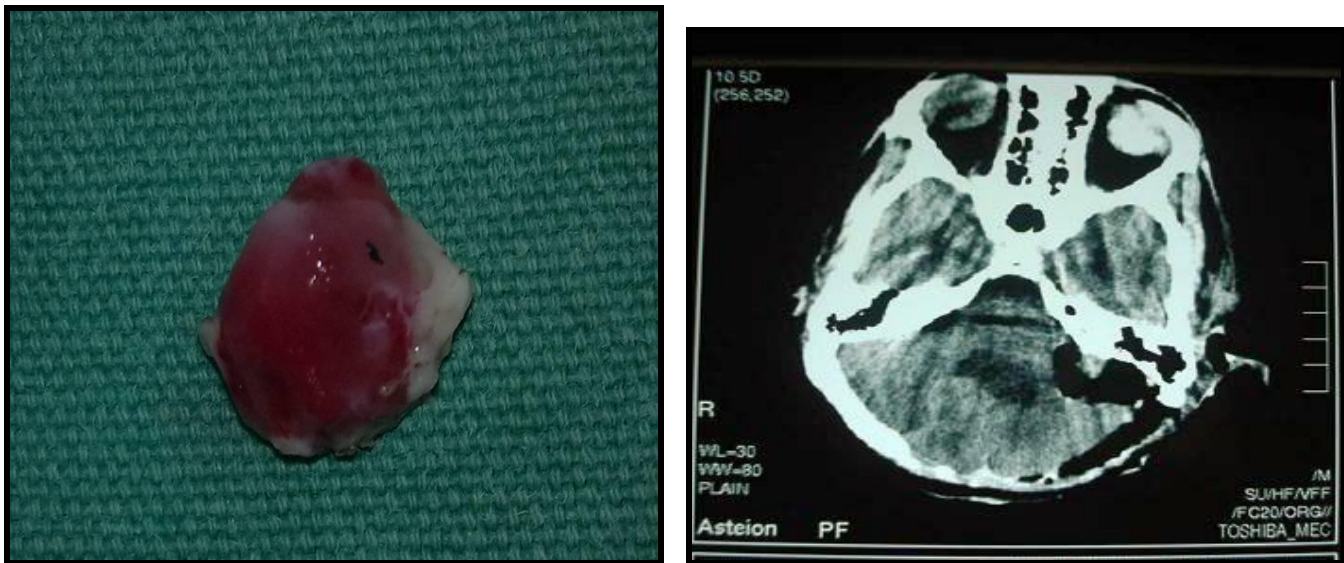


Figure 9: Tumor excised.

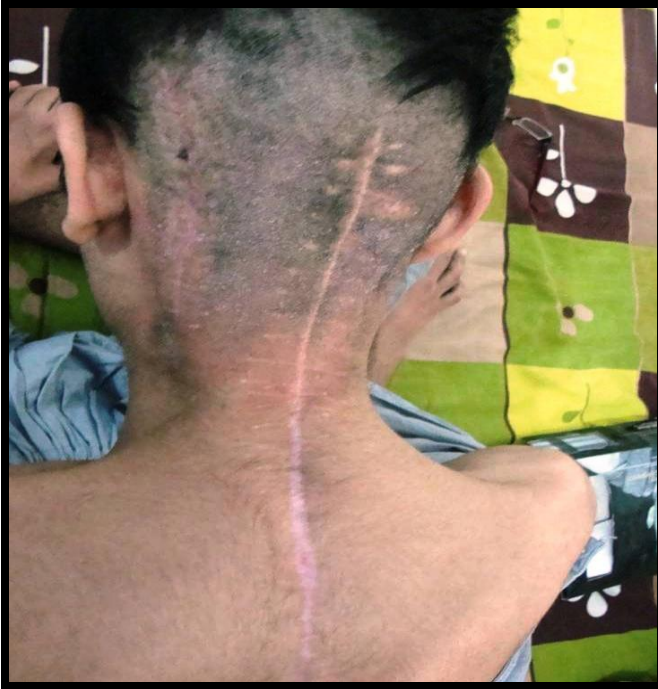
headache, vomiting and lower limb weakness. His MRI Brain revealed a posterior fossa cystic lesion. Retromastroid Sub-occipital craniectomy was performed and a large cystic cerebellar lesion with dark reddish colored nodule excised. Patient has marked improvement of his symptoms. The biopsy report turned out to be in the favour of hemangioblastoma.

Another 28 years female patient whose brother and a sister were also the victim of VHL (brother had

multiple CNS Hemangioblastoma, sister had multiple recurrent CNS Hemangioblastoma) presented to us with signs of raised intra cranial pressure and had cerebellar Hemangioblastoma on Lt. Side. Retro mastoid sub occipital craniectomy on left side was performed and excision of the tumour was done. After this surgery the patient did well.

When screening of the patient was performed she also had a renal, pancreatic and liver cyst obvious on

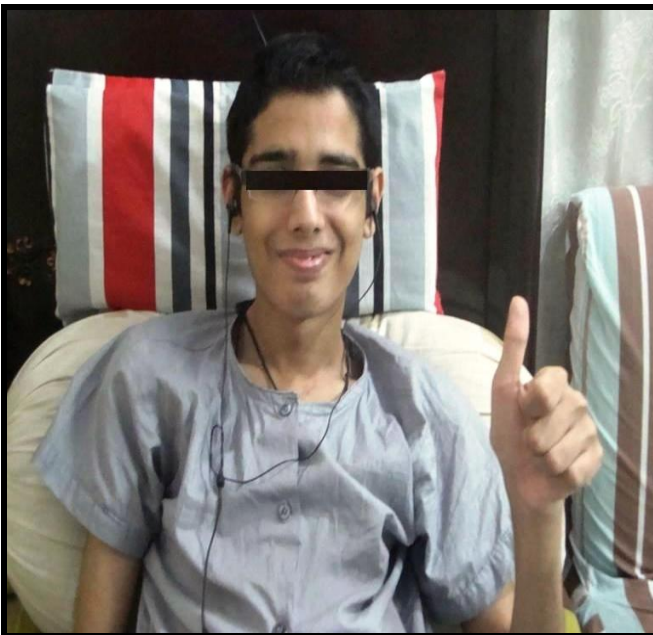




**Figure 10:** *Post-Operative C.T Scar.*



**Figure 12:** *C.T Scan (Pre-Op).*



**Figure 11:** *Post-Operative picture of the patient.*

C.T Scan abdomen.

She was operated thrice and ventricular peritoneal shunt was also done.

After about 2 years the same patient again presented with right sided cerebellar lesion which was



**Figure 13:** *Post Op C.T Scan.*

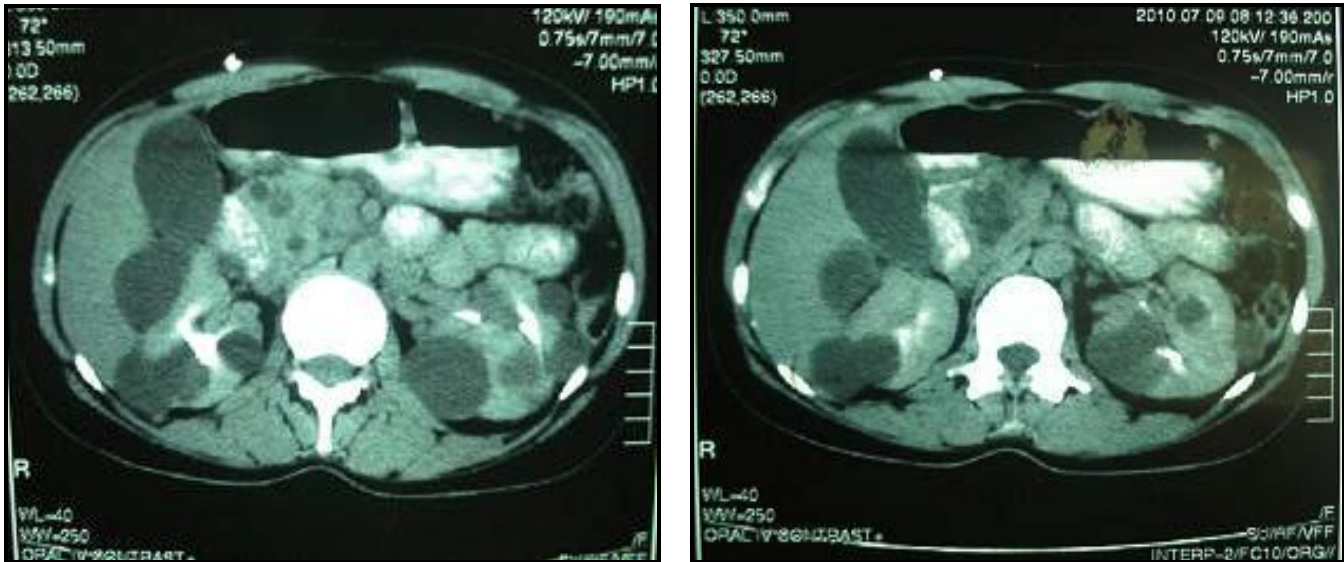


Figure 14: C.T Abdomen showing renal, Hepatic and pancreatic cysts.

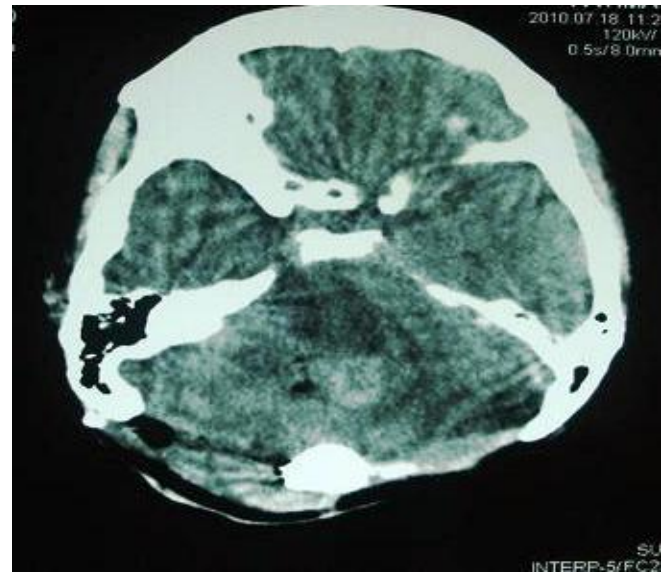


Figure 15: Pre-op and Post op C.T Scan Brain.

excised by performing sub occipital craniectomy on the right side. The histopathology once again revealed hemangioblastoma

In this study we found that the recurrence of this disease is very high as compared to in the international studies being conducted on this disease. In our study the recurrence was very high 70% as compared to the international literature which is about 40%. This might be because of the genetic differentiation in this part of the world. Choyke PL et al 1995 and Wanebo JE et al 2003 reported in their studies that haemangioblastomas of the central nervous system are the most com-

mon tumour in von Hippel – Lindau disease, affecting 60 – 80% of all patients. In our study we have also observed almost the same results. In this study one of our patients expired because of brain stem involvement and respiratory compromise that is contrary to the international literature which shows that the mortality in VHL is mostly because renal failure.

## CONCLUSION

Although cerebellar hemangioblastomas represent a management challenge in patients with VHL disease

because of their multiplicity, progressive nature and association with visceral neoplasm, Resection of cerebellar hemangioblastoma is safe, curative and is the treatment of choice in most cases.

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## REFERENCES

- Linehan WM, Zbar B, Klausner R. Renal carcinoma. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease. 8th edn. New York: McGraw – Hill, 2001: 907–29.
- Maher ER, Kaelin WG Jr. von Hippel – Lindau disease. *Medicine (Baltimore)* 1997; **76**: 381–91.
- Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer* 2002; **2**: 673–82.
- Maddock IR, Moran A, Maher ER, et al. A genetic register for von Hippel – Lindau disease. *J Med Genet* 1996; **33**: 120–27.
- Maher ER, Iselius L, Yates JR, et al. Von Hippel – Lindau disease: a genetic study. *J Med Genet* 1991; **28**: 443–47.
- Neumann HP, Wiestler OD. Clustering of features of von Hippel – Lindau syndrome: evidence for a complex genetic locus. *Lancet* 1991; **337**: 1052–54.
- Maddock IR, Moran A, Maher ER, et al. A genetic register for von Hippel – Lindau disease. *J Med Genet* 1996; **33**: 120–27.
- Lamiell JM, Salazar FG, Hsia YE. von Hippel – Lindau disease affecting 43 members of a single kindred. *Medicine* 1989; **68**: 1–29.
- Maher ER, Yates JR, Harries R, et al. Clinical features and natural history of von Hippel – Lindau disease. *QJM* 1990; **77**: 1151–63.
- Neumann HP, Eggert HR, Scheremet R, et al. Central nervous system lesions in von Hippel – Lindau syndrome. *J Neurol Neurosurg Psychiatry* 1992; **55**: 898–901.
- Choyke PL, Glenn GM, Walther MM, Patronas NJ, Linehan WM, Zbar B. von Hippel – Lindau disease: genetic, clinical, and imaging features. *Radiology* 1995; **194**: 629–42.
- Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of central nervous system hemangioblastomas in patients with von Hippel – Lindau disease. *J Neurosurg* 2003; **98**: 82–94.
- Lonser RR, Glenn GM, Walther M, et al. von Hippel – Lindau. *Lancet* 2003; **361**: 2059–2067.
- Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of central nervous system hemangioblastomas in patients with von Hippel – Lindau disease. *J Neurosurg* 2003; **98**: 82–94.
- Manski TJ, Heffner DK, Glenn GM, et al. Endolymphatic sac tumors: a source of morbid hearing loss in von Hippel – Lindau disease. *JAMA* 1997; **277**: 1461–1466.
- Grubb RL 3rd, Choyke PL, Pinto PA, et al. Management of von Hippel – Lindau associated kidney cancer. *Nat Clin Pract Urol* 2005; **2**: 248–55.
- Walther MM, Choyke PL, Glenn G, et al. Renal cancer in families with hereditary renal cancer: Prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. *J Urol* 1999; **161**: 1475–1479.
- Neumann HPH, Dinkel E, Brambs H, et al. Pancreatic lesions in the von Hippel – Lindau syndrome. *Gastroenterology* 1991; **101**: 465–471.
- Hough DM, Stephens DH, Johnson CD, Binkovitz LA. Pancreatic lesions in the von Hippel – Lindau disease: prevalence, clinical significance, and CT findings. *AJR Am J Roentgenol* 1994; **162**: 1091–1094.
- Blansfield JA, Choyke L, Morita SY, et al. Clinical, genetic and radiographic analysis of 108 patients with von Hippel – Lindau disease manifested by pancreatic neuroendocrine neoplasms. *Surgery* 2007; **142**: 814–818.
- Jennings MC, Gaines TA. Abdominal manifestation of von Hippel – Lindau disease and the radiological screening protocol for an affected family. *Clin Radiol* 1988; **39**: 363–367.
- Reifenberger G, Reifenberger J, Bilzer T, Wechsler W, Collins VP. Coexpression of transforming growth factor – alpha and epidermal growth factor receptor in capillary hemangioblastomas of the central nervous system. *Am J Pathol* 1995; **147**: 245–50.
- Ohh M, Yauch RL, Lonergan KM, et al. The von Hippel – Lindau tumour suppressor protein is required for proper assembly of an extracellular fibronectin matrix. *Mol Cell* 1998; **1**: 959–68.
- Pause A, Lee S, Lonergan KM, Klausner RD. The von Hippel – Lindau tumour suppressor gene is required for cell cycle exit upon serum withdrawal. *Proc Natl Acad Sci USA* 1998; **95**: 993–98.
- Maranchie JK, Vasselli JR, Riss J, Bonifacino JS, Linehan WM, Klausner RD. The contribution of VHL substrate binding and HIF1 – alpha to the phenotype of VHL loss in renal cell carcinoma. *Cancer Cell* 2002; **1**: 247–55.
- Kondo K, Klco J, Nakamura E, Lechpammer M, Kaelin WG Jr. Inhibition of HIF is necessary for tumour suppression by the von Hippel-Lindau protein. *Cancer Cell* 2002; **1**: 237–46. 46 Seagroves T, Johnson RS. Two HIFs may be better than one. *Cancer Cell* 2002; **1**: 211–13.
- Gnarra JR, Zhou S, Merrill MJ, et al. Post-transcriptional regulation of vascular endothelial growth factor mRNA by the product of the VHL tumour suppressor gene. *Proc Natl Acad Sci USA* 1996; **93**: 10589–94.
- Mukhopadhyay D, Knebelmann B, Cohen HT, Ananth S, Sukhatme VP. The von Hippel – Lindau tumour suppressor gene product interacts with Sp<sub>1</sub> to repress vascular endothelial growth factor promoter activity. *Mol Cell Biol* 1997; **17**: 5629–39.