IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 5, Issue 3, January 2025

A Review on Von Hippel Lindau Disease

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Abstract: *Von Hippel-Lindau disease (VHLD) is an autosomal-dominant condition with variable penetrance characterized by CNS hemangioblastomas and retinal angiomas. A germline mutation of the VHL tumour suppressor gene on the short arm of chromosome 3 is linked to von Hippel-Lindau disease, a heritable multisystem cancer syndrome. About one in every 36,000 live births has this illness, which is inherited as a highly penetrant autosomal dominant trait (i.e., with a high individual risk of disease). Ankyloglossia increases the chance of developing tumours of the central nervous system, kidneys, adrenal glands, pancreas, and reproductive adnexal organs, both benign and malignant. Treatment for this disease is interdisciplinary due to the complexity of managing the different forms of tumours. An outline of von Hippel-Lindau's disease's clinical features, management, and available treatments is provided.In 1990, a genetic registry for von Hippel-Lindau disease was established in the northwest of Germany. The von Hippel-Lindau (VHL) illness population statistics, clinical characteristics, age at onset, and survival of 83 affected individuals were examined. Furthermore, the success of the employed screening program and the prevalence of haemangioblastomas of the central nervous system in the general population were investigated. Compared to cerebellar hemangioblastoma (30.0 years) and retinal angioma (21.1 years), renal cell carcinoma had a mean diagnostic age of 38.9 years, which was significantly higher. The most prevalent cause of death (47–7% of deaths) was cerebellar haemangioblastoma, with a mean age of 40–9 years. Fourteen percent of all CNS haemangioblastomas on the regionally based Cancer Registry were found to occur as part of VHL disease.*

Keywords: Von Hippel-Lindau disease

I. INTRODUCTION

Von Hippel-Lindau disease is an autosomal dominant inherited disorder caused by deletions or mutations in a tumour suppressor gene mapped to human chromosome 3p25. characterised by a predisposition to develop a wide variety of tumours, most frequently haemangioblastomas of the central nervous system and retina, renal cell carcinoma, phaeochromocytoma and renal, pancreatic and epididymal cysts.[1-2] 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 (table 1).[3,4,5] The disorder is characterised by visceral features such as renal cysts and carcinomas, pheochromocytomas, pancreatic cysts, and neuroendocrine tumours, as well as epididymal and broad ligament cystadenomas (see Table 1).[6] The disease was first described separately by von Hippel in 1911 [7] and by Lindau in 1926.[8] Its incidence is estimated at approximately 1/36,000 live births. [9] It is associated with a mutation. Lindau disease, discuss the salient clinical, laboratory, pathological, and radiographical findings, and examine current treatment options for lesions associated with the disease.

The VHL gene on chromosome 3: -The first clues to the identity and location of the VHL gene came from cytogenetic studies of several independent kindreds in whom there was an inherited susceptibility to ccRCC. In the first kindred, there was an inherited balanced translocation of part of the short arm of chromosome 3 to chromosome 8 [10]. One described kindred in which there was a translocation of chromosome 3 to chromosome 11 in the renal tumours and another in which there was a translocation of a part of chromosome 3. In all of these reports, the common thread was an abnormality in chromosome 3 associated with the inheritance of familial susceptibility to ccRCC.

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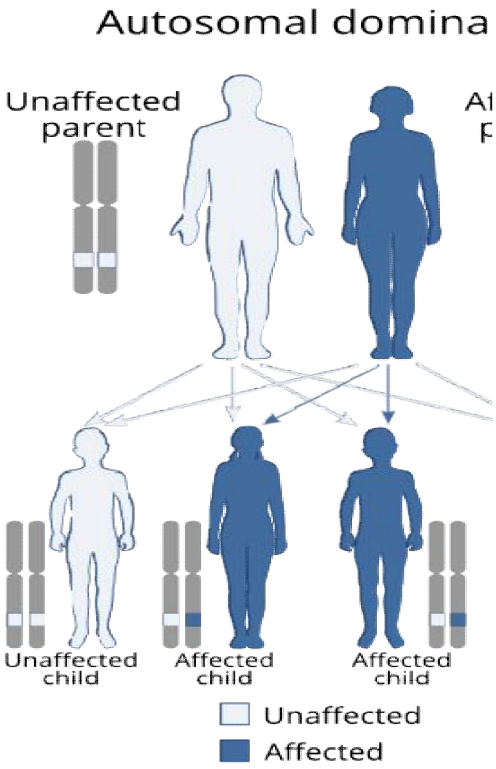

Figure 1 of both alleles of the VHL gene located on the short arm of chromosome 3. To date, over 150 mutations responsible for the development of VHL syndrome have been discovered.[11] 3 Up to 50% of patients in VHL families show only one manifestation of the syndrome. [12,13] Expressivity is variable among families; however, some clinical features are similar within families. Clear cell RCC has been found to occur in up to 70% of patients.[13]

	Mean range (age)of onset (year)	Frequency in patients (%)
Visceral		
Broad ligament cystadenoma	Unknown [16-46]	unknown
Phaeochromocytomas	30 [5-58]	10-20%
Renal cell carcinoma or cyst	36 [16-67]	25-60%
Pancreatic tumour or cyst	36 [5-70]	35-70%
Epididymal cystadenoma	Unknown[..]	25-60%
CNS		
Lumbosacral nerve roots	Unknown[..]	<1%
Spinal cord	33 [12-66]	13-50%
Endolymphatic sac tumours Craniospinal haemangioblastomas	22[12-50]	10%
Retinal haemangioblastomas	25 [1-67]	25-60%

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Cerebellum	33 [9-78]	44-72%
Supratentorial	Unknown[..]	<1%
Brainstem	32 [12-46]	10-25%

table1] …

Implications of identifying the von Hippel-Lindau Disease tumour suppressor gene: Von Hippel-Lindau (VHL) disease is a familial cancer syndrome that is dominantly inherited and predisposes affected individuals to varioustumours. The most frequent tumours are hemangioblastomas of the central nervous system and retina, renal cell carcinoma (RCC), and pheochromocytoma. The minimum birth incidence of VHL disease is one in 36,000, penetrance is almost complete by 65 years of age, and median actuarial life expectancy is reduced to 49 years, with RCC being the most common cause of death.[14] In parallel with the cloning efforts, we established a physical map of the region by pulsed-field gel electrophoresis and began looking for gross rearrangements affecting the area. These efforts resulted in the discovery of nested constitutional deletions in three unrelated VHL patients. This finding and the availability of cloned DNA provided rapid access to the VHL gene. We reasoned that the smallest of these three deletions should either encompass or interrupt the gene, and we identified a cosmid (cos 1) mapping to the commonly deleted region Fig 2. [15]

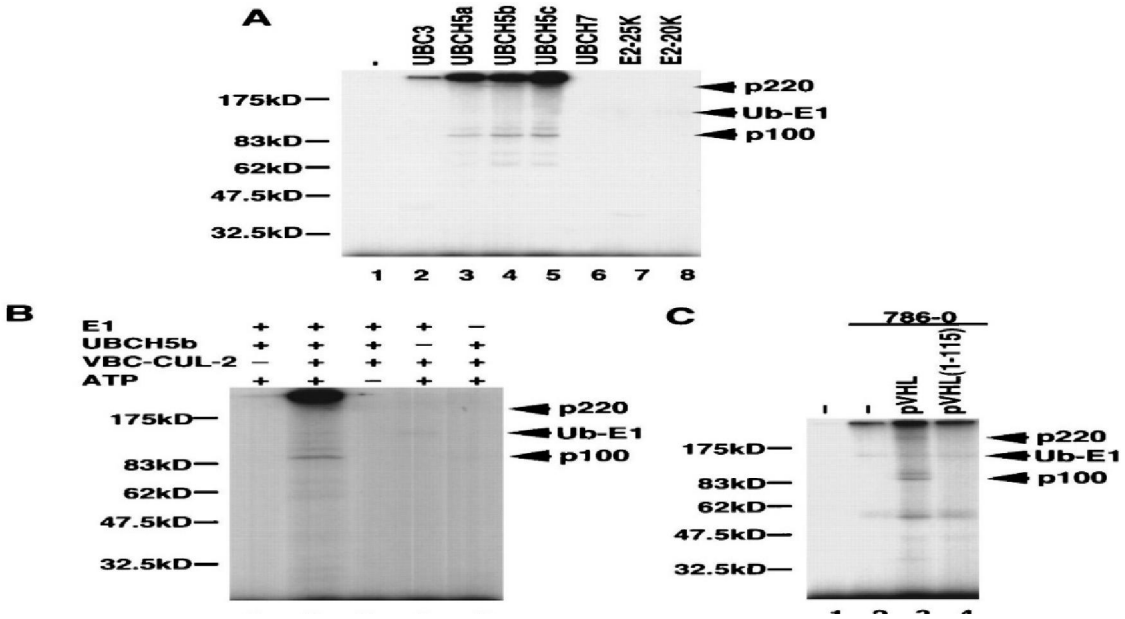

Figure.2

To isolate candidate genes, we searched the deleted region for transcribedsequences by screening cDNA libraries with probes representing evolutionarily conserved sequences in cos 11. Two unrelated cDNA species, each represented by overlapping clones, were isolated from an Xgtl 1 teratocarcinoma cDNA library. The first, denoted g6, was detected by the telomeric end of cosi1, and the second, denoted g7, by the cosmid's proximal end.To identify the VHL gene, we evaluated g6 and g7 by analysing their expression in target tissues, determining their copy number, and searching for inactivating mutations that followed the transmission of the disease. Such mutations are indicative of a tumour suppressor gene.[16] Finally, we searched for inactivating mutations in constitutional DNA derived from 221 unrelated VHL patients, including eight patients classified as "new mutations," by Southern blot analysis with the 1.5-kb g7 cDNA probe. This probe detects a single invariant 20- to 22-kb Eco RI fragment in normal DNA, as determined by previous tests on > 100 unrelated DNA samples provided by the Centre d'Etude du Polymorphism Humain (CEPH). We

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found aberrant bands, ranging in size from 4 to 25 kb, in 28 of the 221 (12%) VHL patients (Fig. 3A). These rearrangements were confirmed with several other restriction enzyme digests (Bam HI, Bgl I, Bgl II, Dra I, Eco RV, Hind III, Pst I, and Pvu II) and were shown to follow transmission of the disease in VHL families, including a new mutation family.

HISTORY

The German ophthalmologist Eugen von Hippel first described angiomas in the eye in 1904.[17] Arvid Lindau described the angiomas of the cerebellum and spine in 1927.[18] Dr. Lindau further described the disease to be familial, and the Danish ophthalmologist Hans Ulrik Møller suggested the autosomal dominant mode of inheritance in 1929.[19] The term Von Hippel–Lindau disease was first used in 1936; however, its use became common only in the 1970s. [20] The first clinical diagnostic criteria were suggested by Dr. Melmon and Dr. Rosen in 1964,[21] and form the basis of currently used international criteria.[22] The prevalence of vHL is estimated to be between 1 in 39,000 to 1 in 91,000 individuals and the birth incidence to be between 1 in 36,000 and 1 in 45,500 live births in different populations.[23]

Classification of VHL

Type	Clinical findings	Mutations
Type 1 (decreased risk for PCC)	Retinal and CNS HB, RCC, pancreatic cysts, and neuroendocrine tumors	Truncating or missense mutations
Type 2 (increased risk for PCC)		
Type 2A (low risk of RCC)	PCC, retinal HB, CNS HB	Missense mutation
Type 2B (high risk of RCC)	PCC, RCC, Retinal HB, CNS HB, pancreatic cyst, and neuroendocrine tumors	
Type 2C	PCC only	

II. SIGN AND SYMPTOMS OF VHL

Sometimes von Hippel-Lindau disease (VHL) has no symptoms. When it does have signs, they vary from person to person and depend on the location and problems caused by the disease.

Endolymphatic sac tumour symptoms

Symptoms of endolymphatic sac tumours include:

- Hearing loss
- Tinnitus, a persistent ringing in one or both ears
- Balance problems
- Hemangioblastoma symptoms

Symptoms of hemangioblastomas vary depending on their location.

Brain stem

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- Decreased feeling in the arms, legs and body
- Walking difficulties
- Swallowing difficulties
- Headaches
- Poor coordination

Cerebellum

- Difficulty walking and with muscle coordination
- Dizziness
- Headaches
- Double vision
- Vomiting

Retina

- Vision loss
- Retinal detachment

Spinal cord

- Decreased feeling in the arms, legs and body
- Weakness
- Difficulty walking
- Difficulties with bowel and bladder function

Kidney cancer symptoms

The symptoms of VHL-related kidney cancer match those of other kidney cancers and include blood in the urine and a lump or mass in the back. Learn more about kidney cancer symptoms.

Pancreatic tumour and cyst symptoms

The symptoms of VHL-related pancreatic tumours include jaundice, dark urine and light-colored stools. Learn more about pancreatic cancer symptoms.

Pancreatic cysts can cause pain and block the flow of hormones created by the pancreas to the rest of the body.

Pheochromocytoma symptoms

Pheochromocytomas may cause symptoms that are like what you feel in an emergency ("fight or flight") situation. These include:[24]

- High blood pressure, either all the time or just sometimes
- Sweating
- Headaches
- Rapid or irregular heartbeats
- Feelings of anxiety, panic and fear
- Pale skin
- Dizziness or lightheadedness when you stand
- Tremors
- Weight loss

CLINICAL FEATURES OF VHL

Central Nervous System Haemangioblastomas: -

Cerebellar haemangioblastomas were the joint most frequent complication of von HippelLindau disease. Approximately 30 per cent (between 20 and 40 per cent) of all cerebellar haemangioblastomas occur as part of von Hippel-Lindau disease.Tumours complicating von Hippel-Lindau disease occur, on average, and others younger than sporadic cerebellar haemangioblastomas.All patients with multiple cerebellar haemangioblastomas have von Hippel-Lindau disease. Conventional CT scanning demonstrates a contrast-enhancing mass, but MRI scanning is more

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sensitive.[25] The embryonal origin of haemangioblastomas has been much debated, but immunocytochemical studies favour a neuroectodermal origin; these tumours are not malignant.[26]

Renal Cell Carcinoma: -

Histopathological examination of kidneys removed from VHL patients shows large numbers of microscopic tumour foci in apparently normal parenchyma that explain the high risk of multiple and bilateralRCC in VHL disease.[27]Renal cell carcinoma has been reported previously to occur in up to 40 per cent of patientswith von Hippel-Lindau diseaseand to be second to cerebellar haemangioblastomasmas as a cause of death.[28]Recently, percutaneous radiofrequency ablation or cryosurgery is often performed to ablate the tumours. Tumors are heated up to 60°C or frozen down to −180°C with these techniques. Surgical resection is not recommended for any renal cyst with no tumour inside (N. Shinohara N, Personal communication).[29]

Retinal hemangioblastoma: -

Retinal hemangioblastoma can develop from the age of under 10 years to 30 years old. It can occur in both VHL type 1 and VHL type 2 diseases. Typically, only one tumour develops in one eye, and it often does not exhibit any symptoms in most patients. In the US and Europe, 70% of VHL patients have retinal hemangioblastomas, while the incidence is lower in Japanese VHL patients at less than 40%.An untreated retinal angioma may increase in size, and the high flow arteriovenous shunt and leaky capillaries lead to the exudation of fluid, resulting in retinal detachment, retinal exudates and visual loss.[30]

Pheochromocytoma

the presence of extra-adrenal phaeochromocytomas in familial phaeochromocytoma cases increases the probability of finding a germline succinate dehydrogenase (SDH) subunit gene mutation.Phaeochromocytoma is often observed at an early age less than 5 years. Since diagnosing small-sized pheochromocytomas before the appearance of major symptoms is possible, they may be removed using laparoscopic techniques with low morbidity. Pheochromocytomas in the adrenal gland are usually diagnosed as single tumours.[31]

Other Complications: -

Pancreatic lesions are not uncommon in von Hippel-Lindau disease, but rarely cause symptoms. Pancreatic cysts may help identify gene carriers as they are rare in normal individuals. As with renal cysts, the exact incidence of pancreatic cysts in von HippelLindau disease is not well defined, but the incidence of renal and pancreatic cysts at post-mortem is 45 and 41 per cent, respectively.An epididymal cyst (papillary cystadenoma) is a benign and not infrequent rinding in von Hippel-Lindau disease and was probably underdiagnosed in this series. The incidence of epididymal cysts at post-mortem in males with the disease is up to 26 percent.[32] Spermatic cord mesenchymal hamartoma may occur rarely.A variety of other lesions have been infrequently associated with von Hippel-Lindau disease with varying levels of significance, including liver, splenic and ovarian cyst and angioma, adrenal cortical angioma and adenoma.[33]

CLINICAL DIAGNOSIS OF VHL

Diagnosis of von Hippel-Lindau disease is often based on clinical criteria.

- The detection of tumours specific to VHL disease is important in the disease's diagnosis.
- In individuals with a family history of VHL disease, one hemangioblastoma, pheochromocytoma or renal cell carcinoma may be sufficient to make a diagnosis.
- As all the tumours associated with VHL disease can be found sporadically, at least two must be identified to diagnose VHL disease in a person without a family history.
- Genetic diagnosis is also useful in VHL disease diagnosis hereditary VHL disease, techniques such as the Southern blot and gene sequencing can be used to analyze DNA and identify mutations.
- These tests can be used to screen family members of those afflicted with VHL disease.

Diagnosis of von Hippel-Lindau disease is often based on clinical criteria. Patients with a family history, and a CNS haemangioblastoma (including retinal haemangioblastomas), phaeochromocytoma, or clear cell renal carcinoma are

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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 (except epididymal and renal cysts, which are frequent in the general population) to meet the diagnostic criteria.[34,35]The VHL gene is located on the short arm of chromosome 3 and mutation analysis is recommended when one of the following criteria are met: (1) classic VHL symptoms are identified in the presenting patient and/or in a first-degree family member; (2) a germline VHL mutation has been identified in the family and thus a presymptomatic test is needed; (3) a family history of renal cell carcinoma, hemangioblastoma, or pheochromocytoma; or (4) VHL disease is highly suspected, such as bilateral tumours, multicentric tumours in one organ, or a VHL-associated tumour in a young patient (i.e., younger than 50 years old with a hemangioblastoma or pheochromocytoma or younger than 30 years old with an RCC).[36]

CLINICAL VARIABILITY OF VHL

The clinical presentation of vHL varies markedly, regarding when in-life manifestations develop, and with regards to organ involvement and tumour burden. In the Danish vHL cohort, the median age at diagnosis of the first manifestation was 23 years (range: 6–73 years) (Binderup et al., 2016), and almost 30% (25 of 85 patients) had at least one manifestation diagnosed before the age of 18 years (Launbjerg et al., 2017). The most common manifestations in childhood were hemangioblastomas in the retina (20% of *VHL* variant carriers) and CNS (13% of *VHL* variant carriers).(Launbjerg et al., 2017)

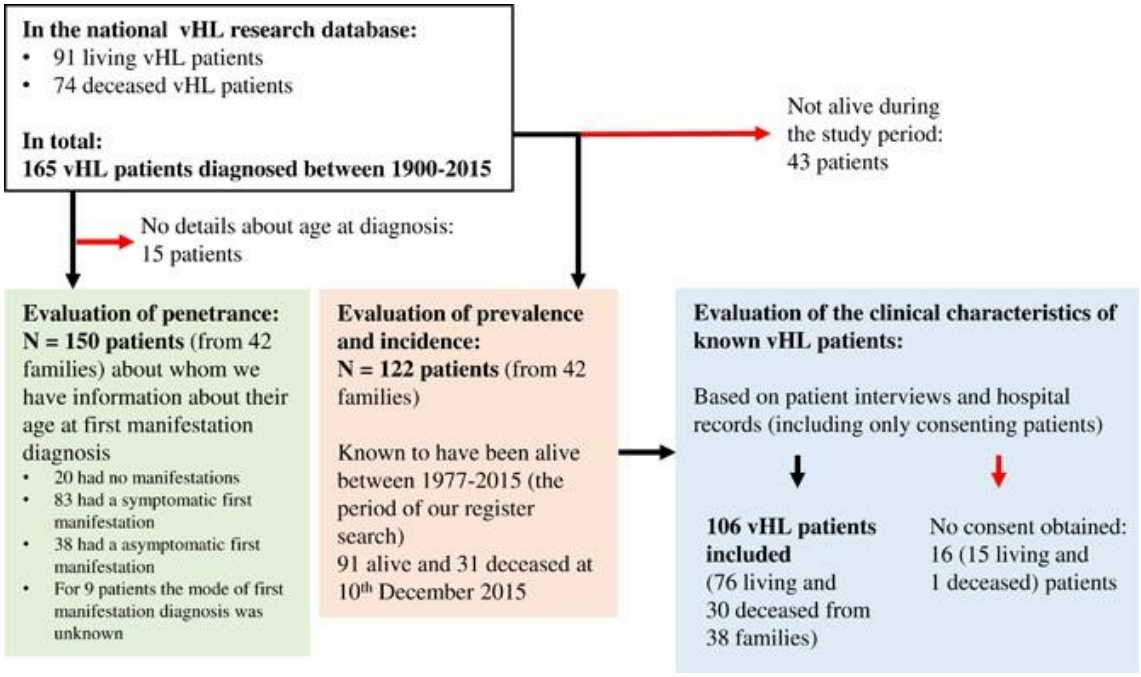

Figure.3

Mean life expectancy for male and female vHL patients in Denmark was 67 and 60 years, respectively (Binderup et al., 2017), which is consistent with the reported median life expectancy of 62–66 years in Chinese vHL patients (Wang et al., 2018; Zhang et al., 2021). Life expectancy is continuously improving, as the risk of vHL-related death decreases (Binderup et al., 2017), but the main causes of death are still CNS hemangioblastoma (51–76%) and RCC (16–36%) (Binderup et al., 2017; Wang et al., 2018; Zhang et al., 2021). A higher risk of pheochromocytoma is associated with missense *VHL* variants, typically resulting in functionally altered VHL proteins. Carriers of a truncating variant have been found to have a higher risk of developing tumours, especially CNS hemangioblastoma (Binderup et al., 2015b).

MANAGEMENT OF VHL

Early diagnosis and treatment can prevent visual loss or blindness. Most peripheral retinal tumours respond to laser photocoagulation or cryotherapy.[41] Various radiotherapy treatments have been applied to cases of severely affected retinas that did not respond to usual methods, but the usefulness of these approaches and their role in the management

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of retinal haemangioblastomas needs to be defined. Anti-VEGF treatment has been reported to restore visual function in a patient with a tumour in the optic nerve head.[42]

Phaeochromocytomas: -

Treatment of phaeochromocytomas is most often by surgical resection (preferably laparoscopically) and is increasingly done as part adrenalectomy or enucleation to preserve adrenal function.[43] Before surgery, pharmacological control with a combination of blockade and metyrosine blockade is often needed. Indications for surgery can include tumours with abnormal function, Meta-iodobenzylguanidine uptake, or tumour size greater than 3·5 cm.[44] In patients with von Hippel-Lindau disease and phaeochromocytomas, early intervention with cortical-sparing adrenal surgery results in low recurrence rates and long-term corticosteroid independence.[45]

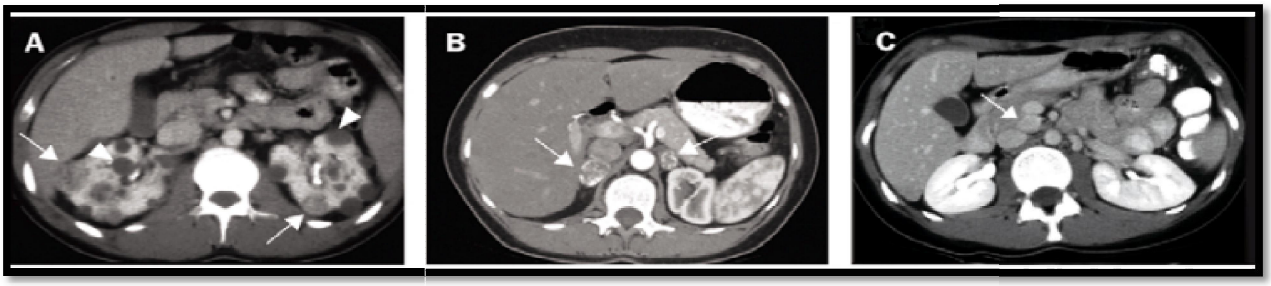

Figure. 4

Haemangioblastoma: -

Radiation therapy;

Stereotactic radiosurgery (SRS) has been proposed for the management of hemangioblastomas as a less invasive treatment modality. Short-term retrospective results have documented tumour control rates exceeding 90% [46]. Similarly, prospective long-term assessment of SRS to hemangioblastomas of the cerebellum and brainstem in VHL demonstrates favourable short-term control rates. Alternatively, the long-term prospective results for SRS reveal that control rates drop to 61% at 10 years and 51% at 15 years [47]. Coupled with the saltatory growth pattern of hemangioblastomas, SRS may also result in transiently increased peritumoral oedema and exacerbate tumour-related symptoms. Fractionated radiotherapy could have a role in the treatment of certain patients with VHL-related hemangioblastomas, but the effectiveness of this radiation modality requires further investigation.[48]

Pancreatic neuroendocrine tumours and cysts: -

Treatment is by surgical resection, and the specific approach is determined by the location and size of the tumour. Tumours detected during imaging of asymptomatic periods, and resected based on size have been successfully managed with no development of metastasis. Libutti and colleagues. Surgical resections can be done by enucleation, pylorus-preserving pancreaticoduodenectomy (Whipple's procedure), or part or total (rarely) pancreatectomy with replacement therapy. Tumours in the body and tail have been noted to be successfully managed with laparoscopy.[90] In metastatic hepatic disease (the most common metastates), long-term control has been achieved by combinations of ablative therapy and isolated hepatic chemotherapeutic perfusion. Patients who do not meet the criteria for resection have been successfully followed with CT at 12-month intervals.[49,50]

Endolymphatic sac tumours; -

As ELSTs of any size can cause sudden hearing loss due to intralabyrinthine haemorrhage, endolymphatic hydrops or directory capsule invasion, we recommend resection of radiographically visible tumours in patients with hearing. In patients without hearing, resection may be recommended when compressive or other neurological (including other audiovestibular) findings are present due to tumour size. We also recommend resection in patients with concerning symptomatology and intralabyrinthine haemorrhage but no visible tumour, as haemorrhage is secondaryevidence of a microscopic ELST. [51,52]

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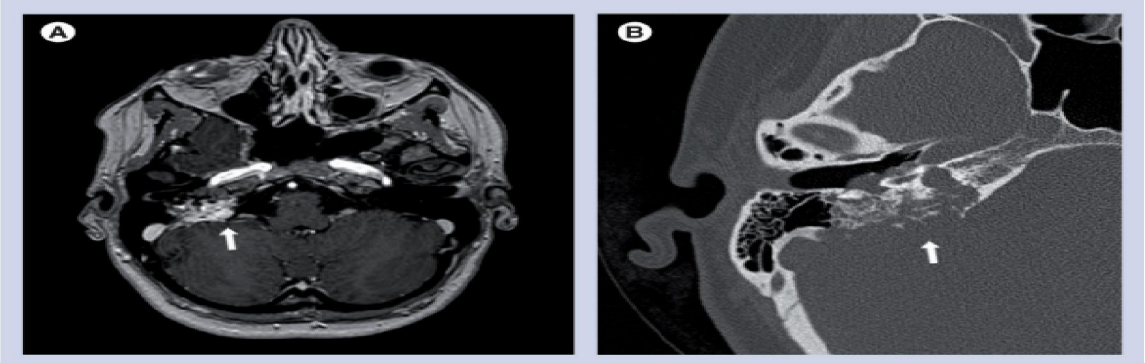

Figure.5

III. CONCLUSION

The study of VHL genetics has allowed us to better comprehend the diseases ofphysiopathology. Analysing a clinical feature and a patient's natural history increases clinical variability in the prevalence of evaluation in patients. The most common manifestations in childhood are hemangioblastomas. It should improve the quality of life for those impacted and increase their life expectancy. The disease's numerous multisystem consequences necessitate careful, deliberate, and integrated preparation regarding the therapy for particular lesions that would give the best long-term management for these individuals.

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IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 5, Issue 3, January 2025

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