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VON HIPPEL-LINDAU DISEASE, DESCRIPTION, GENETICS, MOLECULAR BASIS, CLASSIFICATION AND MANIFESTATIONS OF THE DISEASE

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SUMMARY

Introduction: *Von Hippel-Lindau disease (VHL) is autosomal dominant tumor syndrome that debuts mostly in young adults , patients with this disease are linked to the triggering of various types of benign and malignant neoplasms in multiple locations, systems and organs, in particular affecting more the nervous system and other internal organs. Approximately this tumor syndrome shows an incidence rate of 1 in 36,000 live births with a penetrance greater than 90%. The molecular basis of VHL disease is the impairment of VHL protein function and the consequent clustering of hypoxia-inducible factors with subsequent consequences on cell differentiation and metabolism.*
Objective: to present current information related to Von Hippel-Lindau disease, description, genetics, molecular basis, classification and manifestations of the disease.
Methodology: *a total of 33 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 26 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: Von Hippel-Lindau, VHL, tumor suppressor gene, pheochromocytoma, hemangioblastomas.*
Results: *VHL has an incidence of approximately 1 in 36,000 live births, with a penetrance of over 90%. These present tumors are initiated by inactivation of biallelic VHL and are related to pathologic activation of hypoxic gene response pathways.*
Conclusions: *Von Hippel-Lindau disease is an autosomal dominant disorder that is generated by mutations in the VHL tumor suppressor gene. Within the field intrafamilial variation may evidence correctly shaped genotype-phenotype connections for renal cancer and pheochromocytoma risks. Visceral cysts (renal, pancreatic and epididymal) are frequent, however organ function involvement is rare. They usually occur with hemangioblastomas of the central nervous system and retina, as well as renal cancers. Unusually it includes non-functioning pancreatic endocrine cancers, adrenal and extra-adrenal pheochromocytomas, endolymphatic sac tumors, as well as head and neck paragangliomas.*

KEYWORDS: *Von Hippel-Lindau, VHL, gene, suppressor, tumor, pheochromocytoma, hemangioblastomas.*

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INTRODUCTION

The understanding of the molecular mechanisms of tumor growth is becoming increasingly influential in the development of diagnosis and treatment of human neoplasms. One of the diseases in which this plays a fundamental role is Von Hippel-Lindau disease (VHL) which is an autosomal dominant tumor syndrome that usually occurs in young adults. This syndrome increases the likelihood in those who present it of triggering both malignant and benign tumors in various organs and systems; especially in the nervous system and internal organs. VHL has an incidence of approximately 1 in 36,000 live births, with a penetrance of over 90%. This disease is so named thanks to the collaboration of the German ophthalmologist Eugen von Hippel, who described and identified the retinal characteristics and Arvid Lindau, a Swedish pathologist, who discovered the association between cerebellar and retinal hemangioblastoma with cysts and tumors in visceral organs. Treatment and operative recommendations have been improved over time, in recent years pharmacological therapies have evolved strongly, however many therapies are still in an experimental stage.

The classification system for this disease is clinically based and is divided into two main groups:
Type 1: those predominantly without pheochromocytoma.
Type 2: those with predominantly pheochromocytoma.
The molecular basis of von Hippel-Lindau disease is the suppression of VHL protein activity and subsequent storage of hypoxia-inducible factor with subsequent effects on cell differentiation and metabolism. Tumorigenesis in those affected with VHL disease exhibits elementary principles in the afflicted systems and organs. Inactivation of the VHL germline leads to the insistence of microscopic structures arrested in development. These microscopic cell assemblies already show inactivation of biallelic VHL and subsequent positive regulation of hypoxia inducible factor (HIF) and downstream endings such as VEGF, EPO(1,2).

METHODOLOGY

A total of 32 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 26 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: Von Hippel-Lindau, VHL, tumor suppressor gene, pheochromocytoma, hemangioblastomas.

The choice of bibliography exposes elements related to Von Hippel-Lindau disease, description, genetics, molecular basis, classification and manifestations of the disease.

DEVELOPMENT

Von Hippel-Lindau (VHL) disease is an autosomal dominant disease that can produce multiple neoplasms in affected individuals. Germline pathogenic variants in the VHL gene associate those affected with specific varieties of benign tumors, malignant tumors and cysts in different organs and systems such as:

- Central nervous system hemangioblastomas.
- Hemangioblastomas of the retina.
- Clear cell renal cell carcinomas and renal cysts.
- Pheochromocytomas.
- Tumors of the endolymphatic sac.
- Cysts, cystadenomas and neuroendocrine tumors of the pancreas.
- Cystadenomas of the epididymis.
- Cystadenomas of the broad ligament.

The VHL gene is a tumor suppressor gene located on the short arm of chromosome 3 on cytoband 3p25-26. Pathogenic variants of VHL occur in all 3 exons of the gene. Most patients inherit a germline pathogenic variant of VHL from an affected parent and a normal (wild-type) copy of VHL from the unaffected parent. Von Hippel-Lindau disease-related neoplasms fit into Knudson's "two-hit" hypothesis, which states that the clonal origin, or the first cell to become neoplastic, occurs only after the 2 VHL alleles are inactivated in a cell. The germline pathogenic variation that occurs in VHL is the first "hit", which shows up in the totality of body cells. The second "hit" is the somatic mutation, which occurs in a particular tissue at a given time after the birth of a prospective patient. This alters the normal, or wild-type, VHL allele, forming a cell of clonal neoplastic origin, possibly developing a tumor mass (3-9).
Von Hippel-Lindau disease has the following clinical classification:
VHL Type 1: those predominantly without pheochromocytoma.
VHL Type 2: those with predominantly pheochromocytoma.
2A (with renal cancer).
2B (without renal cancer). They develop only pheochromocytomas(1,2,10).
Renal cell carcinomas form in about 70% of humans with VHL disease during their lifetime. In the surgical setting, the risk-benefit for the well-being of the affected person must be assessed clinically, although surgical treatment is generally recommended. Partial nephrectomy reduces the risk of metastatic disease in patients with renal tumor masses that increase in size to more than the 3 cm diameter limit and in rapidly proliferating renal tumors. A nephron-sparing approach is used in the resection of renal masses when feasible, but does not initiate the surgical procedure in renal cell carcinoma tumors smaller than 3 cm in diameter because they present a minimal risk of body metastases. Patients with this type of disease are usually surgically intervened several times during their lifetime, these are performed resection of tumor masses in the kidneys and excision of other neoplasms related to this autosomal dominant disease. Systemic therapy would potentially help individuals with renal cell carcinomas associated with VHL disease by preventing tumor enlargement to greater than 3 cm in diameter, thereby decreasing the requirement for surgery and the danger of renal failure and subsequent metastases. Systemic therapy would possibly give similar improvements for

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individuals with other neoplasms associated with VHL disease(9,11-13).

Von Hippel-Lindau disease targets a special subgroup of organs by the usual progression of specific tumor varieties with abundant vascularization. Multiple and bilateral tumor masses occur frequently: retinal hemangiomas with 60% mean age of onset 25 years, cerebellar and spinal hemangiomas 65% mean age of onset 33 years, endolymphatic sac tumors 10% age of onset 22 years, renal clear cell carcinomas and cysts 45% age of onset 39 years, pheochromocytomas 20% age of onset 30 years, pancreatic cysts, microcystic serous adenomas, neuroendocrine tumors with 35-70% onset at 36 years of age and cystadenomas of the epididymis and broad ligament in more than 50% of men (1,14,15).

Each offspring of an individual with VHL has a 50% chance of inheriting the pathogenic VHL variant allele from his affected father. The age of onset of von Hippel-Lindau disease (VHL) varies both among different families and among members of the same family. This fact informs the guidelines for age of onset and frequency of presymptomatic surveillance testing. Of all the manifestations of VHL, retinal hemangioblastomas and pheochromocytomas (PHEO) have the earliest age of onset; therefore, targeted screening is recommended in children younger than 10 years. At least one study has shown that the incidence of new lesions varies according to the age of the patient, the underlying pathogenic variant and the organ involved(5,12).

This multisystem disorder requires the synchrony of a multidisciplinary medical team, as treatment can be challenging, being paramount to prevent morbidity and mortality. Correct diagnosis in a timely manner improves prognosis and reduces complications(13).

Table 1. Example of a routine surveillance protocol for von Hippel–Lindau disease (modified from Maher).

1. Screen for retinal angioma: Annual ophthalmic examinations, beginning in infancy or early childhood.
2. Screen for CNS hemangioblastoma: MRI scans of the head for every 12–36 months, beginning in adolescence.
3. Screen for renal cell carcinoma and pancreatic tumors: MRI (or ultrasound) examinations of the abdomen every 12 months, beginning from the age of 16 years.
4. Screen for pheochromocytoma: Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites.
   More intense surveillance (eg, annual measurement of plasma normetanephrine levels, adrenal imaging, beginning from the age of 8 years should be considered in families at high-risk for pheochromocytoma).

Source: Maher ER, Neumann HP, Richard S. von Hippel–Lindau disease (13,16).

Retinal Hemangiomas

Retinal hemangioblastomas are benign tumors that can occur randomly, as well as in patients with VHL. The neoplasms present around 50% bilaterality and multiplicity. The histologic presentation is similar in both retinal hemangioblastomas and CNS hemangioblastomas. The high expression of vascular endothelial growth factor (VEGF) in these masses causes an increase in the number of local blood vessels, accompanied by vascular leakage and exudation, and subsequently retinal detachment. Almost all peripheral retinal hemangioblastomas can be controlled with cryotherapy or laser photocoagulation. For larger neoplasms, vitrectomy is indicated. As for non-surgical treatment, the beta-blocker or non-selective beta-blocker drug known as propranolol has been used for retinal hemangioblastomas. Usually the prognosis of patients with VHL is optimal when they present timely detection and treatment(1,2,17-19).

Central nervous system (CNS) hemangioblastomas.

Hemangiomas are usually the first to appear in people with VHL compared to other conditions being index tumors of the disease. Multiple hemangioblastomas in people with VHL occur periodically. Contrast MRI of the spine and head is used to diagnose them. CNS hemangiomas occur in different locations and with the following frequency:

Cerebellum in 45 %.
Spinal cord in 36%.
Cauda equina in 11 %.
Encephalic trunk in 7 %.

The burden of CNS hemangioblastoma in VHL disease is related to incomplete germline deletions and males. In posterior fossa tumors the main symptoms are dysmetria, ataxia, slurred speech and nystagmus; they also have the possibility of developing increased intracranial pressure or brainstem herniation due to cerebrospinal fluid obstruction. The neurological symptoms of spinal hemangioblastomas are usually focal neurological losses, paresthesias and weakness. Surgical treatment should be performed if possible in all symptomatic tumors and in all tumors that generate cerebrospinal fluid obstruction, however, it is not necessary to perform excision of all the tumors properly speaking of the asymptomatic ones. When surgical treatment is not feasible, radiotherapy can be used as an alternative(2,5,20-22).

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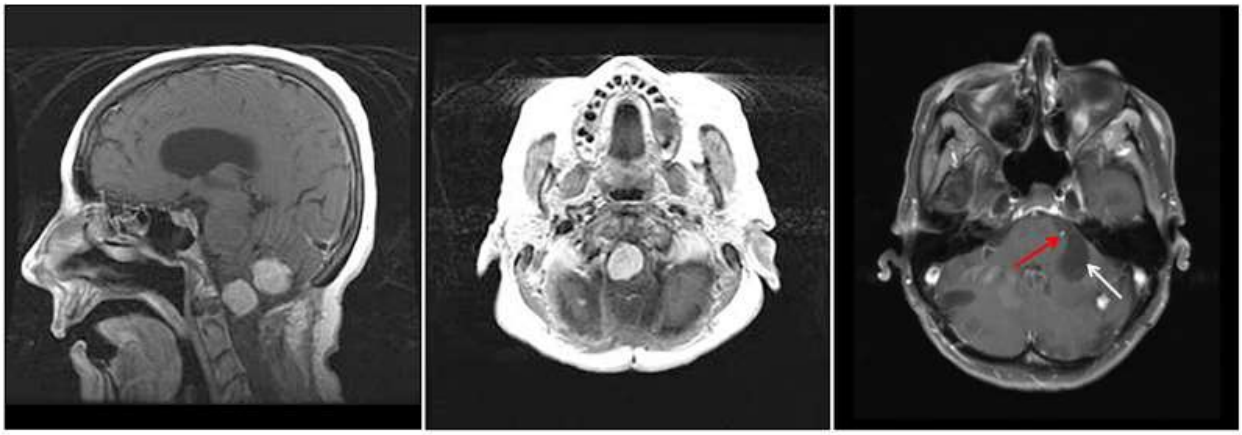
Figure 1. Hemangioblastomas in patients with VHL. Left view of brainstem and cerebellar lesions. Middle view of a brainstem lesion. Right shows a cerebellar lesion (red arrow) with a dominant cystic component (white arrow).



Source: PDQ Cancer Genetics Editorial Board. Von Hippel-Lindau Disease (PDQ®): Health Professional Version(5).

Tumors of the endolymphatic sac

Almost all of them behave in a benign way, these tumors appear in the vestibular aqueduct and can be directed towards the extraosseous part of the lymphatic sac, inner ear and the petrous bone. The fact that they are benign does not mean that they should go unnoticed, because these lesions can increase their size locally in the temporal bone presenting an invasive behavior. Patients may present the following symptoms:

Hearing loss or hearing loss in 100 %.

Tinnitus 77 %.

Imbalance 62 %.

Facial paresis 8%.

In almost 50 % of those affected, the symptoms, especially hearing loss, appear suddenly, perhaps caused by acute intralabyrinthine hemorrhage. Removal by posterior retrolabyrinthine petrosectomy can be resolute and can prevent the onset, deterioration and impairment of hearing and improve vestibular symptoms(1,5).

Renal clear cell carcinomas and cysts.

About 55% of people with von Hippel-Lindau disease hardly have multiple renal cell cysts. Renal cell carcinomas show as combined cystic and solid masses, those related to VHL are mainly multifocal and bilateral. Masses larger than 3 cm increase in grade as they grow and are associated with metastasis(5,7,23).

Pheochromocytomas (PHEO).

The average age for the diagnosis of pheochromocytoma and progressive multifocal leukoencephalopathy is around 30 years. Approximately 25-30% of all patients with VHL develop pheochromocytoma and of these 44% have disease in both adrenal glands (5).

Pancreatic cysts, serous microcystic adenomas and neuroendocrine tumors.

Patients with Von Hippel Lindau often develop single pancreatic cysts, multiple serous cystadenomas and pancreatic neuroendocrine tumors. In those with VHL who present with pancreatic cysts, there is almost never symptomatic bile duct obstruction. Multiple serous cystadenomas have benign features and usually do not require any intervention. Pancreatic neuroendocrine tumors in most cases are not functional, however, they metastasize, especially to the liver and lymph nodes; these tumors should be kept under surveillance through imaging tests and if they are larger than 3 cm they require intervention(5,7).

Cystadenomas of the epididymis and broad ligament.

Cysts in the epididymis are frequent in adult males, they usually present abundant spermatoceles or fluid. In Von Hippel Lindau disease the epididymis may develop more differentiated cystic neoplastic cystic masses which are called papillary cystadenomas. Painless scrotal swelling and slow enlargement are the most common forms of presentation within symptomatic ependymal cystadenomas. Unlike the aforementioned, broad ligament tumors only occur in females with VHL, yet they are also called papillary cystadenomas because they are histologically the same as epididymal cystadenomas. These can present an indolent behavior, however sometimes they can become large in size(2,5).

Surveillance.

Individuals affected with Von Hippel Lindau syndrome should be kept under surveillance, especially for those with a pathogenic variant of VHL and relatives at risk because they are genetically related and their status is unknown. Age appropriate evaluations and testing are recommended. After 12 months of age, ophthalmologic, neurologic and hearing screening, as well as blood pressure control. From 5 years of age onwards, it is

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suggested to perform contrasted thin-slice nuclear magnetic resonance in the internal auditory canal in those who present repeated otic infections, in addition to audiological evaluation every 2 or 3 years, 24-hour urine for fractionated metanephrines and plasma once a year. Surveillance examinations in individuals of 16 years of age that are indicated are brain, spine and abdominal MRI every 2 years and abdominal ultrasound once a year. In pregnant women, an intensified surveillance for cerebellar pheochromocytoma and hemangioblastoma should be performed during pregnancy and preconception; it is advisable to perform a non-contrast MRI especially of the cerebellum at 4 months of gestation(5,24).

When the pathogenic variant is known in a family, there is the possibility of using molecular genetic tests to recognize the genetic status of the relatives at risk, so as not to require surveillance of the family that has not been affected by the pathogenic variant. It is suggested not to perform contact sports activities in patients with adrenal or pancreatic lesions, as well as not to smoke or use tobacco products since they are considered a risk factor for renal cancer, and not to use industrial toxins or chemical products since they modify the organs affected by the disease(24).

Genetic counseling.
About 20% of those with VHL syndrome are the result of a de novo pathogenic variant and 80% represent those inherited from one parent.

In this autosomal dominant syndrome, parental mosaicism with unknown incidence has been reported. A patient with VHL has approximately a 50% chance of inheriting the pathogenic variant of the disease, so prenatal testing can be performed in possible at-risk pregnancies(24).

Targeted drugs have the potential to provide new therapeutic advantages for individuals with VHL disease in the future, such as tyrosine kinase inhibitors in sporadic renal cell carcinoma that primarily target the VEGF pathway. At the moment these drugs are under evaluation in clinical trials with encouraging preliminary results in certain tumors(13,25,26).

CONCLUSIONS

Von Hippel-Lindau disease is an autosomal dominant disorder that is generated by mutations in the VHL tumor suppressor gene. These present with tumors that are initiated by inactivation of biallelic VHL and are associated with pathological activation of hypoxic gene response pathways. Within the field intrafamilial variation may evidence correctly shaped genotype-phenotype connections for renal cancer and pheochromocytoma risks. Visceral cysts (renal, pancreatic and epididymal) are frequent, however organ function involvement is rare. They usually occur with hemangioblastomas of the central nervous system and retina, as well as renal cancers. Unusually, they include non-functioning pancreatic endocrine cancers, adrenal and extra-adrenal pheochromocytomas, endolymphatic sac tumors, as well as head and neck paragangliomas.

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