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Syndrome Von Hippel-Lindau: Literature Review

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Resumo

A sindrome de von Hippel-Lindau (VHL) e uma doenca hereditaria autossomica dominante de elevada penetrância. A mutacao esta localizada no gene VHL, um supressor tumoral. A doenca caracteriza-se pelo desenvolvimento de cistos e tumores em varias partes do corpo e embora a maioria destes tumores contemplem caracteristicas benignas, os individuos com DVHL apresentam alta susceptibilidade a varios tipos de câncer , incluindo carcinoma renal de celulas claras e tumores neuroendócrinos do pâncreas. O desenvolvimento de hemangioblastomas do SNC, de retina e de outras lesões como feocromocitoma e tumores do saco endolinfatico apresentam-se como quadros tipicos de VHL.

Palavras-chaves: Doenca de von Hippel-Lindau, Hemangioblastoma de Sistema Nervoso Central, Hemangioblastoma de Retina, Tumor endócrino de Pâncreas, Feocromocitoma.

Abstract

The von Hippel-Lindau syndrome (VHL) is an autosomal dominant hereditary disease of high penetrance. The mutation is located in the VHL gene, a suppressor tumoral. The disease is characterized by the development of cysts and tumors in several parts of the body and although the most of them have benign characteristics, individuals with DVHL have a high susceptibility to present different tipes of cancers, including renal clear cell carcinoma and pancreas neuroendocrine tumors. The development of CNS hemangioblastomas, retina and others injuries as pheochromocytoma and endolymphatic sac tumors represent typical frames of VHL.

Keywords: *Von Hippel-Lindau Disease; CNS Hemangioblastoma; Retina Hemangioblastoma; Endocrine Tumor of Pancreas; Pheochromocytoma*

Introduction

In 1864 ophthalmologists reported angiomatous lesions of the retina that caused blindness and were associated with cerebelares injuries. Von Hippel, a German ophthalmologist, was the first to recognize the natural history of the disease [2,3]. However who made the discovery that hemangioblastomas of the retina and cerebellum were part of a set of angiomatous lesions of the nervous system and that this condition was hereditary was Arvid Lindau, a Swedish ophthalmologist. Due to its discovery, family cerebellar hemangioblastomas are still called tumor "Lindau"[4]. In 1964 when Melmon and Rose discovered a large family carrier and named disease as von Hippel-Lindau. This pathology presents genetically as an autosomal dominant disease as a result of a mutation in VHL gene [5]. The mutation leads to the development of various benign and malignant tumors addition of cysts in several organs [5].

The disease Von Hippel-Lindau (DVHL) is a syndrome of autosomal dominant inheritance with high penetrance (100% at 65 years) [6]. It is a rare condition, with a prevalence of 1/53,000 and annual incidence at birth 1/36,000, and the ratio of family/sporadic cases is 11 to 14/13 without predominance of any ethnic group or gender[7-9].

The initial symptoms usually appear between 18 and 30 years old, but are subject to great variability in this question and also in how the disease presents itself. Pleiotropism is found even among elements of the same family, sharing a specific mutation.8The carriers are predisposed to develop neoplasms benign and malignant hypervascularized synchronous or metachronous. They are between the most common clinical manifestations of the central nervous system hemangioblastomas (CNS) and retina, renal carcinoma, renal cysts, pheochromocytoma, cystic and solid tumors of the pancreas, cystadenoma of epididymis or broad ligament of the uterus as well as endolymphatic sac tumors [6-17]. The main cause of CCR are the hereditary pheochromocytomas [11,15,16].

Clinical Presentation

Neumann in 1991 [18] classifies the syndrome into three types according to the nature of the tumors found: Type I: CNS and retinal hemangioblastomas, cysts, and renal carcinomas and pancreatic cystic disease; and in the absence of pheochromocytoma, representing the most common clinical form. Type IIA: hemangioblastomas CNS and retina, pheochromocytoma and tumors of pancreatic islets; in the absence of kidney carcinoma and better prognosis. Type IIB: hemangioblastomas CNS and retina, pheochromocytoma, kidney and pancreatic tumors, these patients have all manifestations of the syndrome and represent the least common form.

The clinical presentations of this condition, patients has all the manifestations of the disease, is variable and rarely with approximately 50% of patients only have one of the manifestations. There is no difference according to gender and the clinic presentation [19]. As most frequent initial conditions are hemangioblastomas cerebellum and retina, kidney carcinoma followed. Life expectancy is approximately 49 years [6], being among the leading causes of death renal cancer and central nervous system tumors.19 Hereafter the main clinical presentations:

Hemangioblastoma of Central Nervous System

Hemangioblastomas are benign tumors classified as grade I by WHO and correspond 1-2% of the primary tumors CNS [20]. Peak incidence occurs between 35 and 45 anos [21], with a predominance of male patients in the ratio of 2:11 [20]. The posterior fossa is the most affected region, followed by spinal cord injuries and occasionally supratentorials [22]. In posterior fossa tumors are located in the worm and cerebellar hemispheres and in ventriculo [23]. Manifest clinically quarter by obstruction of cerebrospinal fluid flow and consequent intracranial hypertension [23]. The most common signs and symptoms are headache, vomits, dizziness, ataxy and march disorders [20,23,24].

Are associated with Von Hippel-Lindau disease by 20%, as in sporadic cases in 80% of cases [16]. angiography, magnetic resonance imaging and computed tomography are the neuroimage tests of choice for the diagnosis of hemangioblastomas [13,25-27]. The macroscopic appearance is well-defined, formed by highly vascularized reddish nodules located in the wall of the large cists [20,24,28]. In the histology, are composed of stromal cells and foamy lush capillary network [20,23,29].

Stromal cells, tumor characteristics, have variable size nucleus, with occasional atypical or hyperchromia. They are characterized by their content consists of cytoplasmic vacuoles with lipid character. Due to the high vascular component, intratumoral bleeding are common. Necrosis and calcification are uncommon. The histogenesis of hemangioblastomas is inknown [20,24,30].

Although benign, present recurrence rate above 25% [20,24] besides the fact that patients receiving diagnostic DVHL and multicentric tumors under 30 years are closely related to higher rates of recidiva [20].

The treatment of these tumors is surgery or radiotherapy. The surgery is the complete removal of the tumor, with improvement in symptoms in 88% of cases. The likelihood of recurrence at the same site occurs in 22% of patients. Radiation therapy is beneficial after partial surgical removal of the tumor. The stereotactic radiosurgery is indicated in small solitary tumors (less than 3) or multiple saves and adjacent normal parenchyma irradiation, but may contribute to a transient increase in vascular permeability and subsequent development of edema and cyst peritumoral [8,9,13,26].

Retinal Hemangioblastoma

Often multiple and bilateral, arise in approximately 50% of cases of DVHL and are often the earliest manifestation of the disease. Normally it is not present at birth. These tumors are sporadic in 65% of cases and 35% are associated with multiple DVHL [19] are in 1/3 patients, and in all cases they do multiplicity of the von Hippel- Lindau syndrome [24].

The beggining of symptoms occurs between the ages of 25 years and is rare in children under 10 years, but may occur in 5% of casos [7-11,19,31,32] are bilateral tumors in 30 50% of casos [6,19]. The preferred location of the tumor is the temporal peripheral retina and is easily recognized by its reddish appearance, globular, with an artery and a vein tortuous draining tumor [33].

The most common symptoms are: visual acuity, retinal detachment, macular edema, cataract, glaucoma, uveitis, and phthisis bulbi ophthalmitis in the final stages [34] in addition to severe visual loss by exudation [7-9,26,31,32]. However, most patients are asymptomatic. The diagnosis is made by fundus examination and fluorescein angiography, which should always be performed when the fundus examination is not normal [34].

The HCR remains the leading cause of visual morbidity. The detection and early treatment may alter the outcome visual [33]. There is also the possibility of developing retinal vascular hamartomas, characterized by small vascular lesions without devious blood vessels [31].

Kidney disease

The DHL renal lesions include cysts, carcinomas, adenomas and angiomas [7]. As cystic lesions correspond to 60 to 75% of the tumors and solid are mixed to the remainder [7]. cysts are considered benign lesions while solid tumors are potentially malignant. The biggest challenges involve the possibility of the cysts develop into carcinoma; there are reports that the cystic lesions originating from the proximal tubule epithelium may contain carcinomatous cells while those arising from the distal tubule not have malignancy [35]. Therefore they appear to be two types of cysts, who have malignant potential and the other not. The possibility of transformation of cystic lesion in fully solid lesion is very low at 1 is 2% maximum [19]. Importantly, solid and cystic lesions with solid components are always renal carcinoma. The age of onset of renal tumors is approximately 37 years old [19].

Pheochromocytoma

On average 25% of pheochromocytomas are hereditary, and included in this percentage, 11% are attributable to patient DVHL [11,36]. The frequency of this disease varies widely depending on the type of mutation implicated and may be the initial and unique manifestation of DVHL [8,31,36]. In this disease the tumor is often bilateral, and 90% are located in the adrenal, and may arise in glomus jugular, carotid body and periaortic tissues. These have cited low-grade malignancies, only 5% [37]. Similar to what occurs with other hereditary tumors integrated into DVHL, pheochromocytoma comes earlier than expected in sporadic tumors (20 vs 43.9 years old). There are reports of some cases of pheochromocytoma in children, in the context of DVHL [7,8,11,26,35].

Compared with other causes of hereditary pheochromocytoma, DVHL in patients have become more often asymptomatic. In fact, around 30% of cases may even be asymptomatic and have normal levels of catecholamines. Symptomatic patients report headaches, palpitations, excessive sweating, paleness, nausea and hypertension arterial attacks [8,9,11,26].

The diagnosis is based on measurement of plasma and urinary catecholamines, fractionated plasma metanephrines, total and fractionated urinary metanephrines and chromogranin associated with radiological tests such as CT or RM1 [8,35].

Symptoms may begin before ten years of life and can present clinically as sustained hypertension, hypertensive crisis, tachycardia, headaches or can be asymptomatic. The treatment consists in the total or partial adrenalectomy (preferably laparoscopic), preceded by two weeks of α and eventually blocking subsequent β-adrenergic [3,7].

Pancreatic tumors

They are present in 32% of cases of DVHL being more typical cysts, corresponding to 70% of pancreatic tumors cases [36]. Include serous cystadenomas (present in about 12% of patients with DVHL), hemangioblastomas (< 1%) and ductal adenocarcinomas (< 1%) and PE (10-17%) [8,9,14,36].

Pancreatic cysts are rare in the population and their presence is an indicator of DVHL [19]. Occurs between 20 and 40 [19]. are usually asymptomatic, but may present with abdominal discomfort, exocrine pancreatic insufficiency, pancreatitis and biliary obstruction. Tumors consisting of islet cells, although also asymptomatic in most cases, can produce a number of substances such as insulin, gastrin and glucagon and cause corresponding clinical malignant syndrome [19]. They are in 42% of cases and metastasis are targeted to liver and bone [39]. The radiological diagnosis is by ultrasound, CT and MRI. Suspicions detected by ultrasound should be evaluated by TC [19].

The treatment is surgery where solid tumors with functional compressive symptoms or syndrome. Percutaneous drainage or biliary stent placement is justified only before symptoms suggestive of compression [8,9].

There is an important correlation between endocrine tumors most often included in DVHL: about 40% of patients with PE also have pheochromocytoma, a fact that is attributable to common embryonic origin, at the level of neural crest [9,11,39].

Cystadenoma of epididymis

Are benign tumors that affect 40% of men with DVHL. They normally have asymptomatic behave, but when symptomatic the most common clinical manifestations are: pain, edema, scrotal mass and even infertility [8,9,40,41].

It is detected by physical examination or ultrasound. Treatment is by complete surgical resection, since it can undergo transformation to cistadenocarcinoma [41]. In women, the pathologic equivalent of epididymal cystadenoma is papillary cystadenoma of the broad uterus ligament [42]. Other rarer lesions: Cavernous hemangiomas and liver hemangioblastoma, lung hemangioblastomas, omentum cysts, hemangiomas skeleton, cysts and ovarian hemangiomas, medullary carcinoma and thyroid papillary dermis of hemangiomas, nevus pigment, cysts and splenic angioma, angioma and adenoma of the adrenal cortex adenocarcinoma and pancreas hemangioblastomas [19].

Diagnostic

DVHL patients with a family history of having any of the following injuries: hemangioblastoma of the CNS or retina, RCC, pheochromocytoma, pancreatic cyst or tumor, cystadenoma of the epididymis or tumor of the endolymphatic sac, is sufficient to establish the diagnosis of DVHL. Patients with no family history of the disease, the diagnosis requires at least two hemangioblastomas CNS and/or retina or hemangioblastoma of the CNS or retina associated with a visceral injury (RCC, pheochromocytoma, cysts or pancreatic tumor or cystadenoma of the epididymis) [7,12,13,26,40].

It can also be made through molecular diagnosis with the identification of a germline mutation in the VHL gene associated with a distinctive clinical tumor.10,42O genetic study aimed molecular diagnosis is of great value, since 50% of patients DVHL have only one manifestation of the disease [8,11,12,40]. Patients who have an isolated apparently sporadic tumors, the DVHL was confirmed in about 30% of retinal hemangioblastomas, 25 to 30% of CNS hemangioblastomas, 20% the endolymphatic sac tumors, 11% of pheochromocytomas and 2% of CCR [42]. Genetic testing should be performed when there is at least one of the cases.

Etiopathogenesis

The DVHL shows a pattern of autosomal dominant transmission with 100% penetrance will close after 65 years old [7,8,10,26]. The VHL gene is located on chromosome 3p25-26. It is a tumor suppressor gene with exons [3]. Their product, widely expressed in normal tissues, is a protein of 213 amino acids which is one of the regulatory subunits (elonguinas) of RNA polymerase II. The RNA polymerase II transcribing RNA in the genes that will be translated into proteins. The VHL gene product could inhibit the elongation of the mRNA

is being transcribed (synthesized by the polymerase II). It also regulates expression of VEGF, PDGF-B and GLUT-1 post-transcriptional level. In normal cells, increased expression of these factors is associated with hypoxic conditions [8,9,26].

Individuals who should undergo genetic screening. 1. In families with germline mutation of the VHL gene 8.12 2. If there is a family history of CRC, hemangioblastoma or pheochromocytoma 12.14 3. In presence of multiple tumors classifiable in DVHL diagnosed in the patient and/or in a fisrt degree relative [12,41] If the patient has bilateral tumors, multicentric or come early (before age 30 for CCR or before age 50 for hemangioblastoma and feocromocitoma [8,9,13,41].

Table 1: *RCC: Renal cell carcinoma; VHL: Von Hippel-Lindau disease; VHL: Von Hippel-Lindau.*

Genotype – Phenotype Correlaction

The DVHL provides great phenotypic variability, and mutations affecting the same codon may determine distinct phenotypes, giving us the idea that there are other factors involved, particularly the substituted amino acid type and the presence of modifier genes or environmental factors [12]. It is usually classified as type 1 in the absence of pheochromocytoma or type 2, pheochromocytoma in the presence of which is less frequent, corresponding to 7 to 20% of cases [8,12,13].

The DVHL type 1 was the most of the times by changing nonsense, deletion or frameshift and a minority of cases is missense, but modification of the hydrophobic residue affected enough to cause disruption of pVHL protein structure and loss of function. In DVHL type 2, the majority are missense mutations with replacement of one amino acid from the surface of pVHL, yielding a partially functional protein normal size [7,8,10,11].

Type 2 can be divided into three categories.8The type 2A is characterized by high risk for pheochromocytoma and low risk for RCC and endocrine pancreas tumors [8,11,12]. The type 2B associated with high risk of pheochromocytoma, CCR and endocrine pancreas tumors [8,12,43]. Finally 2C type, called familiar pheochromocytoma isolated [8,12,36].

The type and location of the mutation can confer different risks normally associated with DVHL tumors. The risk of pheochromocytoma is higher in patients with missense mutations compared to nonsense mutations, frameshift or deletions. However the type of mutation does not appear to influence the severity of the disease and rate of mortality [43].

Follow - Up

It needs continuous and lifelong segment of patients with DVHL because of the unpredictability of the onset of the disease lesions and what is associated. The genetic tests are of paramount importance both to the patient and for his family because, with the prior knowledge of the genotype can have the idea of the phenotype associated [9,10,43,44]. Hereafter there is a possible protocol to be followed.

Complementary diagnostic test	Age of onset	Revaluation
RM neuroaxis	11 ages	Every two years (possibly early if you develop complaints suggestive of injury) [12,13,15,40].
Eye exam	birth	Yearly [12,13,42].
urinary catecholamines [15,26,40-42].	2-5 ages	Annual (and whenever it detects elevated TA) [12,15,26,40].
Fractionated plasma metanephrines (normetanephrine) [26,36]		
abdominal ultrasound	8 ages	
RM abdominal	18 ages	Yearly [12,26,42].
audiometry	15 ages	Only if there relevant complaints [26,42].
CT or MRI cranioencefalic directed to the inner ear	–	If patient develops tinnitus, vertigo or loss of auditory acuity [12,26].

Table 2: *MR: Magnetic Resonance; DA: Blood Pressure; CT: Computed Tomography.*

Following Protocol DVHL individuals

Poulsen., *et al*. found that the risk of intercurrent events relating to CNS lesions was reduced from 7.2% to 2.7% when the interval of the skull MRI was performed every year instead of two to two years as the most studies suggest [26,45].

Conclusion

In VHL disease genotype does not always predict the associated phenotype, making the diagnosis difficult and restricting the establishment of monitoring protocols tailored to the patient. Patients with DVHL can manifest neoplasms located in the same agency or not, may undergo multiple surgical interventions and are thus susceptible to bleeding risk beyond naturally associated with resection of hemangioblastomas, other complications of the therapeutic procedure, mainly iatrogenic causes. Early detection of lesions is extremely important for the diagnosis and planning of appropriate therapeutic intervention, since the growth of the lesions will condition an increase complication that compromise the quality of life and survival of patients.

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