Von Hippel-Lindau Syndrome in a Private Cancer Service in São Paulo: Case Report

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Síndrome de von Hippel-Lindau em um Serviço Privado de Câncer em São Paulo: Relato de Caso

Síndrome de von Hippel-Lindau en un Servicio Privado de Cáncer en São Paulo: Informe de Caso

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ABSTRACT

Introduction: Von Hippel-Lindau (VHL) syndrome is an autosomal dominant hereditary pathology that involves the growth of tumors in different regions of the human body due to mutation of the VHL gene. **Case report:** Male patient, 38 years old, complained of recurrent headache for 3 years, with progressive worsening. A lesion in the cerebellum was diagnosed, whose magnetic resonance imaging found an expansive formation in the posteroinferior portion of the left cerebellar hemisphere. Multislice tomography of the abdomen was performed, showing splenic nodular formation with marginal enhancement. Cervical spine imaging demonstrated a small nodule located in the cervical (intramedullary) cord adjacent to cervical vertebra 3 (C3). In view of the findings, the patient underwent total macroscopic resection of the cerebellar lesion, with an anatomopathological report of World Health Organization (WHO) grade 1 cerebellar hemangioblastoma, which is a benign tumor with lower risk of aggressiveness and recurrence. Immunohistochemical test showed positive cluster of differentiation 34 (CD34), cell proliferation index positive (Ki67) (<5%), positive alpha inhibin and epithelial membrane antigen (EMA) negative. As the patient had no family history of cancer, a new generation sequencing was performed due to the radiological findings, which identified the pathogenic variant VHL c.292T>C found in germ lineage; although the family was unaware of any past family history of the syndrome, the patient's diagnosis was confirmed. **Conclusion:** The set of clinical findings and the variant in the VHL gene confirm the diagnosis of the syndrome.

Key words: von Hippel-Lindau disease; germ-line mutation; hemangioblastoma.

RESUMO

Introdução: A síndrome de von Hippel-Lindau (VHL) é uma patologia hereditária autossômica dominante que envolve o crescimento de tumores em diversas regiões do corpo humano em razão da mutação no gene VHL. **Relato do caso:** Paciente, sexo masculino, 38 anos, há três anos queixava-se de cefaleia recorrente, com piora progressiva. Foi diagnosticado com uma lesão em cerebelo cuja ressonância magnética cerebral encontrou uma formação expansiva na porção posteroinferior do hemisfério cerebelar esquerdo. Foi realizada tomografia *multislice* de abdome, que evidenciou formação nodular esplênica com realce marginal. A imagem da coluna cervical demonstrou pequeno nódulo localizado na medula cervical (intramedular) adjacente à vértebra cervical 3 (C3). Diante dos achados, o paciente foi submetido à ressecção macroscópica total da lesão do cerebelo, com laudo anatomopatológico de hemangioblastoma cerebelar grau 1, de acordo com a classificação da Organização Mundial da Saúde (OMS), que é um tumor benigno com baixa agressividade e recorrência. O teste imuno-histoquímico mostrou *cluster of differentiation* 34 (CD 34) positivo, índice de proliferação celular (Ki67) positivo (<5%), alfa inibina positiva e *epithelial membrane antigen* (EMA) negativo. Como o paciente não tinha história familiar de câncer, em função dos achados radiológicos, foi realizado sequenciamento de nova geração identificando a variante patogênica VHL c.292T>C, constatado em linhagem germinativa que, apesar do desconhecimento de história familiar positiva para a síndrome, confirmou o diagnóstico do paciente. **Conclusão:** O conjunto de achados clínicos e a variante no gene VHL confirmam o diagnóstico da síndrome.

Palavras-chave: doença de von Hippel-Lindau; mutação em linhagem germinativa; hemangioblastoma.

RESUMEN

Introducción: El síndrome de von Hippel-Lindau (VHL) es una patología hereditaria autosómica dominante que consiste en el crecimiento de tumores en diferentes regiones del cuerpo humano debido a una mutación en el gen VHL. **Informe del caso:** Paciente, masculino, 38 años, consulta por cefalea recurrente desde hace 3 años, con empeoramiento progresivo. Se diagnosticó lesión en cerebelo, cuya resonancia magnética encontró una formación expansiva en la porción posteroinferior del hemisferio cerebeloso izquierdo. Se realizó tomografía multicorte de abdomen, que mostró formación nodular esplénica con realce marginal. Las imágenes de la columna cervical demostraron un pequeño nódulo ubicado en el cordón cervical (intramedular) adyacente a vértebra cervical 3 (C3). Ante los hallazgos se procedió a la resección macroscópica total de la lesión cerebelosa, con informe anatomopatológico de hemangioblastoma cerebeloso grado 1, de acuerdo con la clasificación de la Organización Mundial de Salud (OMS) que es un tumor benigno con baja agresividad y recurrencia. La prueba inmunohistoquímica mostró *cluster of differentiation* 34 (CD34) positivo, índice de proliferación celular (Ki67) positivo (<5%), alfa inhibina positivo y *epithelial membrane antigen* (EMA) negativo. Como el paciente no tenía antecedentes familiares de cáncer, debido a los hallazgos radiológicos, se realizó una secuenciación de nueva generación identificando la variante patogénica VHL c.292T>C, encontrada en el linaje germinal, que, a pesar del desconocimiento de antecedentes familiares positivos para el síndrome, confirmó el diagnóstico del paciente. **Conclusión:** El conjunto de hallazgos clínicos y la variante en el gen VHL confirman el diagnóstico del síndrome.

Palabras clave: enfermedad de von Hippel-Lindau; mutación de línea germinal; hemangioblastoma.

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INTRODUCTION

The Von Hippel-Lindau (VHL) syndrome is an autosomal dominant hereditary pathology that involves the growth of tumors in different regions of the human body[1]. The mutation occurs in the VHL tumor suppressor gene on chromosomal locus 3p25.3[2,3]. The disease generates a predisposition to the development of hypervascular neoplasm, the most common are: retinal and central nervous system (CNS) hemangioblastomas, renal cells carcinoma, renal cysts, pheochromocytoma and solid pancreatic cystadenomas[4].

In 1991, Neumann classified this syndrome according to the frequency of the tumors[5]. Currently, there are five subtypes described: the most common clinical form is type 1, caused by truncated deletions or mutations, with high risk to clear cells renal cells carcinoma and retinal and CNS hemangioblastomas and low risk for pheochromocytoma; type 1B, caused by contiguous genetic exclusions which encompass VHL with high risk of retinal and CNS hemangioblastomas and low risk of pheochromocytoma and clear cells renal cells carcinoma; type 2, caused by missense mutations with high risk for pheochromocytoma divided in 2A – high risk for retinal and CNS pheochromocytoma and low risk for clear cell renal cells carcinoma and 2B – high risk for pheochromocytoma, retinal and CNS hemangioblastomas and clear cells renal cells carcinoma; 2C – high risk for pheochromocytoma and low risk of retinal and CNS hemangioblastomas and clear cells renal cells carcinoma[6].

The expressivity of the disease varies according to the type of mutation encountered. The most common subtype of renal carcinoma is in clear cells, a frequent cause of death[7].

Clinical diagnosis can be made in a patient with positive family history, a single retinal or cerebellar hemangioblastoma and in patients without family history with two or more clinical characteristics of the syndrome[7].

The objective of this case report is to clarify the medical community on how the VHL syndrome presents in clinical practice and facilitate the recognition and diagnosis by health professionals.

CASE REPORT

The present case is related to a former healthy 38-years old male patient who complained of recurrent head ache with progressive worsening for three years. He sought a neurologist who diagnosed cerebellar lesion and referred him to additional investigation.

A cranial magnetic resonance revealed a 27 × 26 × 25 mm expansive formation in the posteroinferior portion of the left cerebellar hemisphere, characterized by isosignal at T1, hypersignal at T2/FLAIR, multilobulated and prominent heterogeneous contrast enhancement, with intralesional vascularization as shown in Figure 1.

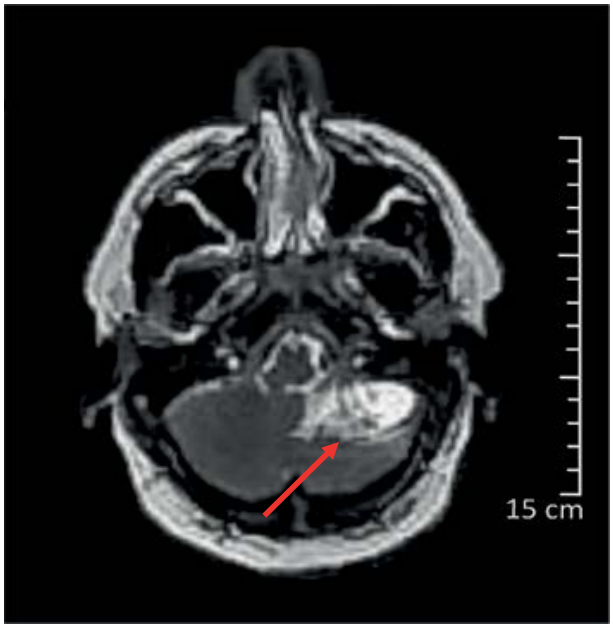

Figure 1. Cranial magnetic resonance showing hemangioblastoma at the left cerebellar hemisphere

Multislice tomography of the upper abdomen was performed showing slightly lobulated splenic nodular formation (normal topography, dimensions and density) with marginal enhancement up to 2.9 cm. Other organs had no significant alterations.

Cervical, thoracic and lumbar spine imaging revealed a well-defined small isointense nodule in T1 and hyperintense in T2 with avid-contrast enhancement measuring 0.9 cm located at the cervical cord (intramedullary) adjacent to cervical vertebra 3 (C3).

Due to the findings, the patient was submitted to total macroscopic resection with World Health Organization (WHO) grade 1 cerebellar hemangioblastoma report[8], which is a benign tumor with lower risk of aggressiveness and recurrence. Immunohistochemical test showed positive cluster of differentiation 34 (CD 34), positive cell proliferation index (<5%), positive alpha inhibin and negative epithelial membrane antigen (EMA).

Because of the findings suggestive of VHL syndrome, a geneticist evaluated the patient and requested new generation sequencing which identified the variant *chr3:10142139* T>C (VHL c.292T>C, NM_000551), in heterozygosis of the gene VHL which promotes the substitution of the amino acid tyrosine at codon 98 by histidine (VHL p.Tyr98His)[9]. According to the criteria of the American College of Medical Genetics (ACGM)[10],

the variant *chr3:10142139* T>C (VHL c.292T>C, NM_000551) is considered pathogenic.

Other cranioencephalic magnetic resonance of control was performed, showing signals of bilateral occipital craniotomy, orifice of occipital trepanation at right, volumetric reduction of the left cerebellar hemisphere associated with prominence of cerebellar follies, in addition to images of hypersignal in T2, predominance of hypersignal with some foci of hypersignal with concomitant FLAIR, characterizing areas of gliosis and foci of encephalomacia.

Currently, the patient is in ophthalmologic, neurologic and abdomen follow-up (annual, based in clinical evaluation) and radiologic (biannual – neuroaxis and abdomen resonance but can be replaced by abdomen tomography or ultrasound if resonance is unavailable) according to the last guidelines[11].

The study complied with Resolution 466/2012[12] of the National Health Council and was approved by the Institutional Review Board of "*Notre Dame Intermédica Saúde S.A.*" and "*Invitare Pesquisa Clínica Auditoria e Consultoria Ltda.*" report number 4,869,492 (CAAE (submission for ethical review): 49966321.0.0000.8098).

DISCUSSION

VHL syndrome is an autosomal dominant inherited pathology and mutations of the gene VHL mapped to the short arm of the chromosome 3. Latif et al.[13] identified rearrangements of the gene VHL, a part due to deletions, one of these in-frame of three nucleotides. Crossey et al.[14] identified 40 different types of mutations, the two most frequent are: arg238-to-gln and arg238-to-trp. Lenglet et al.[15] identified complex mutations in heterozygosis in E1-prime of the gene VHL, obtaining the substitutions leu128-to-val (L128V) and leu138-reportsto-pro (L138P). The VHL codifies the protein VHL (pVHL), tumor suppressor gene involved in the pathways of cellular signaling. There are two isoforms of protein VHL: VHL30 and VHL19 and both are important for tumor suppressor effects[4].

Mostly, the individual affected inherits the allele mutated from a parent also carrier of VHL (80% of the cases), the other cases arise from *de novo* mutations[16]. The abnormal production of pVHL generates the transcription of several genes and increase of the production of growth factors, including erythropoietin, vascular endothelial growth factor, platelet-B derived growth factor and other genes involved in the capture and metabolism of the gliosis, leading to the formation of hypervascular cysts and tumors characteristics of VHL[17].

It is a rare, challenging disease for medical diagnosis due to the appearance of infrequent tumors which, if observed as isolated entities, may not raise suspicion of the syndrome. It affects 1:36,000 to 1:45,000 born alive with prevalence from 1:38,0000 to 1:91,000. Most of the patients manifests the syndrome earlier than 70 years of age. Half of the carriers are identified before the onset of the clinical manifestations because of the current possibility of molecular diagnosis[18].

Thus, VHL is defined by the formation of various hypervascular benign and occasionally malignant tumors at the CNS and visceral organs, further to multiple pancreatic and renal cysts[7,18].

The diagnostic criteria proposed for the syndrome include molecular and clinical findings: family history of VHL with common characteristics as retinal or CNS hemangioblastoma or visceral lesion (renal cells carcinoma, pheochromocytoma, pancreatic neuroendocrine tumor or cysts or cystadenoma of the epididymis). To satisfy the diagnostic criteria, two or more retinal or CNS hemangioblastoma need to be present associated with visceral lesion for those without VHL family history[4,19].

Hemangioblastomas are benign vascular neoplasms which may occur in patients with VHL, mainly cerebellar (16-69%) and retinal (49%-62%). However, this tumor can also appear at the brainstem (5-22%), spinal cord (13-53%), cauda equina (11%) or supratentorial (1-7%)[20] (Table 1). Usually, they appear between the second and third decades of life and quite often are the first manifestations of the syndrome[3,17].

These tumors can be asymptomatic but may also manifest symptoms by the mass effect and compression of adjacent structures as headaches, nausea and vomits or sensory and/or motor deficits and ataxia and consequently are related to morbidity and mortality of the VHL syndrome[3,17,18]. The diagnosis at the CNS is through magnetic resonance and in solid tumors, isosignal in T1 and hypersignal in T2 and with cystic component with hyposignal in T1 and hypersignal in T2[5]. Overall, the treatment is surgical resection[17].

The patient had cysts in the arm. The involvement of viscera is an important aspect of the patients with VHL syndrome. Although no renal carcinoma was found, benign cysts and clear cells carcinomas stand out in the syndrome.

The likelihood of developing renal cells carcinoma until 60 years of age is 60%, the main cause of death for these patients. Initially they are asymptomatic, evolving to hematuria, flank pain or palpable abdominal mass (Table 1). Contrast computed tomography is utilized for the diagnosis. Patients with renal cells carcinoma can develop metastases, preferentially at the bones, lungs and

liver[3]. The treatment involves surgical resection for tumors larger than 3 cm.

Pheochromocytomas arise from chromaffin cells in the medulla of adrenal glands occurring in 16-20% of the patients and usually appear in the second decade of life[17,20] (Table 1). These tumors produce catecholamines causing hypertension, tachycardia, palpitation, headaches, sweating, paleness and nausea but can also be asymptomatic[17,18]. Lab studies show excess of catecholamines which, together with suggestive image confirm the diagnosis[20]. The condition may cause potentially fatal complications as arrythmia and acute coronary syndrome and the treatment of choice is surgery.

In addition, pancreatic lesions have been reported, rarely malignant, further to epididymal cystadenomas and of broad ligament cystadenomas[17].

The patient was classified as subtype 2A (not the most common) of the VHL syndrome, corroborated by the genetic mutation found, the most common is subtype I. The finding of CNS hemangioblastomas raised the initial suspicion for the syndrome although the patient did not present other expected clinical findings – retinal hemangioblastoma and pheochromocytoma (Table 1).

Liu et al.[9] reported the first Chinese family with mutation VHL p.Tyr98His (Y98H) widely considered in patients with type 2A VHL mutation. Four generations were evaluated, totaling 15 carriers of the mutation of which only four were diagnosed with type 2 typical pheochromocytomas. It also investigated that there are still a small number of patients carriers of the mutation who present renal cells carcinoma, most frequent of subtype 2A, indicating that the genotype-phenotype incompatibility is not impossible, also demonstrated in the present case report[9] (Chart 1).

Table 1. Frequency of clinical manifestations of the Von Hippel-Lindau Syndrome

Clinical Manifestation	Frequency %
CNS Hemangioblastomas	44
Retinal hemangioblastomas	45-59
Pheochromocytomas	16-20
Pancreatic tumors	32
Clear cell renal cell carcinoma	30

Source: Gatti et al.[5]
Caption: CNS= central nervous system.

It is a rare VHL type 2A after the identification of the variant VHL c.292T>C. Typical manifestations of the syndrome, thorough clinical tests and analysis of the mutations can help the diagnosis and in fact, confirm the syndrome. The guideline VHL Alliance[21] suggests annual clinical follow-up with anamnesis and physical exam in the first five years from the diagnosis, including blood and wrist pressure, retina and urinary metanephrines exams. Imaging tests as brain, spine and total abdomen contrast resonance should be conducted every two years from 30 to 65 years of age.

Historically, survival is lower than the general population and life expectancy of 49 years, however, it is a study conducted more than 25 years ago. A recent retrospective study with Danish men and women born in 2000 with VHL syndrome showed life expectancy of 67 and 60 years, respectively[19].

Chart 1. Classification of the Von-Hippel-Lindau Syndrome according to the nature of the tumor

Subtype	Type of mutation	Typical phenotype
Type 1	Exonic deletions, variants of truncation of missense proteins causing instability of proteins	Retinal hemangioblastoma CNS hemangioblastoma Clear cell renal cell carcinoma
Type 1 B	Deletions of contiguous genes including VHL and BRK1	Retinal hemangioblastoma CNS hemangioblastoma
Type 2A	Missense surface substitutions pVHL p. ex.: p.Tyr98His	Retinal hemangioblastoma CNS hemangioblastoma Pheochromocytoma
Type 2B	Missense: p.Arg167Trp, p.Arg167Gln	Retinal hemangioblastoma CNS hemangioblastoma Clear cells renal cell carcinoma Pheochromocytoma
Type 2C	Missense: p.Val84Leu	Pheochromocytoma

Sourc: Nielsen et al.[6]
Captions: CNS = central nervous system; VHL = von Hippel-Lindau.

At last, an important aspect because of the high frequency of multiple tumors in various organs and systems is the multidisciplinary care to the patient with VHL with patient-centered rehabilitation program for better quality-of-life[22].

The role of several medical specialties as neurosurgeon, ophthalmologist, urologist, nephrologist and clinical is crucial. In addition, the effect is potentialized to improve the patient's health when associated with physiotherapy, occupational therapy or psychology[22-24]. Timeline and the course of the disease have great implications on activities of the daily life, permeating social and functional aspects. In that sense, psychological support is required to deal with mental health issues created by the disease-related uncertainties[22]. Functional issues associated with CNS lesions or surgical removal that can provoke neurologic deficits and functionality impairment should be treated by occupational physiotherapist with direct approach to improve the symptoms[24].

The treatment of choice of the case and other patients is the exeresis of tumors caused by VHL with benign characteristics mostly or with reduced metastases[17].

VHL syndrome-targeted therapies currently under investigation are promising perspectives to inhibit the growth of the primary tumor and angiogenesis. Monoclonal antibodies as bevacizumabe and ranibizumab are drugs intended to act on the natural history of the disease, but yet with inconclusive results utilized as adjuvant.

Inhibitors of tyrosine-kinase, targeted drugs which block the cascades of transduction of the cellular sign based in the tumor pathway of the vascular endothelial growth factor (VEGF) on VHL (semaxanib, sunitinib, pazopanib, erlotinib, dovitinib, sorafenib) have positive results with improvement of the symptoms and even regression of the tumors. RNA aptamers which inhibit one of the isoforms of VEGF were tested in clinical trials and in a Phase I study. Modifiers of biological response increase or modulate the autologous immune response of the host to the VHL syndrome and some of these modifiers tested *in vitro* and in small groups of patients with VHL – roquinimex, thalidomide, IFN-α-2a, inhibitors of HIF2α, octreotide, clarithromycin and immune therapy are under evaluation[25].

CONCLUSION

The finding of retinal or CNS hemangioblastoma, pheochromocytoma or renal cells carcinoma associated or not with positive family history should be highly suspicious of VHL syndrome diagnosis. Rare diseases are challenging to the daily routine of the physician.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and/or interpretation of the data, wording and/or critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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