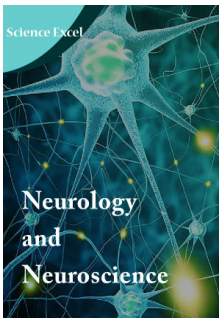
Neurology & Neuroscience

Case Report



Cerebellar Hemangioblastoma in A Patient With Von Hippel-Lindau Syndrome

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- Received Date: 11 Feb 2025
- Accepted Date: 18 Feb 2025
- Publication Date: 20 Feb 2025

Abstract

Von Hippel-Lindau syndrome (VHL) is an autosomal dominant hereditary disease characterized by a variety of benign/malignant tumors, mainly hemangioblastomas, renal, pancreatic, and hepatic alterations, as well as pheochromocytoma. The disease is associated with high morbidity and mortality and can affect multiple family members. Due to the potential for serious complications and psychosocial impacts, early diagnosis is crucial for monitoring tumor lesions, multidisciplinary treatment, and appropriate genetic counseling.

Introduction

Von Hippel-Lindau syndrome (VHL) is a rare, autosomal dominant genetic disorder with a prevalence of 1 in 36,000. It is characterized by cysts and/or benign tumors in multiple organs with potential for malignant transformation. The main findings are: hemangioblastomas located in the retina and central nervous system (CNS), cysts or solid tumors in various sites (pancreas, liver, kidneys, lymphatic tissue), and pheochromocytoma [1-2]. Diagnosis is made in the presence of some of the classic tumors in individuals with a family history or in the presence of two tumors in those without a family history. Treatment and prognosis vary depending on the alterations presented [3-4].

Case Report

A 37-year-old male patient presented with gait ataxia, nystagmus, and urinary incontinence for 6 months. He had a prior cognitive disorder and was diagnosed 5 years ago with systemic hypertension and multiple renal nodules, progressing to chronic renal failure with the need for kidney transplantation. Previous abdominal CT showed multiple cystic formations in both kidneys (Figure 1).

A cranial MRI was performed, revealing an expansive cystic lesion centered on the cerebellar vermis and right cerebellar hemisphere, causing compression of the fourth ventricle with consequent dilation of the supratentorial ventricular system and transudation of cerebrospinal fluid (Figures 2 and 3).

Initially, a ventriculoperitoneal shunt (VPS) was performed, with clinical improvement of the patient. About one month after the VPS, a microsurgical approach was conducted for the cerebellar lesion, revealing clear cystic peritumoral content and hypervascularized solid content. The lesion biopsy confirmed the diagnosis of hemangioblastoma.

The combination of clinical signs and symptoms, including bilateral renal cysts and cerebellar hemangioblastoma, led to the diagnostic hypothesis of VHL syndrome. Genetic testing of the patient confirmed the mutation. The patient continues follow-up care with two first-degree sisters who also tested positive for the mutation in the VHL genetic test.

Discussion

SVHL syndrome was first described by Eugen Von Hippel in the late 19th century due to retinal angiomatous disease and was complemented by Arvid Lindau, who associated retinal lesions with cerebellar alterations [2]. It is caused by a pathogenic variant in the tumor suppressor gene located on chromosome 3p25. Inhibition of the tumor suppressor gene on the short arm of chromosome 3 results in cellular hypoxia, leading to increased transcription of pro-tumor molecules that promote vascular abnormalities [5,6].

The most common tumors associated with VHL disease are hemangioblastomas located in the retina and CNS (cerebellum,

Citation: Cavalcante JBF, Cembraneli PN, Cembraneli IN, et al, Cerebellar Hemangioblastoma in A Patient With Von Hippel-Lindau Syndrome. Neurol Neurosci. 2025;6(2):0191.

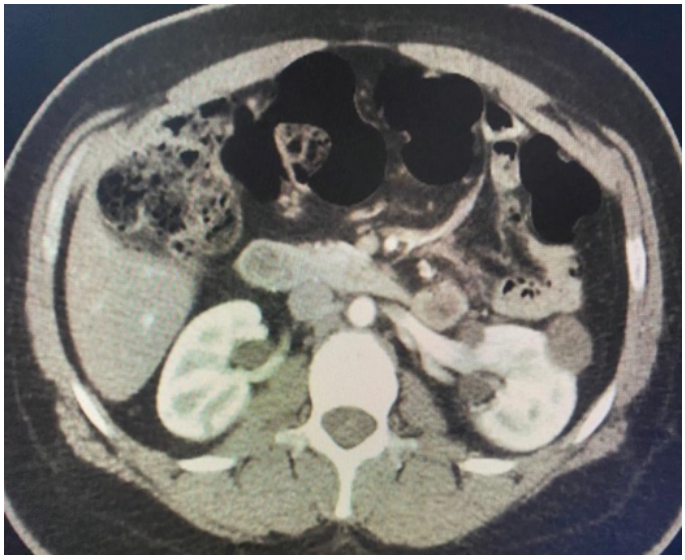

***Figure 1**. Sagittal, coronal, and axial cranial CT scan showing a bone defect due to decompressive craniectomy, with a midline shift and compression of the brain parenchyma.*

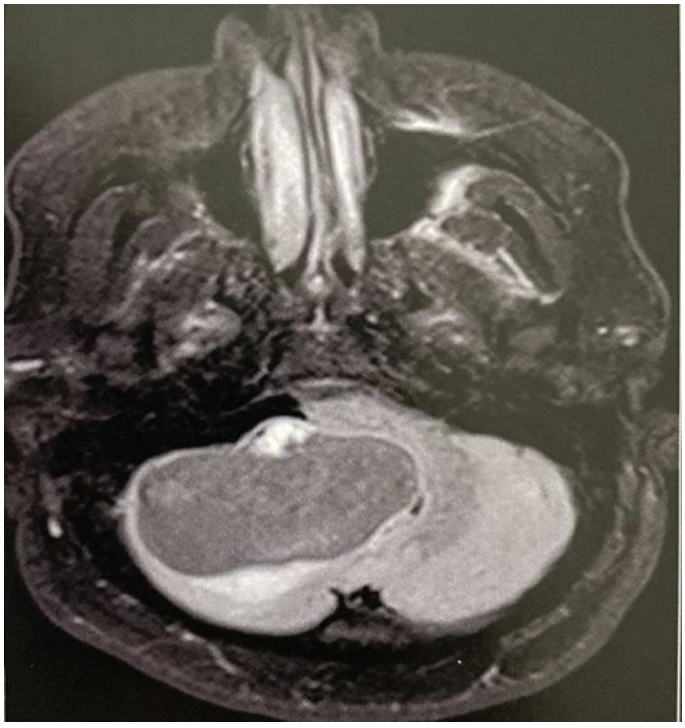

***Figure 2**. T1-weighted cranial MRI, axial section, showing a cystic lesion in the cerebellar region with an intramural nodule.*

brainstem, or spinal cord), clear cell renal carcinoma (CCR), pheochromocytoma, non-secretory pancreatic neuroendocrine tumors, and endolymphatic sac tumors. Visceral cysts (renal, pancreatic, and epididymal) occur frequently and may suggest the diagnosis when detected alongside other tumors [7-8].

Diagnostic criteria include the presence of two hemangioblastomas (in the CNS or retina) or one hemangioblastoma combined with a visceral manifestation. About 50% of individuals with VHL syndrome present with only a single manifestation of the syndrome, and in these cases, genetic testing is crucial for establishing the diagnosis. In

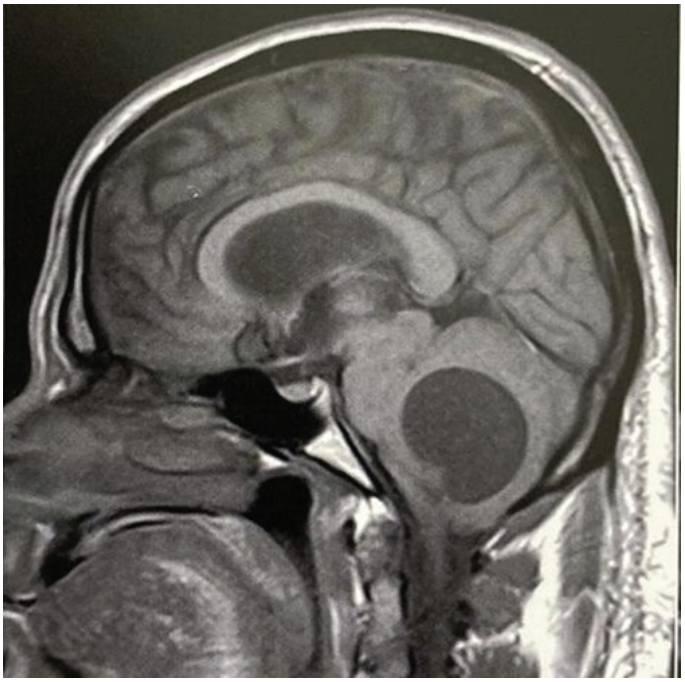

***Figure 3.** T1-weighted cranial MRI, sagittal section, showing a cystic lesion in the cerebellar region with compression of the brainstem and fourth ventricle.*

familial cases, only one manifestation is sufficient for diagnosis [9,10].

VHL syndrome is classified as type 1 or type 2, with the differentiation based on the presence or absence of pheochromocytoma. Type 2 is less common, representing 7 to 20% of cases [11,12].

Most mutations responsible for type 1 VHL syndrome carry a low risk for pheochromocytoma development. In type 2 VHL syndrome, associated with a high risk of pheochromocytoma, the disease can be further subdivided into three categories: Type 2A, which has a high risk for pheochromocytoma and low risk for CCR and pancreatic endocrine tumors; Type 2B, associated with a high risk for pheochromocytoma, CCR, and pancreatic endocrine tumors; and Type 2C, characterized by isolated familial pheochromocytoma [7,8,11-14].

CNS hemangioblastomas in patients with VHL syndrome occur in 60-80% of patients, with a mean age of 39 years, and the most common locations are the cerebellum, medulla, and brainstem [15-17].

The clinical presentation varies with tumor location and can include headaches, dizziness, ataxia, dysmetria, nystagmus, ptosis, vomiting, dysphagia, paroxysmal hypertension, paresthesias, hypo- or hypertonia, paraplegia, pain, or hyperesthesia. Diagnosis is established by MRI of the neuroaxis (cranium, cervical, thoracic, and lumbar spine). The relative unpredictability of cyst and tumor appearance in VHL disease necessitates lifelong follow-up for these patients [15-19].

Surgical treatment should be indicated for symptomatic lesions. Preoperative arterial embolization is used in some cases to prevent hemorrhage, which is commonly associated with hypervascularized tumors. For hemangioblastomas smaller than 3 centimeters without peritumoral cysts, or for multiple or inaccessible lesions, stereotactic radiosurgery may be considered. However, this treatment modality carries a higher

risk of recurrence. Additionally, it may contribute to transient vascular permeability and subsequent edema and peritumoral cyst formation [15-19].

Histologically, these benign tumors consist of stromal cells supported by a dense vascular network, with hyperchromatic nuclei, atypia, and rare mitoses, and the cytoplasm filled with lipid vacuoles. They resemble clear cell CCR microscopically, which may complicate the distinction between a primary CNS tumor and a metastasis. The peritumoral cyst contains clear to hemorrhagic fluid [3,9,15-19].

Despite classification, there is considerable phenotypic variation, often within the same family, making screening and early diagnosis critical for reducing the morbidity and mortality of the disease. Patients aged 0-4 years should undergo fundoscopy and clinical evaluation (blood pressure and neurological examination) annually; for ages 5-15 years, plasma/urinary metanephrines, abdominal ultrasound after age 8, abdominal MRI if biochemical alterations are present, and audiological evaluation if symptomatic should be performed. All patients over 15 years old should undergo annual abdominal and neuroaxis MRIs [20].

For VHL patients under annual surveillance, early detection and treatment pathways for symptomatic retinal hemangioblastomas and CCR are well-established. For CNS hemangioblastomas, detecting an asymptomatic lesion usually does not lead to surgical removal. Therefore, regular monitoring is usually initiated, and surgery is delayed until symptoms develop (hemangioblastomas associated with a cyst are more likely to become symptomatic) [21].

The main causes of death are due to CCR metastases, neurological lesions from CNS hemangioblastomas, and the surgical approaches that the patient may undergo [22,23].

Conclusion

VHL syndrome is characterized by benign and malignant tumors, with or without specific endocrine alterations, including hemangioblastoma, CCR, and pheochromocytoma. Manifestations frequently occur in adult patients; however, screening should begin in childhood when there is suspicion or a family history. Imaging tests and genetic testing are the main resources for diagnosis, follow-up, and treatment. Follow-up should be done with a multidisciplinary team due to the complexity of the disease.

Conflict of Interests

The authors have no conflict of interests to declare

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