Trigeminal nerve hemangioblastoma in the setting of undiagnosed von Hippel–Lindau disease: illustrative case

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BACKGROUND  Von Hippel–Lindau disease (VHL) is an autosomal dominant tumor predisposition syndrome caused by mutations in the VHL gene. Patients with VHL are predisposed to developing numerous neoplasms, including central nervous system hemangioblastomas that typically arise within the cerebellum, brainstem, or spinal cord. The authors present the unusual case of a 69-year-old patient with a hemangioblastoma of the trigeminal nerve as his initial presentation of VHL.

OBSERVATIONS  A 69-year-old male presented with progressive right-sided V3 paresthesias, gait disturbance, and diplopia. Magnetic resonance imaging demonstrated an enhancing 0.5-cm nodule within the right trigeminal nerve and an associated peritumoral cyst exerting mass effect on the cerebral peduncle. Neural axis imaging demonstrated pia-based enhancing lesions concerning for multiple spinal hemangioblastomas. The patient underwent an uncomplicated retrosigmoid craniotomy for trigeminal nerve hemangioblastoma resection. The patient had postoperative improvement in his gait, diplopia, and facial paresthesias. Genetic testing revealed that the patient was heterozygous for a pathological mutation in the VHL gene.

LESSONS  Hemangioblastomas in adults over 50 years of age should prompt a workup for VHL. Recognizing that cranial nerves are a possible site of hemangioblastoma occurrence is important for neurosurgeons and radiologists alike. Resection of cranial nerve hemangioblastomas is technically challenging but can lead to symptom improvement for patients.

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KEYWORDS  von Hippel–Lindau disease; case report; hemangioblastoma; trigeminal nerve

Von Hippel–Lindau disease (VHL) is an autosomal dominant tumor predisposition syndrome characterized by a germline mutation in the VHL tumor suppressor gene on chromosome 3p. Patients with VHL are prone to the development of numerous visceral cysts, central nervous system (CNS) hemangioblastomas (HBs), pheochromocytomas (Pheos), pancreatic neuroendocrine tumors (PNETs), renal cell carcinomas (RCCs), and endolymphatic sac tumors (ELSTs). VHL is rare, affecting 1 in 36,000 live births, but it is highly penetrant, with more than 90% of affected individuals demonstrating one or more sequelae of the disorder by 65 years of age. While the majority of patients with VHL have a known family history of the disorder, up to 20% of individuals can present with the condition de novo. Therefore, it is imperative that physicians and neurosurgeons are aware of the potential manifestations of VHL disease.

Several clinical criteria have been published for the diagnosis of VHL, including the Dutch, Danish, and international criteria. The Dutch criteria suggest that in the absence of a family history of VHL, two or more VHL-related manifestations (HB, Pheo, RCC, retinal HB, PNET, ELST) are required to confirm a clinical diagnosis of VHL. In both the Danish and international criteria, however, two or more CNS HBs are sufficient to make a clinical diagnosis of VHL. Genetic testing can be informative in establishing a diagnosis of VHL if a pathological germline mutation in the VHL gene on the short arm of chromosome 3 is identified.
The majority (60%–80%) of patients with VHL will have at least one CNS-related HB. VHL HBs tend to occur in the cerebellum (45%), spinal cord (36%), cauda equina (11%), or brainstem (7%). Less than 1% of VHL-related HBs will occur in the infundibulum, along the optic nerve, or along a peripheral nerve root. Excluding optic nerve HBs, HBs associated with other cranial nerves have rarely been reported.

Here, we present the case of a 69-year-old man who presented with a symptomatic trigeminal nerve HB and underwent successful excision of his tumor with improvement in his preoperative symptoms.

Illustrative Case

A 69-year-old otherwise healthy male presented with progressive right-sided facial paresthesias, ataxia, and diplopia. His medical history was noncontributory; however, his mother had died of RCC more than 20 years prior. On physical examination, he appeared well. He had diminished light touch over his right face in the V1, V2, and V3 distributions. He had right-sided dysmetria and was unable to perform tandem gait. The remainder of his cranial nerve and neurological examination was unremarkable.

Magnetic resonance imaging (MRI) demonstrated a 0.5-cm enhancing nodule within the right trigeminal nerve with a peritumoral cyst that was exerting mass effect on the cerebral peduncle, cerebellum, and pons (Fig. 1). Differential diagnoses included HB, pilocytic astrocytoma, and metastatic disease. Additional neural axis imaging was therefore performed and was notable for multiple pia-based enhancing lesions along the thoracic spinal cord and cauda equina (Fig. 2). Computed tomography of the chest, abdomen, and pelvis did not demonstrate any evidence of RCC, other primary tumors, or metastatic disease. The dilated retinal fundoscopic examination was unremarkable. The differential diagnosis at this point was multiple CNS HBs versus leptomeningeal carcinomatosis. Six-month interval surveillance for the patient’s spinal disease was planned, with annual monitoring thereafter. Surgery for the spinal lesions would be reserved for the onset of clear symptom development. As the patient did not have any evidence of a primary tumor and otherwise appeared well, it was believed that multiple HBs and a new diagnosis of VHL were likely. Given the symptomatic nature of the patient’s posterior fossa cyst and trigeminal tumor, retrosigmoid craniotomy with tumor resection and cyst aspiration was recommended to establish a definitive diagnosis and improve the locoregional mass effect along the brainstem and cerebellum.

The patient underwent an uncomplicated right retrosigmoid craniotomy for resection of the trigeminal tumor with concurrent cyst aspiration. Intraoperatively, a cherry red tumor situated within the fascicles of the trigeminal nerve was identified (Fig. 3) and resected without complication. The resected tumor was intimately associated with the trigeminal nerve and was composed of numerous blood vessels admixed with vacuolated, inhibin-positive stromal cells (Fig. 4). A gross-total resection was achieved (Fig. 1) with significant improvement in the posterior fossa cyst. The patient did well, with resolution of his ataxia and diplopia. His paresthesias over the V1 and V2 distributions resolved within 1 month of surgery. Six months after surgery, his V3 paresthesias persisted but had improved. Postoperative genetic testing showed that the patient was heterozygous for the p. Y98H (c.292T>C) pathogenic mutation in the VHL gene, confirming the diagnosis of VHL.
Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

HBs are benign, rare tumors of the CNS with an overall incidence of 0.1 cases per 100,000 person-years. While the majority of newly diagnosed HBs are sporadic and are not associated with VHL, the presence of a newly diagnosed HB should prompt consideration of an underlying tumor predisposition syndrome. Patients with VHL require multidisciplinary management to screen for RCC, Pheo, and ELST with neural axis imaging. Herein, our patient presented with a symptomatic HB that prompted neural axis imaging, which ultimately demonstrated multiple spinal HBs, findings consistent with VHL. Although most patients with VHL present earlier in life, there is significant phenotypic variability among patients and even among first-degree relatives. It is therefore plausible that the patient reported herein had a mild disease course throughout most of his adult life. Furthermore, while the patient did not have a family history of VHL, the presence of RCC in his mother raises the question of whether her RCC was the result of unrecognized VHL.

Our case is also notable for the patient’s HB arising from the trigeminal nerve. Excluding optic nerve HBs, to our knowledge, there have been fewer than 10 cases of cranial nerve–associated HBs. Liu et al. also reported a series of 35 patients with trigeminal neuralgia caused by cerebellopontine angle tumors. One of these patients had an HB, but the outcome of subtotal resection in this patient was not specifically reported. Roberti et al. reported a sporadic HB emanating from the trigeminal nerve. This patient presented with facial numbness and an associated headache. Brain MRI revealed an HB in Meckel’s cave. The patient underwent endovascular treatment to decrease feeder vessel supply, followed by gross-total resection of the tumor with a partial labyrinthectomy petrous apicectomy approach. Postoperatively, this patient experienced persistent V3 numbness, as did our patient, with additional conductive hearing loss. Although there are few known cases, the existing reports of HBs involving the trigeminal nerve have resulted in a significant improvement in related symptoms upon resection of the lesion.

While these prior reports and the current case involved the treatment of cranial nerve HBs with resection, there may be indications for alternative treatments in select cases. Stereotactic radiosurgery has been reported as a treatment for recurrent and residual intracranial HBs. Antiangiogenic therapy with agents, such as bevacizumab, can be used when surgical options are limited or the patient has multiple progressive HBs warranting systemic therapy. Finally, the recently Food and Drug Administration–approved hypoxia-inducible factor-2α inhibitor belzutifan can be considered for patients with VHL-associated RCC and CNS HBs.

The primary limitations of this study are its sample size and subsequent limited generalizability to a larger population of patients. Additionally, this retrospective study is limited by the available data in the medical record.

This case adds to the limited knowledge of HBs arising from cranial nerves. HBs should be considered in the differential diagnosis when a cystic mass with a mural nodule is identified arising from a cranial nerve. In cases of suspected VHL, preoperative screening for Pheo should be performed. Microsurgical resection of symptomatic cranial nerve–associated HBs is technically challenging, but if performed by an experienced surgeon, it can lead to an improvement in preoperative symptoms.

Lessons

A trigeminal nerve HB is a rare occurrence that may serve as a presentation of VHL. Although VHL typically presents in the first few decades of life, any patient with multiple HBs should prompt a workup for VHL. While resection of these trigeminal HBs can be technically challenging, this intervention can result in significant resolution of the patient’s symptoms.

References


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Conception and design: Busch, Matos Cruz, Shepard. Acquisition of data: Busch, Matos Cruz, Gyure, Shepard. Analysis and interpretation of data: Busch, Gyure, Yu, Shepard. Drafting the article: Busch, Shepard. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Busch. Administrative/technical/material support: Matos Cruz, Shepard. Study supervision: Matos Cruz, Shepard.

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