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Spinal cord hemangioblastomas in von Hippel–Lindau disease

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Abstract

Background. von Hippel-Lindau disease (VHL) is an autosomal dominant familial neoplasia syndrome. The most common manifestation of VHL is central nervous system hemangioblastomas. VHL patients will often develop multiple hemangioblastomas along their craniospinal axis over their lifetime. Spinal cord hemangioblastomas account for nearly half of all nervous system hemangioblastomas in VHL.

Methods. The authors conducted a literature review and summation of available articles on spinal cord hemangioblastomas associated with VHL.

Results. The embryological origins, epidemiology, natural history, surgical outcomes, nonsurgical treatments, and future directions in spinal cord hemangioblastomas are discussed.

Conclusions. Hemangioblastomas in VHL are optimally managed with a multidisciplinary approach that includes surgical resection of symptomatic lesions. Novel treatments are gaining traction, but must be studied further for efficacy and safety.

Keywords

hemangioblastoma | spinal cord | von Hippel-Lindau disease

Central nervous system (CNS) hemangioblastomas are benign vascular neoplasms.[1] These tumors develop sporadically (60%–70% of cases) or in association with von Hippel–Lindau disease ([VHL]; 30%–40% of cases).[2–4] Ninety-nine percent of CNS hemangioblastomas are found below the level of the tentorium along the craniospinal axis. They are most frequently found in the cerebellum (45%–50% of nervous system hemangioblastomas), spinal cord (35%–40%), brain stem (2%–5%), and cauda equina (8%–10%).[5–8] Irrespective of the anatomic origin, these tumors exhibit a saltatory growth pattern (characterized by periods of growth and quiescence).[9] Tumor-associated symptomatology is most commonly linked with a peritumoral cyst or syrinx formation.[5,8,9] Hemangioblastoma-associated signs and symptoms are variable and dependent on the anatomic location of the lesion. Despite their benign pathology, CNS hemangioblastomas represent a significant source of morbidity and mortality.

The management of spinal cord hemangioblastomas in VHL can be complex due to the frequent multiplicity and variable nature of these tumors along the craniospinal axis. Nevertheless, surgical resection is the treatment of choice for symptomatic sporadic and VHL-associated nervous system hemangioblastomas. We discuss the molecular/genetic mechanisms, epidemiology, clinical manifestations, treatment strategies, and outcomes for VHL-associated spinal cord hemangioblastomas.

Molecular and Genetic Mechanisms

The *VHL* gene (tumor suppressor gene) is located on the short arm of chromosome 3 (3p25-26).[10] The gene encodes for the VHL protein (pVHL) that is critical for regulatory function in the hypoxia-inducible factor (HIF) pathway. pVHL acts to degrade the HIF-2α subunit and prevent persistent hypoxia signaling in tissues. When pVHL is mutated, it cannot perform this function, leading to increased and continuous HIF expression that is associated with tumor propagation.[11,12] Tumor formation

and progression occur when HIF-related genes become upregulated, including growth signals, angiogenesis-supporting factors (such as vascular endothelial growth factor [VEGF]), and glucose metabolism genes.[2,13] Because of unregulated HIF signaling in VHL tumors, which lack heterozygosity of the *VHL gene*, tumor cell propagation is supported and driven in a hypoxic environment enriched with growth factors and neovascularization.

Embryologic Origin of Hemangioblastomas

Because of their multiplicity and highly conserved anatomic distribution, it has been suggested that hemangioblastomas may have an embryologic origin.[14–16] Specifically, Lindau and Cushing hypothesized that an embryologic precursor cell was the origin of hemangioblastomas based on the histologic features and conserved anatomic distribution. They further hypothesized that this cell could develop into endothelial (vessel) and red blood cells that are seen in hemangioblastomas.[17] However, it was not confirmed until Choi and colleagues discovered that during normal embryologic development, hematopoietic and endothelial cells have a common cell precursor, which they termed a "*hemangioblast*."[15] Embryologic hemangioblasts are defined by the expression of 3 markers, including stem cell leukemia (Scl), FLK1 (VEGF receptor 2), and brachyury. These embryologic cells are present only during mesodermal development in patients who do not have VHL.

To define the origin of hemangioblastomas based on a hypothesis by Lindau and Cushing, Park and colleagues characterized neoplastic cells (defined by loss of heterozygosity) from resected hemangioblastomas in VHL patients.[18] They found that neoplastic cells demonstrated expression of the 3 characteristic markers that define embryologic hemangioblasts.[18] To confirm their pluripotent potential, hemangioblastoma neoplastic cells were grown in cell culture. The tumor-derived hemangioblasts differentiated into erythrocytes, granulocytes, and endothelial cells, confirming their ability to develop into hemangioblastomas. Moreover, Merrill and colleagues determined that intratumoral mast cells are also derived from hemangioblasts that have undergone loss of heterozygosity.[19] These findings support the concept that hemangioblasts are the arrested mesodermal embryologic cells of origin and retain their ability to differentiate into cell types found in hemangioblastomas.

Epidemiology and Clinical Manifestations

Epidemiology

VHL has an incidence of approximately 1 in 36 000 live births (total prevalence of 1 in 38 000 to 1 in 91 000 persons).[1,2,20,21] Approximately 20% of the new VHL cases are due to de novo germline mutation and 80% are familial.[13] VHL is transmitted in an autosomal dominant manner. Typically, VHL has a symptomatic clinical onset in the third to fourth decade of life with over 90% developing a characteristic sign of the disease by 34 years of age.[2,22] VHL patients will have nearly complete penetrance by the age of 60 years.[20,23] Over 90% of VHL patients will develop a CNS hemangioblastoma during their lifetime (the average age at symptom onset from spinal cord hemangioblastoma in VHL is 33 years of age). Overall (both sporadic and VHL-associated), the mean age of symptomatic spinal hemangioblastoma development is 48 years of age (range, 45.2–50.9 years).[24] Spinal cord hemangioblastomas have male predominance (1.4 to 1 ratio).[25]

Surveillance

VHL patients require serial observation, laboratory testing, imaging, and care by multidisciplinary teams (Table 1).[8] The VHL Alliance recommends that any adult with VHL should

Table 1. Multidisciplinary Screening Recommendations for Patients Diagnosed with VHL (adapted from Chittiboina and Lonser 2015[2] and Binderup et al., 2022[26])

Age	Recommendation				
	Eye clinical exam	CNS clinical exam	Hearing exam	Imaging	Lab testing
0–4 years old	Annual retinal evaluation: Can be performed via many techniques, but most commonly via ophthalmoscopy with or without wide angle funduscopy	Annual general pediatric examination	N/A	N/A	N/A
5–14 years old			Annual hearing examination	MRI of the CNS (brain and neuroaxis) including the inner ear with contrast: Baseline scan at age 10 years	Annual plasma metanephrine and plasma normetanephrine
>15 years old		Annual neurological evaluation	Annual or Biannual: Hearing examination	Every second year: MRI of the CNS (brain and neuroaxis) including the inner ear with contrast AND Imaging of the abdomen Either US or MRI abdomen can be performed	

Note: MRI = magnetic resonance imaging; US = ultrasound examination.

be surveilled annually for abdominal and ophthalmologic pathologies, with a magnetic resonance (MR)-imaging scan of the entire neuroaxis every 2 years to screen for new CNS manifestations (or upon sign/symptom formation).[13,26] The Alliance also recommends baseline evaluations in adolescent (5–14 year old) patients based on expert consensus. These recommendations are guided by the fact that early detection and judicious management of CNS hemangioblastomas can provide the best long-term functional outcome.[23] Because of improvements in detection, surveillance, and understanding of the natural history of the disease, VHL patients born after the year 2000 have an increased life expectancy of 67 years for women and 60 years for men.[27] This is significantly improved from the historical estimated life expectancy of 52 years.[28]

Natural History

The natural history of CNS hemangioblastomas, including spinal cord hemangioblastomas, is characterized by long periods of quiescence interrupted with rapid growth ("*saltatory*" growth pattern). To define the natural history of VHL-associated nervous system hemangioblastomas, Lonser and colleagues performed a prospective natural history study at the National Institutes of Health. This study found that VHL patients develop an average of 0.4 tumors/year/patient.[5] However, there was a significant decline in new tumor formation after the fourth decade of life. Although 94% of hemangioblastomas remained asymptomatic, 6% developed symptoms during the study period (7.5 years) and required treatment.[5] This study demonstrated that it was not possible to predict which tumors would become symptomatic requiring surgery and that imaging progression was not an indication for resection. These findings indicate that judicious surgery of early symptom forming tumors can minimize the need for surgery and its attendant risks over a lifetime.

Clinical Presentation

The most common presenting signs/symptoms of spinal hemangioblastoma in descending order of frequency are sensory changes, pain, motor changes, and/or bowel/bladder dysfunction. The signs/symptoms are related to tumor location, Specifically, 66% of spinal cord hemangioblastomas are found in the dorsal root entry zone and 96% are located posterior to the dentate ligaments.[5,7,8] As such, symptoms are related to compression of the dorsal columns, that is, balance issues, dysesthesia, and proprioceptive issues. Hemangioblastomas most often possess both intramedullary and extramedullary components, followed by primarily extramedullary and primarily intramedullary locations.[8,29] Occasionally, sacral hemangioblastomas that remodel the bone locally and cause progressive sacral destruction can be encountered.[30] The anatomic distribution of hemangioblastomas is shown in Figure 1.

Imaging Presentation

The MR imaging is the best modality to define and assess spinal cord hemangioblastomas. Hemangioblastomas have a characteristic appearance on MR imaging. They avidly enhance on T1-weighted postcontrast images. Spinal cord hemangioblastomas may be associated with edema and/or peritumoral cysts (or syringes) that are best defined on T2/FLAIR MR imaging.[29,31,32] Arteriography, with its small but attendant risks, is rarely necessary to diagnose nervous system hemangioblastomas. Arteriography can be used to define vascularity (vascular "*road map*") in very large hemangioblastomas. Furthermore, we and others do not routinely use preoperative tumor embolization due to the inherent risks associated with it and the high rate of successful resection without hemorrhagic complications with microsurgery.[8,33,34] Similarly, adjuncts such as indocyanide green angiography have been used to evaluate the extent of hemangioblastoma resection and identify associated vessel anatomy during resection. However, it has not changed extent of resection or complication rates.[35]

Because VHL patients often have multiple spinal hemangioblastomas that may or may not be symptomatic, it is important to correlate imaging findings with precise neurologic examination to define symptom/sign-producing tumors when present. Surgeons can best define symptom-causing tumors via careful neurologic exam correlation with MR imaging findings. Mossel and colleagues found that larger tumors (mean, 300 mm^2 or more), peritumoral edema, and/or the presence of spinal cysts were more likely to be associated with neurologic symptoms.[36]

Treatment Strategies and Outcomes

Often, VHL patients will develop multiple spinal hemangioblastomas over their lifetime. The indication for surgical treatment is early signs/symptom formation. The data support surveillance for asymptomatic patients and treatment of only symptomatic patients, due to the slow and unpredictable progression of spinal hemangioblastomas.

Surgical Resection

CNS hemangioblastomas are treated with microsurgical resection (Figure 2). The goal of surgery is the complete removal of the tumor.[5,32,37–39] During resection, the surgeon performs circumferential microsurgical dissection of vascular supply via cautery and sharp transection of the feeding vessel. This allows for the tumor to be resected en bloc with minimal blood loss. Given that most tumors are located posteriorly and/or posterolaterally, the preferred approach is a laminectomy for surgical access. Laminectomy and laminoplasty have been compared in the literature and there are no difference in progressive deformity rates between them.[40] Ventrally located tumors, may need to be approached via lateral or anterior surgical corridors. Because hemangioblastomas of the cauda equina and nerve roots have an intrafasicular origin, the nerve root of origin must be resected for complete excision of the tumor. Fortunately, the vast majority

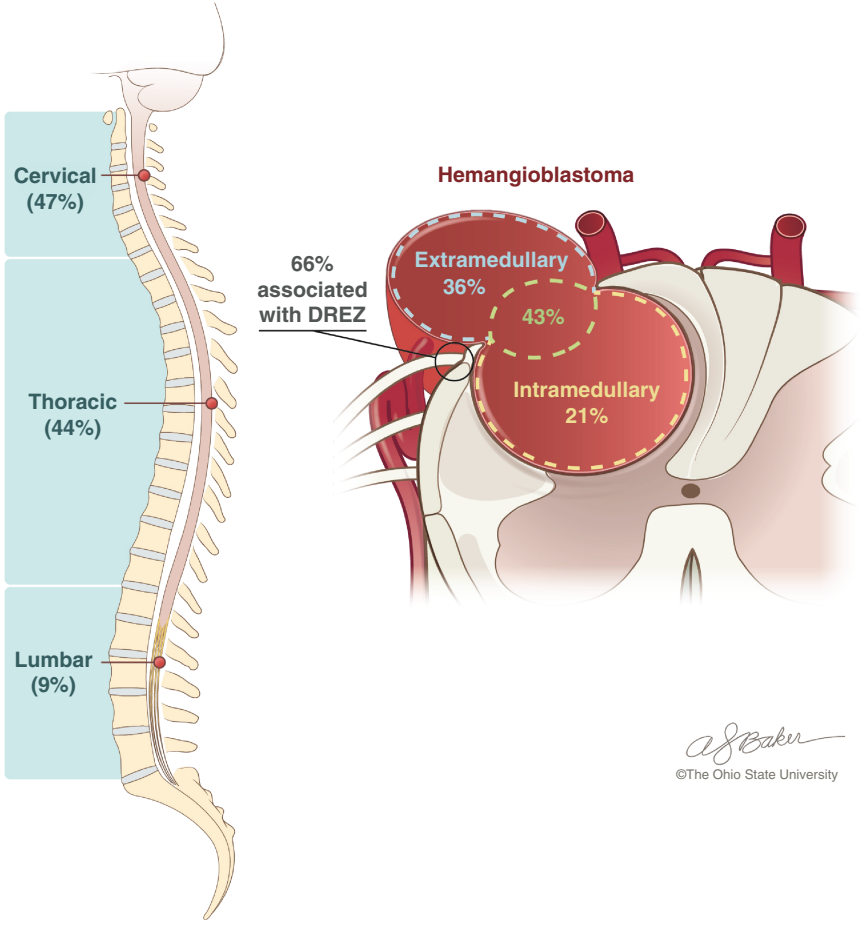

Figure 1. Visual representation of spinal region location and cross-sectional anatomic location of spinal cord hemangioblastomas (percentages obtained from Mehta et al.[8]). Spinal hemangioblastomas are seen mostly in the cervical spinal cord and become less common in the thoracic, lumbar, and sacral regions. Most are associated with the dorsolateral portion of the cord, and more than half are near the dorsal root entry zone.

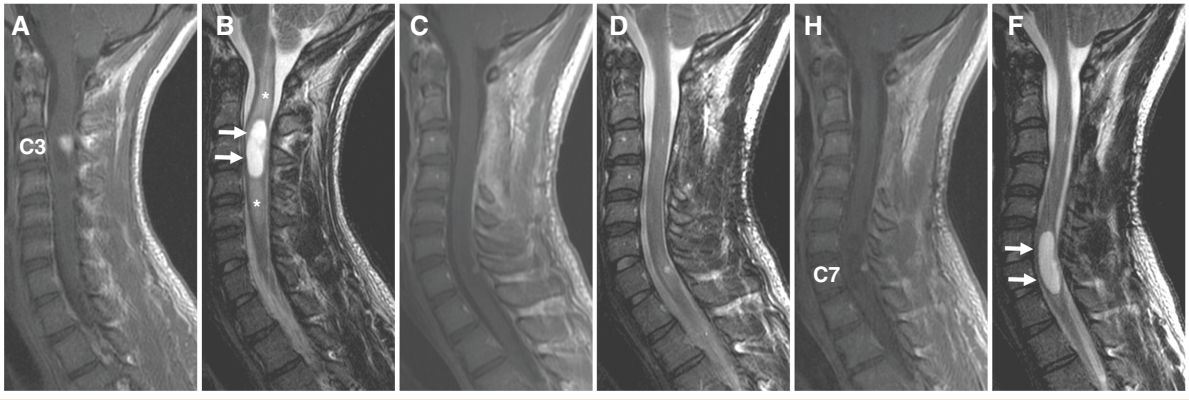

Figure 2. Sagittal T1- and T2-weighted magnetic resonance (MR) imaging of the cervical spine in a von Hippel–Lindau disease patient demonstrating an intramedullary hemangioblastoma. Preoperative contrast-enhanced imaging (**A**) and T2-weighted imaging (**B**) show a hemangioblastoma with associated syrinx (*arrows*) and spinal cord edema (*asterisks*). Laminectomies were performed for access. Postoperative imaging obtained at 7 months follow-up confirmed complete resection (**C**) and demonstrated syrinx and edema reduction (**D**). Twenty month follow-up (**E** and **F**) showed progression of another hemangioblastoma at C-7 with syrinx development (*arrows*). ***Figure adapted from Mehta et al.[8]

of these tumors arise from sensory roots and may be resected with minimal to no neurologic deficit in our experience.[30,41]

Associated syringomyelia will resolve once the offending tumor is removed. There is no need to fenestrate the cyst (although this may happen during resection) or resect the cyst/syrinx wall. Prior studies have shown that 96% of syrinx cavities will collapse or shrink after tumor resection.[8]

Other adjuncts for surgery have been used to improve upon established surgical techniques. Some groups have begun using minimally invasive (MIS) approaches to reduce operative morbidity and blood loss associated with hemangioblastoma resection. High degrees of efficacy can be achieved with MIS approaches, for example, Kruger et al. demonstrated 94.5% neurological stability or improvement and a 100% gross total resection rate in their series of 18 MIS-treated patients (16/18 VHL).[42] Intraoperative ultrasound can be utilized to localize the lesion after lamina removal, and again when the lesion is resected to evaluate for residual if there is concern. Intraoperative neuromonitoring can be utilized to identify tumor edge and may inform the surgeon of when dissection is too aggressive or when to expect postoperative neurological changes, but it has not improved or changed outcomes to a significant degree according to a recent systematic review.[35]

Surgical Outcomes

Resection is a highly effective, safe, and durable treatment for spinal cord hemangioblastomas. Mehta and colleagues found that after resection of 218 spinal cord hemangioblastomas in 108 VHL patients, complete resection was achieved for 99.5% of tumors with a 96% rate of clinical stability or improvement.[8] However, 60% of patients will experience transient deficits (not function-limiting) in the immediate postoperative period.[8] They also found that ventral tumors and completely intramedullary tumors had a higher risk of postoperative functional decline. Overall, microsurgical resection is the gold standard given its high degree of success and stability or improvement of neurological symptoms.

Nonsurgical Management

General

Nonsurgical treatments have been used for spinal hemangioblastomas, including radiation therapy (most often stereotactic radiosurgery [SRS]) and systemic therapies that target pathways associated with VHL tumorigenesis.

Radiation Therapy

Asthagiri and colleagues performed a prospective multicenter trial examining the effectiveness of SRS for the treatment of cerebellar and brainstem hemangioblastomas in VHL. The study included 20 VHL patients with 44 hemangioblastomas. They found that the SRS-treated hemangioblastomas achieved local control rates at 2, 5, 10, and 15 years of 91%, 83%, 61%, and 51%, respectively. Compared to the natural history of VHL-associated hemangioblastomas, they found no difference between the natural history of untreated hemangioblastomas and SRS-treated tumors after 10 years indicative of a diminished impact over long-term follow-up.[43] Consequently, SRS should be reserved for patients who cannot safely undergo definitive surgical resection.[8] When patients do undergo SRS, they should be monitored at regular intervals for radiation-associated symptoms and/or swelling and managed appropriately with steroids and/or operative intervention.

Chemotherapy

Previously, trials have used VEGF inhibitors to treat VHL-associated tumors, including nervous system hemangioblastomas. These studies have not shown benefits in controlling nervous system hemangioblastomas but were associated with symptomatic relief due to decreased tumor permeability and peritumoral edema.[44,45] Recently, belzutifan has been used to successfully treat VHL-associated tumors.[46,47] Belzutifan is a small-molecule inhibitor of the HIF 2α subunit. It has shown efficacy in treating VHL-associated tumors. Specifically, it was shown to provide a 30% objective response rate in CNS hemangioblastomas over 21.8 months of median follow-up in 50 patients.[46] Based on these data, the FDA has approved for the use of belzutifan in the treatment of VHL-associated tumors. However, it is not indicated for the treatment of hemangioblastomas that require surgical resection.[48] Currently, belzutifan should be utilized in patients with progressive VHL-associated hemangioblastomas that are currently asymptomatic or unresectable. There is no direct guidance on the size or multiplicity of tumor thresholds for the use of the drug.

Future Directions

An important area of exploration includes the HIF-VEGF pathway. Groups have evaluated the effects of VEGF-targeting drugs (bevacizumab, cabozanitinib, etc.) but have not seen success in the management of hemangioblastomas[27,49,50] Targeting of the β-adrenergic receptor pathway is also being explored. Propanolol is being explored as a potential therapeutic for VHL-associated tumors because of its broad antagonistic effects on the β-adrenergic receptors, leading to down-regulation of vascular signaling.[51] Similarly, ICI-118551, a small-molecule inhibitor of the β2 adrenergic receptor, is being investigated as a therapeutic agent for hemangioblastoma treatment. Cuesta and colleagues published that the use of this molecule in vitro was able to reduce the viability of hemangioblastoma-derived cells in culture by triggering apoptosis.[52] Finally, modulators of protein degradation are being investigated in the treatment of VHL-related hemangioblastomas.[53] A recent

Phase 0 trial evaluated vorinostat in 7 VHL patients with symptomatic hemangioblastomas (patients with germline missense mutations). The patients received vorinostat for 7 days before surgery and tumors were resected. Tumors treated with vorinostat had increased active pVHL expression with concomitant reductions in HIF2α expression, indicating rescue from pVHL functional loss.[54] Additional studies of vorinostat and other novel therapeutics will be required to define their roles in the treatment of hemangioblastomas related to VHL.

Conclusions

VHL-associated spinal cord hemangioblastomas are benign tumors that can cause significant morbidity. Careful surveillance, multidisciplinary management, and resection at early sign/symptom formation are critical to provide the best possible outcome and lasting functional stability. Ongoing research may provide new systemic treatments for patients to be used as adjuncts or replacements for resection.

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