Functional Outcome After Resection of Von Hippel-Lindau Disease-Associated Cauda Equina Hemangioblastomas: An Observational Cohort Study

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BACKGROUND: Cauda equina hemangioblastomas in von Hippel-Lindau (VHL) disease can cause significant neurological signs and symptoms. Despite their associated morbidity, the management of these tumors remains incompletely defined.

OBJECTIVE: To determine optimal management, we analyzed the functional outcomes after resection of these tumors.

METHODS: VHL patients who underwent surgical resection of cauda equina hemangioblastomas at the National Institutes of Health and the University of Virginia were included. Clinical and radiological follow-up was performed at 6- to 12-month intervals after surgery.

RESULTS: Fifteen patients underwent 18 operations for 21 cauda equina hemangioblastomas (median follow-up 5.9 years). Patients often presented with multiple symptoms, including pain (67%), numbness (50%), urinary complaints (33%), and weakness (11%). Median preoperative tumor volume was 1.2 cm³. Four tumors at 3 operations were not resected due to a motor nerve root origin. Gross total resection was achieved in 14 surgeries (93% of operations when resection was attempted). New mild (non-function limiting) neurological symptoms were noted after 11 operations (61%), which most often (64%) resolved within 2 weeks of surgery. At 6-month follow-up, 15 patients (83%) were stable, 2 (11%) were improved, and 1 (6%) was worse. Histological analysis revealed that all tumors originated from within the involved nerve fascicle.

CONCLUSIONS: VHL-associated cauda equina hemangioblastomas have an intrafascicular origin and require interruption of the rootlet of origin for complete resection. Motor nerve root involvement may preclude complete resection but strategies including bony decompression and/or interruption of vascular supply may provide a therapeutic option. Nevertheless, most VHL patients with symptom-producing lesions improve with resection.

KEY WORDS: Cauda equina, Hemangioblastoma, Lumbosacral, Nerve root, von Hippel-Lindau disease

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Von Hippel-Lindau (VHL) disease is a tumor suppressor gene syndrome characterized by mutations in the *VHL* gene that result in central nervous system (CNS) and systemic tumors. VHL patients are predisposed to the development of multiple hemangioblastomas of the cerebellum, brainstem, and spinal cord that

can give rise to neurological sequelae. Hemangioblastomas may also arise from spinal nerve roots, including the cauda equina. Although cauda equina hemangioblastomas are present in the majority of patients with VHL (62%), few patients (2%) develop symptoms related to a cauda equina hemangioblastoma.¹ This may be due to greater space for growth within the lumbar cistern, as well as a diminished likelihood of tumor-associated cyst development, which is the most common cause of hemangioblastoma-associated symptoms in other CNS regions.^{1,2}

ABBREVIATIONS: CNS, central nervous system; MRI, magnetic resonance imaging; VHL, von Hippel-Lindau

When symptomatic, cauda equina hemangioblastomas can be challenging lesions to resect. Previous studies have suggested that cauda equina hemangioblastomas often involve sensory nerve roots.^{3,4} Nevertheless, involvement of motor nerve roots is possible and can increase the morbidity of complete surgical resection. Consequently, it is critical to understand the anatomical origin (motor and/or sensory nerve roots) of cauda equina hemangioblastomas and the long-term outcomes of resection. To date, only case reports and small series (6 or less patients, including sporadic cases) have been reported.³⁻¹¹ To define optimal management strategies and the outcome of resection of cauda equina hemangioblastomas in VHL, we analyzed the short- and long-term functional outcomes in patients who underwent surgical treatment.

METHODS

Patients

Patients with VHL disease who underwent surgery for resection of cauda equina hemangioblastomas at the National Institutes of Health (IRB-approved protocols 79-N-0089 and 03-N-0164, NCT00060541) between 1984 and 2015 and at the University of Virginia (IRB-approved protocol HSR# 13737) between 2007 and 2015 were identified. Informed consent to participate in clinical research studies was obtained from all patients. Six cases that were previously reported, in part, were included with additional follow-up to most accurately assess the long-term functional outcome and durability of surgical management.⁴ All patients had a confirmed diagnosis of VHL.

Clinical Evaluation

Detailed neurological examinations were performed before surgery and in the postoperative period. Patients were followed in 6- to 12-month intervals after surgery. To determine neurological function after surgery and distinguish this outcome from the progression of additional CNS tumors in VHL disease, functional outcome was recorded immediately (0-30 days) after surgery, in the short-term (6 months) after surgery, and over the long-term (most recent follow-up) after surgery. The short-term (6 months) outcome was used to assess the outcome of surgery in this cohort. Functional outcome was determined by the clinical grading scale described by McCormick.¹²

Imaging

Tumor location and size were determined by preoperative contrast-enhanced T1-weighted magnetic resonance imaging (MRI). Tumor volume was determined by the product of greatest anteroposterior diameter × greatest craniocaudal diameter × greatest mediolateral diameter × 0.5.¹³ Recurrence was determined based on MRI at last follow-up.

Surgical Technique

Surgical resection was performed as described previously.⁴ Briefly, a laminectomy was performed at the level of the tumor based on preoperative fluoroscopy. Ultrasound was then used to confirm the adequacy of the dural exposure. Following dural opening, microdissection was performed to isolate the tumor from uninvolved nerve roots. The involved nerve rootlet(s) was then tested for motor function using

electromyography (including anal sphincter, external urinary sphincter, and lower extremities), as well as testing for intravesicular pressure (detrusor contraction). If involved roots did not show evidence of motor function with stimulation, they were cauterized, sectioned, and removed with tumor. In cases of motor nerve rootlet involvement, the tumor was left in situ.

Statistical Analysis

Statistical analyses were performed using the software GraphPad Prism (Prism version 6.0, GraphPad Software, Inc.; La Jolla, California). All results were reported as median or mean ± standard deviation, unless otherwise specified. The effect of preoperative variables on outcome was not determined due to a paucity of events.

RESULTS

Patients

Fifteen consecutive patients with VHL (8 males, 7 females) who underwent surgery for cauda equina hemangioblastomas were included. These patients underwent a total of 18 operations for 21 hemangioblastomas (Table 1). The most common

TABLE 1. Clinical and Tumor Characteristics at the Time of Surgery

Variable	Operations (n = 18)
Age at surgery, median, years	45.5
Mean ± SD	40.7 ± 10.3
Range	24 to 58
Female ^a	7 (47%)
Prior operations for CNS tumors ^a , median	1
Mean ± SD	2.9 ± 3.7
Range	0 to 11
Symptomatic at time of surgery	18 (100%)
Symptoms at presentation	
Hypesthesia	9 (50%)
Dysesthesia/pain	12 (67%)
Weakness	2 (11%)
Bowel/bladder complaints ^b	6 (33%)
Length of follow-up, median, years	5.9
Mean ± SD	7.0 ± 3.9
Range	1.8 to 13
Number of tumors, median	1
Mean ± SD	1.1 ± 0.4
Range	1 to 2
Combined tumor volume, median (cm ³)	1.2
Mean ± SD	2.6 ± 3.6
Range	0.3 to 15
Largest tumor volume, median (cm ³)	1.2
Mean ± SD	2.5 ± 3.4
Range	0.2 to 15
Nerve root cyst	1 (6%)
Tumor entering neural foramen	6 (33%)
Preoperative embolization	1 (6%)

SD, standard deviation.

^aOf 15 patients.

^bAll urinary complaints.

FIGURE 1. MRI of a cauda equina hemangioblastoma with associated nerve root cyst. Sagittal T1-weighted postcontrast (left) and T2-weighted imaging demonstrate a contrast-enhancing hemangioblastoma at L2 (white arrows) with an associated cystic mass (white arrowhead). Axial T2-weighted imaging (right) rostral to tumor demonstrates a cystic mass (white arrowhead) displacing the cauda equina anteriorly and laterally.

presenting symptom before surgery was dysesthesia or pain (12 patients, 67% of operations). Patients also presented with hypesthesia (9 patients, 50%), urinary complaints (6 patients, 33%), and/or weakness (2 patients, 11%). Median follow-up was 5.9 years (mean, 7.0 ± 3.9 years; range, 1.8–13 years).

Tumor Characteristics

Twenty-one symptom-producing hemangioblastomas were identified on preoperative MRI. Median combined preoperative tumor volume was 1.2 cm^3 (mean $2.6 \pm 3.6 \text{ cm}^3$; range $0.3\text{--}15 \text{ cm}^3$). One patient had a tumor-associated nerve root cyst identified preoperatively (Figure 1). Twelve patients had primarily intrathecal tumors, 4 patients had tumors that extended from the lumbar cistern into the neural foramen, and 2 patients with multiple lesions had both tumors located completely intrathecally and others extending into the neural foramen. Preoperative arteriography with embolization was used in 1 patient with a large tumor (volume 15 cm^3 ; Figure 2).

Surgical Findings

Intraoperative neurophysiological monitoring was used in 15 operations (83%, Table 2). Neuromonitoring was deferred in 1 patient who was paraplegic at surgery and 2 patients due to surgeon preference. Four tumors (19%) at 3 operations were not resected due to a motor nerve root origin. One patient with 2 intrathecal tumors involving motor rootlets underwent selective microsurgical interruption of arterial feeders to both tumors. Tumor arterial feeders were identified by their tortuosity, subarachnoid location, and by their termination in tumors. This patient's presenting dysesthesia improved after surgery; however,

her hypesthesia remained unchanged and these tumors remained stable in size over 5.7 years of follow-up. A second patient with a right-sided S1 neuroforaminal tumor found to involve the motor root underwent bony decompression alone. Her presenting symptom of right-sided leg pain resolved despite an increase in tumor size (diameter 1.2 cm to 1.7 cm) over 4 years of follow-up. Finally, a patient with a 4.2 cm intrathecal tumor that was adherent to multiple motor roots underwent lumbosacral decompression alone, and was treated with postoperative radiation (44 Gy, 22 sessions). Two years later, due to tumor growth and progressive gait instability requiring a walker, the patient was treated with selective embolization and re-irradiation (18 Gy, 3 sessions). Tumor size has remained stable over an additional year of follow-up.

Of the remaining 15 operations where tumor resection was attempted, gross total resection was achieved in 14 (93%; Figure 2), with near-total resection performed in 1 case without neuromonitoring. At 3 operations where complete resection was achieved and 1 operation with near-total resection, internal debulking of the tumor was performed to facilitate safe resection. In each of the 14 operations where complete resection was achieved, sensory nerve rootlets involving the tumors were transected to effect complete resection of the tumor.

Functional Outcome

New neurological symptoms were noted after 11 operations (61%) including new numbness (6 of 18 operations; 33%), pain (1; 6%), weakness (2; 11%), new/worsened urinary symptoms (3; 17%), and/or muscle spasms (1; 6%). In most cases, new symptoms (7 of 11 operations with new symptoms; 64%) were

FIGURE 2. Preoperative axial (left) and sagittal (center) T1-weighted post-contrast MRI demonstrating a large (volume: 15 cm³) cauda equina hemangioblastoma (white arrowheads) involving and eroding the sacrum. Due to the size of this lesion, selective embolization was performed preoperatively. Gross total resection was achieved and no recurrence has been observed through 13 years of follow-up (most recent imaging, right).

TABLE 2. Surgical Findings and Characteristics

Variable	Operations (n = 18)
Neuromonitoring used	15 (83%)
Number of tumors resected, median	1
Range	0 to 2
Motor roots involved ^a	3 (20%)
Nerve roots interrupted	15 (83%)
Debulking required ^b	4 (27%)
Gross total resection achieved ^b	14 (93%)
Estimated blood loss, median (mL)	150
Mean ± SD	230.0 ± 217.7
Range	50 to 750

SD, standard deviation.

^aOf 15 surgeries where neuromonitoring was used.

^bOf 15 surgeries where resection was attempted.

TABLE 3. Short-Term Clinical Outcomes

Preop McCormick grade	6-month McCormick grade				Total
	I	II	III	IV	
I	10 ^a	–	–	–	10
II	1	4 ^a	1	–	6
III	1	–	–	–	1
IV	–	–	–	1 ^a	1
Total	12	4	1	1	18

^aStable postoperative McCormick clinical grade.

self-limited (resolved 2 days to 2 weeks postoperatively) and not function limiting. At 6-month follow-up (McCormick Scale), 15 patients (83%) were stable, 2 patients (11%) were improved, and 1 patient (5%) was worse compared to their preoperative status (Table 3). Functional decline in this 1 patient was likely related to progression of additional CNS hemangioblastomas, as he had remained functionally stable in the first month after surgery. Thirteen patients (72%) reported subjective improvement in their preoperative presenting symptoms.

Long-Term Outcome

During the follow-up period, 1 recurrence was noted after intended gross-total resection (1 of 14 cases, 7%). This patient underwent re-operation 8 years after the index surgery, and gross total resection was achieved without recurrence (follow-up, 16 months). The additional case with near-total debulking had no tumor regrowth noted over 5.9 years of imaging follow-up.

Complications

Complications included bilateral pleural effusions in 1 patient, pulmonary embolism in 1 patient, a pseudomeningocele in 1 patient (repaired 6 weeks after surgery), and an epidural hematoma that developed in 1 patient, resulting in pain (evacuated 5 days after surgery).

Histopathological Findings

In all cases where tumor was resected, a histopathological diagnosis of hemangioblastoma was confirmed. Nerve root infiltration by tumor was observed in all cases (Figure 3).

DISCUSSION

Cauda Equina Hemangioblastomas in VHL

In a recent prospective evaluation of 225 patients with VHL, 261 nerve root hemangioblastomas involving the cauda equina were identified in 139 (62%) patients.¹ Despite this frequency, relatively few patients (5 patients; 2%) became symptomatic from a cauda equina hemangioblastoma during a 10-year follow-up period. The biological and anatomic basis for this discrepancy may include the large potential space for growth in the lumbar cistern and the infrequency of tumor-associated cysts, which are the most frequent cause of hemangioblastoma-associated symptom formation in other CNS regions.^{1,2} Due to the paucity of cases requiring therapy, treatment options and outcomes have been poorly defined.

Prior Studies

The management of cauda equina hemangioblastomas has been previously described only in case reports and small clinical series.^{3–11} These series included 6 or fewer patients, frequently mixed sporadic and VHL-associated cases, and in some instances included nerve root tumors in the cervical or thoracic region. Given the limited scope of these reports, little is known regarding the details of the presentation, outcomes of surgery, and optimal management of symptomatic cauda equina hemangioblastomas. In particular, the incidence and importance of motor nerve root involvement, which can have a significant effect on the outcome of surgery, is undefined. Gläsker and colleagues,³ reporting the

surgical outcomes of 2 cases of cauda equina hemangioblastomas, have suggested that these tumors arise preferentially from sensory roots. Additionally, Biondi and colleagues,⁵ reporting the outcomes of preoperative embolization and surgery of 4 cases of cauda equina hemangioblastomas (3 sporadic), conclude that embolization may lead to more favorable outcome after surgery. We previously reported the outcomes of surgery for 6 patients with VHL-associated cauda equina hemangioblastomas; however, follow-up was limited (mean follow-up, 23 months).⁴

Current Study

General Characteristics

We analyzed 15 consecutive patients with VHL who underwent 18 operations for symptomatic cauda equina hemangioblastomas. Patients most frequently presented with pain (67%), numbness (50%), and urinary complaints (11%). Unlike symptomatic spinal cord hemangioblastomas, these tumors were often large (mean largest tumor volume: 2.5 cm³ vs 0.8 cm³) at symptom onset. Nerve root cysts were uncommon (1 patient, 6%; Figure 1). However, neuroforaminal involvement was present in 6 cases (33%). Median follow-up in this cohort was 5.9 years, allowing for analysis of the long-term outcomes of surgery.

Surgical Management

Preoperative embolization was used in 1 case in this series. Given the risk associated with this additional procedure, we have reserved spinal arteriography and embolization for select cases with very large tumor volume. Motor roots were found to be involved with tumor in 4 of 21 (19%) tumors in which neuromonitoring was utilized. This observed rate of motor involvement is higher than the rate of ventral involvement found with spinal cord hemangioblastomas (6%).¹⁴ Thus, neuromonitoring can be useful for resection of cauda equina root heman-

gioblastomas. Furthermore, patients should be counseled that motor involvement could preclude safe or complete tumor resection. Management of tumors involving motor roots can be challenging—surgical options depend on individual lesion characteristics. Selective interruption of arterial feeding vessels may devascularize the tumor and curb growth. Alternatively, in cases of neuroforaminal involvement, bony decompression may also improve symptoms.

Functional Outcome

Surgery in these cases was, in general, safe. Most patients (94%) were stable or improved with surgical management. Only 1 patient (6%) experienced a decrement in functional outcome. These functional outcomes were similar to the outcomes previously reported for surgery of symptom-producing spinal cord hemangioblastomas in VHL.¹⁴ However, the rate of gross total resection of cauda equina hemangioblastomas (vs intramedullary hemangioblastomas; over 99% complete resection rate) was lower (78%) and was attributable to involvement of motor nerve roots (complete tumor resection was not attempted in these cases).¹⁴

Management in VHL

VHL patients typically require multiple surgeries for CNS hemangioblastomas over their lifespan.¹ Due to the potential morbidity of surgery for these lesions, optimal management requires using resection only when necessary. We have previously shown that if treatment of VHL-associated hemangioblastomas were based on radiographic progression alone, patients, on average, would undergo up to 4 unnecessary operations within a 10-year period.¹⁵ Furthermore, despite the frequency of cauda equina hemangioblastomas in VHL (62% of patients), symptomatic cauda equina hemangioblastomas are an uncommon finding (2% of patients). Therefore, to avoid unnecessary surgery or radiation, these tumors should only be treated as they become symptomatic. Surgery remains the primary treatment modality. Radiation therapy, which has been previously shown to potentially control some hemangioblastomas of the brain and spine may be considered for progressive cases with extensive motor nerve rootlet involvement.^{16,17} Although the precise utility of radiation therapy in VHL has not been determined, this therapy may have less value in the treatment of cauda equina hemangioblastomas that are often large at symptom onset (median volume: 1.2 cm³).¹⁴

CONCLUSION

Cauda equina hemangioblastomas in VHL most frequently involve sensory nerve roots and surgical resection is the primary

therapeutic modality for these lesions. Most VHL patients undergoing resection of symptomatic cauda equina hemangioblastomas improve with surgery.

Disclosures

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