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Original research article

Surgical treatment of sporadic and von Hippel–Lindau syndrome-associated intramedullary hemangioblastomas

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ABSTRACT

Object: Intramedullary hemangioblastomas are rare lesions. They can be related to von Hippel–Lindau syndrome or they may be sporadic. This study describes surgical treatment for this infrequent tumor.

Methods: Twelve consecutive patients received surgery to remove sporadic or von Hippel–Lindau syndrome-associated intramedullary hemangioblastomas. Patients were evaluated at four time points: before treatment, on postoperative day one, on the day of discharge, and at a follow-up examination.

Results: The patients showed good preoperative neurological status. The cohort had a slight female predominance. All tumors spanned at least one spinal segment. In all cases, total tumor removal was achieved, and a good outcome was obtained. None of the following factors had a significant effect on outcome: age, sex, tumor size, the presence of a syrinx, or the presence of von Hippel–Lindau syndrome.

Conclusions: The surgical removal of intramedullary hemangioblastomas resulted in satisfactory long-term functional outcomes. The best results were obtained before neurological symptoms occurred. Thus, we suggest that surgery should be considered for managing asymptomatic, surgically accessible, space-occupying lesions in sIH group, and isolated, space-occupying lesions in vHLS-IH group.

1. Introduction

Intramedullary hemangioblastomas are rare neoplasms. They account for about 2% of all spinal cord tumors [1]. Hemangioblastomas are highly vascularized tumors, and due to their vascular permeability, they produce peritumoral cysts, which occur in about 50% of cases [2]. About 70% of intramedullary hemangioblastomas are isolated (sporadic, sIH), and 30% are associated with von Hippel–Lindau

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Abbreviations: vHLS, von Hippel–Lindau syndrome; IH, intramedullary hemangioblastoma; sIH, sporadic intramedullary hemangioblastoma; mMS, modified McCormick scale.

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syndrome (vHLS-IH) [3]. The rarity of these tumors has precluded a precise definition of a detailed treatment scheme. The natural history of these tumors is difficult to define, because they have unpredictable growth rates [4]. The aim of this study was to evaluate the short- and long-term results of the surgical removal of sIH and vHLS-IH, with attention to outcome in patients with asymptomatic vHLS-associated tumors.

2. Materials and methods

This retrospective study reviewed medical charts for 12 consecutive patients that received surgery for sporadic-IH ($n = 6$) and vHLS-IH ($n = 6$).

2.1. Clinical evaluation

Patients were evaluated at four time points: before treatment, on postoperative day one, on the day of discharge (early outcome), and at a follow-up examination (late outcome). The early and late outcomes were compared separately for patients with sIH and vHLS-IH. Follow-up data were obtained from medical charts, from telephone interviews with the patients, and from interviews during individual visits. Patients were assessed with a modified McCormick scale (mMS, Table 1) [5]. The follow-up period ranged from 3 to 10 years (average 5 years). Complete follow-up data were obtained in all cases.

2.2. Imaging evaluation

All patients underwent contrast-enhanced MRI before and after operative treatment. Spinal angiography was performed in eight (67%) patients.

2.3. Surgery

All tumors were removed via a posterior approach. Patients were placed in a prone position for removing tumors located in the thoracic spine and at the level of the atlanto-occipital junction. Patients were placed in a sitting position for removing tumors located in the cervical spine and at the cervico-thoracic junction. Three patients received laminectomies with an extended suboccipital craniotomy. Surgery was initiated with a midline dural incision over the dorsal surface of the spinal cord, followed by lateral dural sutures. Then, an incision was performed through the arachnoid and pia mater, at a location that depended upon the location of the most superficial part of the tumor ($n = 6$ midline incisions and $n = 6$ non-midline incisions). When the tumor was identified, the arterial feeders were gently coagulated during dissection. The tumor was microsurgically detached from the surrounding tissue, shrunken with bipolar coagulation at low power, and removed en bloc in all cases. It was not necessary to employ an ultrasound aspirator or laser. Concomitant intramedullary syrinxes were not directly dissected. The dura was closed in a watertight fashion. Laminoplasty was not applied. The wound was closed in a standard fashion. Motor and somatosensory evoked potentials were monitored during all procedures. Preoperative embolization was not used.

Table 1 – Modified McCormick scale [5].

Grade	Modified McCormick scale
I	Intact neurologically, normal ambulation, minimal dysesthesia
II	Mild motor or sensory deficit, functional independence
III	Moderate deficit, limitation of function, independent w/external aid
IV	Severe motor or sensory deficit, limited function, dependent
V	Paraplegia or quadriplegia, sometimes w/flickering movement

Fig. 1 – C1–C3 hemangioblastoma before and after treatment.

Fig. 2 – Th6 hemangioblastoma before and after treatment.

2.4. Statistical analysis

Fisher's exact test was used to evaluate significance. A p-value <0.05 was taken as statistically significant. Also, p-values between 0.06 and 0.07 were defined as a trend (Figs. 1 and 2).

3. Results

3.1. Patients and symptoms

We analyzed data for five men (42%) and seven women (58%), ages 18–59 years (mean 34 years). Six patients (50%) had sIH

Table 2 – Neurological status on postoperative day one, relative to the preoperative condition.

Before surgery (McCormick classification)	Neurological status on postoperative day one				
	McCormick Grade I	McCormick Grade II	McCormick Grade III	McCormick Grade IV	McCormick Grade V
Grade I	6	1	1	0	0
Grade II	0	1	2	0	0
Grade III	0	0	1	0	0
Grade IV	0	0	0	0	0
Grade V	0	0	0	0	0

(mean age 22 years; 2 men, 4 women), and 6 patients had vHLS-IH (mean age 46 years; 3 men, 3 women).

Ambulatory status was classified as grade I ($n = 8$), grade II ($n = 3$), and grade III ($n = 1$), according to the preoperative mMS. Four (33%) patients presented with neurological deficits; three had progressive single limb paresis; and one had a sensory deficit. Eight patients were neurologically intact before surgery; of these, five had vHLS-IH. Only one patient with vHLS-IH presented with a neurological deficit. In four cases, previously diagnosed vHLS was the indication for a diagnostic evaluation that led to the discovery of an intramedullary tumor.

Patients with associated syringomyelia had the following preoperative neurological status: mMS grade I ($n = 4$; 50%), grade II ($n = 3$; 37.5%), grade III ($n = 1$; 12.5%). All patients without syrinxes ($n = 4$) were neurologically intact (mMS grade I).

3.2. *Tumors*

Hemangioblastomas accounted for 20% of all intramedullary tumors (12/60) found in our Department during the study period.

The tumor sizes varied substantially. Tumors spanned one spinal segment in 5 patients (42%), two segments in two patients (17%), three segments in three patients (25%), 4 segments in one patient (8%), and six segments in one patient (8%). The mean tumor length was 2.3 vertebral segments.

The tumor was located in the cervical spinal cord in 6 patients (50%), at the cervico-thoracic junction in 2 patients (17%), and in the thoracic region in 4 patients (33%).

Intramedullary syrinxes accompanied the tumor in eight cases (67%). In six cases, the syrinx extended above the tumor; in two cases, tumors were located in the upper cervical spine, and the syrinx was located below the tumor.

Total resection of the tumor was achieved in all cases.

3.3. *Neuromonitoring*

Every patient underwent intraoperative neurophysiological monitoring performed with an ISIS IOM System (Inomed). The corticospinal tract was assessed with motor evoked potentials, elicited with a transcranial, constant current, electrical stimulation, delivered in a 5-train sequence. Motor evoked potentials were recorded with subdermal needle, monopolar electrodes inserted into the thenar, tibialis anterior, and abductor halucis muscles, bilaterally. The sensory tract was assessed with somatosensory evoked potentials, elicited by stimulating the medial and tibial nerves, bilaterally.

No significant changes in intraoperative neurophysiological recordings were noted for 11 patients. In one case, a significant change was observed in the intraopertive neurophysiological recording. In that case, the somatosensory evoked potential amplitude dropped by 60%, compared to the baseline neurophysiological recording obtained before the dural incision. This drop was correlated with a worsening postoperative clinical status.

3.4. *Neuroprotection*

An intravenous infusion of methylprednisolone was started routinely on the day of surgery. After the bolus, continuous infusion was performed for 24 h ($n = 4$) or for 48 h ($n = 3$). For the patient with the significant drop in intraoperative potential and the subsequent postopertive deficit, the infusion was prolonged for 96 h. The average infusion time was 46 h. There were no complications involving steroid administration in our series.

3.5. *Neurological status evaluations*

3.5.1. *Neurological status postsurgery*

Immediately after surgery, compared to the preoperative status, neurological status remained stable in eight (67%) patients and worsened in four (33%) patients. Among the eight patients with stable neurological status, three patients (37.5%) had asymptomatic vHLS-IH, and five patients (62.5%) had sIH, Among the four patients with worsened neurological status, three (50%) had vHLS-IH, and only one (17%) had sIH (Table 5).

On postoperative day 1, neurological status was graded according to the mMS (Table 2).

3.5.2. *Neurological status on the day of discharge*

Compared to postoperative day 1, at discharge, one patient had regressed from paraparesis (mMS grade III to grade II). All other patients remained stable. These mMS grades were considered early outcome (Table 3).

3.5.3. *Neurological status at follow up*

Compared to the early outcome, at follow up, neurological status improved in six patients (50%), and it remained unchanged in six patients (50%). All but one patient ($n = 11$; 92%) achieved mMS grade I. One patient (8%) was classified as mMS grade II at the last check-up, but died 10 months after the surgery. The cause of death was unrelated to the intramedullary tumor. The long-term results in relation to preoperative status are shown in Table 4.

Table 3 – Early postoperative outcome. Neurological status on the day of discharge, relative to the preoperative condition.

Before surgery	Early outcome		
	McCormick Grade I	McCormick Grade II	McCormick Grade III
Grade I	6	1	1
Grade II	0	2	1
Grade III	0	0	1
Grade IV	0	0	0
Grade V	0	0	0

Table 4 – Long-term neurological status, relative to the preoperative status.

Before surgery	Follow up		
	McCormick Grade I	McCormick Grade II	McCormick Grade III
Grade I	8	0	0
Grade II	3	0	0
Grade III	0	1[a]	0
Grade IV	0	0	0
Grade V	0	0	0

[a] One patient died in the period of neurological deficit regression, due to esophageal cancer. He was classified as McCormick grade II in the last evaluation.

3.6. *Outcome*

Postoperative complications included one case of a CSF leak. It was treated successfully with lumbar drainage. This wound healed correctly, based on long-term observations. Among all 12 patients, no tumor recurrence was diagnosed during the mean follow-up period of 5 years. There were no statistical differences in the early and late outcomes between the sIH and vHLS-IH groups (Tables 6 and 7).

3.6.1. *Sporadic hemangioblastomas*

Among patients with sIH, on postoperative day one, three were classified as mMS grade I, one as grade II, and two as grade III. At follow up, neurological status improved in three patients (50%; Table 5), compared to preoperative status. Consequently, of the six patients, five achieved mMS grade I and one achieved mMS grade II.

3.6.2. *vHLS-related hemangioblastomas*

Among patients with vHLS-IH, on postoperative day one, three were classified as mMS grade I, one as mMS grade II, and two as mMS grade III. At follow up, three patients with postoperative neurological deficits improved (Table 5), and all patients reached mMS grade I.

3.6.3. *Syrinxes*

Among eight patients with associated syrinxes, the neurological status on postoperative day 1 was as follows: mMS grade I ($n = 3$), mMS grade II ($n = 1$), and mMS grade III ($n = 4$). All these

Table 5 – Comparison of changes in neurological condition compared to preoperative status in subgroups of patients with vHLS-IH and sIH.

	vHLS-IH			sIH		
	Improvement	Stable	Deterioration	Improvement	Stable	Deterioration
Postoperative day one	0	3	3	0	5	1
Follow up	3	3	0	3	3	0

Table 6 – Analysis of factors that might influence the short-term outcome of surgical tumor excision.

Factor	Neurological status on the day of discharge (McCormick classification)		P-value (Fisher exact test)
	Grade I	Grades II–III	
Age <35	4 (57%)	3 (43%)	NS
Age ≥35	2 (40%)	3 (60%)	
Female sex	4 (57%)	3 (43%)	NS
Male sex	2 (40%)	3 (60%)	
Preoperative deficit /+/	0 (0%)	4 (100%)	0.06
Preoperative deficit /–/	6 (75%)	2 (25%)	
Spinal levels ≤2	4 (57%)	3 (43%)	NS
Spinal levels >2	2 (40%)	3 (60%)	
Syrinx /+/	3 (37.5%)	5 (62.5%)	NS
Syrinx /–/	3 (75%)	1 (25%)	
Sporadic	3 (50%)	3 (50%)	NS
vHLS-related	3 (50%)	3 (50%)	

NS: no significant difference between subgroups.

Table 7 – Analysis of factors that might influence the long-term outcome of surgical tumor excision.

Factor	Follow up (McCormick classification)		P-value (Fisher exact test)
	Grade I	Grades II–III	
Age <35	7 (100%)	0 (0%)	NS
Age ≥35	4 (80%)	1 (20%)	
Female sex	7 (100%)	0 (0%)	NS
Male sex	4 (80%)	1 (20%)	
Preoperative deficit /+/	3 (75%)	1 (25%)	NS
Preoperative deficit /–/	8 (100%)	0 (0%)	
Spinal levels ≤2	7 (100%)	0 (0%)	NS
Spinal levels >2	4 (80%)	1 (20%)	
Syrinx /+/	7 (87.5%)	1 (12.5%)	NS
Syrinx /–/	4 (100%)	0 (0%)	
Sporadic	5 (83%)	1 (17%)	NS
vHLS-related	6 (100%)	0 (0%)	

NS: no significant difference between subgroups.

patients showed improved conditions at follow-up; seven patients reached mMS grade I and one mMS grade II. Of the four patients without intramedullary syrinxes, three were assessed as mMS grade I, and one as mMS grade II, on postoperative day 1. At follow-up, all achieved mMS grade I. There were no significant differences in outcomes between patients with and without coexisting intramedullary syrinxes (Tables 6 and 7).

3.7. *Factors correlated with outcome*

The early postoperative results were not significantly different between subgroups of patients with differences in age, sex, tumor size, syrinx presence, or vHLS presence. Nevertheless, we found a trend toward more favorable results among patients that were neurologically intact before treatment compared to those with preoperative neurological deficits ($p = 0.06$, Table 6). The long-term treatment results were favorable for all patients. Consequently, we found no statistically significant differences between subgroups of patients (Table 7). The long-term results did not depend significantly on preoperative neurological status; however, the only patient with a sustained deficit (mMS grade II) at follow-up, had presented with paraparesis before surgery (mMS grade III).

4. Discussion

There is no generally accepted strategy for treating asymptomatic intramedullary hemangioblastomas in recent literature [6–11]. In particular, it can be difficult to decide whether to perform consecutive resections to remove multiple tumors in patients with vHLS. Because a preoperative neurological deficit is often irreversible [6], we decided to resect all tumors, including those accidentally discovered.

In the series described by Ammerman [7], 5 years of observation showed that 90% of tumors larger than 4.7 mm in diameter became symptomatic and required treatment. In the same study, after 10 years of observation, they found that 98% of hemangioblastomas were symptomatic. In our cohort, all tumors had main diameters greater than 5 mm. Therefore, we decided to start treatment shortly after diagnosis.

Recent studies have demonstrated that good preoperative status is crucial for satisfactory outcome [6,8,11]. Samii and Klekamp [6] showed that the most important determinant in long-term outcome was the preoperative level of neurological function. Ammerman et al. [8] stated that treating hemangioblastomas before the appearance of neurological symptoms resulted in improved neurological outcomes. Van Velthoven et al. [11] noted that surgical morbidity could be eliminated only when surgery was performed before significant disability occurred. Only one patient in our group had a significant neurological deficit (McCormick grade III) before surgery. The majority of our patients had mild neurological symptoms or asymptomatic tumors. The good postoperative treatment results confirmed that our decision to perform immediate surgery was justified.

The goal of surgery is complete tumor removal. The extent of resection is an important factor in the outcome [7,9,11]. Roonprapunt [7] stated that incomplete tumor removal might result in significant morbidity and mortality. Mehta [9] suggested that, because incomplete resection of a hemangioblastoma always results in recurrence, tumors should always be radically removed.

In the present study, 10 cases (83.3%) had tumors that occupied less than 4 spinal segments. Although tumor size is not generally recognized as a good prognostic factor for intramedullary hemangioblastomas, it is possible that a small size may favor good treatment results. Four patients without neurological deficits before treatment had tumors that occupied only one spinal segment. These patients were neurologically intact in the early postoperative period.

Our findings that syrinxes did not influence the outcome were consistent with those reported by Samii and Klekamp [6] and Van Velthoven et al. [11]. However, Samii and Klekamp [6] noticed more rapid recovery in patients with intramedullary hemangioblastoma and coexisting syringomyelia. In

our series, eight patients (67%) had intramedullary hemangioblastomas accompanied by syrinxes, but the syrinxes did not influence the outcomes.

In our series, vHLS coexisted with intramedullary hemangioblastoma in six cases (50%). Recent studies have shown that only 30% of patients with intramedullary hemangioblastoma had genetically confirmed vHLS [12,13]. Clark et al. studied a series that had equal numbers of patients with sIH and vHLS-IH [14]. Because the operative treatment results were similarly satisfactory in both groups, the coexistence of vHLS had no significant influence on outcome.

Our long-term results were satisfactory in all patients. Therefore, we found no significant correlations between the follow up results and sex, age, tumor location, or symptom duration. Nevertheless, in the early postoperative period, we found a trend toward a better outcome among patients that were neurologically intact before treatment. Moreover, Brotchi found that, in over 90% of cases, those with moderate neurological deficits before surgery displayed good treatment results [15]. Our results also suggested that surgical risk was related to the neurological condition before surgery.

The results obtained in our patients with vHLS confirmed the rationale for early treatment. For multiple vHLS-related tumors, the surgical treatment removed all large (space-occupying) asymptomatic lesions. Nevertheless, many authors argue that only a neurological deficit progression can justify surgery for patients with vHLS [8,9,16–20,4]. Ammerman [8] and Mehta [9] argued that surgical resections based on radiological progression may lead to many unnecessary resections. Huang [16] suggested that only symptomatic lesions can justify surgical removal, due to the risk of postoperative neurological deficits. Lonser [18] suggested that, due to the multiplicity of surgical procedures that are necessary in patients with vHLS over their lifetime, only selective removal of symptomatic lesions should be considered.

The natural history of intramedullary hemangioblastoma is not precisely known. Thus, decisions about operative treatment should always consider the risk of a sudden appearance of a neurological deficit. Due to phases of rapid tumor progression [4], it is difficult to determine the best time to surgically remove an asymptomatic lesion. In our series, no patient exhibited a permanent severe neurological deficit postsurgery. Therefore, we considered that, in these patients, the operative risk was low. Similarly, in the series studied by Van Velthoven et al. [11], no patients deteriorated compared to preoperative status. In the study by Lonser [18], only 9% of patients exhibited a worse condition compared to the preoperative condition. The cohort analyzed by Bostrom [2] showed outcomes similar to our results. Based on our outcomes, we concluded that treatment should be considered for asymptomatic tumors that are surgically accessible and exhibit a mass effect.

In patients with vHLS and multiple intramedullary tumors, the determining factor for commencing treatment should be radiologically documented tumor progression, not a neurological manifestation [7,11,16,20]. As Van Velthoven et al. stated, neurological deficits are often irreversible [11]; therefore, it seems unreasonable to wait for their appearance. Lonser suggested that patients with vHLS merit life-long observation to detect tumor progression before neurological deficits appear [18]. In particular, the radiologically documented growth of a peritumoral cyst is dangerous and requires surgical removal, in the opinion of Weil [20]. Thus, the favorable results we found with the surgical removal of asymptomatic intramedullary hemangioblastomas in both sIH and vHLS-IH supported the notion that modern treatment should adopt a more aggressive attitude. Our policy in managing small, asymptomatic, vHLS-IH is to perform close surveillance with serial MRIs each year to detect any significant tumor progression before a clinical presentation.

5. Conclusions

This study showed that the surgical removal of IH resulted in satisfactory long-term functional outcomes. Moreover, operative treatments were similarly favorable for both sIH and vHLS-IH lesions. We recommend that surgery should be considered for managing asymptomatic, surgically accessible, space-occupying lesions in sIH group, and isolated, space-occupying lesions in vHLS-IH group, because the best results are obtained by removing the lesion before neurological symptoms occur.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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