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Radiologic Characteristics of Spinal Hemangioblastomas in von Hippel Lindau Disease as Guidance in Clinical Interventions

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OBJECTIVE: **Hemangioblastomas in the central nervous system are the most common manifestation of von Hippel-Lindau (VHL) disease. Because the growth rate of hemangioblastomas is unpredictable, regular follow-up is mandatory, focusing on clinical symptoms and imaging of the central nervous system. However, clinical symptoms may be subtle and nonspecific, and data about the relationship between the radiologic findings and clinical symptoms are sparse. This study aims to evaluate if and how findings of magnetic resonance imaging (MRI) regarding spinal hemangioblastomas are associated with symptoms of VHL disease, with special attention to peritumoral edema and spinal cysts.**

METHODS: **Serial spinal MRI scans of 43 genetically or clinically established VHL patients with at least 2 years of follow-up were reevaluated to examine the volume, growth rate, and location of spinal hemangioblastomas and the presence, size, and growth rate of peritumoral edema and cysts. Findings were compared with clinical symptoms using the Fisher exact test.**

RESULTS: **We observed a total of 77 spinal hemangioblastomas in 28 patients. Eight of the 28 patients showed peritumoral edema and spinal cysts, and 1 patient showed peritumoral edema without cyst formation; 6 of these 9 patients showed clinical symptoms. Both peritumoral edema and spinal cysts were associated with clinical symptoms ($P = 0.023$ and $P = 0.011$, respectively).**

CONCLUSIONS: **The presence of peritumoral edema and/or spinal cysts shown on MRI in VHL patients with spinal hemangioblastomas is associated with symptoms in more than half of the patients and may alert the clinician to intensify clinical and radiologic surveillance.**

INTRODUCTION

Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder caused by a germline mutation of the VHL tumor suppressor gene.[1] The incidence of VHL disease is estimated to be between 1 in 36,000 newborns.[2,3] VHL disease leads to the development of multiple vascularized lesions in the central nervous system (CNS: cerebellum, brainstem, and spinal cord) and tumor formation in visceral organs (pancreas, kidney, adrenals, and epididymis/broad ligament).[4]

Among CNS tumors related to VHL are hemangioblastomas associated with significant neurologic morbidity and mortality.[5] Hemangioblastomas are highly vascular, benign tumors that can occur sporadically or as a manifestation of VHL disease.[6] In VHL patients, hemangioblastomas are localized in the cerebellum, spinal cord, and medulla.[7] The surveillance and timing of treatment of CNS hemangioblastomas in VHL patients must be balanced carefully, weighing the risks of interventions against clinical benefits because patients often suffer from multiple lesions. Moreover, since spinal hemangioblastomas often remain asymptomatic for an extended period, the timing

Key words
- Peritumoral edema
- Spinal cyst
- Spinal hemangioblastoma
- Von Hippel-Lindau disease

Abbreviations and Acronyms
CNS: Central Nervous System
IQR: Interquartile Range
MRI: Magnetic Resonance Imaging
VHL: Von Hippel-Lindau

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of treatment is challenging. Another complicating factor is their unpredictable growth rate. In general, hemangioblastomas follow a stuttering growth pattern, in which periods of accelerated growth alternate with periods of no growth.[8] Radiologic progression is thus in itself no indication for intervention.

Spinal hemangioblastomas can lead to significant morbidity due to pressure on adjacent structures in the spinal cord, and symptoms depend on the anatomic location of the tumors.[9] Over the past 20 years, the morbidity and mortality rates of these highly vascular tumors have decreased significantly because of early detection and new and improved treatments like resection, arterial embolization, and stereotactic ablation.[10-13] Microsurgical resection is still the treatment of choice for hemangioblastomas of the spinal cord, although the risk of bleeding during resection, with a chance of subsequent infarction of the cord, is relatively high.[14,15] Larger VHL-related hemangioblastomas are more often associated with postoperative morbidity and worse clinical outcome than small (<500 mm^3) hemangioblastomas.[15] Clinical symptoms may be subtle and nonspecific, and no clinical or radiologic marker can fully predict whether a spinal hemangioblastoma or associated cyst may progress and become symptomatic, requiring intervention. Therefore regular imaging of the CNS with magnetic resonance imaging (MRI) and observation of clinical symptoms is mandatory. However, it is unclear whether current imaging protocols regarding follow-up of spinal hemangioblastomas in VHL patients are sufficient since the association between clinical symptoms and radiologic findings is not fully understood. VHL disease is rare; reports on radiologic findings, interventions, and clinical symptoms are limited; and it is complicated to reach a sufficient sample size to make solid conclusions. A recent study by Wang et al[16] presented surgical outcomes in 18 patients with spinal hemangioblastomas and stated that syringomyelia throughout the entire spinal cord might be considered an indication for surgical treatment besides the presence of clinical symptoms. However, only 2 of the 18 study subjects were diagnosed with VHL disease. Since VHL patients, contrary to patients suffering from a solitary hemangioblastoma, often develop multiple hemangioblastomas, the indication for surgical treatment should be made carefully because it is not desirable to treat every single hemangioblastoma. This study aims first to evaluate the association of MRI findings of spinal hemangioblastomas and symptoms in VHL disease, with special attention to peritumoral edema and spinal cysts. Secondly, we present a single-center outcome of interventions performed in VHL patients with spinal hemangioblastoma.

CLINICAL MATERIAL AND METHODS

Study Population

All patients aged 18 and older with clinically or genetically diagnosed VHL disease and diagnosed with a spinal hemangioblastoma, under surveillance at the Endocrinology Department of University Medical Center Groningen between January 2000 and December 2017 with more than 2 years of follow-up at the moment of inclusion, were eligible for this study. The moment of study entrance was defined as the date on which a spinal hemangioblastoma was first detected on MRI. To provide insight into our patient population, we retrospectively evaluated genetic mutations, VHL-related tumors, symptoms, survival, and causes of death using patients' charts.

Symptoms

Symptoms associated with a spinal hemangioblastoma were defined as localized pain, hypesthesia, weakness, ataxia, hyperreflexia/areflexia, autonomic dysfunction, or gait impairment.[1] Symptoms were scored only when established and attributed to a spinal hemangioblastoma by a neurologist and were scored before and 1 year after the intervention. Symptoms were retrospectively classified according to the McMorwick scale (Table 1).[17]

Radiologic Reevaluation

According to the Dutch surveillance program of VHL patients, an MRI of the spinal cord is performed at least every 1–2 years.[17] A dedicated neuroradiologist (A.P.A.A.), blinded for the outcome, reevaluated all MRIs of the patients included in this study. Precontrast and postcontrast T1-weighted and T2-weighted sequences performed between 2000 and 2017 were evaluated for the presence and size of spinal hemangioblastomas and associated peritumoral edema and spinal cysts. Hemangioblastoma volume was calculated using a T1-weighted postcontrast MRI, and the presence of peritumoral edema was scored using T2-weighted sequences. In addition, the localization and size (maximum diameter in 2 planes) of peritumoral edema and spinal cysts were assessed using the standard Line Measurement tool (Vue PACS, version 12.2, Carestream Health, Inc). Maximum diameters of the spinal hemangioblastomas and cysts were measured in all 3 planes (axial, sagittal, coronal). A few hemangioblastomas were not invariably visible during reassessment on several consecutive scans. Their invisibility was attributed to the slice thickness of the MRI scan, and they were therefore considered to be present in those scans. Only the most recently performed MRI scan was reevaluated in VHL patients not diagnosed with a spinal hemangioblastoma. For assessment of the growth pattern, a minimum of 4 consecutive scans was required. Hemangioblastomas that were

Table 1. McCormick Scale

Grade	Definition
I	Neurologically normal, mild focal deficit not significantly affecting function of the involved limb; mild spasticity or reflex abnormality; normal gait
II	Sensorimotor deficit affecting the function of involved limb; severe pain or dysesthetic syndrome affecting patient's quality of life; mild to moderate gait difficulty
III	More severe neurologic deficit, requires cane or brace for ambulation; significant bilateral upper extremity impairment; patient may or may not function independently
IV	Severe deficit, requires wheelchair or cane or brace with bilateral upper extremity impairment; usually not independent

Adapted from McCormick et al.[17]

not visible on 4 consecutive scans were excluded from this section. Spinal MRI scans were defined as "incomplete" when only T1-weighted images without contrast were performed.

Tumor Growth

For every subject, tumor growth pattern was studied with at least 4 consecutive serial MRI scans and determined with mathematic characterization. On the basis of the method used by Lonser et al,[8] they were interpreted as follows (**Figure 2**): "No growth" was defined as a difference in tumor size $\leq$7.5 mm^3 between baseline and overall time of follow-up. "Saltatory growth" was defined as periods of tumor growth divided by no growth intervals of more than 50%. A hemangioblastoma was defined as having "linear growth" if the R^2 (R_1^2) of the regression of tumor size was $\geq$0.85 and $\geq R^2$ (R_2^2) of the regression of log-transformed tumor size. A hemangioblastoma growth pattern was defined as "exponential growth" if R_2^2 was $\geq$0.85 and $>R_1^2$.

Statistical Analysis

We used descriptive statistics to describe patient characteristics, hemangioblastoma features, and intervention outcomes. Statistical analyses were performed with SPSS software, release 16.0 (SPSS, Inc., Chicago, Illinois, USA). Normality of data was evaluated using the Shapiro-Wilk test. Variables following a normal distribution were described as mean $\pm$ standard deviation. Skewed distributed variables were described using median and interquartile range (IQR).

The Fisher exact test was used to examine associations between categorical variables (hemangioblastoma growth patterns, location of the spinal hemangioblastoma, presence of peritumoral edema, and spinal cysts). The nonparametric Mann-Whitney U test was used to evaluate statistical differences between groups. Statistical significance was determined by a 2-tailed probability value of $<$0.05.

Ethical Considerations

Dutch law required no informed consent for this retrospective database study. Institutional review board approval was obtained before the start of data collection. Patient identity was protected by generation of a specific anonymous study code.

RESULTS

Patient Characteristics

For our study, we included twenty-eight (17 male, 11 female) of 43 VHL patients who were clinically followed in the University

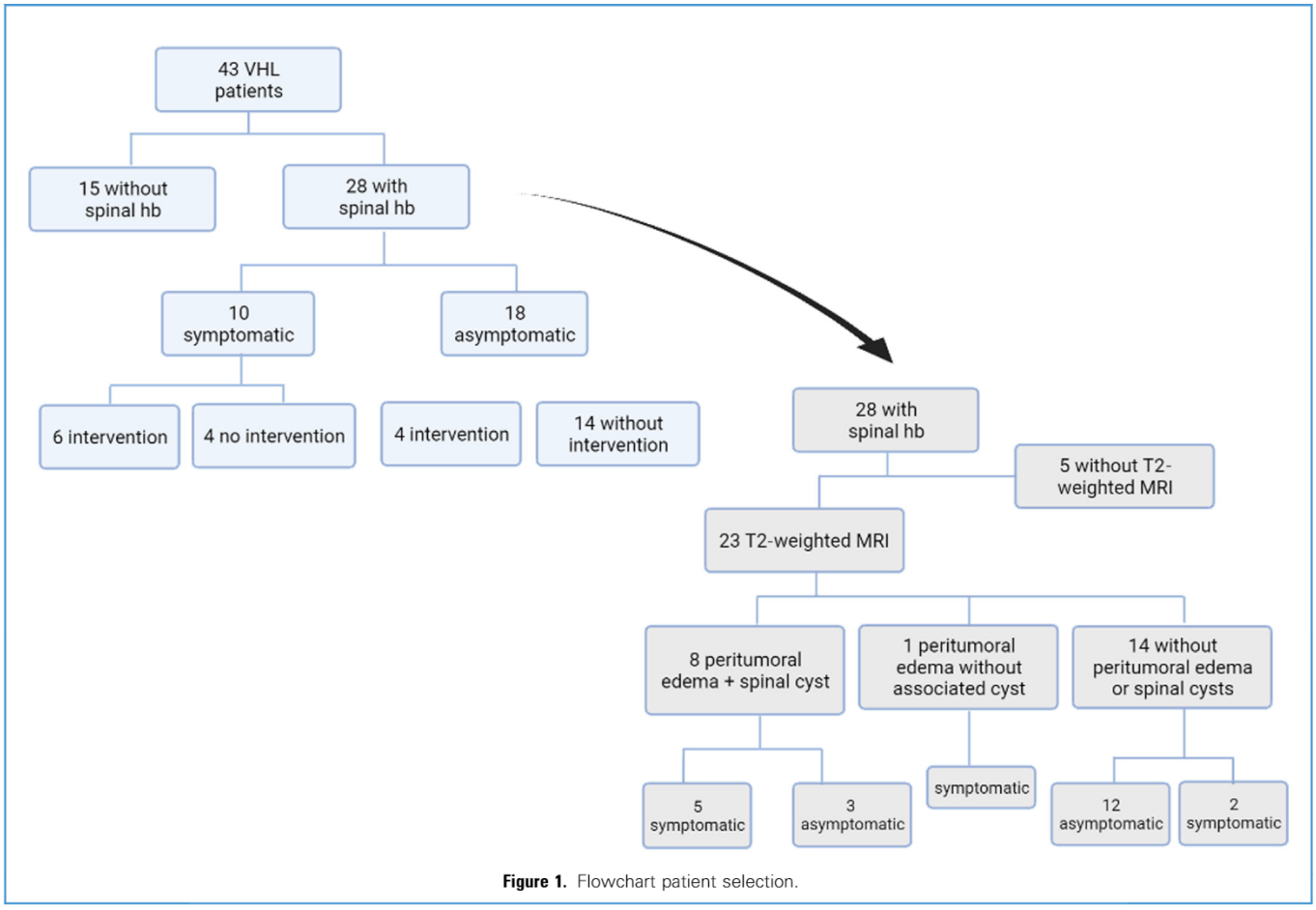

Figure 1. Flowchart patient selection.

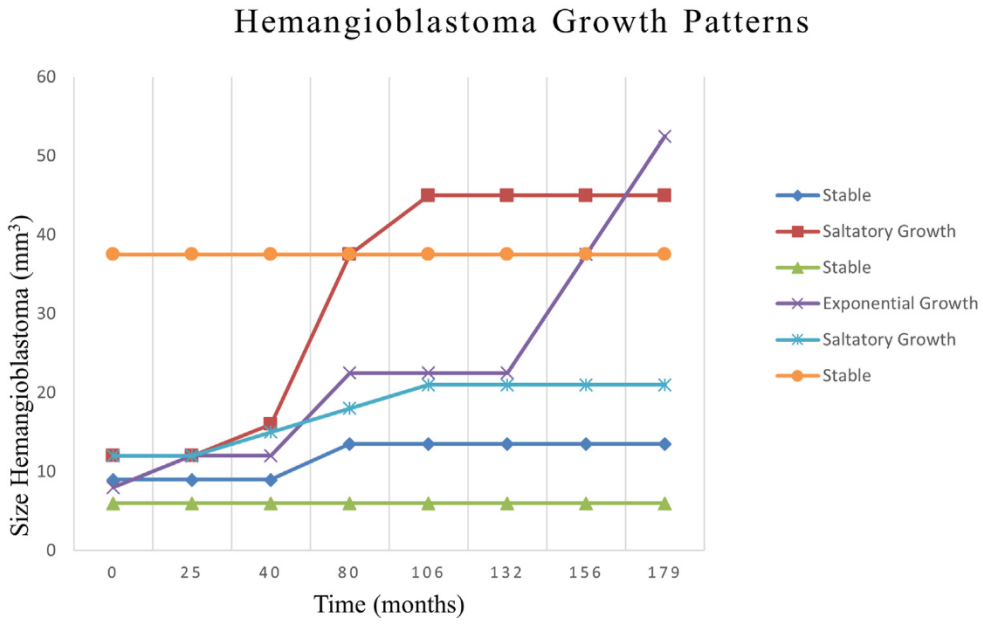

Figure 2. Example of several growth patterns of 6 hemangioblastomas present in 1 patient, including no growth, saltatory growth, and exponential growth.

Medical Center Groningen for more than 2 years and had 1 or more spinal hemangioblastomas (Table 2, Figure 1). Fifteen VHL patients did not show a spinal hemangioblastoma and were therefore excluded from the study. Their mean age at the moment of study entrance was 34 ± 16 years. Median follow-up, from the first MRI showing a spinal hemangioblastoma until the end of the study period, was 12 years (IQR 9–17 years). During follow-up, 8 of 28 patients (28.6%) with a mean age of 61 years died: from renal cell carcinoma (3 patients), cardiovascular disease (2 patients), rectum carcinoma (1 patient), pancreatic neuroendocrine tumor (1 patient), and cerebellar hemangioblastoma (1 patient). Of these 8 patients, none died because of the spinal hemangioblastoma.

Hemangioblastoma

We found 77 intramedullary spinal hemangioblastomas in 28 patients. Twenty-two patients had multiple spinal hemangioblastomas, and 6 had a single spinal hemangioblastoma. Of the total 77 hemangioblastomas, 37 (48.1%) had a cervical location, 26 (33.7%) thoracic, 13 (16.9%) lumbar, and one (1.3%) was located at the borderline between the cervical and the thoracic part of the spinal cord, at level C7-Th1. The size of hemangioblastomas in patients with symptoms ($n = 10$; median 63.0 mm^3, IQR 5.3–30.3 mm^3) was significantly greater than the size of hemangioblastomas in patients with no symptoms ($n = 18$; median 8.5 mm^3, IQR 35.3–641.6 mm^3) ($P = 0.002$) (Figure 3).

Clinical Symptoms and Intervention

Nine of the 28 patients (32.1%) with 1 or more spinal hemangioblastoma(s) experienced symptoms related to the presence of a spinal hemangioblastoma (Table 3). Five of these underwent surgical intervention, and 3 remained untreated. Four patients were asymptomatic before the intervention and were treated on the basis of radiologic progression. One of these patients developed symptoms after the surgical intervention. Because of comorbidities and poor physical condition, 2 of 10 symptomatic patients did not undergo intervention, although they did experience symptoms caused by their spinal hemangioblastomas. One of these patients died due to comorbidities after 9 months of follow-up; symptoms due to the spinal hemangioblastoma were not recorded during these 9 months. In the other patient, the symptoms caused by the spinal hemangioblastoma stabilized during follow-up (57 months) until the end of the study period. In 1 of the 16 patients who did not undergo intervention, the symptoms were minimal (weak hypesthesia) and therefore not considered an indication for surgical treatment; this patient died after a follow-up of 30 months due to a rectum carcinoma. Neurologic symptoms were not described at the end of the 30 months.

Tumor Growth

Thirty-four of 77 hemangioblastomas were excluded for this part of the study on the basis of inclusion criterion that the hemangioblastoma had to be visible on 4 consecutive scans. Of the remaining 43 hemangioblastomas, 18 (41.9%) remained stable during the study period, with a median follow-up of 113 months (IQR 50–152); 25 (58.1%) progressed in various growth patterns during the study period, with a median follow-up period of 131 months (IQR 71–154). Fourteen (56.0%) of the progressing hemangioblastomas showed a saltatory growth pattern, 4 showed

Table 2. Clinical Characteristics

Subjects Diagnosed with von Hipple-Lindau Disease $N = 43$		
Patient Characteristics	**Spinal Hemangioblastoma $N = 28$**	**No Spinal Hemangioblastoma $N = 15$**
Age	34 (±16)	37 (±17)
Gender	17 male	6 male
	11 female	9 female
Died during follow-up	8	0
Comorbidities	23 cerebellar hemangioblastomas	9 cerebellar hemangioblastomas
	6 pheochromocytomas	4 pheochromocytomas
	2 pancreas neuroendocrine tumors	2 pancreas neuroendocrine tumors
	10 renal cell carcinomas	2 renal cell carcinomas
	2 endolymphatic sac tumor	5 endolymphatic sac tumor
Mutation	14 c-89	7 c-89
	6 c.500G>A	1 c.500G>A, p.Arg167Gln
	1 c.259	1 235
	1 c.269A>T	1 367G>A
	2 c.341	2 c467A>G
	1 358A>G	1 497T>C
	1 c.1-?-340+?del p.(?)	2 Deletion VHL gene
	1 c.463+2T>C(IVS2+2T>C)	1 Unknown
	1 Deletion VHL gene	

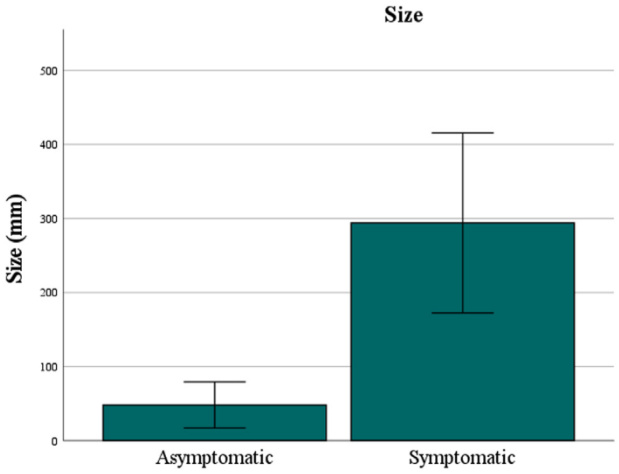

Figure 3. Size of hemangioblastoma.

(16.0%) linear growth, and seven (28.0%) showed exponential growth (see **Figure 2** for an example of growth patterns in 1 patient). The median growth rate was 1.93 mm³/year (IQR 0.89–4.02) for hemangioblastomas with a saltatory growth pattern, 5.25 mm³/year (IQR 2.80–16.84) for lesions with a linear growth pattern, and 7.53 mm³/year (IQR 5.20–95.07) for those with an exponential growth pattern. No association was found between clinical symptoms and growth patterns ($P = 0.30$) or between growth pattern and localization of the spinal hemangioblastoma ($P = 0.69$). However, a significant difference was found between the growth rates per year for asymptomatic (median 0.69 mm³/year, IQR 0–2.01) and symptomatic hemangioblastomas (median 3.91 mm³/year, IQR 1.44–78.87) ($P = 0.015$) (**Figure 4**).

Peritumoral Edema and Cysts

A hemangioblastoma-associated spinal cyst was seen on MRI in 10 of 28 patients (35.7%) with spinal hemangioblastomas (see **Figure 1**). In 23 patients, a T2-weighted image was available to measure peritumoral edema. Nine of these 23 patients (39.1%) showed peritumoral edema, and 8 of these 9 patients showed both peritumoral edema and a spinal cyst. In 6 cases, both the spinal cyst and peritumoral edema were visible on the first scan during the study period. In 2 patients, the development of spinal cysts was preceded by the presence of peritumoral edema. All spinal cysts were accompanied by peritumoral edema (**Figure 5**). However, for 2 patients with a spinal cyst, no T2-weighted images were available and peritumoral edema could not be assessed. An association between both the presence of spinal cysts and the experience of symptoms ($P = 0.01$) and the presence of peritumoral edema and the experience of symptoms ($P = 0.02$), was present (**Figures 6** and **7**).

Interventions and Outcomes

Nine patients underwent an intervention (**Table S1**, available online at …). Five of these patients were symptomatic before the intervention; 4 experienced no symptoms, and their intervention was based on radiologic progression. In 6 patients, the hemangioblastoma was removed surgically, 1 patient was treated with superselective endovascular embolization, and 1 case was treated with a combination of embolization and resection. All surgical cases were operated through a standard posterior approach (laminectomy or hemilaminectomy). No fixation/instrumentation was needed. The aim of surgery in cases with progressive cystic transformation of the intramedullary hemangioblastoma was the opening of the cyst through a small myelotomy, followed by the resection of the hemangioblastoma. As with all cases of spinal cord surgery, operation is performed under intraoperative neurophysiologic monitoring, which included D-wave monitoring as a standard in our center. Embolization is not a standard approach but was performed in 2 cases to facilitate the operative resection. In 1 of these cases, it was decided not to proceed to surgery because of

Table 3. Symptomatic Patients, Severity of Symptoms Classified by McMorwick Scale[17]

Subject	Inter-vention	Symptoms	Severity of Symptoms at Start of Study Period	Severity of Symptoms before Intervention	Severity of Symptoms after Intervention (First Follow-Up Visit)	Severity of Symptoms at the End of Study Period	Follow-Up (months)
1	Yes	Pain	II	II	II	Not specified	72
2	Yes	Pain, hypesthesia	I	II	I	I	62
3	Yes	Weakness	II	II	II	Not specified	64
4	Yes	Ataxia, paresis	No symptoms	No symptoms	No symptoms	IV	166
5	Yes	Hypesthesia, areflexia	II	II	I	Not specified	203
6	Yes	Pain, hypesthesia	II	II	I	Not specified	257
7	Yes	Ataxia, hypesthesia	II	II	I	II	53
8	No	Hypesthesia, weakness	I	No intervention	No intervention	II	152
9	No	Pain, hypesthesia, ataxia	II	No intervention	No intervention	Not specified	243
10	No	Ataxia	III	No intervention	No intervention	III	195

the localization of the spinal hemangioblastoma in close proximity to the anterior spinal artery. In 1 patient, the safe surgical removal of the hemangioblastoma was judged too dangerous; exploration was restricted to fenestration of the intramedullary cyst, leaving the hemangioblastoma untouched. In the period of 1 year after the intervention, the neurologic condition improved in 4 patients. After the intervention, 1 patient experienced persistent paresthesia and 1 had persistent drop foot. Of the 4 asymptomatic patients who underwent an intervention, 3 were still asymptomatic at the end of the study period. One patient developed ataxia and paresis of the right upper extremity, caused by other spinal hemangioblastomas.

DISCUSSION

The current study provides a detailed overview of retrospectively studied MRI characteristics and clinical findings of spinal hemangioblastomas in VHL patients in a VHL expertise center. We found an association between the presence of peritumoral edema, spinal cysts, and clinical symptoms. Furthermore, we found large size and rapid growth rate of individual hemangioblastomas to be associated with symptoms. Our findings suggest that these specific MRI signs may indicate a need for intensified clinical and MRI monitoring. Our results are in line with those of a previous prospective study in a large cohort of VHL patients. In this cohort, the location of CNS hemangioblastomas and the presence of edema and peritumoral cysts were described as the main factors leading to symptomatic spinal hemangioblastomas.[8] For cerebellar hemangioblastomas, edema and cysts also seem to be associated with the presence of symptoms.[18]

In the current study, we showed that peritumoral edema precedes, or accompanies, a spinal cyst; moreover, we observed no spinal cyst without the presence of peritumoral edema, consistent with the hypothesis of Lonser et al[19] that peritumoral edema may be a precursor of cyst formation. Having correlated imaging data of CNS hemangioblastomas and cysts with pathological findings after surgery, Lonser hypothesized that the formation of a cyst could be the result of increased vascular permeability and

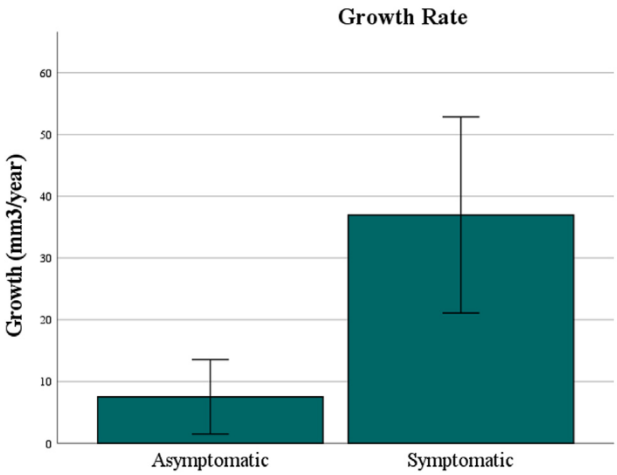

Figure 4. Growth rate (mm^3/year) of hemangioblastoma.

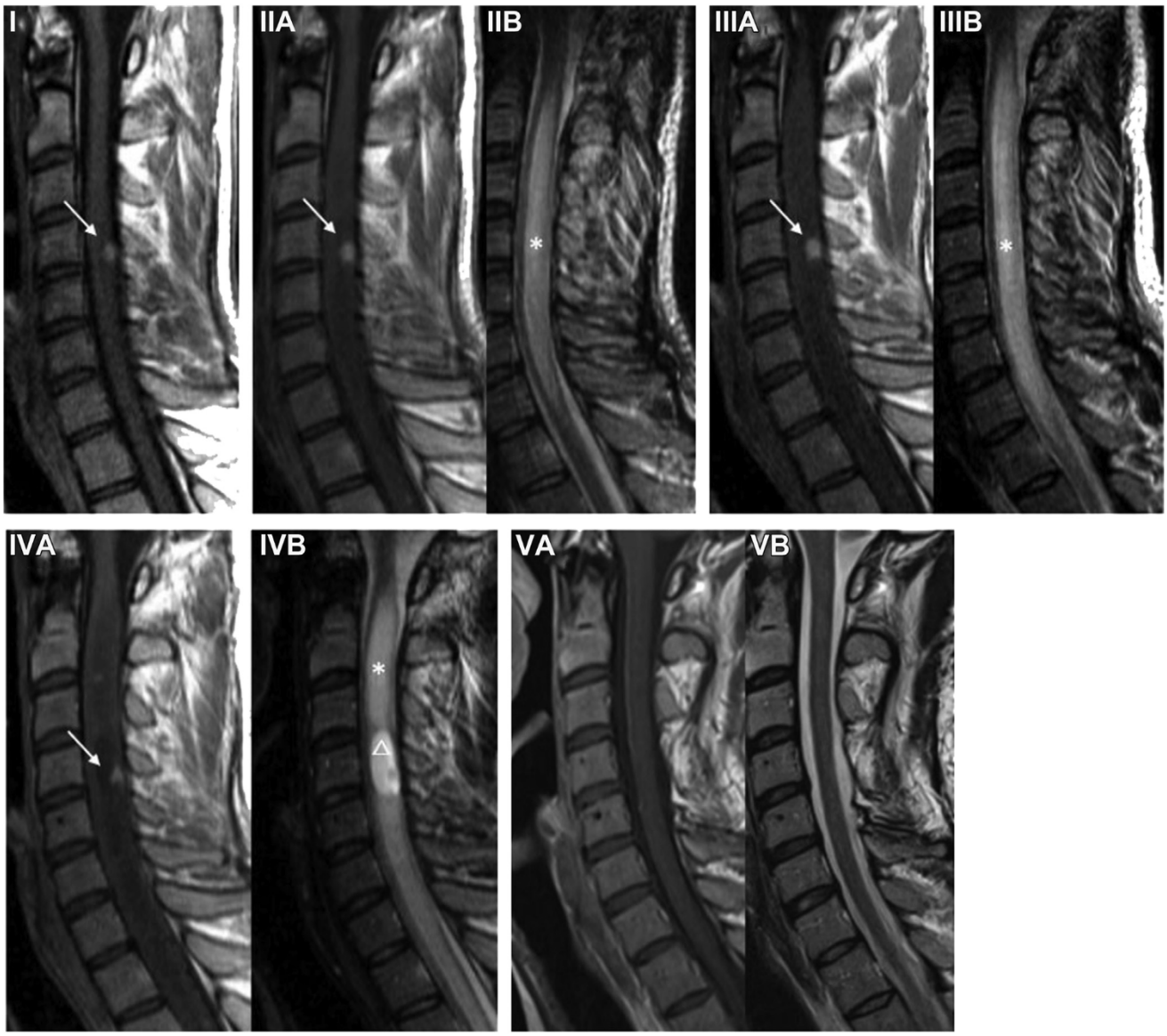

Figure 5. (**I**) Sagittal contrast-enhanced magnetic resonance imaging (MRI) of cervical spinal cord in 21-year-old von Hippel-Lindau patient demonstrates growth of peritumoral edema and hemangioblastoma-associated spinal cyst. T1-weighted MRI in May 2001 shows presence of small hemangioblastoma (*white arrow*) at level C4 (no T2-weighted image available). (**II**) T1- (**A**) and T2- (**B**) weighted MRI in September 2005 show, besides presence of spinal hemangioblastoma at level C4, also the development of peritumoral edema (*white asterisk*). (**III**) T1- (**A**) and T2- (**B**) weighted MRI in September 2008 show progression of peritumoral edema surrounding the spinal hemangioblastoma. (**IV**) T1- (**A**) and T2- (**B**) weighted MRI in August 2009 show development of spinal cyst (*white triangle*). (**V**) T1- (**A**) and T2- (**B**) weighted MRI in September 2014 show postoperative state with the disappearance of the edema and the cyst after removal of the intramedullary hemangioblastoma at C4.

interstitial pressure in the underlying hemangioblastoma, leading to plasma extravasation and distribution of fluid to the surrounding tissue, and finally resulting in the formation of a new cyst.[19]

In spinal hemangioblastomas in general, it is not so much their presence or growth but neurologic symptoms that are considered an indication for treatment.[20] However, since most patients had multiple hemangioblastomas and comorbidities, our data also illustrate that the decision to treat calls for a personalized approach involving carefully weighing of individual pro and con arguments and that surgery can also be considered when clear/evident progression is present without symptoms. In our study, 4 asymptomatic patients with spinal hemangioblastomas were treated for progressive growth as seen on serial MRIs. At the

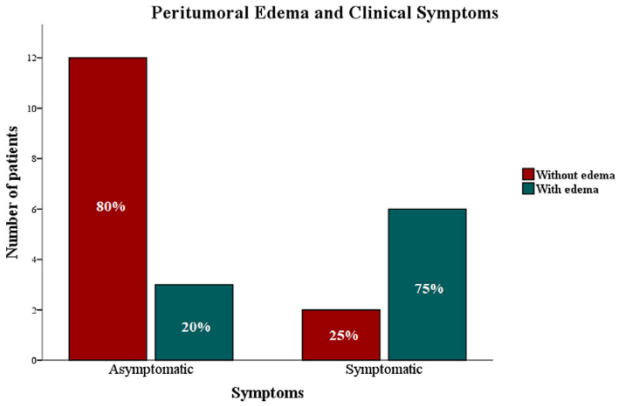

Figure 6. Peritumoral edema.

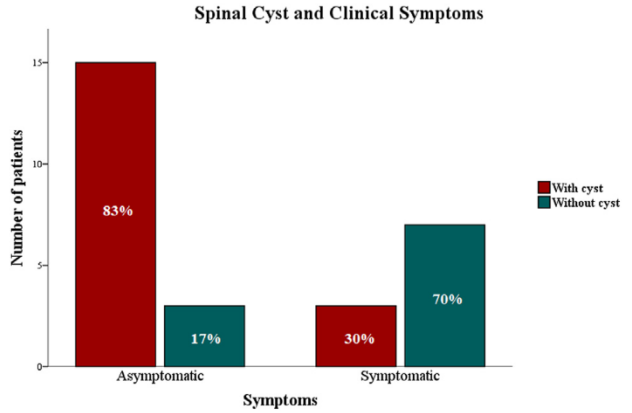

Figure 7. Spinal cyst.

end of the study period, 3 of them were still asymptomatic. One patient developed ataxia and paresis of the upper right extremity, caused by other spinal hemangioblastomas. Further, van Velthoven et al[21] described 6 asymptomatic patients treated solely based on observed radiologic progression of their spinal hemangioblastoma.[21] Two of these patients developed symptoms in the period before the intervention took place, and these symptoms remained after surgery. In all our cases, symptomatic patients improved after their intervention, but symptoms never resolved completely. These cases, taken together with the cases of the asymptomatic patients who underwent an intervention and remained asymptomatic, might imply that we should not solely focus on symptoms in the decision whether to treat spinal hemangioblastomas or not.

Our study describes a significant difference in growth rate between symptomatic and asymptomatic spinal hemangioblastomas. The study also shows that more than half of hemangioblastomas that showed progression have a saltatory growth pattern, with alternating periods of growth and stabilization, thereby making growth an unreliable predictor. The current study showed no association between specific growth patterns and the experience of symptoms. Therefore in the follow-up of spinal hemangioblastomas, their growth and growth patterns are considered suboptimal radiologic markers.

A limitation of this study is its retrospective analysis and classification of symptoms. Most of the symptoms were not standardized in the medical charts, complicating the retrospective classification of symptoms based on the McMorwick scale. Moreover, studies on diagnostics and treatment of spinal cord hemangioblastomas in patients with VHL disease are limited. Since VHL disease is rare, only relatively small populations have been studied and data are often combined with information obtained in the management of sporadic hemangioblastomas.[17,22,23] However, by presenting MRI characteristics and clinical findings in a VHL expertise center, the current study makes a useful contribution to the general knowledge regarding spinal hemangioblastomas in VHL disease.

CONCLUSION

Current treatment of spinal hemangioblastomas balances between an intervention and a wait-and-see strategy; this underscores that these patients need to be followed and treated in centers of expertise. In our study, the presence of peritumoral edema and/or spinal cysts on MRI scans of VHL patients with spinal hemangioblastomas was found to be associated with symptoms in more than half of the patients. This may alert clinicians to intensify radiologic and neurologic follow-up of patients without clinical symptoms and provide timely interventions to prevent irreversible clinical symptoms.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Pascalle Mossel: Conceptualization, Methodology, Formal analysis, Investigation, Writing — original draft, Visualization, Project administration. **Anouk N.A. van der Horst-Schrivers:** Methodology, Formal analysis, Writing — review & editing. **Maran J.W. Olderode-Berends:** Writing — review & editing. **Rob J.M. Groen:** Writing — review & editing. **Eelco W. Hoving:** Writing — review & editing. **Auke P.A. Appelman:** Conceptualization, Methodology, Formal analysis, Investigation, Writing — review & editing, Visualization. **Thera P. Links:** Conceptualization, Methodology, Formal analysis, Writing — review & editing, Project administration, Supervision.

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