INTRODUCTION

Hemangioblastomas are vascular tumors that can be found throughout the central nervous system including spinal cord that account for approximately 2% of primary spinal cord tumors. They are benign neoplasms (World Health Organization Grade I), but can cause significant morbidity and mortality through mass effect according to the intraspinal lesion. Von Hippel-Lindau (VHL) disease denotes an important subset of patients who present with hemangioblastomas in the central nervous system (CNS). Hemangioblastomas of the spinal cord occur more commonly as sporadic isolated lesions (70-80% of cases) rather than as multiple lesions in the cerebellum and retina as part of the VHL disease. The von Hippel-Lindau mutation analysis was done in three patients and two of them showed VHL gene abnormality. Tumors were located in the cervical cord in five cases and in the thoracic cord in four cases. All patients underwent surgical intervention, and total removal was achieved in six cases. All patients showed improvement or, at least, clinically stationary state. Surgical complications did not develop in any cases.

Conclusion: Spinal hemangioblastoma in this series has been safely and effectively removed via a posterior approach. Postoperatively, clinical outcome was excellent in the majority of cases. The VHL mutation analysis was useful in patients with family history and in those with multiple hemangioblastomas.

KEY WORDS: Hemangioblastoma · Von Hippel-Lindau disease · Mutation analysis.
Surgical Treatment of Spinal Cord Hemangioblastoma

JH Na, et al.

MATERIALS AND METHODS

Between December 1994 and March 2006, nine patients were treated for spinal cord hemangioblastomas including five patients with VHL disease. Four men and five women were included in the study, ranging from 17 to 66 years in age (mean age, 37.8 years). The sex, age at the time of onset, initial symptom, duration, location of the tumor, association with VHL disease and the presence of syrinx are summarized in Table 1. Clinical diagnosis for VHL disease was made according to the criteria that Melmon and Rosen described. If a family history of the CNS or retinal hemangioblastoma exists, only one hemangioblastoma or visceral lesion (renal tumors, pancreatic cysts or tumors, pheochromocytoma, papillary cystadenomas of the epididymis) is required to make the diagnosis of VHL disease. For an isolated case without a clear family history, two or more CNS and/or retinal hemangioblastoma or one hemangioblastoma and a visceral manifestation are required. The von Hippel-Lindau mutation analysis was performed in three patients.

Table 1. Clinical data for nine patients with hemangioblastomas of spinal cord

<table>
<thead>
<tr>
<th>No.</th>
<th>Age /Sex</th>
<th>Chief complaint</th>
<th>Duration (Mo)</th>
<th>Multiplicity /location</th>
<th>Intraspinal lesion</th>
<th>VHl/ Associative Ds.</th>
<th>Syrinx/ location</th>
<th>Pre-op Angio.</th>
<th>Surgical resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/F</td>
<td>Upper back pain, both hand paresthesia</td>
<td>3</td>
<td>-/C3–4</td>
<td>IDEM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>GTR</td>
</tr>
<tr>
<td>2</td>
<td>40/M</td>
<td>Both U/Ext. weakness, paresthesia</td>
<td>12</td>
<td>-/T7–8</td>
<td>IM</td>
<td>+/</td>
<td>C2–L1</td>
<td>-</td>
<td>STR</td>
</tr>
<tr>
<td>3</td>
<td>22/F</td>
<td>Back pain, Rl. leg pain</td>
<td>10</td>
<td>-/T11–L1</td>
<td>IM</td>
<td>+/</td>
<td>T8–L1</td>
<td>+</td>
<td>GTR</td>
</tr>
<tr>
<td>4</td>
<td>45/M</td>
<td>Lt. leg paresthesia</td>
<td>24</td>
<td>+/T4, T9–10, T12–L1</td>
<td>IM</td>
<td>+/</td>
<td>C3–T12</td>
<td>+</td>
<td>STR</td>
</tr>
<tr>
<td>5</td>
<td>17/F</td>
<td>Lt. leg weakness, hypesthesia</td>
<td>36</td>
<td>-/C7–T1</td>
<td>IM</td>
<td>+/</td>
<td>C4–T12</td>
<td>+</td>
<td>STR</td>
</tr>
<tr>
<td>6</td>
<td>42/M</td>
<td>Lt. U/Ext. pain, C4–6 paresthesia</td>
<td>9</td>
<td>-/C5</td>
<td>IM</td>
<td>-</td>
<td>C4–6</td>
<td>+</td>
<td>GTR</td>
</tr>
<tr>
<td>7</td>
<td>66/M</td>
<td>Lt/Ext. Weakness, paresthesia</td>
<td>1</td>
<td>-/C7–T1</td>
<td>IDEM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>GTR</td>
</tr>
<tr>
<td>8</td>
<td>21/F</td>
<td>Neck pain, both U/Ext. tingling sense, U/Ext. weakness</td>
<td>8</td>
<td>-/T2–3</td>
<td>IM</td>
<td>+/</td>
<td>C4–T10</td>
<td>+</td>
<td>GTR</td>
</tr>
<tr>
<td>9</td>
<td>35/F</td>
<td>Lt. shoulder pain, headache</td>
<td>5</td>
<td>-/C–M</td>
<td>IDEM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>GTR</td>
</tr>
</tbody>
</table>

U/Ext. : upper extremity; L/Ext. : lower extremity; Rl. : right; Lt. : left; C : cervical; T : thoracic; L : lumbar; C–M : cervico–medullary; IDEM : intradural and extramedullary; IM : intramedullary; RCC : renal cell carcinoma; HB : hemangioblastoma; GTR : gross total removal; STR : subtotal removal

Fig. 1. Preoperative magnetic resonance imaging (MRI) : T2-weighted sagittal image (A) showing a hyperintense lesion with spinal cord swelling from lower medulla to T2-3 level. Gadolinium-enhanced sagittal image (B) reveals well enhancing mass, approximately 1 cm diameter at the C5 spinal cord level. Preoperative right vertebral angiography (C) demonstrates hypervascular tumor staining fed by the ascending cervical artery of right thyrocervical trunk. Postoperative MRI : T2-weighted sagittal image (D) shows a marked diminution of the hyperintense lesion that existed previously in the preoperative MRI. The swelling of the cervical cord was nearly disappeared.
Mutations in the VHL gene was determined by direct sequencing of all coding exons and flanking intronic sequences. Serial neurological examination was done and preoperative and postoperative MRI studies were performed in all patients. Preoperative spinal angiography was performed in four patients, and preoperative embolization in two (Fig. 1). Preoperative and intraoperative somatosensory-evoked potentials (SSEP) were performed in four cases.

Indications for operation included the presence of lesion consistent with a spinal cord hemangioblastoma on MR imaging in a patient with objective and usually progressive neurological deficit. All patients underwent surgical removal through posterior approach via laminectomy.

Patients were followed from 4 to 39 months (mean follow-up period, 22.4 months) postoperatively. The neurological function of patients was graded according to the clinical scale described by McCormick, et al. The grade was evaluated before surgery, at the time point of discharge, and in the follow-up period for all patients.

RESULTS

The clinical features of the cord hemangioblastomas were similar to those of other spinal cord tumors. Initial symptoms in our series appeared as a combination of several sensory/motor manifestations. Sensory disturbance was encountered in seven patients (78%), pain in five patients (55%), and motor disturbances in four patients (45%). The duration between onset of initial symptom and diagnosis ranged from 1 month to 36 month (mean 12.9 month). Tumors were located in the cervical cord including cervico-medullary junction area in five patients and in thoracic area in four patients. In six cases, they were located intramedullary and in three cases intradural extramedullary. Based on a review of MR imaging, syrinx was accompanied in six patients (66%).

Five of nine patients (55%) met the criteria for the diagnosis of VHL disease. Two patients presented the family history of CNS or retinal hemangioblastoma. In three patients, multiple lesions of CNS hemangioblastomas were seen on MR imaging. In five patients, additional organ systems were involved including kidney (three cases), retina (two cases), pancreas (three cases), adrenal gland (one case) and epididymis (one case) (Table 1). VHL mutation analysis was performed in three patients and two of them showed gene abnormality. Two different mutations of the VHL gene, including 1 missense (c.586A>T;p.Lys196X) and frameshift insertion (c.223_224insT;p.Ile75TyrfsX57), were detected in two patients (Fig. 2).

On the operation field, abnormally dilated and tortuous vessels were found on the surface of the tumors. In all cases, tumors had a capsule and there was a border demarcating clearly the tumor from the normal spinal cord. Syrinx and
edema were seen in spinal cord close to the tumor. In three patients (case 2, 4 and 5) tumors were subtotally removed and for other patients tumors were totally removed. There was no perioperative mortality. Table 2 represents the preoperative, postoperative and last follow-up grade changes according to McCormick, et al. Most patients remained at their preoperative grade level or improved. There was no significant difference in surgical outcomes for patients with VHL disease compared to those with sporadic tumors. Intraoperative findings also did not differ between two groups. Two patients, who underwent subtotal removal (case 4, 5) showed stationary and improved outcome, respectively.

DISCUSSION

Hemangioblastomas can occur throughout CNS system that originate primarily in the cerebellum (83-95%), spinal cord (3.2-13%), and medulla oblongata (2.1%)25. In about 40% of patients with VHL disease, a hemangioblastoma is the manifestation of the disease24,29. Spinal hemangioblastoma can occur in 13-59% of patients with VHL disease depending on the families selected for study. These tumors occur more commonly as sporadic isolated lesions (70-80% of cases) rather than as multiple lesions in the cerebellum and retina as part of the dominantly inherited familial cancer syndrome, von Hippel-Lindau disease (16-25% of cases)6,20. In our series, five of nine patients (55%) with spinal cord hemangioblastomas were affected by VHL disease. The age of the patients at the time of diagnosis was not different from the data from other reports, ranging from 17 to 66 years, and hemangioblastoma in VHL disease was manifested in early adulthood, ranging from 17 to 40 years5,14,15,19,20.

Recently, the importance of early detection of VHL disease has been emphasized20. The majority of mutations in the VHL disease patients are represented by point mutations including missense, nonsense mutations, splicing, microinsertions or microdeletions10,12,31. The VHL gene resides on the short arm of chromosome 3 and encodes a ubiquitously expressed 4.7-kilobase (kb) messenger RNA (mRNA) that encodes 3 alternatively spliced exons14,31,32. In our study, five patients were clinically associated with VHL disease. Two of them showed gene abnormality in VHL gene mutation analysis. Two different mutations of the VHL gene were detected in each patient: insertion T on exon 1 of the VHL gene (c.223_224insT), resulting in a frameshift mutation (p.Ile75TyrfsX57) and a heterozygous A to T transversion in exon 3 of the VHL gene (c.586A > T), resulting in a Lys196X nonsense mutation (Fig. 2). We confirmed these in the genetic mutation web site (http://molgen-www.uia.ac.be/CMTMutations) and these mutations were novel not described previously. None of the novel variants were observed in 100 control chromosomes by direct sequencing of the corresponding exons. We are investigating the resultant VHL proteins (pVHL) formed by these mutant genes and their significance on the tumorigenesis.

The most common neurological symptoms at presentation were sensory disturbance and pain as those in the other spinal cord tumor. A difference in neurological symptom was not observed between patients harboring sporadic hemangioblastomas and those harboring hemangioblastomas as a manifestation of VHL disease. Regards to the location of the tumor, intramedullary hemangioblastomas were reported as rare cases in previous review4,18,20,26,28,30,32,34-36, but in our study intramedullary location (66%) was the most common.

Magnetic resonance imaging (MRI) is an examination of choice for spinal hemangioblastomas, and is helpful in preoperative planning and the differential diagnosis of spinal cord neoplasms and vascular lesions. On contrast-enhanced images, hemangioblastomas usually show a typically bright enhancing mass, clearly delineated from the surrounding spinal cord tissue. On T1-weighted images, hemangioblastomas produce signals that are isointense or slightly hyperintense, and on T2-weighted images the signals are hyperintense and the signals of the associated edema and cyst are hypointense22,25,30.

Although radiosurgery has been used to treat multiple hemangioblastoma, particularly in the cerebellum25, complete microsurgical removal is the treatment of choice for spinal cord hemangioblastomas26,35. It has been shown that preoperative spinal angiography and embolization may be used as an adjunct to surgery20. Although the number of our cases is small, spinal angiography and embolization helped determine the location and the nature of the tumor and anatomy of the feeding artery and delineate vascular supply. Surgical removal via posterior approach has been advocated in the majority of cases to achieve complete removal because a posterior laminectomy provides adequate exposure of the tumor11,25,35. Spinal cord hemangioblastomas are almost always associated with a syrinx or significant edema13,25. In our study, 66% of the patients exhibited the tumor associated edema and syrinx. Cases associated edema and syrinx are more space-occupying than those only with solid part of the tumor. Consequently, the mass effect producing neurological symptoms derives from the cyst rather than the tumor itself. On removal of hemangioblastomas in association with syrinx, the syrinx is spontaneously opened and always stops growing and usually regresses in size. Thus, additional opening of the syrinx, or surgical removal of the syrinx is not necessary20,26,32. In our series, a posterior approach via laminectomy was performed in all cases, and total removal was achieved in six cases. On postoperative MR imaging, it was found that the syrinx was regressed spontaneously.
in six cases. No patient's condition worsened after surgery, and complications did not develop in any cases in our series.

**CONCLUSION**

Spinal hemangioblastoma in this series could be safely and effectively removed via a posterior approach. Postoperatively, edema and syrinx resolved spontaneously and clinical outcome was excellent in the majority of cases. For early diagnosis and family consultation, the VHL mutation analysis was useful in patients with family history and in those with multiple hemangioblastomas. Cautious neurological observation and timely selective removal are necessary for spinal cord hemangioblastoma.

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**References**