# Hemangioblastomas of the Central Nervous System in von Hippel-Lindau Syndrome and Sporadic Disease

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**OBJECTIVE: The presentation, screening, management, and clinical outcomes of patients who presented to our institution from 1973 to 1999 with central nervous system (CNS) hemangioblastomas in von Hippel-Lindau (VHL) syndrome and sporadic disease were analyzed.**

**METHODS: The surgical pathology database of our institution was searched to identify all patients with histologically verified CNS hemangioblastomas occurring from 1973 to 1999. The medical, radiological, surgical, pathological, and autopsy records from these patients were reviewed retrospectively and statistically analyzed.**

**RESULTS: Forty patients (21 males and 19 females) presented with CNS hemangioblastomas. Twenty-five patients (62%) harbored sporadic hemangioblastomas. Fifteen patients (38%) had VHL syndrome. These 40 patients presented with 61 hemangioblastomas (8 patients had multiple lesions). Ten patients (25%) harbored spinal cord hemangioblastomas (5 patients had multiple lesions). Patients with VHL disease tended to present with neurological symptoms and signs at a younger age than patients with sporadic disease ($P = 0.09$), to present with multiple lesions (53%), and to develop new lesions (rate, 1 lesion/2.1 yr). Hemangioblastomas of the spinal cord were more prevalent in patients with VHL syndrome ($P = 0.024$). Neuroradiological screening of patients with VHL syndrome allowed identification of more than 75% of new lesions before they became symptomatic. Sixty-six surgical procedures were performed (12 patients required multiple operations). Six patients with VHL syndrome required surgery for new lesions. Surgical complications occurred in six patients (15%). Symptom resolution or arrest of progression at 1 year was documented in 88% of patients. Recurrence of symptoms from partially resected lesions occurred in eight patients (20%). No deaths associated with surgery occurred. One patient with sporadic disease and one patient with VHL syndrome (5%) died as a result of late medical complications from CNS hemangioblastomas.**

**CONCLUSION: Surgical outcomes for patients with CNS hemangioblastomas are favorable. However, management of hemangioblastomas is a more difficult and prolonged endeavor for patients with VHL syndrome. In patients with VHL syndrome, neuroradiological screening allows identification of lesions before they become symptomatic. Because patients with VHL syndrome are at risk for development of new lesions, they require lifelong follow-up.** (Neurosurgery 48:55–63, 2001)

**Key words:** Central nervous system, Hemangioblastoma, Screening, Spinal, von Hippel-Lindau syndrome

Hemangioblastomas of the central nervous system (CNS) can present as sporadic lesions or as manifestations of von Hippel-Lindau (VHL) syndrome (2, 5, 12, 19, 22, 25, 28). In either situation, hemangioblastomas can cause significant morbidity and mortality through mass effect on nearby structures (1, 7, 25, 32). Fortunately, the morbidity and mortality caused by CNS hemangioblastomas have been reduced as a result of diagnostic and therapeutic advances introduced during the last 25 years (3, 11, 25, 29).

Extensive progress has been made in determining the underlying genetic cause of sporadic and VHL-associated CNS hemangioblastomas. The gene mutated in autosomal domi-

nant VHL syndrome has been identified and is located on chromosome 3p (17, 31). This gene is a tumor suppressor and probably is altered in sporadic cases of CNS hemangioblastomas as well (15, 18). It is thought that the VHL protein mechanism of action involves inhibition of transcriptional elongation through interaction with the elongin B and C proteins (8, 14).

Recent clinical advances have improved outcomes for patients with CNS hemangioblastomas and emphasized the importance of early detection of VHL syndrome (2, 11, 25). In addition to CNS hemangioblastomas, other manifestations of VHL syndrome include retinal hemangioblastomas, renal and pancreatic cysts, renal carcinoma, pheochromocytoma, pancreatic islet cell tumors, endolymphatic sac tumors, and papillary cystadenoma of the epididymis (2, 19, 21, 22, 34). Early diagnosis is essential because several conditions, such as retinal hemangioblastoma and renal carcinoma, are treated more effectively if detected early (2, 10, 11, 20).

The purpose of this study was to analyze the presentation, screening, management, course, and surgical outcomes of patients with sporadic and VHL-associated CNS hemangioblastomas. Specifically, we determined the prevalence of VHL syndrome in patients requiring surgical resection of CNS hemangioblastomas at our institution during the last 25 years. The characteristics of patients who presented with sporadic versus VHL-associated CNS hemangioblastomas were compared. The progression of VHL syndrome was investigated. In patients with VHL syndrome, the sensitivity of neuroradiological screening for detection of CNS hemangioblastoma development and progression was determined. The association between clinical variables and outcomes was analyzed.

## PATIENTS AND METHODS

The surgical pathology database of the Johns Hopkins Medical Institution contains all surgical pathology reports from this institution. This database was searched to identify all patients with histologically verified CNS hemangioblastomas that occurred between 1973 and 1999. This search resulted in the identification of 40 patients with hemangioblastomas of the CNS that required surgical resection. The medical, radiological, surgical, pathological, and autopsy records from these 40 patients were reviewed retrospectively. Data pertaining to clinical presentation, therapeutic management, and outcomes were collected. The medical information recorded for each patient included age at presentation, symptoms at presentation, and the duration of these symptoms. Additional manifestations of VHL syndrome at presentation, including retinal hemangioblastomas, renal or pancreatic cysts, renal carcinoma, pheochromocytoma, endolymphatic sac tumor, or papillary cystadenoma of the epididymis, were recorded. Any family history of these manifestations was recorded.

Diagnoses of VHL syndrome were made according to the criteria that Melmon and Rosen (22) described. According to these criteria, in the absence of a family history of CNS or retinal hemangioblastoma, the diagnosis of VHL syndrome requires the presence of at least two CNS and/or retinal hemangioblastomas or one hemangioblastoma and one of the following manifestations of VHL disease: renal carcinoma, pheochromocytoma, pancreatic cyst, or papillary cystadenoma of the epididymis. In a patient with a family history of CNS or retinal hemangioblastoma, a diagnosis of VHL syndrome requires only the presence of one hemangioblastoma or other manifestation of VHL syndrome.

The radiological records of these patients were reviewed to determine the number, location, and size of any CNS hemangioblastomas at presentation. Radiological images obtained at presentation were available for 37 of the 40 patients. Computed tomographic (CT) scans obtained at presentation from six patients were analyzed, and magnetic resonance imaging (MRI) scans were available from 31 patients. The presence and size of any associated cyst, syrinx, or additional lesions were determined. Hemangioblastoma size was determined by examining a T1-weighted MRI scan after enhancement with gadolinium or a CT scan after administration of contrast medium. Cyst size was determined from a T1-weighted MRI or CT scan.

Analysis of therapeutic management included documentation of the use of endovascular embolization or radiosurgery. Analysis of surgical outcomes included determination of the occurrence of serious complications of surgery, length of hospitalization, and length of time until resolution of presenting symptoms. A serious complication was defined as one that extended the patients' length of hospitalization by more than 15 days or caused significant morbidity or death. The time until recurrence of symptoms from partially resected hemangioblastomas was calculated. The progression of CNS hemangioblastomas in patients with VHL syndrome who required surgical resection of at least one hemangioblastoma was analyzed. The rate of development of new CNS hemangioblastomas also was determined.

Fisher's exact test and the Mann-Whitney *U* test were used as indicated for statistical analysis of the data. StatView 4.5 (SAS Institute, Cary, NC) statistical software for the Macintosh (Apple Computer, Inc., Cupertino, CA) was used for statistical analysis.

## RESULTS

### Presentation

Forty patients (21 males and 19 females) required surgical resection of CNS hemangioblastomas at this institution from 1973 to 1999 (*Table 1*). These 40 patients presented with 61 lesions (8 patients had multiple lesions). Ten patients (25%) presented with spinal hemangioblastomas (5 patients had multiple lesions). The mean age at onset of neurological symptoms was 43 years (range, 13–75 yr). The most common neurological symptoms at presentation were headache (53% of patients), dizziness and disturbances of equilibrium (53%), and nausea (30%). The mean duration of symptoms before medical attention was sought was 8 months. The mean size of solid and mural-enhancing lesions detected at presentation was 13 mm. Cysts were present in 18 patients (45%; mean size, 36 mm). Representative lesions are shown in *Figure 1*. The average length of follow-up from presentation was 72 months.

**TABLE 1. Epidemiology and Presenting Characteristics of 40 Patients Requiring Surgical Resection of a Central Nervous System Hemangioblastoma from 1973 to 1999[a]**

| | |
|---|---|
| Total no. of patients | 40 |
| No. of males (%) | 21 (52%) |
| No. of females (%) | 19 (48%) |
| Mean age at presentation of neurological symptoms (range) | 43 yr (13–75 yr) |
| No. of VHL patients (% of total) | 15 (38%) |
| Most common neurological symptoms at presentation (% of total affected) | Headache (53%)<br>Disturbances of equilibrium (53%)<br>Nausea (30%) |
| Mean duration of symptoms before presentation (range) | 8 mo (1–60 mo) |
| Mean size of solid or mural-enhancing lesion at presentation (range) | 13 mm (2–40 mm) |
| No. of patients with cystic lesions (% of total), mean size (range) | 18 (45%), 36 mm (20–60 mm) |
| Mean length of follow-up (range) | 72 mo (1–408 mo) |
| Sporadic disease | 39 mo (1–151 mo) |
| VHL syndrome | 128 mo (11–408 mo) |

[a] **VHL, von Hippel-Lindau.**

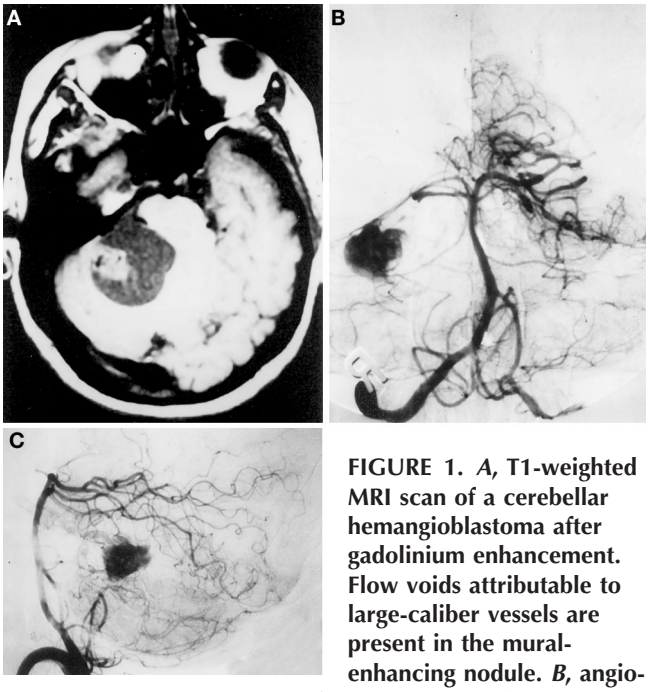


**FIGURE 1.** ***A*****, T1-weighted MRI scan of a cerebellar hemangioblastoma after gadolinium enhancement. Flow voids attributable to large-caliber vessels are present in the mural-enhancing nodule.** ***B*****, angiogram (anteroposterior view) of the same cerebellar hemangioblastoma.** ***C*****, angiogram (lateral view) of the same cerebellar hemangioblastoma.**

Patients with sporadic CNS hemangioblastomas were followed up for an average of 39 months, and patients with VHL syndrome were followed up for an average of 128 months.

Sporadic hemangioblastomas were observed in 25 patients (62%), and 15 patients (38%) from 13 different families harbored CNS hemangioblastomas as one manifestation of VHL syndrome. Eleven (78%) of 14 patients with VHL syndrome who provided information had a positive family history of VHL syndrome. The diagnosis of VHL syndrome was attributed to CNS hemangioblastomas in 9 (60%) of the 15 patients with VHL syndrome. Of the remaining six patients, two presented with renal carcinoma, three presented with retinal hemangioblastomas, and one presented with pheochromocytoma. Eight (53%) of 15 patients harbored multiple CNS hemangioblastomas at their initial presentation with neurological symptoms (mean number of lesions, 5).

A comparison was made between the presenting characteristics of patients harboring sporadic CNS hemangioblastomas versus those harboring CNS hemangioblastomas as a manifestation of VHL syndrome (*Table 2*). A difference was not observed between the prevalence of either sex with VHL syndrome as compared with patients with sporadic hemangioblastomas ($P = 0.57$; Fisher's exact test). Patients with VHL syndrome tended to experience neurological symptoms at an earlier age (mean, 36 yr) than patients with sporadic CNS hemangioblastomas (mean, 45 yr; $P = 0.09$; Mann-Whitney $U$ test) did. Spinal hemangioblastomas were more prevalent in patients with VHL syndrome than in patients with sporadic disease ($P = 0.024$; Fisher's exact test). A significant difference was not detected between the two groups in the distribution of other CNS hemangioblastomas or in the prevalence of cystic lesions (Fisher's exact test).

## VHL syndrome progression

Ten (67%) of 15 patients with VHL syndrome developed additional CNS hemangioblastomas during follow-up as observed on MRI or CT scans (*Table 3*). A total of 75 additional CNS hemangioblastomas developed in these patients. Lesions developed in six of the seven patients who initially presented with a solitary CNS hemangioblastoma and in four of eight patients who presented with multiple hemangioblastomas. The rate of hemangioblastoma development in patients developing new lesions was one lesion every 1.5 years, and the rate of lesion development for the entire VHL cohort was one lesion every 2.1 years. Additional hemangioblastomas occurred in all parts of the CNS: 29 spinal hemangioblastomas and 40 cerebellar hemangioblastomas developed as well as one hemangioblastoma each in the midbrain, pons, third ventricle, lateral ventricle, thalamus, and sellar region.

Additional hemangioblastomas continued to develop during the entire course of patient follow-up. Ten (67%) of 15

**TABLE 2. Epidemiology and Presenting Characteristics of Patients with Sporadic Disease versus von Hippel-Lindau Syndrome[a]**

| | Sporadic Disease | VHL Syndrome |
|---|---|---|
| No. of patients (% of total) | 25 (62%) | 15 (38%) |
| No. of males (% of sporadic disease or VHL syndrome patients) | 14 (56%) | 7 (47%) |
| No. of females (% of sporadic disease or VHL syndrome patients) | 11 (44%) | 8 (53%) |
| Mean age at presentation of neurological symptoms[b] | 45 yr | 36 yr |
| No. of patients[c] with each lesion (% sporadic disease or VHL syndrome patients): | | |
| Cerebellar hemangioblastoma | 17 (68%) | 8 (53%) |
| Medullary hemangioblastoma | 4 (16%) | 1 (7%) |
| Spinal hemangioblastoma[d] | 3 (12%) | 7 (47%) |
| Supratentorial hemangioblastoma | 1 (4%) | 2 (13%) |
| No. of patients with cystic lesions (% sporadic disease or VHL syndrome patients) | 12 (48%) | 6 (40%) |

**[a] VHL, von Hippel-Lindau.**

**[b] A statistical trend exists ($P = 0.09$, Mann-Whitney $U$ test).**

**[c] Sum is greater than total number of patients since eight VHL syndrome patients presented with more than one central nervous syndrome hemangioblastoma.**

**[d] A statistically significant difference exists ($P = 0.024$, Fisher's exact test).**

**TABLE 3. Presentation and Course of Central Nervous System Manifestations in von Hippel-Lindau Syndrome[a]**

| | |
|---|---|
| No. of VHL patients | 15 |
| No. of VHL patients whose first manifestation was a CNS hemangioblastoma (% of total) | 9 (60%) |
| No. of VHL patients who presented with multiple hemangioblastomas (% of total) | 8 (53%) |
| No. of VHL patients who developed additional CNS hemangioblastomas (% of total) | 10 (67%) |
| Mean no. of additional hemangioblastomas per patient | 8 |
| Rate of additional hemangioblastoma formation | 1 lesion/2.1 yr |
| No. of VHL patients who required additional surgery for new hemangioblastomas (% of total) | 6 (40%) |

**[a] VHL, von Hippel-Lindau; CNS, central nervous system.**

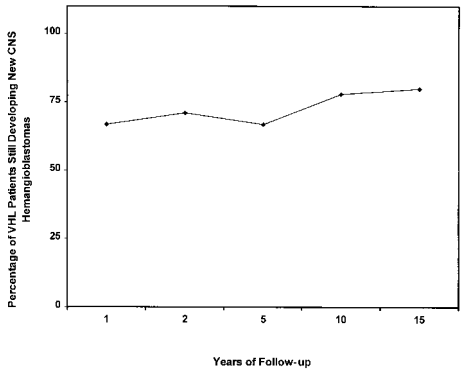


**FIGURE 2. Graph showing percentage of patients with VHL syndrome who developed new CNS hemangioblastomas during the follow-up period. Ten (67%) of 15 patients with VHL syndrome who were followed up for longer than 1 year developed a new CNS hemangioblastoma after 1 year. Ten (71%) of 14 patients with VHL syndrome who were followed up for longer than 2 years, 8 (67%) of 12 patients with VHL syndrome who were followed up for longer than 5 years, 7 (78%) of 9 patients who were followed up for longer than 10 years, and 4 (80%) of 5 patients who were followed up for longer than 15 years developed a new hemangioblastoma after 2, 5, 10, and 15 years, respectively.**

patients with VHL syndrome who were followed up for more than 1 year developed additional hemangioblastomas after 1 year. Ten (71%) of 14 patients with VHL syndrome who were followed up for longer than 2 years, 8 (67%) of 12 patients with VHL syndrome who were followed up for longer than 5 years, 7 (78%) of 9 patients who were followed up for longer than 10 years, and 4 (80%) of 5 patients who were followed up for longer than 15 years developed additional hemangioblastomas (*Fig. 2*).

Other manifestations of VHL syndrome occurred in these patients during follow-up. Seven patients (47%) developed retinal hemangioblastomas. Two patients (13%) developed pheochromocytomas. Renal carcinoma occurred in three patients (20%), and one patient (7%) developed an islet cell tumor. New retinal hemangioblastomas were observed up to 202 months after initial presentation. A pheochromocytoma occurred in one patient 93 months after presentation. In another patient, renal carcinoma occurred at 240 months and a pancreatic islet cell tumor developed 168 months after presentation.

## Neuroradiological screening of patients with VHL syndrome

Patients with VHL syndrome were screened using computed tomography or MRI at 1- to 2-year intervals to detect development of additional CNS hemangioblastomas and

monitor progression of existing lesions. In the six patients with VHL syndrome who originally presented with a nonneurological manifestation of VHL, screening allowed the identification of the initial CNS hemangioblastomas in five patients (83%) before symptoms developed. These lesions were first detected an average of 106 months after presentation (range, 4–276 mo). In two (33%) of these patients, asymptomatic lesions were resected because screening revealed rapid enlargement of the lesions. In the entire cohort of patients with VHL syndrome, additional hemangioblastomas developed in 10 patients (67%) after initial neurological presentation. Six (60%) of these patients required an average of three additional operations for hemangioblastomas that developed during follow-up. Overall, screening allowed identification of 74% of the lesions that eventually required surgical resection before they became symptomatic.

### Outcomes for CNS hemangioblastomas

The forty patients with CNS hemangioblastomas required 66 operations. Twelve patients (30%) required multiple operations for recurrence of symptoms from a partially resected lesion or development of a new hemangioblastoma. Resolution of symptoms or arrest of symptom progression was documented in 66% of patients 1 month postoperatively, in 86% of patients at 6 months, and in 88% of patients at 12 months. Serious complications of surgery occurred in six patients (15%), including cerebrovascular infarction secondary to obstructive hydrocephalus in two patients, meningitis in two patients, sepsis complicated by disseminated intravascular coagulation in one patient, and blindness in one patient.

Radiography revealed recurrence in 11 (17%) of 63 lesions that were operated on at any time. These 11 lesions occurred in 10 patients. Of these 11 lesions, eight lesions in eight patients became symptomatic and required additional surgery. In these patients, symptoms recurred an average of 53 months (range, 1–145 mo) after initial surgery. Five (62%) of these eight lesions were resected completely during the second operation, resulting in resolution of symptoms. The other three lesions were resected partially and became symptomatic an average of 19 months after surgery (range, 14–24 mo). It was necessary to reoperate on two of these three lesions, and again they were only partially resected. Symptom progression continued in these three patients.

Two patients (5%) died as a result of late medical complications of CNS hemangioblastomas. As revealed by autopsy, one patient died of sporadic disease from a medullary hemangioblastoma that regrew after two operations and endovascular embolization. One patient with VHL syndrome developed multiple CNS hemangioblastomas during a 20-year period and died from an intracerebral hemorrhage originating from one of these lesions.

### Adjuvant therapy

Endovascular embolization was used to treat four patients: two with spinal hemangioblastomas, one with a medullary hemangioblastoma, and one with a cerebellar hemangioblastoma. In each case, the decision to use embolization was made after angiography demonstrated that the tumor was supplied primarily by one or two major feeding vessels. Endovascular therapy generally was used in conjunction with surgical resection of the tumor. In one patient with a VHL-associated sacral hemangioblastoma, however, endovascular embolization alone arrested symptom progression 1 month after treatment, and surgery was not necessary. Serious complications secondary to embolization occurred in one patient who developed a Wallenberg's syndrome deficit after embolization of her medullary hemangioblastoma.

Radiosurgery was used in four patients (27%) with VHL syndrome to treat symptomatic lesions that were unsuitable for surgical resection because of their deep location and small size. Twelve lesions were treated with radiosurgery in these four patients. Five lesions were spinal, three were cerebellar, and four were supratentorial hemangioblastomas. Treatment arrested symptom progression in two patients (1.5 yr and 5 yr of follow-up). One patient experienced symptom progression 2 years after treatment. The one patient with VHL syndrome who died from an intracerebral hemorrhage died 7 years after therapy.

### Outcome analysis

A difference was not observed in any surgical outcomes between patients harboring sporadic lesions and those with VHL. The percentage of patients with resolution of symptoms at 1, 6, or 12 months in the two groups was similar ($P = 0.47$, $P = 0.29$, and $P = 0.99$, respectively; Fisher's exact test). A difference was not detected with regard to the prevalence of partially resected lesions ($P = 0.46$; Fisher's exact test) or time to recurrence of symptoms ($P = 0.56$; Mann-Whitney $U$ test). A difference in the number of serious surgical complications or deaths between the two groups was not observed ($P = 0.99$ and $P = 0.99$, respectively; Fisher's exact test).

No differences were observed in clinical outcomes (resolution of symptoms, prevalence of incomplete resections, time to symptom recurrence, and complications from surgery or death) between males and females (Fisher's exact test). The location of the presenting lesion was not prognostic (Fisher's exact test). Additional surgery attributed to symptom recurrence or new lesion development was not associated with an increased risk of serious complications ($P = 0.99$ and $P = 0.41$, respectively; Fisher's exact test). There was no difference in outcome for patients presenting with cystic lesions as compared with patients with solid lesions for resolution of symptoms at 1 month, 6 months, or 12 months ($P = 0.99$, $P = 0.68$, and $P = 0.68$, respectively; Fisher's exact test), or with regard to the frequency of recurrence, complications, or death ($P = 0.99$, $P = 0.36$, and $P = 0.18$, respectively; Fisher's exact test).

## DISCUSSION

Hemangioblastomas of the CNS comprise approximately 2% of primary CNS tumors and approximately 7 to 10% of primary posterior fossa tumors (6, 26, 28). Hemangioblastomas account for approximately 2% of primary spinal cord

tumors (9, 12, 23, 35, 36). Although hemangioblastomas are infrequent, they are an important clinical entity because the morbidity and mortality associated with them can be reduced significantly if these lesions are appropriately diagnosed and treated (3, 12, 25, 29, 32). As demonstrated in this series of 40 patients with CNS hemangioblastomas, surgical outcomes are generally favorable.

Patients with VHL syndrome are an important subset of patients who present with CNS hemangioblastomas. In this series, 15 (38%) of the patients who required surgical resection of a CNS hemangioblastoma had VHL syndrome. This proportion is higher than those reported in other published series, in which 3 to 25% of CNS hemangioblastomas were associated with VHL syndrome (4, 25, 29, 32). Although the high prevalence of patients with VHL syndrome in this series is probably the result of a referral bias to our institution, it emphasizes the importance of screening all patients who present with CNS hemangioblastomas for other manifestations of VHL syndrome. The early diagnosis and treatment of these manifestations will result in improved clinical outcomes for these patients.

Retinal hemangioblastomas are typically the first manifestation of VHL syndrome (2, 11, 20, 22, 24). In this study, however, CNS hemangioblastomas were the most common presenting manifestation of VHL syndrome (64% of the VHL patients). The high prevalence of CNS hemangioblastomas as the presenting manifestation of VHL syndrome probably results from referral patterns. However, this prevalence emphasizes the need to screen all patients presenting with CNS hemangioblastomas for VHL syndrome.

Few characteristics of patients harboring CNS hemangioblastomas were predictive of VHL syndrome. One previous study demonstrated that patients with VHL syndrome tend to present with CNS hemangioblastomas at a younger age than do patients with sporadic disease (25). We also observed a strong trend to earlier presentation for the patients with VHL syndrome in this series ($P = 0.09$). In contrast to other studies, the presence of spinal hemangioblastomas was significantly associated with VHL syndrome ($P = 0.024$) (11, 25, 29). A high degree of suspicion for VHL syndrome should be raised in young patients with hemangioblastomas and in patients with spinal hemangioblastomas. In addition, multiple lesions are diagnostic of this condition.

In the outcome analysis, a clinical variable could not be identified that was associated with resolution of symptoms, incomplete resection, serious complications, or mortality. In this series, patients with VHL syndrome did not have a worse surgical prognosis than patients with sporadic disease. Additional operations for lesion regrowth or new lesion formation were not associated with an increased risk of serious complications. We could not confirm a difference in outcomes, as suggested in previous studies, between patients who presented with cystic lesions as compared with solid lesions (3, 13, 26–28, 33). These studies, however, reported results from patients who presented with CNS hemangioblastomas before recent improvements in diagnostic techniques and therapeutic management. Clinical variables once associated with outcome may no longer be predictive in light of advances in neuroradiology, microsurgical techniques, neuroanesthesia, and critical care management that have improved surgical outcomes in difficult cases.

Adjuvant therapy, including endovascular embolization and radiotherapy, were used only in selected patients. Endovascular embolization was used for those few patients in whom the hemangioblastoma was fed by one or two large vessels that were located away from the surgical approach and were not expected to be encountered immediately during resection. Radiosurgery was used only for hemangioblastomas that were symptomatic, small, and deeply located. In our experience, each patient must be evaluated individually to determine whether any adjuvant therapy is warranted and is likely to result in a better outcome than surgery alone.

Although the surgical outcomes for patients with CNS hemangioblastomas were favorable, VHL syndrome caused significant morbidity. Additional manifestations of VHL syndrome, including retinal hemangioblastomas, renal carcinoma, pheochromocytoma, and an islet cell tumor, occurred in these patients. Additional CNS hemangioblastomas requiring resection or adjuvant therapy developed in all areas of the CNS, even many years after presentation. However, neuroradiological screening of patients with VHL at 1- to 2-year intervals allowed identification of more than 75% of presymptomatic new lesions that eventually would require surgery.

In all patients presenting with a CNS hemangioblastoma, the entire neuraxis should be evaluated for the presence of additional hemangioblastomas using enhanced MRI. Patients should be referred to the appropriate specialists and screened for additional manifestations of VHL syndrome as directed by one of the major screening protocols (2, 16, 20). The National Institutes of Health screening protocol includes a urinary catecholamine evaluation, ophthalmoscopy, and an abdominal CT scan and ultrasound evaluation (2). If a patient is diagnosed with VHL syndrome, periodic follow-up is required including a biannual urinary catecholamine evaluation, an annual ophthalmoscopy, a biannual enhanced MRI examination of the CNS, and an annual abdominal CT scan and ultrasound evaluation (2). A medical geneticist should coordinate the management and screening, determine whether genetic testing is appropriate, and provide counseling for the patient and the patient's family. Because VHL syndrome is transmitted in an autosomal dominant manner and is infrequently the result of de novo mutations in the *VHL* gene, an extensive effort should be made to screen first-degree relatives of the proband for the disease (2, 17, 30). Based on the results of this screen, other members of the extended family may be at risk for VHL syndrome and should be screened.

## CONCLUSION

Our experience reinforces the concept that although the surgical outcomes for CNS hemangioblastomas are generally favorable, the management of lesions associated with VHL

syndrome is a much more difficult and prolonged endeavor. Neuroradiological screening of patients with VHL syndrome is useful for identifying hemangioblastomas before they become symptomatic. Lifelong follow-up is required, and familial screening and counseling are of paramount importance.



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## COMMENTS

von Hippel-Lindau (VHL) disease is caused by loss-of-function mutations of the *VHL* gene located on chromosome 3p25 (2). Its protein product, pVHL, acts as a tumor suppressor protein, forming a complex with elongin B and C (1) and negatively regulating hypoxia-inducible messenger ribonucleic acid (6). Clinically, it is characterized by the formation of vascular tumors, including retinal and central nervous system hemangioblastomas (cerebellar, spinal, and brainstem). Other features include cysts of the kidneys, liver, and pancreas, clear cell renal cell carcinomas, pheochromocytomas, and endolymphatic sac tumors.

The authors present a retrospective series of 40 patients with hemangioblastomas, and they compare various clinical aspects in patients with sporadic disease versus those with VHL disease (38%). Their diagnosis of VHL disease was clinically based. The authors conclude that although surgical outcomes for CNS hemangioblastomas are generally favorable, VHL patients require lifelong surveillance to detect these lesions before they become symptomatic. The authors confirm most of the findings reported in the literature regarding VHL disease (4, 5, 7), reemphasizing long-term follow-up in patients diagnosed with VHL disease. In the authors' series, 67% of patients with VHL disease developed new central nervous system lesions, with a calculated rate of one new lesion developing every 2.1 years. Similar to previously published series, patients with VHL disease presented at a younger age than those with sporadic disease (36 versus 45 yr), with multiple lesions (53%), with spinal hemangioblastomas (47 versus 12%), and with new lesions (1 lesion/2.1 yr) throughout the follow-up period. Presymptomatic screening with MRI identified more than 75% of presymptomatic new lesions, leading to appropriate treatment. The authors found no difference in surgical outcome between patients with sporadic disease as compared with patients with VHL disease, and additional operations required in VHL patients were not associated with an increased risk of serious complications. These findings will serve as important guidelines for any neurosurgeon treating a patient with VHL disease.

Molecular genetic analysis for *VHL* gene mutations has been reported to be superior to clinical information in the diagnosis of VHL disease (3). This analysis provides an essential diagnosis and enables screening for other manifestations of VHL disease such as renal cell carcinoma; in addition, it provides prognostic information. Most VHL families may be characterized by the presence (Type 2; 7 to 20% of families) or absence (Type 1) of pheochromocytomas (2). In contrast to Type 2 families who have been found to have missense mutations, most Type 1 families are affected by deletions or premature termination mutations (2). These represent the first phases of genotype-phenotype correlation for VHL disease. The next level in managing VHL disease, as with many other genetic disorders, is the use of molecular genetic analysis to identify patients at risk of developing future symptoms. This will correlate certain types of mutations with a more aggressive clinical course and allow more intensive treatment of individuals harboring these mutations, including more frequent screening, and it will lead to the next phase of molecular neurosurgery.

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This article is an excellent overview of hemangioblastomas of the central nervous system in a series of 40 patients treated during a 26-year period. This study is retrospective, but it provides clear knowledge of the natural history of two aspects of this disease. This article contains some interesting points, such as

the information that patients with VHL disease develop a new lesion every 2.1 years on average. Therefore, close follow-up is very important. Furthermore, radiological screening permits identification of 74% of lesions that require surgery. In VHL disease that presents with non-neurological forms, the sensitivity of radiological screening is still superior (identification rate, 83%).

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The authors' experience reveals that although hemangioblastomas are histologically benign tumors, their operative management can be challenging. In this series, 15% of patients experienced significant surgical complications, and 17% of tumors recurred after surgery, which implies that they could not be removed completely. The observation that patients with VHL disease develop a new tumor at an average of every 2.1 years is important for physicians in planning treatment and follow-up. It is also a valuable contribution to the body of knowledge on this disease.

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