

Neurosurgical treatment of von Hippel-Lindau-associated hemangioblastomas: benefits, risks and outcome

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Aim. Von Hippel-Lindau (VHL) disease is a genetic syndrome predisposing to central nervous system (CNS) hemangioblastomas and several lesions in many organs. The cases of all VHL individuals operated on in the Neurosurgical Unit of Padua Hospital since year 2000 were reviewed in order to define which features lead to surgical treatment and to examine surgical outcome during postoperative follow-up.

Methods. The authors evaluated 20 VHL subjects (7 males and 13 females, age at surgery 32±10 years) who underwent 28 operations in order to remove 48 CNS hemangioblastomas and 1 endolymphatic sac tumor. Among the 49 resected lesions, 21 (42%) were cerebellar, 9 (18%) at brainstem, 19 (38%) spinal (7 cervical, 6 dorsal, 6 at concauda level), and 1 (2%) endolymphatic sac tumor in the petrous bone. Patients were graduated according to Karnofsky Performance Status (KPS) at admission, at discharge and during the last follow up visit. Genetic testing revealing the presence of a VHL disease-causing mutation was a prerequisite for inclusion in the study.

Results. Nineteen individuals (95%) were symptomatic. Symptomatic hemangioblastomas were associated with a cyst or a syrinx in 22/27 circumstances (81%). Total removal, as confirmed by postoperative magnetic resonance imaging (MRI), was achieved in all but one lesion. Following surgery, at follow-up (38±20 months), patients improved their neurological status in 75% of cases, 20% remained stable and 5% worsened; 16 patients (80%) are able to carry on normal activity with or without minor symptoms, 3 patients require some grade of assistance, 1 patient died because of bronchopneumonia.

Conclusion. VHL-associated hemangioblastomas generally affect a young adult population and can be successfully removed, either when symptomatic, or when

they reach a critical volume. Microsurgery of hemangioblastomas has a favourable impact on survival and quality of life of VHL patients, although it is strongly influenced by preoperative conditions. Transient surgical complications are possible, particularly with brainstem and spinal cord hemangioblastomas.

KEY WORDS: Hemangioblastoma - Von Hippel-Lindau disease - Neoplasm - Microsurgery.

Von Hippel-Lindau disease (OMIM 193300) is a neoplastic multisystemic autosomal-dominant syndrome resulting from a defect of the VHL gene. Affected individuals carry a VHL disease-causing mutation and are predisposed to develop central nervous system (CNS) lesions like cerebellar, spinal, brainstem and supratentorial hemangioblastomas, retinal angiomas, endolymphatic sac tumors, and visceral lesions like clear cell renal carcinomas, pheochromocytomas, renal and pancreatic cysts, neuroendocrine tumors, epididymal and broad ligament cystadenomas.¹ The disease has an estimated incidence between 1/36 000 and 1/52 000 livebirths,^{2,3} and a very high penetrance, as 100% of the carriers of a VHL dis-

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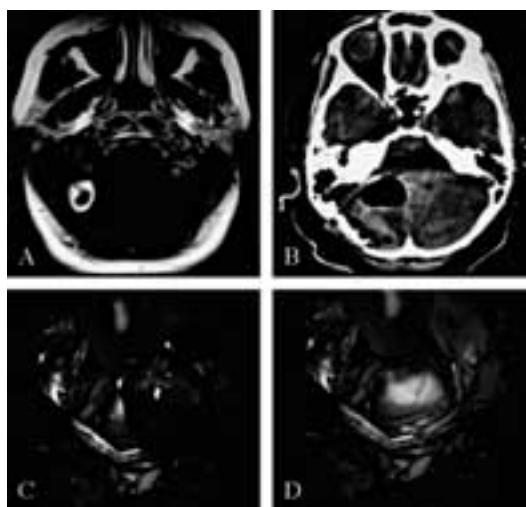


Figure 1.—Surgical removal of a cerebellar hemangioblastoma: A) preoperative MRI, B) postoperative CT, C) en bloc removal, D) residual cystic cave.

ease-causing mutation develop clinical manifestations by the age of 65.⁴ The disease takes its name from the German ophthalmologist Eugen von Hippel who, in 1911, described the retinal hemangioblastoma as a cystic capillary angiomatosis of congenital origin,⁵ and from the Swedish pathologist Arvid Lindau who, between 1926 and 1927, associated retinal and CNS hemangioblastomas with renal, pancreatic and epididymal cysts.^{6,7} In 1992, Grossniklaus demonstrated that retinal hemangioblastomas are histologically identical to CNS hemangioblastomas.⁸ The tumor-suppressor VHL gene has been identified by Latif *et al.* in 1993.⁹ Thanks to CNS microsurgery developments, clear cell renal cell carcinoma has exceeded CNS hemangioblastomas as the first cause of death (50% and 30% respectively) in VHL patients.¹⁰

The aim of this study was to review all cases of VHL patients who underwent surgery in our Neurosurgical Unit in order to assess the clinical behaviour of VHL disease-associated CNS lesions, establish features that lead to surgical treatment and examine surgical outcome.

Materials and methods

Subjects

Von Hippel-Lindau disease exposes affected individuals to an increased risk of developing cystic and neo-

plastic lesions in several organ systems. Therefore, it is a complex, multisystemic disease, which requires many competences, hardly manageable by a single physician. For this reason all VHL disease affected patients are managed by a multispecialistic team, composed by endocrinology, neurosurgery, urology and nephrology, ophthalmology, otosurgery, general surgery and molecular genetic specialists (VHL Padua Network).

Up to now, 115 patients are followed by the VHL Padua Network. Between 2000 and 2006, in the Operative Unit of Neurosurgery of Padua Hospital, 20 patients (7 males and 13 females) affected by VHL disease underwent 28 surgical operations in order to remove 48 CNS hemangioblastomas and 1 endolymphatic sac tumor.

Patients evaluation

Patients were evaluated by means of an accurate neurological examination and magnetic resonance imaging (MRI) both before and after surgery. Follow-up evaluations are planned at intervals of 3, 6, 12 and 24 months, and then every 2 years unless closer examinations are necessary. Overall physical conditions of each patient are scored according to Karnofsky Performance Status (KPS) at the moment of admission and during the last follow up evaluation. As VHL is a multisystemic disease, patients are periodically followed by many specialists. During the first evaluation, a detailed clinical and family history is collected. The evaluation protocol includes, VHL genetic testing, the evaluation of blood-test, erythropoietin, urinary methanephrens and normethanephrens, chromogranin A; in addition, audiometric and ophthalmological examinations, and cerebral, spinal and abdominal magnetic resonance imaging are performed.

Molecular analysis

A complete molecular analysis of the VHL gene was performed for each patient, after obtaining regular informed consent, in order to include in this study only VHL affected individuals. According to the literature, the authors consider molecular genetic analysis the most specific method to confirm or exclude VHL disease, particularly when the family history is negative or the patient is affected by a single CNS hemangioblastoma, without any visceral lesion.¹¹

VHL gene testing performed on high molecular weight genomic DNA extracted from peripheral blood

TABLE I.—*Clinical findings of patients operated on for a CNS hemangioblastoma.*

Pat.	Op.	Location	Associated cyst or syrinx	Preop KPS	Final KPS	Final outcome	Follow up (mos)	Temporary complications	Permanent complications
1	1	Thoracic spine	/	70%	90%	Improved	45	Worsening of hypesthesia and hyposthenia	
2	2	Ponto-cerebellar angle	/	50%	0%	Worse	50	IX and X cranial nerves palsy	
3	3	Cerebellum	cyst	50%				Worsening of hyposthenia	
	4	Cerebellum	cyst	50%				Aseptic meningitis	
	5	Dorsal spine	/	50%	50%	Stable	26		
4	6	Pons, cerebellum	/	60%	60%	Stable	41	IX and X cranial nerves palsy	VII cranial nerve central palsy, diplopia
5	7	Endolymphatic sac	/	80%	100%	Improved	47	Dizziness	
6	8	Bulbar		70%					
	9	Bulbar	Cyst, syrinx	80%	90%	Improved	96	Paresis of arm and hypoesthesia	
7	10	Bulbar	Syrinx	10%				IX and X cranial nerves palsy	
	11	2 cerebellum, 1 cervical spine	Cyst	10%				X cranial nerve palsy	
	12	2 cerebellum, 1 cervical spine	Cyst	30%	70%	Improved	69		
8	13	Cerebellum	Cyst	90%					
	14	Dorsal spine	Syrinx	90%					
	15	Dorsal spine	Syrinx	90%	90%	Stable	43		Painful dysesthesia
9	16	Cerebellum	Cyst	80%	100%	Improved	53		
10	17	Cerebellum	Cyst	80%	100%	Improved	25	Diplopia	
11	18	Cerebellum	Cyst	80%	100%	Improved	26		
12	19	Cervical spine	Syrinx	100%	100%	Stable	23	Disesthesia	
13	20	Spinal cone	Cyst	80%				Feet disesthesia	
	21	Cervico-thoracic spine	Cyst	80%	90%	Improved	34	Migrant paresthesia	
14	22	Cerebellum	Cyst	70%	100%	Improved	48	Polyuria	
15	23	Ponto-cerebellar angle	Cyst	70%	100%	Improved	22	IX and X cranial nerves palsy	
16	24	Cerebellum	Cyst	90%	100%	Improved	15		
17	25	1 cerebellum, 1 bulbar, 2 cervical	Syrinx	80%	100%	Improved	17		
18	26	Bulbar	Syrinx	80%	100%	Improved	2	Hand paresis and dysesthesia	
19	27	Bulbar	Syrinx	80%	90%	Improved	5	Hand paresis and dysesthesia	Hand hypoesthesia
20	28	Bulbar	Cyst	30%	100%	Improved	2		

Pat.: patient; Op: operation; Preop KPS: preoperative Karnofsky performance status.

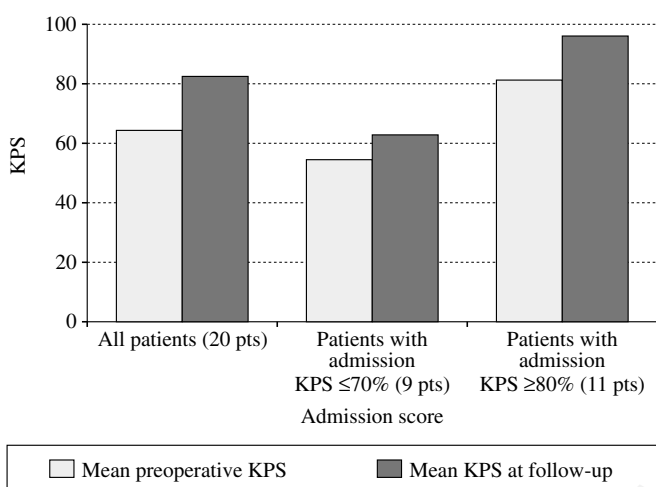


Figure 2.—KPS evolution in relation with admission score: patients presenting with a KPS score $\leq 70\%$ at admission had a mean KPS score at follow up lower than patients with a KPS score $\geq 80\%$ ($73 \pm 33\%$ vs $97 \pm 4\%$; $P < 0.05$).

leukocytes with standard technique, has been carried out with the use of quantitative Southern blot or real-time quantitative polymerase chain reaction (PCR) for detection of partial or complete gene deletions, and PCR amplification of the entire coding sequence and intron-exon junctions, followed by Single Strand Conformation Polymorphism (SSCP) analysis for the identification of small deletions/insertions and point mutations. Direct sequencing of mutated fragments was performed on ABI Prism 310 Perkin-Elmer Automatic Sequencer®.

Surgical treatment

Neurosurgical treatment was decided after extensive diagnostic procedures in order to define the possible systemic involvement of the disease and to establish therapeutical priorities on occasion. Cerebellar and bulbar hemangioblastomas have been operated either in prone or seated position through a median or retromastoid suboccipital craniotomy; adequate exposure of the single or multiple lesions was tailored on individual basis. Preoperative angiography and endovascular embolization were never utilized. Once the dura is opened, the surgical strategy is somewhat similar to that of an arteriovenous malformations (AVM) excision: afferent vessels are recognized, coagulated and divided, while the larger arterialized veins should be spared till last dis-

section stages in order to avoid vascular engorgement of the lesion and its subsequent bleeding. Actually, hemangioblastomas have a fragile wall and may bleed profusely if a piecemeal removal is attempted before their total devascularization (Figure 1). Properly low bipolar setting with adequate irrigation should be utilized, especially in brainstem and spinal locations. At surgery, the associated cyst should be entered first in order to gain additional space thus making the tumor dissection easier. As a rule, cyst removal was never attempted, as it will shortly disappear once the nodule has been taken out. We made an exception to this rule in two cases where the cyst, associated with obex location of the solid hemangioblastoma, trapped the fourth ventricle, so that excision of the cyst was mandatory for hydrocephalus resolution.

Statistical analysis

All data are presented as mean \pm standard deviation. T Student test was used in order to provide statistical analysis.

Results

Twenty patients (7 males and 13 females, age at surgery 32 ± 10 years, range 22-63 years) underwent 28 surgical operations for the removal of 48 CNS hemangioblastomas and 1 endolymphatic sac tumor. Table I summarizes the most significant clinical findings. In 27 cases patients needed surgery because of the onset of symptoms due to lesion growth and 1 patient for the presence of an asymptomatic although rapidly expanding hemangioblastoma. A cystic component or a syrinx was associated with symptomatic hemangioblastomas in 22 out of 27 cases (81%).

The most common signs and symptoms before surgery were headache,¹³ hypo- or paresthesia,¹⁰ dizziness,⁹ nausea/vomiting, hypostenia,⁸ pain,⁶ gait ataxia,³ chronic food intake aversion;² the patient affected by endolymphatic sac tumor had worsening hypacusia and auricular pain. One patient had no symptoms. Two patients were in coma at admission; in one patient coma was secondary to *ab ingestis* pneumonia, due to brainstem compression at obex region, in the other patient coma was associated with acute hydrocephalus. If one considers symptomatic patients, surgery was necessary 9 ± 21 months (range 0-96 months) after the onset of symptoms; in 23 cases (79%), patients needed surgical treatment briefly (2 ± 2

months) after the first disease manifestation. The onset age of the first CNS manifestations is 28 ± 9 years (range 12-55 years); CNS involvement was the first VHL manifestation in 15 patients (75%). Among the 49 resected lesions, 21 (42%) were cerebellar, 9 (18%) at brainstem, 19 (38%) spinal (7 cervical, 6 dorsal, 6 at cono-cauda level), and 1 (2%) endolymphatic sac tumor in the petrous bone.

Patients were hospitalized for 14 ± 11 days (range 5-63 days) after surgery. The mean postoperative follow up was 38 ± 20 months (range 7-79 months). MRI confirmed total removal in all but one case, a cono-caudal ventrally located hemangioblastoma which remnant remained stable and asymptomatic during follow-up.

Postoperative complications should be distinguished in temporary and persistent. Temporary complications, consistent with a complete resolution during follow-up, occurred in 17 out of 28 surgical procedures cases (60%), and were represented by worsening of motor and/or sensory impairment (8 cases), cranial nerves palsy (6 cases), aseptic meningitis, dizziness, polyuria. Persistent complications, *i.e.* still present at last follow-up, were observed in 3 out of 20 patients (15%): sensory impairment (2 patients), cranial nerve palsy (1 patient). Permanent new neurological deficits occurred after surgical removal of brainstem hemangioblastomas and of intramedullary locations; no permanent morbidity was associated with exclusively cerebellar lesions removal.

At long-term final outcome, collected at last follow-up, it was observed that 15 patients (75%) improved their conditions, 4 patients (20%) persisted stable, 1 patient (5%) died 10 months after surgery because of bronchopneumonia.

Patients with lower KPS on admission showed a less favourable functional outcome. In particular, we observed that patients presenting with a KPS score $\leq 70\%$ at admission had a mean KPS score at follow-up lower than patients with a KPS score $\geq 80\%$ ($73 \pm 33\%$ vs $97 \pm 4\%$; $P < 0.05$. Figure 2).

Discussion

Clinical features

VHL disease is a rare familial tumour syndrome involving multiple organ systems.² Therefore, neurosurgical treatment of VHL patients is part of a multidisciplinary management. Figure 3 summarizes the therapeutical approach used in this case. Indication

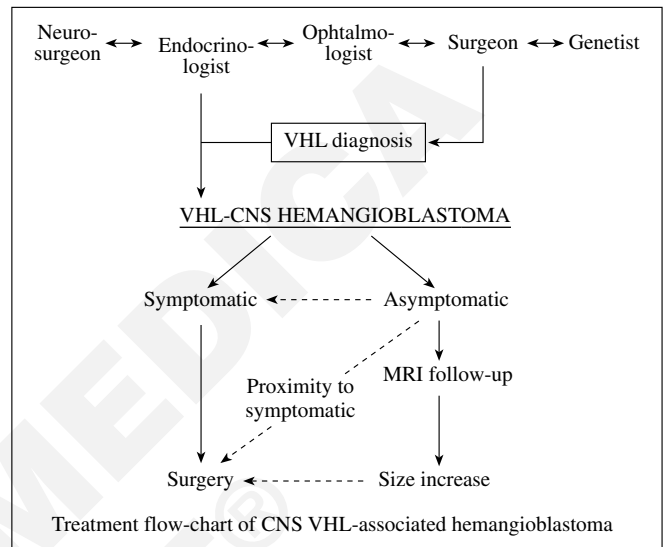


Figure 3.—Treatment flow-chart of CNS VHL-associated hemangioblastoma.

for surgical treatment of VHL-associated CNS hemangioblastomas is strictly related both with the complex nature of the underlying disease context and with the single hemangioblastoma natural history. Actually, since individuals affected by VHL may need different organ tumours treatment at close intervals, a multidisciplinary approach is mandatory so that clinical priority assessment may be judiciously evaluated. For this reason these patients need a serial clinical and imaging monitoring once the genetic diagnosis is established. Our observations show an early age at onset of CNS lesions (excluding retinal angiomas): the mean onset age is 28 ± 9 years (range 12-55 years), and the mean age at surgery is 32 ± 10 years (range 22-63 years). Therefore, the present study confirms that VHL-associated CNS hemangioblastomas develop on average 10 years earlier than sporadic ones, as described in the literature.¹²⁻¹⁶ The authors also noticed that 15 patients (75%) experimented CNS lesions as the first manifestation of VHL disease: this observation emphasizes the importance of an early CNS evaluation in VHL affected patients. For what concerns the single hemangioblastoma natural history, we do not have an observational follow-up long enough to indicate a rate of growth for individual lesions, but their growth pattern has been well studied in other reports:^{4, 15, 17} growth and quiescent phases alternate in an unpredictable manner and symptoms result from the mass effect exerted by

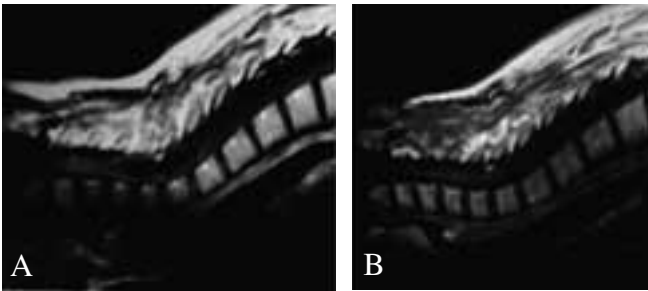


Figure 4.—A) Imaging of an asymptomatic hemangioblastoma of cervical spine (sagittal T1-weighted MRI). B) The same lesion after 10 months: an intramedullary cyst developed, exerting a clear mass effect with related symptoms.

the lesion evolution in relation with its size and its location. Thus symptoms may also have different progression patterns, as some patients present a very quick worsening, whereas some other can live with mild or absent symptoms for long periods; in this context, a remarkable role is caused by the associated cyst. In only 1 (4%) case it was decided to proceed with surgery because of progressive lesion growth during serial controls in an asymptomatic patient. In the authors' experience, among symptomatic patients 81% were operated a few weeks after the beginning of symptoms, suggesting that growth phases are associated with a rapid clinical evolution. In two cases patients were in coma when hospitalized and surgery was urgently undertaken: this was due in one case to *ab ingestis* pneumonia in a lower brainstem location, and in the other case to acute hydrocephalus. Conversely, one patient, affected by an endolymphatic sac tumor, had a slow but progressive hypoacusia worsening over the course of 2 years; in another case hypesthesia and dizziness lasted 8 years, and then worsened immediately before surgery. Two young female patients arrived at surgery after a one-year history of anorexia nervosa, actually caused by the compressive effect of the lesion at the obex.¹⁸

Obstructive hydrocephalus was actually present on admission in 6 out of 20 patients. In one case an external ventricular drainage was positioned 12 hours before surgery and removed a week after operation. In the other five cases hemangioblastoma removal was sufficient to correct CSF obstruction without the need of derivation implant. Only two patients had a ventriculo-peritoneal shunt: in one case due to refusal of further open surgery, and in the second case because of a previously positioned shunt.

In the present series, no patient presented with a bleeding hemangioblastoma; like in sporadic hemangioblastomas, the observation of bleeding lesions in VHL patients, even if possible, is extremely uncommon.¹⁹⁻²² The high incidence of associated cyst in the present series is consistent with previous observations.^{15, 23} If one excludes patient 5, affected by endolymphatic sac tumour, and considers only patients with hemangioblastomas, in as many as 22 cases (81%) either a cystic component or a syrinx was associated; it's often the compressive effect of the cystic component that causes a rapid deterioration of patient's neurological conditions (Figure 4).^{15, 24, 25} The authors usually recommend surgery for patients presenting signs and symptoms directly caused by the tumor or by its associated cyst, and for those with solid or cystic lesions rapidly growing during a few months interval, even if the patient is asymptomatic.²⁴⁻²⁶ In a multiple lesion context the associated asymptomatic lesions were removed whenever they were localized in proximity to the symptomatic ones, without changing the main surgical approach.

Surgical outcome

Although new lesions may occur in VHL individuals, due to the natural history of the disease, no local recurrences were observed in our patients, likely due to radical tumor removal.

In VHL-related lesions, surgical treatment is often mandatory; however, surgery is encumbered by the risk of temporary or permanent complications.^{16, 24, 25} Long tracts and cranial or spinal nerves impairment are more often related to brainstem and spinal cord hemangioblastomas localizations. In particular, permanent surgical morbidity was observed in 2 out of 8 patients operated for brainstem hemangioblastomas locations, and in one out of 9 patients operated for intramedullary locations. On the other hand no permanent surgical morbidity was seen after removal of solely cerebellar lesions.

In order to establish a long-term clinical surveillance, patients were followed up periodically after surgery and postoperative outcome was studied comparing KPS at admission with KPS at the last follow up examination (38 ± 20 months, range 7-79 months). It was observed that, compared with preoperative KPS, symptoms improved in 15 patients (75%), 4 (20%) patients persisted stable, and 1 (5%) patient died 10 months after surgery because of a bronchopneumonia likely unrelated to the previous operation; usual-

ly, mass effect relief or hydrocephalus resolution account for immediate positive outcomes. Temporary complications, although present in 60% of postoperative courses, did not significantly affect the functional evaluation in terms of KPS. This is mainly due to the quick recovery of postoperative symptoms, generally lasting no more than two weeks after surgery. Moreover, these patients frequently have still room to improve their functional status with an adequate neuro-rehabilitative program: at follow-up 16 out of 20 patients (80%) are able to carry on normal activity with or without minor symptoms (KPS 90-100%). These figures, although concerning a small series, recommend surgical treatment of VHL-associated hemangioblastomas as a powerful therapy in terms of survival and of quality of life.

Preoperative conditions proved to be critical for final outcome: at present, in the authors' experience, preoperative neurological status proved to be the better parameter to predict postoperative functional outcome. Patients with slight or absent neurological impairment before surgery have a better probability of maintaining intact their conditions.

At present, microsurgery is the only therapeutic option for symptomatic CNS hemangioblastomas in VHL patients; the role of other therapies, such as radiosurgery²⁷⁻³⁰ and chemotherapy,³¹ in the management of these tumours, although promising, is restricted to growth control of CNS asymptomatic hemangioblastomas or poorly symptomatic deep-seated hemangioblastomas. Since VHL patients indeed face a continuous risk of developing new lesions,^{32, 33} radiosurgery can be a valuable tool especially in a multiple-lesion context with a palliative local tumor control effect.

Conclusions

The age at onset of CNS lesions in VHL patients is on average lower than in cases with the same lesions developed sporadically; cerebellar or spinal tumors are often the first manifestations of the disease.

CNS hemangioblastomas can be successfully surgically removed, with a good prognosis; generally, they must be operated either when they give rise to symptoms, or when the tumor or cyst reach volumes that would increase surgery-associated risks, particularly if lesions are localized in critical areas. Although patients generally have a good surgical outcome, surgery carries an actual risk of compli-

cations, which is rarely permanent. The removal of brainstem and spinal cord lesions is more hazardous than the excision of cerebellum hemangioblastomas.

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Comments

This article is an excellent overview of eman-gioblastomas of the central nervous system in a series of 20 patients affected by von Hippel Lindau disease treated during a 6-year period. This is a retrospective study and provides clear knowledge of the natural history of such disease. The manuscript contains some interesting points, such as the information that patients with VHL disease face a continuous risk of developing new lesions. The Authors' experience reveal that although hemangioblastomas are histologically benign tumors, their operative management can be challenging. In their series 15% of patients experienced

pertinent surgical complications, particularly in brain-stem and intramedullary locations.

Although surgical outcomes for CNS heman-gioblastomas are generally favorable, VHL patients require lifelong surveillance to detect these lesions before they become symptomatic. In such a way, molecular genetic analysis for VHL gene mutation has been reported to be superior to clinical information in the diagnosis of VHL disease. This analysis provides an essential diagnosis and enables screening for other manifestations of VHL disease, such as renal cell carcinoma or endolymphatic sac tumors. In addition, it can provide prognostic information, identifying patients at risk of developing future symptoms. The authors contribute is a valuable work and have to be thanked for their precious support.

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Until recently the relationships between CNS hemangioblastomas and the Hippel-Lindau's disease had not been systematically investigated in clinical practice. On these grounds the authors should be congratulated on their multidisciplinary work carried out in the framework of a well-known genetic disease.. On the basis of the large personal series dealt with in the present report, it can be inferred that hemangioblastomas of CNS requiring surgical management are relatively frequent in patients with Hippel-Lindau disease: 20 patients out of 115. It also appears that in the systematic disease, neurosurgical symptomatology is observed in younger patients than in solitary hemangioblastomas. The pathological features as well as surgical procedures for the excision of the lesions are the same in both cases.

Further longitudinal studies are needed to ascertain whether there are significant differences in the biological behavior between the solitary lesions and those observed in the context of the systematic disease. However, from the practical neurosurgical standpoint, the most relevant remark which can be derived from this report, is that all patients in whom CNS heman-gioblastomas are disclosed thorough investigation should be carried out in order to disclose or rule out a systematic disease.

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