

The natural history of hemangioblastomas of the central nervous system in patients with von Hippel–Lindau disease

JOHN E. WANEBO, M.D., RUSSELL R. LONER, M.D., GLADYS M. GLENN, M.D., PH.D.,
AND EDWARD H. OLDFIELD, M.D.

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke; Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and Department of Neurosurgery, Naval Medical Center, San Diego, California

Object. The goals of this study were to define the natural history and growth pattern of hemangioblastomas of the central nervous system (CNS) that are associated with von Hippel–Lindau (VHL) disease and to correlate features of hemangioblastomas that are associated with the development of symptoms and the need for treatment.

Methods. The authors reviewed serial magnetic resonance images and clinical histories of 160 consecutive patients with VHL disease who harbored CNS hemangioblastomas and serially measured the volumes of tumors and associated cysts.

Six hundred fifty-five hemangioblastomas were identified in the cerebellum (250 tumors), brainstem (64 tumors, all of which were located in the posterior medulla oblongata), spinal cord (331 tumors, 96% of which were located in the posterior half of spinal cord), and the supratentorial brain (10 tumors). The symptoms were related to a mass effect. A serial increase in hemangioblastoma size was observed in cerebellar, brainstem, and spinal cord tumors as patients progressed from being asymptomatic to symptomatic and requiring surgery ($p < 0.0001$). Twenty-one (72%) of 29 symptom-producing cerebellar tumors had an associated cyst, whereas only 28 (13%) of 221 nonsymptomatic cerebellar tumors had tumor-associated cysts ($p < 0.0001$). Nine (75%) of 12 symptomatic brainstem tumors had associated cysts, compared with only four (8%) of 52 nonsymptomatic brainstem lesions ($p < 0.0001$). By the time the symptoms appeared and surgery was required, the cyst was larger than the causative tumor; cerebellar and brainstem cysts measured 34 and 19 times the size of their associated tumors at surgery, respectively. Ninety-five percent of symptom-producing spinal hemangioblastomas were associated with syringomyelia.

The clinical circumstance was dynamic. Among the 88 patients who had undergone serial imaging for 6 months or longer (median 32 months), 164 (44%) of 373 hemangioblastomas and 37 (67%) of 55 tumor-associated cysts enlarged. No tumors or cysts spontaneously diminished in size. Symptomatic cerebellar and brainstem tumors grew at rates six and nine times greater, respectively, than asymptomatic tumors in the same regions. Cysts enlarged seven (cerebellum) and 15 (brainstem) times faster than the hemangioblastomas causing them. Hemangioblastomas frequently demonstrated a pattern of growth in which they would enlarge for a period of time (growth phase) and then stabilize in a period of arrested growth (quiescent phase). Of 69 patients with documented tumor growth, 18 (26%) harbored tumors with at least two growth phases. Of 160 patients with hemangioblastomas, 34 patients (median follow up 51 months) were found to have 115 new hemangioblastomas and 15 patients new tumor-associated cysts.

Conclusions. In this study the authors define the natural history of CNS hemangioblastomas associated with VHL disease. Not only were cysts commonly associated with cerebellar, brainstem, and spinal hemangioblastomas, the pace of enlargement was much faster for cysts than for hemangioblastomas. By the time symptoms appeared, the majority of mass effect-producing symptoms derived from the cyst, rather than from the tumor causing the cyst. These tumors often have multiple periods of tumor growth separated by periods of arrested growth, and many untreated tumors may remain the same size for several years. These characteristics must be considered when determining the optimal timing of screening for individual patients and for evaluating the timing and results of treatment.

KEY WORDS • central nervous system • hemangioblastoma • neoplasm • von Hippel–Lindau disease

VON Hippel–Lindau disease (Mendelian Inheritance in Man No. 193300) is a multisystem familial cancer syndrome, which is inherited as an autosomal-dominant trait with a greater than 90% penetrance and an annual incidence of one per 36,000 live births.^{15,25} Common

Abbreviations used in this paper: CNS = central nervous system; MR = magnetic resonance; NIH = National Institutes of Health; PDGF = platelet-derived growth factor; SD = standard deviation; VEGF = vascular endothelial growth factor; VHL = von Hippel–Lindau.

manifestations of VHL disease include retinal and CNS hemangioblastomas, renal cysts and carcinoma, pheochromocytomas, pancreatic neuroendocrine tumors, endolymphatic sac tumors, and papillary cystadenomas of the epididymis. If a family history of retinal or CNS hemangioblastoma exists, only one hemangioblastoma or visceral lesion needs to be identified to grant the diagnosis of VHL disease.²⁸ For patients without a family history of this disease, two or more hemangioblastomas or one hemangioblastoma and one visceral lesion are sufficient to determine the diagnosis.²⁵ A method of VHL gene mutation analysis is

Hemangioblastomas of the CNS in patients with VHL disease

available and may also be used for genetic testing within families with VHL disease.³⁹

Hemangioblastomas, which can occur throughout the neural axis, are benign vascular tumors composed of endothelial and stromal cell components.¹⁷ Hemangioblastomas have been reported to occur in the cerebellum in 44 to 72% of patients with VHL disease, whereas such lesions in the spine are reported to occur in 13 to 44% of patients with the disease.^{10,20,27} Unlike cerebellar hemangioblastomas, of which only 5 to 31% of tumors are said to be associated with this disease, 80% of spinal cord hemangioblastomas occur with VHL disease.^{27,41}

Treatment of hemangioblastomas associated with VHL disease, whether performed surgically or with radiosurgery, is more likely to be successful and without complication when the tumor or its associated cyst is small. The development of MR imaging has permitted the sensitive detection of CNS hemangioblastomas in patients with VHL disease.^{1,7,10,11,14} Nevertheless, which lesions require treatment and the optimal time to treat them depend on the natural history of these tumors, and this has not previously been addressed. The distinct margins, intense contrast enhancement, and spherical shape of hemangioblastomas on MR images permit the accurate and reliable measurement of tumor volumes and longitudinal assessment of these lesions. This allows us to measure any enlargement due to tumor progression or a reduction in tumor size caused by a response to treatment.

To define the natural history and growth pattern of CNS hemangioblastomas associated with VHL disease and to identify features that will help predict if a specific hemangioblastoma will progress from an asymptomatic to a symptom-producing lesion that requires therapy, we reviewed serial MR imaging studies of 160 consecutive patients with VHL disease who harbored CNS hemangioblastomas and correlated the MR imaging findings with the patients' clinical condition at the time of each imaging study.

Clinical Material and Methods

Patient Population and Imaging

The clinical charts and MR images of all patients with VHL disease who were evaluated at the NIH between January 1986 and January 1997 were reviewed. All MR images of the head and spine were evaluated separately by two authors (J.E.W. and R.R.L.) for hemangioblastomas and associated cysts. To avoid misinterpretation of a blood vessel imaged in cross section as a tumor, the arbitrary threshold size for tumor detection was defined as 0.3 cm in diameter. A lesion thus had to be at least 0.3 cm wide to be included in this analysis. Maximum lesion diameters were measured in three planes and lesion volumes were approximated using the following formula: volume = (length × width × height) × 0.5.²³ Patients' charts were evaluated for documentation of their neurological condition at each follow-up examination and the neurological status of each patient was correlated with findings on MR images of the head and spine that were obtained at that visit. Tumor and cyst sizes were recorded when patients were asymptomatic, symptomatic, and at the time of surgery (which was generally performed when symptoms and signs were present). Tumor growth rates were determined by measuring chang-

es in tumor volume over time on serial MR images when patients were asymptomatic and just before surgery. A detailed description of the MR imaging techniques has been reported.⁹

It should be noted that the number of patients included in this report does not correspond to those of other reports from our group at the NIH in this issue. During the past several years we have removed 329 hemangioblastomas from patients with VHL disease at the NIH. The interval covered by this report and those of the reports by Lonser, et al.,²² Weil, et al.,⁴⁴ and Pluta, et al.,³⁶ began and ended at different times during this experience.

Statistical Analysis

Statistical analyses were performed in the manner defined in *Results*. Statistical significance was determined by a probability value less than 0.05. All mean data presented in this report represent means ± SD.

Results

Patient Characteristics

Two hundred thirty-one patients were identified who met the criteria for the diagnosis of VHL disease, of whom 160 (69%) had CNS hemangioblastomas (79 female and 81 male patients). The mean age of the patients at the time of presentation to the NIH was 33.4 ± 10.2 years. In the patients with VHL disease who harbored hemangioblastomas of the CNS, additional organ systems were involved including the following: kidney (81% of cases), retina (68% of cases), pancreas (55% of cases), epididymis (30% of cases), adrenal gland (15% of cases), and endolymphatic sac (9% of cases). The high percentage of patients with CNS hemangioblastomas who also harbored renal tumors almost certainly reflects a patient-referral selection bias derived from a particular interest in patients with VHL disease and kidney tumors that existed at the NIH during much of the time interval of this study. The mean MR imaging observation period for all patients with CNS hemangioblastomas was 21 ± 27 months (median 7.5 months) and that for 88 patients with at least 6 months follow up was 37 ± 24 months (median 32 months).

Tumor and Cyst Distribution

Among the 231 patients diagnosed with VHL disease, hemangioblastomas were detected in the cerebellum, brainstem, spinal cord, and supratentorial brain in 47, 22, 53, and 4% of patients, respectively, whereas cerebellar and brainstem cysts and spinal cord syringomyelia were noted in 22, 5, and 15% of patients, respectively (Fig. 1A). The distribution of the 655 hemangioblastomas identified by MR imaging in the 160 patients with VHL was as follows: 250 cerebellar hemangioblastomas in 108 patients (68% of 160 patients with hemangioblastomas); 64 brainstem lesions in 50 patients (31% of patients with hemangioblastomas); 331 spinal cord lesions in 122 patients (76% of patients with hemangioblastomas); and 10 supratentorial lesions in 10 patients (6% of patients with hemangioblastomas) (Fig. 1B).

There was a distinct pattern of distribution among the supratentorial, brainstem, and spinal tumors. Three (30%) of

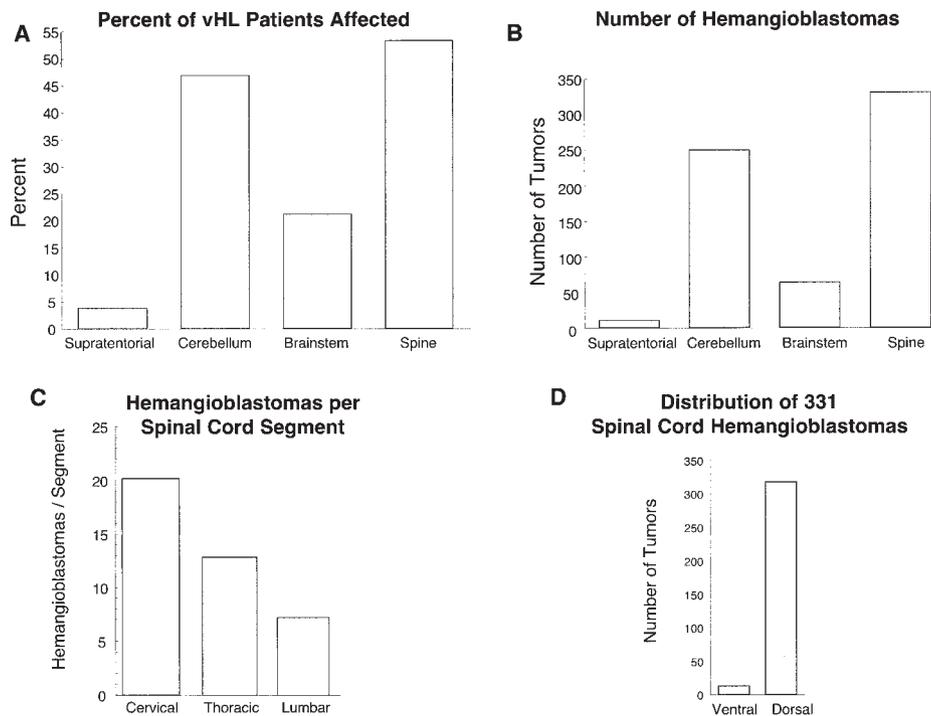


FIG. 1. Bar graphs demonstrating the distribution of 655 hemangioblastomas in 160 patients with confirmed VHL disease in whom there was CNS involvement of at least one hemangioblastoma. A and B: Distribution by the percentage of patients affected (A) and by the number of hemangioblastomas affecting various regions of the CNS (B). C: There is a preferential distribution of hemangioblastomas in the rostral portions of the spinal cord. D: Ninety-six percent of spinal hemangioblastomas are located in the posterior half of the spinal cord.

the 10 supratentorial tumors were located in the region of the tuber cinereum and all 64 brainstem tumors were located in the posterior medulla oblongata; 37 (58%) of the 64 brainstem lesions lay precisely within the region of the obex and area postrema, the specific site within the entire CNS that is most commonly affected by a hemangioblastoma. There was a tendency on the part of spinal tumors to be distributed more rostrally. Of the 331 spinal cord hemangioblastomas, there were 141 cervical (43%), 154 thoracic (47%), and 36 lumbar (11%) tumors. The average number of tumors per vertebral segment of spine diminished from the cervical through the thoracic and lumbar areas (Fig. 1C). Almost all spinal tumors were located in the posterior half of the spinal cord (96%); in only 13 (4%) of the 331 spinal tumors was the epicenter of the lesion located in the ventral half of the spinal cord (Fig. 1D).

Of the 160 patients with tumors, 33 harbored a single tumor and 127 had multiple tumors. Of the 127 patients with multiple tumors, in 25 patients all tumors were confined to a single region, in 73 patients two regions of the neuraxis were involved, and in 29 patients three regions were involved. Thus, there was no tendency for lesions to cluster in the same region or anatomical site in the same patient.

Cysts were frequently associated with hemangioblastomas, regardless of tumor location (Fig. 2A). Occasionally multiple cysts were found in the cerebellum, brainstem, and spinal cord in patients with multiple tumors. For instance, among 56 patients who harbored 77 cerebellar cysts, 12 patients had two cysts, two had three cysts, and one had five cysts. Thirty-nine (32%) of the 122 patients with spinal cord hemangioblastomas had tumor-associated cysts.

Clinical Findings

During the period of imaging review, 81 operations were performed for resection of hemangioblastomas. Of these 81 operations, 23 (28%) were scheduled for removal of cerebellar tumors, 10 (12%) for removal of brainstem tumors, two (2%) for removal of supratentorial tumors, and 46 (57%) for resection of spinal hemangioblastomas (24 cervical [30% of all operations], 18 thoracic [22%], and four lumbosacral [5%] lesions). Although patients without symptoms rarely underwent surgery because of concerns about the large size and associated mass effect of a tumor and/or its associated cyst, most patients (76 patients; 93%) were symptomatic at the time of surgery. Patients with cerebellar lesions presented with gait ataxia (64%), dysmetria (64%), headaches (12%), diplopia (8%), vertigo (8%), and/or emesis (8%). Those with brainstem lesions presented with hypesthesia (55%), gait ataxia (22%), dysphagia (22%), hyperreflexia (22%), headaches (11%), and/or dysmetria (11%). Patients with spinal cord tumors presented with hypesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), pain (17%), and/or incontinence (14%).

Relationship Between Tumor and Cyst Sizes and Their Relative Contributions to Symptoms

Tumor Size and Symptoms. The appearance of symptoms was related to the volume of the mass effect of the lesion. As expected, a serial increase in the size of a hemangioblastoma was observed in cerebellar, brainstem, and spinal cord

Hemangioblastomas of the CNS in patients with VHL disease

lesions, as patients progressed from being asymptomatic to symptomatic (Fig. 3A; $p < 0.0001$, $p < 0.01$, and $p < 0.0001$ for the cerebellum, brainstem, and spinal cord, respectively; unpaired t-test). In addition, the development of symptoms also was related to the size of the space available to accommodate a space-occupying lesion and its associated mass effect in the affected anatomical compartment. At the time of surgery, cerebellar hemangioblastomas (mean tumor volume $3.4 \pm 6.8 \text{ cm}^3$) were much larger than those lesions in the brainstem or spinal cord (mean tumor volumes $0.7 \pm 0.5 \text{ cm}^3$, and $0.8 \pm 1.8 \text{ cm}^3$, respectively; Fig. 3A).

Importance of the Cyst for the Development of Symptoms. Most symptomatic tumors were associated with a cyst (Fig. 2), and in most instances the cyst was larger than the tumor associated with it (Figs. 3B and C, and 4). Among the 250 cerebellar hemangioblastomas, 29 (12%) were associated with symptoms by the time the tumor or its associated cyst had reached peak size; 21 (72%) of these symptom-producing tumors had an associated cyst that was primarily responsible for the symptoms. On the other hand, only 28 (13%) of the 221 cerebellar tumors that remained asymptomatic had tumor-associated cysts ($p < 0.0001$; chi-square test). Similarly, 12 (19%) of the 64 brainstem tumors were associated with symptoms; nine (75%) of these 12 tumors had associated cysts, compared with an incidence of cysts in only four (8%) of the 52 brainstem tumors, which did not produce symptoms ($p < 0.0001$; chi-square test).

Almost all symptom-producing spinal hemangioblastomas had associated syringomyelia (Figs. 2B and 5). Because many patients harboring a spinal hemangioblastoma have multiple tumors, in some patients it was difficult to establish which tumor was producing the symptoms or which was responsible for a syrinx. To ensure reliable analysis we examined the relationship between the presence of a syrinx and the development of symptoms only in patients in whom it was clear which tumor was responsible for the symptoms or syrinx. Among the 257 tumors that could be evaluated, there was a significant correlation between the presence of symptoms and the presence of a syrinx ($p < 0.0001$; chi-square test).

When tumor-associated cysts were present, they accounted for most of the mass burden; the ratios of the average volume of cysts associated with cerebellar and brainstem tumors to the average volume of the hemangioblastomas responsible for the cyst were 4.3 and 12.3, respectively. By the time symptoms occurred and surgery was required, the cyst was usually much larger than the tumor causing it (Figs. 3B and C, and 4). This could be accurately quantified for cerebellar and brainstem tumors, which measured $14.6 \pm 13.5 \text{ cm}^3$ and $8.6 \pm 15.2 \text{ cm}^3$, respectively, at the time of surgery, whereas cerebellar and brainstem cysts averaged 34 (median 5.4) and 19 (median 2.4) times the size of their associated tumors (Figs. 3B and C, and 4). A similar circumstance appeared to occur with the spinal tumors, although it could not be accurately quantified because of the inability to obtain reliable measurements of cyst volume on MR images retrospectively.²² Because patients frequently harbored multiple lesions or cysts in the same region, the overall mass burden to the patient was reflected by the sum of all tumor and/or cyst volumes within an anatomical region; when symptoms appeared, this overall mass averaged

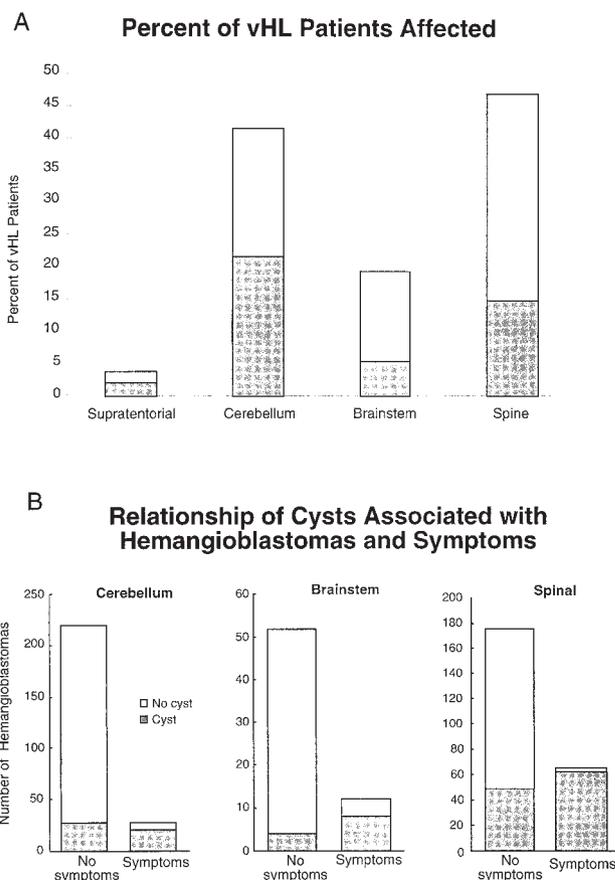


FIG. 2. Bar graphs demonstrating the distribution of cysts. Many patients (A) and hemangioblastomas (B) had associated cysts (gray portion of bar indicates associated cyst). Most symptom-producing hemangioblastomas had an associated cyst.

$16.8 \pm 14.1 \text{ cm}^3$ in the cerebellum and $9.1 \pm 13 \text{ cm}^3$ in the brainstem (Fig. 3B and C).

Induction of a Cyst by a Hemangioblastoma is Related to Tumor Size

The production of a cyst by a tumor was significantly associated with tumor size in the cerebellar, brainstem, and spinal tumors (all $p < 0.0001$; Mann-Whitney test) (Fig. 5). There was considerable overlap in the range of tumor sizes with and without a cyst in all three anatomical zones, however (Fig. 5B and C). Although the accurate prediction of a cyst could not be made based on a specific tumor size in any anatomical region, in the cerebellum there was a transition in the incidence of an associated cyst from 30 to 50% when the tumor size increased from the 400 to 600-mm³ range to the 600 to 800-mm³ range (10–12-mm diameter, Fig. 6A). In the brainstem this transition occurred when the lesion reached a size of approximately 500 mm³ (10-mm diameter, Fig. 6B). With spinal hemangioblastomas the incidence of an associated cyst increased progressively as tumor size increased, but there was no abrupt transition in the likelihood of producing an associated cyst at any tumor size (Fig. 6C).

Tumor and Cyst Growth and Rate of Growth

Tumor and Cyst Growth. Although some tumors enlarged,

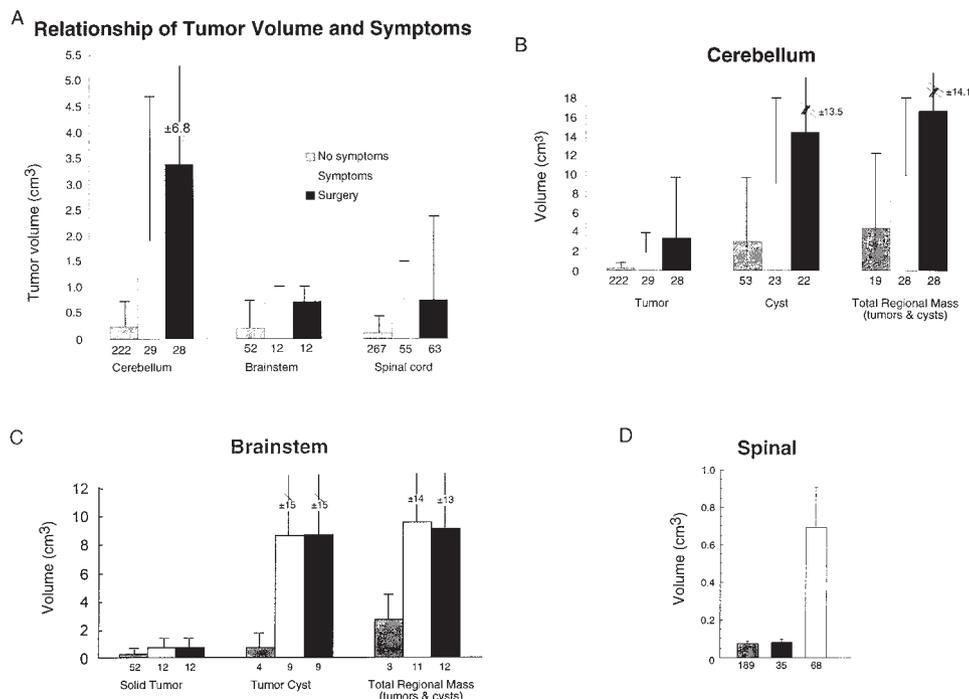


FIG. 3. Bar graphs showing mean hemangioblastoma volumes in the cerebellum, brainstem, and spinal cord when patients were asymptomatic, symptomatic, and at the time of surgery (means \pm SDs). The number of patients is indicated by the numbers beneath each column. A: The development of symptoms and the need for treatment is associated with tumor size in the cerebellum, brainstem, and spinal cord. Note that the size required for symptom production is larger in the cerebellum than in the brainstem or the spinal cord. B and C: The average volumes of cerebellar and brainstem cysts are considerably larger than those of the hemangioblastomas, regardless of whether the lesion produced symptoms. The cyst size and the total regional mass (see text) increases as patients became symptomatic and at surgery (spinal tumors are not included because the size of the cyst [syrinx] associated with a spinal tumor could not be measured accurately). D: Maximum hemangioblastoma size is similar in patients without symptoms and in patients with stable myelopathy associated with previous hemangioblastomas and/or surgery. The average size is substantially greater in tumors that produce symptoms. Note that of 331 spinal hemangioblastomas, in 27 cases it was unclear whether the lesion produced symptoms because the patient was symptomatic from another cord lesion, in three cases the lesion was resected while there were no symptoms, and in nine it was unknown if the lesion produced symptoms.

many did not grow larger during the interval of observation. The tendency for enlargement was greater for cysts than for hemangioblastomas. Among 88 patients who underwent serial imaging for at least 6 months (mean 37 ± 24 months; median 32 months), 164 (44%) of 373 hemangioblastomas and 37 (67%) of 55 tumor-associated cysts were documented to have enlarged. In patients with 6 months or longer follow-up review, 82 (52%) of 159 cerebellar tumors, 21 (55%) of 38 brainstem tumors, 54 (32%) of 167 spinal cord tumors, and seven (78%) of nine supratentorial tumor demonstrated growth. No tumors or cysts spontaneously diminished in size during the interval of observation.

Rates of Tumor and Cyst Growth. In all tumors in which the size of the lesion was documented over time by serial MR imaging, the overall growth rate (the change in volume between the last assessment and the initial MR imaging data available for the lesion divided by the interval between those two consecutive images) and the fastest growth spurt (the most rapid change in volume between any two scans) were determined (Figs. 7–10).

There were no significant differences in the growth rates of hemangioblastomas in the cerebellum, brainstem, and spinal cord. The overall absolute rates of expansion and the intervals of rapid growth in symptom-producing tumors

and cysts were greater than those in their asymptomatic counterparts (Fig. 7). The absolute rate of growth of symptomatic tumors was 5.7, 8.7, and 1.7 times the rates of asymptomatic tumors in the cerebellum, brainstem, and spinal cord (Fig. 7A), respectively. The rates of growth of cerebellar, brainstem, and spinal hemangioblastomas associated with cysts were significantly ($p < 0.05$) greater than the rate of tumors in these areas that were not associated with cysts (Fig. 7B).

Cysts enlarged at much higher rates than hemangioblastomas (Fig. 8). Cerebellar and brainstem cysts grew at rates averaging seven and 15 times greater, respectively, than hemangioblastomas in these areas. Nevertheless, there was no significant difference in the appearance of symptoms or associated cysts and the relative rates of growth of tumors during growth spurts ($p > 0.3$), suggesting that tumor size, rather than rate of growth, was the predominant factor underlying the association of change in tumor size with symptoms or a cyst.

Patterns of Tumor Growth

The clinical circumstance was dynamic in many patients. Hemangioblastomas of the CNS frequently demonstrated a

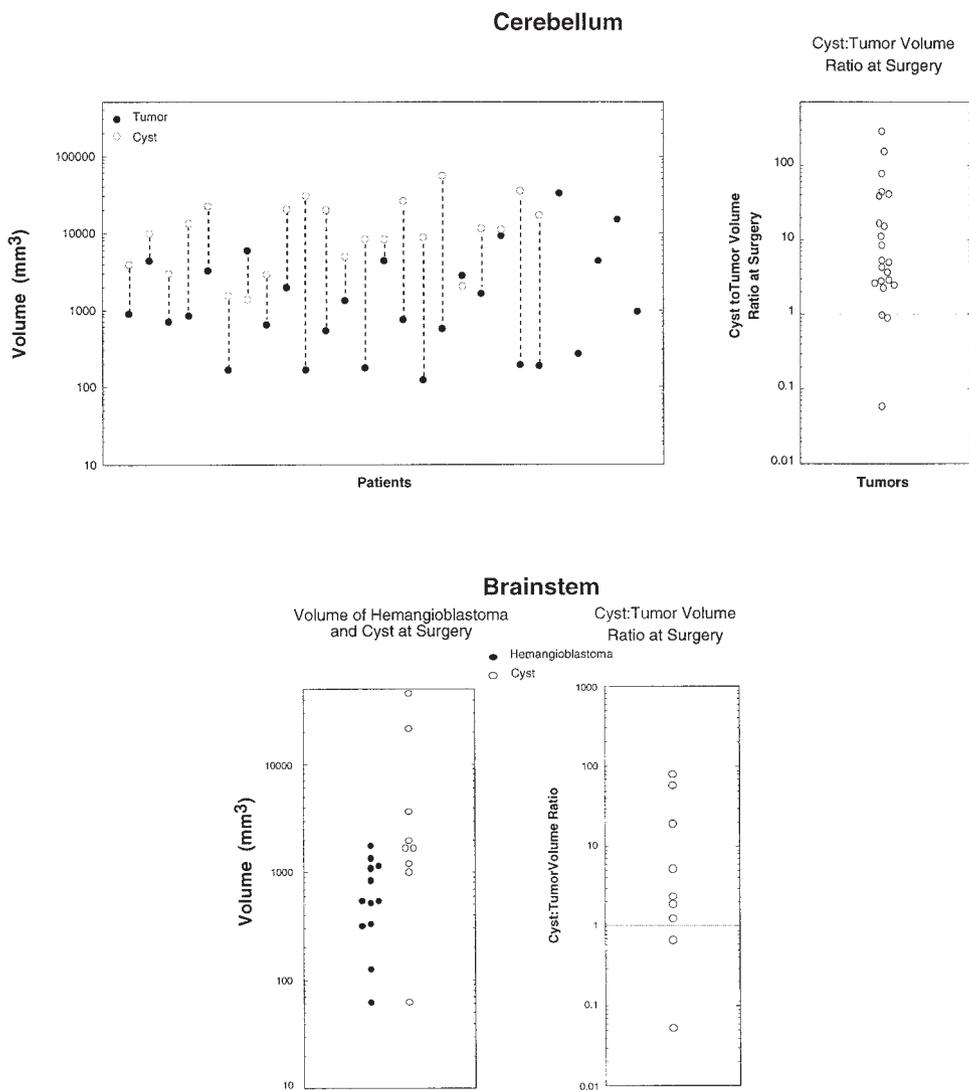


FIG. 4. Graphs depicting relative volumes of hemangioblastomas and cysts in individual patients at surgery. Distribution of individual tumor and cyst volumes and the ratios of cyst volume to the volume of the hemangioblastoma associated with it for cerebellar and brainstem tumors. The volumes of cerebellar (*upper*) and brainstem (*lower*) cysts were consistently and significantly (note log scale) larger than those of the hemangioblastomas that caused them. Shown are 27 hemangioblastomas in the 23 patients who underwent surgery for cerebellar hemangioblastomas (five cerebellar hemangioblastomas did not have associated cysts) and 12 hemangioblastomas in 10 patients who underwent surgery for brainstem hemangioblastomas (three brainstem hemangioblastomas did not have associated cysts). At the time of surgery the cerebellar and brainstem cysts averaged 34 (median 5.4) and 19 (median 2.4) times the size of their associated tumors.

two-step pattern of growth consisting of a period of time during which the lesions enlarged (growth phase) followed by a period of arrested growth (quiescent phase). Plotting volumes of all lesions detected on serial MR imaging from an individual patient displayed the characteristics of this disease process, the tumors, and their associated cysts. Figure 9 demonstrates patients with multiple tumors, each with multiple growth and quiescent phases. Patients harbored as many as 14 simultaneous growing tumors and four cysts from cerebellum, brainstem, and spinal cord regions, as exemplified by the patient whose tumor and cyst growth patterns are shown in Fig. 10. In some patients individual tumors would abruptly begin a growth spurt after an interval of stability (Fig. 9), suggesting the acquisition of an addi-

tional genetic event such as an additional mutation. In contrast, in many patients several tumors would enter growth phases and phases of stability concurrently (Fig. 10), suggesting systemic influences, perhaps hormonal ones. Of the 69 patients with documented tumor growth, 51 patients (74%) harbored tumors with one growth phase, whereas 18 patients (26%) had tumors with at least two growth phases. Conversely, gradual tumor growth without an associated quiescent phase was observed in 34 patients (49%), whereas in 35 patients (51%) the tumors had one or two quiescent phases.

The number of growth phases correlated with the mean follow-up time: 23 ± 21 months for those patients harboring tumors with one growth phase and 57 ± 19 months for

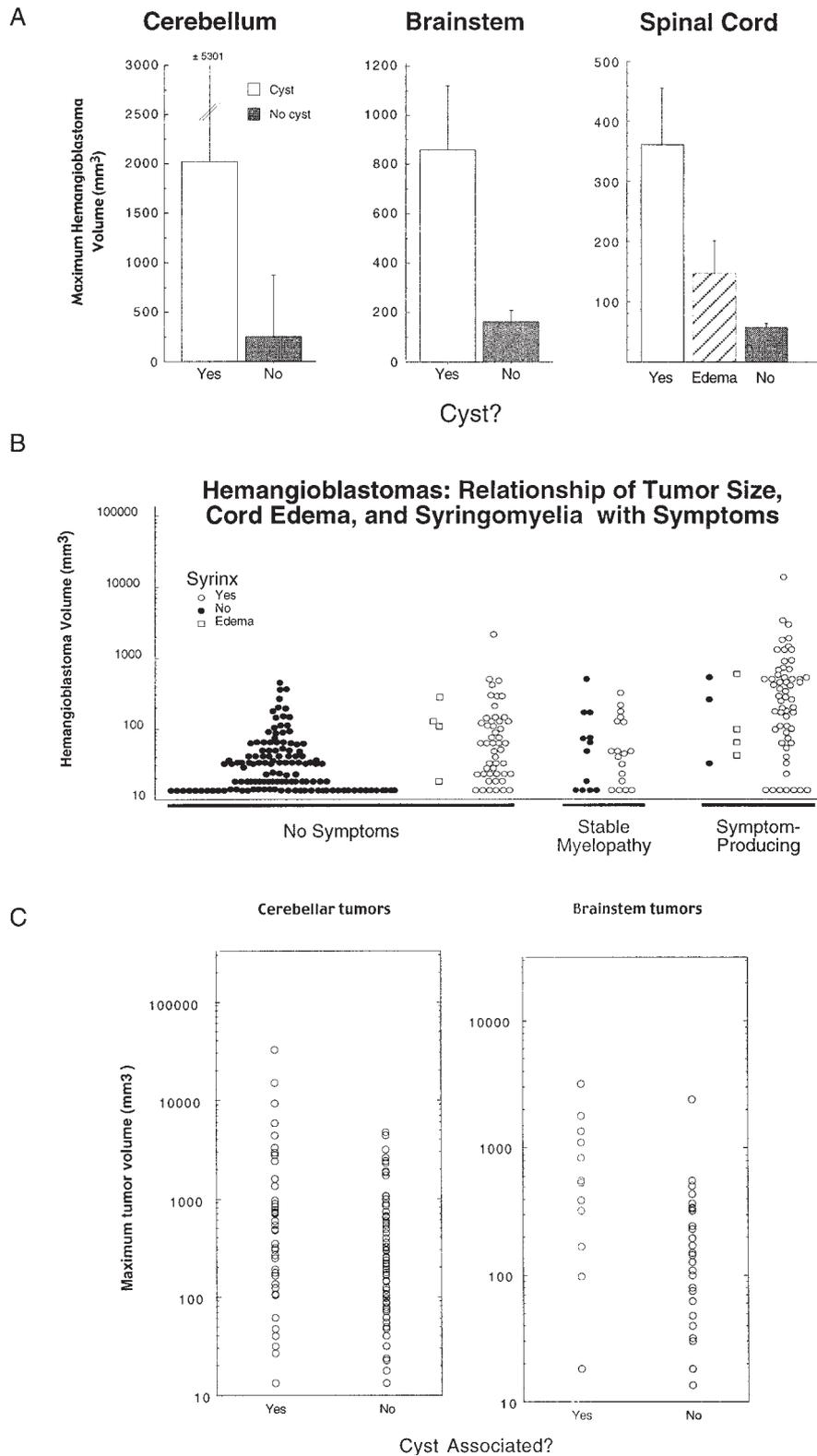


FIG. 5. Graphs demonstrating that the production of a cyst by a tumor is associated with tumor size in the cerebellar, brainstem, and spinal tumors. The mean tumor volumes \pm SDs of hemangioblastomas with and without associated cysts are shown (A). In the spinal cord the average tumor volume increased progressively from tumors without cysts or edema to tumors associated with edema of the surrounding spinal cord, and to tumors associated with cysts. Note that almost all symptom-producing hemangioblastomas of the spinal cord are associated with either edema or a cyst (B) and there is considerable overlap of sizes of tumors with and without associated cysts in the spinal cord, cerebellum, and brainstem (B and C).

Hemangioblastomas of the CNS in patients with VHL disease

those harboring lesions with two growth phases. Similarly, the number of quiescent phases correlated with the mean follow-up time. Patients having zero, one, or two quiescent phases had mean follow-up times of 19 ± 21 , 32 ± 21 , and 59 ± 19 months, respectively. Thus, with a longer period of observation the fraction of tumors with sequential intervals of growth and stability would have increased.

Formation of New Hemangioblastomas

One hundred fifteen new hemangioblastomas (41 cerebellar, 58 spinal, 13 brainstem, and three supratentorial) and 15 new tumor-associated cysts developed in 34 of the 160 patients with hemangioblastomas. The mean follow-up period for these 34 patients was 45 ± 26 months (median 51 months). The distribution of new lesions in the neuraxis closely matched the distribution of all lesions described previously. Of the 88 patients with at least 6 months follow up (mean 37 ± 24 months; median 32 months), 32 patients (36%) were found to harbor 110 new hemangioblastomas and 10 patients (11%) to harbor 14 new tumor-associated cysts. The majority of new tumors (55 [50%]) were spinal, whereas 39 (35%) were cerebellar, 13 (12%) were brainstem, and three (3%) were supratentorial. All new cysts were associated with a preexisting hemangioblastoma.

Most patients (102 of 160) had more than one region of hemangioblastoma involvement. Of 115 new tumors, all occurred in regions associated with previous or current tumor involvement, except for 13 tumors in nine patients. In those nine patients new tumors developed in regions that previously had been uninvolved, including the brainstem (five patients), spine (three patients), supratentorial region (three patients), and cerebellum (one patient). Of the 34 patients with new lesions, five patients initially presented with tumors from a single region. A supratentorial lesion developed in one patient with a cerebellar lesion, whereas one patient with five cerebellar lesions was later found to have two more cerebellar lesions and two spinal lesions. Two spinal tumors developed in one patient with a brainstem lesion. A patient with one spinal tumor was found to have three new spinal tumors, two brainstem tumors, and a supratentorial tumor, whereas another patient who originally had four spinal tumors was found to have four more spinal tumors and one cerebellar tumor. Thus, there was no discernable tendency for new lesions to cluster in a region of previous involvement. Nevertheless, patients in whom new tumors were found harbored an average of nine lesions compared with 4.5 lesions per patient in those in whom no new tumors developed.

Discussion

The natural history of CNS hemangioblastomas in patients with VHL disease has not been well characterized, although the establishment of centers of special expertise in the various aspects of VHL disease, the introduction of MR imaging, and advances in molecular genetics are facilitating the understanding of this disease process. Some of our findings are consistent with observations previously reported, whereas some of our observations differ substantially from previous studies. The 69% rate of CNS hemangioblastomas in patients with VHL disease reported here is comparable to the 48 to 72% reported previously,^{10,20,27,30} and the age of the

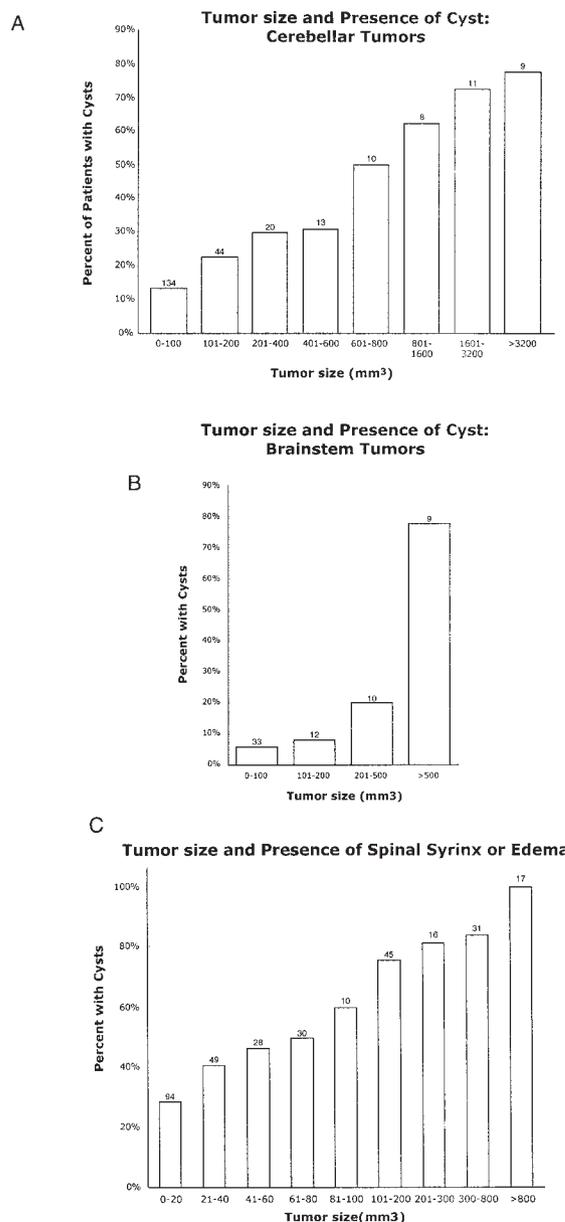


FIG. 6. Bar graphs showing the relationship between tumor size and the presence of a cyst/syrinx or edema. A: Although accurate prediction of a cyst in any anatomical region could not be based on any specific tumor size, in the cerebellum there is a transition in the incidence of an associated cyst from 30 to 50% when the tumor size increases from the 400 to 600-mm³ range to the 600 to 800-mm³ range (10–12-mm diameter). B: In the brainstem this transition occurs when the tumor is approximately 500 mm³ (10-mm diameter). C: With spinal hemangioblastomas the incidence of an associated cyst increases progressively as tumor size increases, but there is no abrupt transition in the likelihood of producing an associated cyst at any tumor size.

patient at the first NIH presentation for VHL disease is similar to the mean age of diagnosis of this disease in patients with CNS lesions (33 years) in other reports (range 30–34 years).^{10,24,30} In contrast, the 53% incidence of spinal cord hemangioblastomas in our patients with VHL disease greatly exceeds the 13 to 15% rates described in previous stud-

A Hemangioblastoma Growth Rate and Presence of Symptoms

B Hemangioblastoma Growth Rate and Presence of Cyst

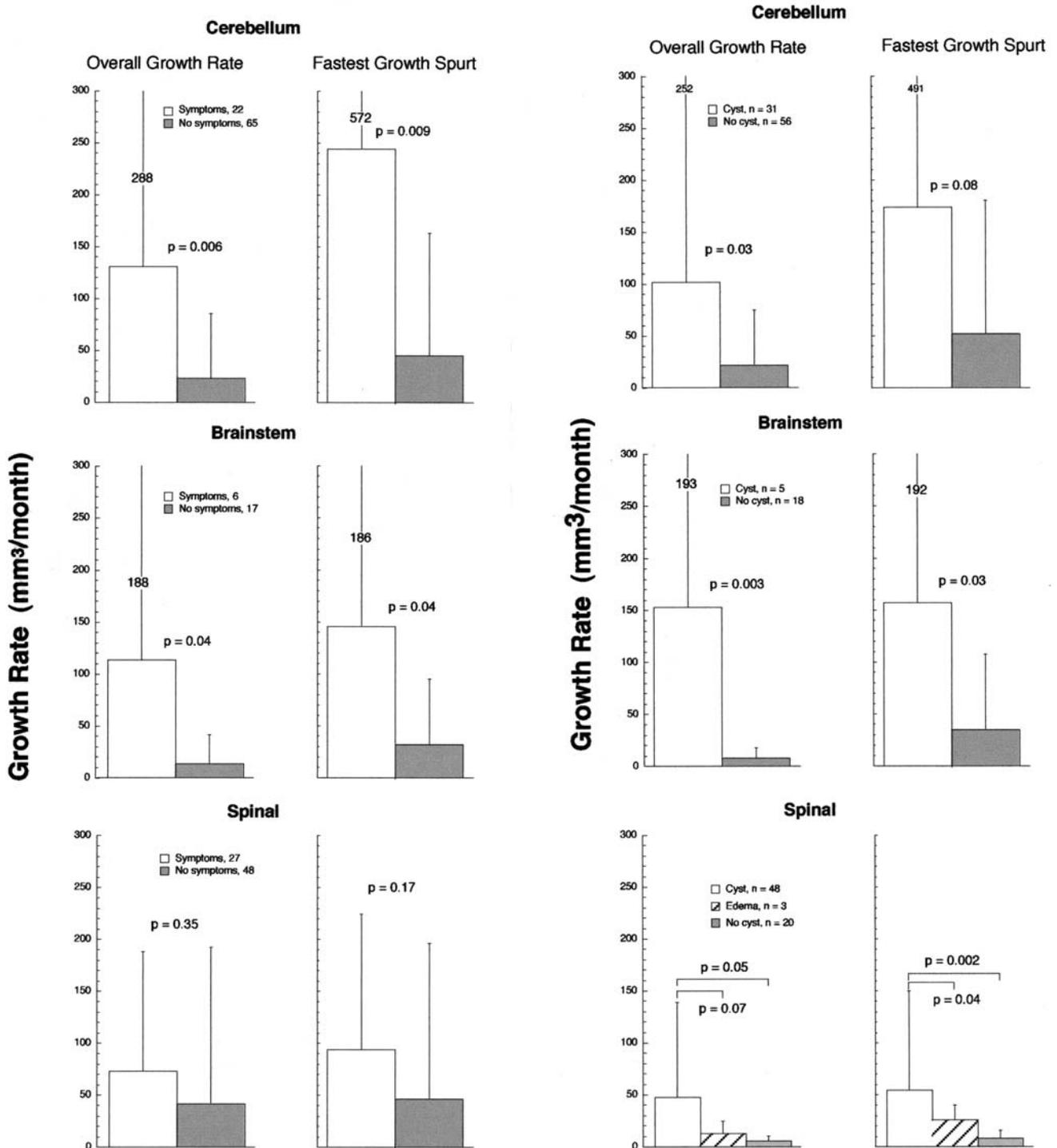


FIG. 7. Bar graphs showing the relationships between the hemangioblastoma growth rate and the presence of symptoms and an associated cyst. A: The overall growth rate and the rate of growth during the interval of most rapid growth (fastest growth spurt) is greater in symptom-producing tumors than in tumors without associated symptoms. B: The rate of growth is also greater in tumors associated with cysts (probability values indicate the result of a comparison made using the unpaired t-test). The number of patients (n) in each category is indicated in the legend for each graph. Note the wide range of rates of growth indicated by the large error bars (mean \pm SD is shown).

Hemangioblastomas of the CNS in patients with VHL disease

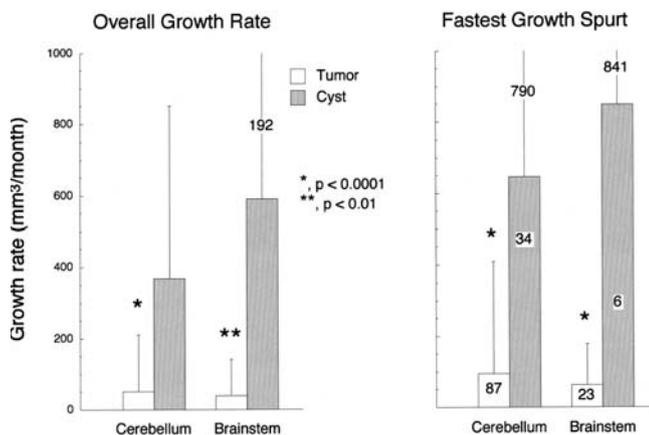


FIG. 8. Bar graphs depicting overall growth rates and peak growth rates (rates of growth during the interval of most rapid growth) of hemangioblastomas and cysts. The growth rate of cysts averages seven to 15 times greater than the average growth rate of hemangioblastomas.

ies, possibly reflecting the frequent, extensive MR imaging performed at our center.^{20,27,31} Although referral patterns may have emphasized patient selection for patients with spinal tumors in a minor way, because the great majority of patients originated in the NIH VHL Clinic, referral to which only a diagnosis of VHL disease is required, it is unlikely that referral patterns were a factor influencing the distributions observed here.

Natural History of Individual Tumors

The observations in this study indicate that these tumors grow in an unpredictable manner. Through serial imaging, we have demonstrated that 44% of hemangioblastomas and 67% of tumor-associated cysts will grow during a median of 32 months of follow up. Nevertheless, the growth of many tumors occurs for a period of several months and then stops for several months. Whereas acoustic neuromas demonstrate a truncated form of this behavior with single phases of growth and subsequent stability of tumor volume on serial imaging,^{42,43} the finding of multiple sequential growth and quiescent phases has not been described previously in CNS hemangioblastomas. We observed up to two growth periods and two quiescent periods in 26 and 51% of patients with growing tumors, respectively. The fact that additional growth or quiescent phases were more likely to develop in patients with longer follow-up periods suggests that these tumors may have more than two phases of growth if observed for a sufficiently long interval. It is unclear why these tumors behave in this fashion, although genetic and humoral factors may play a role.

Genetic Factors. The *VHL* gene, which was sequenced in 1993 and localizes to the short arm of chromosome 3 (3p25-26), is a tumor-suppressor gene.²¹ Each patient with VHL disease inherits a germline mutation of the *VHL* gene from the affected parent and a normal somatic (wild-type) gene from the other parent. Applying Knudson's two-hit hypothesis of tumorigenesis with tumor suppressor genes,¹⁹ germline mutations of the *VHL* gene are present in all cells; however, only those cells that undergo a deletion or mutation of the remaining normal somatic allele and are con-

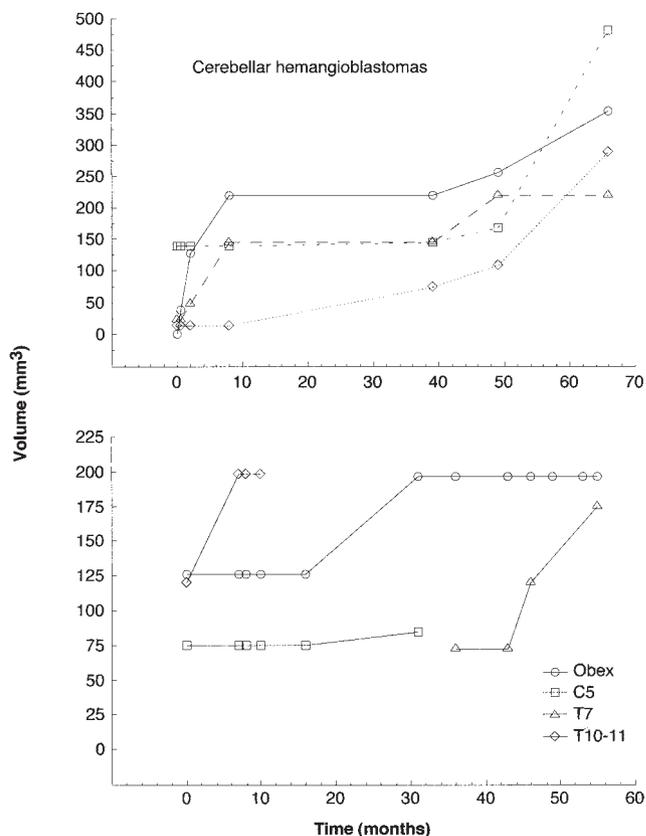


FIG. 9. Graphs demonstrating growth and growth arrest of tumors in individual patients. *Upper:* Multiple phases of growth and growth arrest in a patient harboring four cerebellar hemangioblastomas. Note the simultaneous interval of growth arrest in three of four tumors between 8 and 40 months (> 2.5 years of no growth), which is followed by a period of growth. *Lower:* Multiple phases of growth and growth arrest of hemangioblastomas in the obex and spinal cord in a patient with VHL disease. Note the appearance of a new tumor at the seventh thoracic level (T-7) at 36 months.

stituents of susceptible target organs, such as the kidney, adrenal, pancreas, or CNS, develop into tumors.^{18,19} The CNS, one of the target organs susceptible to somatic mutations, usually contains multiple hemangioblastomas. Thus, a prerequisite for tumor formation is loss of function of both copies of the *VHL* tumor suppressor gene. Our data demonstrate widely variable tumor growth rates. Our observations also indicate that many of these tumors do not enlarge at all over years of careful and precise measurement, whereas others either enlarge rapidly after an interval of no growth or enlarge for several months and then maintain a stable size for many months or even years before growing again. Furthermore, in some patients several tumors enlarge simultaneously over a period of several months and then concurrently stabilize. Moreover, an interval of rapid tumor growth frequently occurs with small preexisting tumors that have been stable for some time; these tumors already had to have homologous loss of function of the *VHL* gene to become tumors. These growth patterns are difficult to explain based simply on the sporadic occurrence of a disabling event on the wild-type allele producing tumor formation. These patterns indicate additional genetic events com-

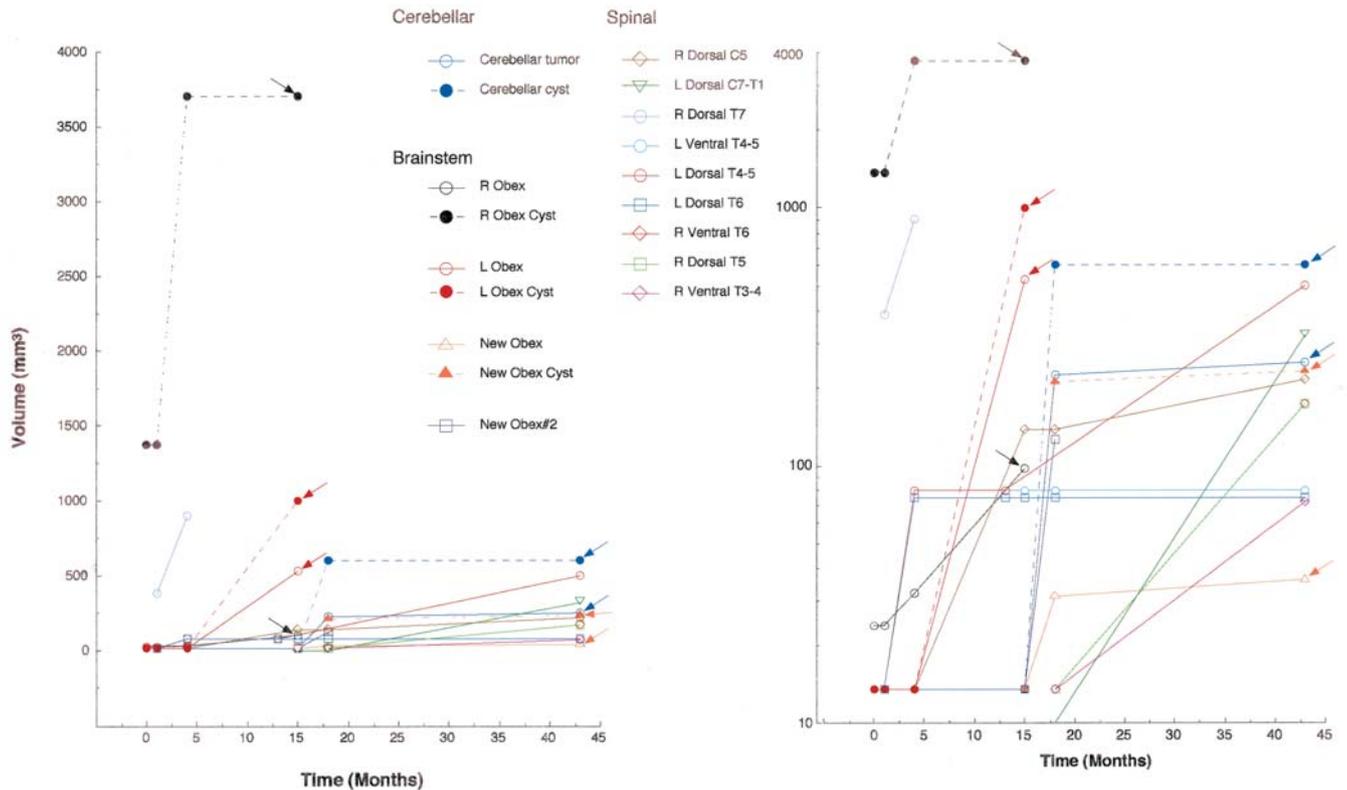


FIG. 10. Graphs demonstrating absolute and relative rates of growth of tumors and associated cysts in a patient with 14 hemangioblastomas (*open symbols connected by solid lines*) in the cerebellum, brainstem, and spinal cord, four of which were associated with cysts (*solid symbols connected by dashed lines*). *Arrows* indicate pairs of hemangioblastomas and associated cysts (each color represents a pair). The linear graph displays the wide range of volumes and the absolute rate of growth of the individual tumors and cysts (*left*). The graph with the log scale on the ordinate shows a comparison of relative changes in tumor volumes over time and permits visualization of the growth patterns of the smaller tumors. Note the pattern of intervals of growth separated by intervals of stable tumor size that last for as long as 3.5 years. The absolute growth rate of cysts is much greater than that for the tumors associated with them, and the absolute rate of the change in volume is greater with larger hemangioblastomas (*left*), but the relative change in size is similar for tumors and cysts and for large and small tumors (*right*). Note also the tendency for tumor and cyst growth to coincide. Termination of the line representing a lesion indicates excision of that lesion. New tumors arose during the interval of observation, as indicated by the appearance of a new symbol after the observation period began.

bined with paracrine or hormonal factors influencing tumor growth and stability. Extensive analysis of renal cell carcinoma cells from patients with VHL disease has demonstrated multiple mutations within the single *VHL* gene locus.^{6,8,37,45,48} If hemangioblastoma cells also have multiple mutations within the *VHL* gene, variable expression of these could lead to variable growth rates.^{9,12} New mutations to an existing hemangioblastoma also could alter its subsequent growth rate. Analysis of somatic mutations in two tumors with widely differing growth rates from a single patient may, in fact, demonstrate differences in the types and number of somatic mutations in the *VHL* gene or in other genes that regulate cell replication. Acquisition of additional genetic events affecting “promoter” genes may also influence tumor growth.¹³ Hormonal variation, such as that which occurs with pregnancy and puberty, has been advanced as a modifier of hemangioblastoma growth.³⁸ Several authors have reported that hemangioblastomas become active during pregnancy,^{16,29,34,38} and elevated progesterone receptor immunoreactivity has been demonstrated in these lesions.³ Based on increased clinical activity, surveillance protocols for patients with VHL disease call for more

frequent follow-up examinations during the reproductive years.^{7,26,27}

Local growth factors such as VEGF, placental growth factor, epidermal growth factor, and PDGF as well as their respective receptors have been shown to be elevated in hemangioblastomas, possibly influencing their growth.^{2,40,46} The finding of dramatic upregulation of VEGF, a potent endothelial growth factor with vascular permeability-inducing activity, in stromal cells and of the corresponding receptors, VEGFR-1 and VEGFR-2, in tumor endothelial cells indicates that angiogenesis and cyst formation in hemangioblastomas may be regulated with paracrine mechanisms.^{40,46} Additionally, Bohling, et al.² found that hemangioblastoma stromal cells contain high levels of epidermal growth factor receptor and PDGF receptor and endothelial cells have elevated levels of placental growth factor, VEGF, and PDGF receptor, indicating the potential for autocrine and paracrine loops regulating these tumors.

Implications for Treatment of Patients

With these noninvasive tumors, symptom production is a

product of lesion (tumor and its associated cyst) size and location. This is the case whether the lesion is in the cerebellum, brainstem, or spine, and whether the lesion is a hemangioblastoma or its associated cyst. As might be expected, the volume necessary to produce symptoms is also a reflection of the space available to accommodate a mass effect in the anatomical compartment that is affected; much smaller lesions in the spinal cord and brainstem produce symptoms than are required to produce symptoms in the cerebellum. Furthermore, not only are cysts commonly associated with cerebellar, brainstem, and spinal hemangioblastomas by the time symptoms appear, the majority of the mass effect-producing symptoms derives from the cyst rather than the tumor responsible for the cyst. Moreover, the larger the tumor, the more likely it is to produce an associated cyst; the cyst grows at a rate several times the rate of growth of the tumor causing it, and it reaches a volume that almost always is several times the volume of the causative tumor by the time symptoms appear. Thus, in most instances it is the cyst that produces most of the mass effect underlying the symptoms and the need for treatment, and that is so whether the tumor is located in the cerebellum, brainstem, or spinal cord.

Because of the importance of the cysts in the evolution of these tumors from an asymptomatic to a symptom-producing stage requiring treatment, and the fact that in our experience and that of others³² the presence of a cyst associated with a hemangioblastoma is a contraindication to treatment with radiosurgery, it is important to identify features of a hemangioblastoma that will predict the development of a cyst and the need for treatment. Identification of such features would permit treatment of tumors at a smaller size, allowing safer surgery or safer and more effective radiosurgery, and it may permit treatment of a greater fraction of tumors with radiosurgery if the tumors that will ultimately require treatment can be identified before cysts develop. Thus, we examined tumor size and rate of growth as predictors of symptoms and of the association with a cyst. Although absolute tumor size and the absolute rate of change in tumor size were associated with symptoms and the presence of a cyst, there was a wide range of tumor sizes and rate of change in tumor size with and without symptoms and with and without associated cysts. No reliable threshold tumor size or threshold rate of growth was identified that reliably predicted an association with either symptoms or a cyst.

The pattern of growth and quiescence that we have observed is also important when interpreting the results of treatment with radiosurgery or antiangiogenic therapy. Stereotactic radiosurgery has recently been used as an alternative to surgical therapy for some hemangioblastomas.^{4,5,32,33,35} Stability of tumor size has been used as a criteria for response to therapy.⁴⁷ Nevertheless, we observed many tumors that had intervals during which no growth occurred, and these intervals were often as long or longer than the intervals required after radiosurgery to determine whether arrest of tumor growth indicates response to therapy. Thus, absence of growth in many tumors after radiosurgery may simply coincide with a quiescent phase of tumor growth and may not represent a response to therapy at all.

Because of the extremely vascular nature of these tumors and their high expression of VEGF (also known as vascular endothelial growth and permeability factor),^{2,40,46} they are

potentially one of the most susceptible tumors to antiangiogenic therapies, and stability of tumor size also has been proposed as a criterion for tumor response to antiangiogenic therapy. The tendency of untreated tumors to have long intervals of stability in size will also have to be considered in that setting.

Understanding the course of hemangioblastoma growth should also influence the optimal interval of radiographic and clinical follow up and the timing of therapeutic intervention of these tumors. For instance, patients may need to be monitored more frequently during intervals of tumor enlargement or after appearance of a cyst, and less often during intervals of stability.

Finally, several important features of tumor growth, such as the influence of puberty, pregnancy, menopause, aging, and hormonal therapy such as birth control pills could not be addressed in this retrospective study, but will require a prospective study that encompasses several years. A prospective study that should capture these important features recently began at the NIH (National Institute of Neurological Disorders and Stroke Protocol No. 00-N-0140).

References

1. Anson JA, Glick RP, Crowell RM: Use of gadolinium-enhanced magnetic resonance imaging in the diagnosis and management of posterior fossa hemangioblastomas. **Surg Neurol** 35:300-304, 1991
2. Bohling T, Hatva E, Kujala M, et al: Expression of growth factors and growth factor receptors in capillary hemangioblastoma. **J Neuropathol Exp Neurol** 55:522-527, 1996
3. Brown DF, Gazdar AF, White CL III, et al: Human telomerase RNA expression and MIB-1 (Ki-67) proliferation index distinguish hemangioblastomas from metastatic renal cell carcinomas. **J Neuropathol Exp Neurol** 56:1349-1355, 1997
4. Chakraborti PR, Chakraborti KB, Doughty D, et al: Stereotactic multiple arc radiotherapy. IV—Haemangioblastoma. **Br J Neurosurg** 11:110-115, 1997
5. Chandler HC Jr, Friedman WA: Radiosurgical treatment of a hemangioblastoma: case report. **Neurosurgery** 34:353-355, 1994
6. Chen F, Kishida T, Yao M, et al: Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. **Hum Mutat** 5:66-75, 1995
7. Choyke PL, Glenn GM, Walther MM, et al: von Hippel-Lindau disease: genetic, clinical, and imaging features. **Radiology** 194:629-642, 1995
8. Crossey PA, Richards FM, Foster K, et al: Identification of intragenic mutations in the von Hippel-Lindau disease tumor suppressor gene and correlation with disease phenotype. **Hum Mol Genet** 3:1303-1308, 1994
9. Decker HJ, Weidt EJ, Brieger J: The von Hippel-Lindau tumor suppressor gene. A rare and intriguing disease opening new insight into basic mechanisms of carcinogenesis. **Cancer Genet Cytogenet** 93:74-83, 1997
10. Filling-Katz MR, Choyke PL, Oldfield E, et al: Central nervous system involvement in Von Hippel-Lindau disease. **Neurology** 41:41-46, 1991
11. Filling-Katz MR, Choyke PL, Patronas NJ, et al: Radiologic screening for von Hippel-Lindau disease: the role of Gd-DTPA enhanced MR imaging of the CNS. **J Comput Assist Tomogr** 13:743-755, 1989
12. Glenn GM, Daniel LN, Choyke P, et al: Von Hippel-Lindau (VHL) disease: distinct phenotypes suggest more than one mutant allele at the VHL locus. **Hum Genet** 87:207-210, 1991

13. Glenn GM, Linehan WM, Hosoe S, et al: Screening for von Hippel-Lindau disease by DNA polymorphism analysis. **JAMA** **267**: 1226–1231, 1992
14. Grunberg A, Rodesch G, Hurth M, et al: Imagerie par resonance magnetique des hemangioblastomes intra-rachidiens. **Neurochirurgie** **40**:155–164, 1994
15. Horton WA, Wong V, Eldridge R: Von Hippel-Lindau disease: clinical and pathological manifestations in nine families with 50 affected members. **Arch Intern Med** **136**:769–777, 1976
16. Kasarskis EJ, Tibbs PA, Lee C: Cerebellar hemangioblastoma symptomatic during pregnancy. **Neurosurgery** **22**:770–772, 1988
17. Kleihues P, Burger PC, Scheithauer BW: **Histological Typing of Tumours of the Central Nervous System, ed 2**. Berlin: Springer-Verlag, 1993, pp 41–42
18. Knudson AG Jr: Genetics of human cancer. **Annu Rev Genet** **20**: 231–251, 1986
19. Knudson AG Jr, Strong LC: Mutation and cancer: neuroblastoma and pheochromocytoma. **Am J Hum Genet** **24**:514–532, 1972
20. Lamiell JM, Salazar FG, Hsia YE: von Hippel-Lindau disease affecting 43 members of a single kindred. **Medicine** **68**:1–29, 1989
21. Latif F, Tory K, Gnarr J, et al: Identification of the von Hippel-Lindau disease tumor suppressor gene. **Science** **260**:1317–1320, 1993
22. Lonser RR, Weil RJ, Wanebo JE, et al: Surgical management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. **J Neurosurg** **98**:106–116, 2003
23. Lundin P, Pedersen P: Volume of pituitary macroadenomas: assessment by MRI. **J Comput Assist Tomogr** **16**:519–528, 1992
24. Maddock IR, Moran A, Maher ER, et al: A genetic register for von Hippel-Lindau disease. **J Med Genet** **33**:120–127, 1996
25. Maher ER, Iselius L, Yates JR, et al: Von Hippel-Lindau disease: a genetic study. **J Med Genet** **28**:443–447, 1991
26. Maher ER, Webster AR, Moore AT: Clinical features and molecular genetics of Von Hippel-Lindau disease. **Ophthalmic Genet** **16**:79–84, 1995
27. Maher ER, Yates JRW, Harries R, et al: Clinical features and natural history of von Hippel-Lindau disease. **Q J Med** **77**: 1151–1163, 1990
28. Melmon KL, Rosen SW: Lindau's disease. Review of the literature and study of a large kindred. **Am J Med** **36**:595–617, 1964
29. Nathan L, Satin AJ, Twickler DM: Cerebellar hemangioblastoma complicating pregnancy. A case report. **J Reprod Med** **40**: 662–664, 1995
30. Neumann HP, Eggert HR, Scheremet R, et al: Central nervous system lesions in von Hippel-Lindau syndrome. **J Neurol Neurosurg Psychiatry** **55**:898–901, 1992
31. Neumann HP, Eggert HR, Weigel K, et al: Hemangioblastomas of the central nervous system. A 10-year study with special reference to von Hippel-Lindau syndrome. **J Neurosurg** **70**:24–30, 1989
32. Niemela M, Lim YJ, Soderman M, et al: Gamma knife radiosurgery in 11 hemangioblastomas. **J Neurosurg** **85**:591–596, 1996
33. Page KA, Wayson K, Steinberg GK, et al: Stereotaxic radiosurgical ablation: an alternative treatment for recurrent and multifocal hemangioblastomas. A report of four cases. **Surg Neurol** **40**: 424–428, 1993
34. Palmer JJ: Haemangioblastomas. A review of 81 cases. **Acta Neurochir** **27**:125–148, 1972
35. Patrice SJ, Sneed PK, Flickinger JC, et al: Radiosurgery for hemangioblastoma: results of a multiinstitutional experience. **Int J Radiat Oncol Biol Phys** **35**:493–499, 1996
36. Pluta RM, Iuliano B, DeVroom HL, et al: Comparison of anterior and posterior surgical approaches in the treatment of ventral spinal hemangioblastomas in patients with von Hippel-Lindau disease. **J Neurosurg** **98**:117–124, 2003
37. Richards FM, Crossey PA, Phipps ME, et al: Detailed mapping of germline deletions of the von Hippel-Lindau disease tumor suppressor gene. **Hum Mol Genet** **3**:595–598, 1994
38. Robinson RG: Aspects of the natural history of cerebellar hemangioblastomas. **Acta Neurol Scand** **41**:372–380, 1966
39. Stolle C, Glenn G, Zbar B, et al: Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. **Hum Mutat** **12**:417–423, 1998
40. Stratmann R, Krieg M, Haas R, et al: Putative control of angiogenesis in hemangioblastomas by the von Hippel-Lindau tumor suppressor gene. **J Neuropathol Exp Neurol** **56**:1242–1252, 1997
41. Sung DI, Chang CH, Harisiadis L: Cerebellar hemangioblastomas. **Cancer** **49**:553–555, 1982
42. Thomsen J, Tos M: Acoustic neuroma: clinical aspects, audiotesticular assessment, diagnostic delay, and growth rate. **Am J Otol** **11**:12–19, 1990
43. Wazen J, Silverstein H, Norrell H, et al: Preoperative and postoperative growth rates in acoustic neuromas documented with CT scanning. **Otolaryngol Head Neck Surg** **93**:151–155, 1985
44. Weil RJ, Lonser RR, DeVroom HL, et al: Surgical management of brainstem hemangioblastomas in patients with von Hippel-Lindau disease. **J Neurosurg** **98**:95–105, 2003
45. Whaley JM, Naglich J, Gelbert L, et al: Germ-line mutations in the von Hippel-Lindau tumor-suppressor gene are similar to somatic von Hippel-Lindau aberrations in sporadic renal cell carcinoma. **Am J Hum Genet** **55**:1092–1102, 1994
46. Wizigmann-Voos S, Breier G, Risau W, et al: Up-regulation of vascular endothelial growth factor and its receptors in von Hippel-Lindau disease-associated and sporadic hemangioblastomas. **Cancer Res** **55**:1358–1364, 1995
47. Yamamoto M, Jimbo M, Ide M, et al: Is unchanged tumor volume after radiosurgery a measure of outcome? **Stereotact Funct Neurosurg** **66** (Suppl 1):231–239, 1996
48. Zbar B, Kishida T, Chen F, et al: Germline mutations in the Von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. **Hum Mutat** **8**:348–357, 1996

Manuscript received April 23, 2002.

Accepted in final form September 9, 2002.

Address reprint requests to: Edward H. Oldfield, M.D., Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 5D37, Bethesda, Maryland 20892-1414. email: OldfieldE@ninds.nih.gov.