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Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease

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Abstract

Object—The tumors most frequently associated with von Hippel-Lindau (VHL) disease are hemangioblastomas. While they are associated with significant neurological impairment and mortality, their natural history and optimal management have not been fully defined.

Methods—Patients with VHL were enrolled in a prospective study designed to define the natural history of CNS hemangioblastomas. In the present analysis, serial imaging, laboratory, genetic, and clinical data were evaluated in those with at least 2 years of follow-up data.

Results—At study entrance 225 patients (111 males, 114 females) harbored 1921 CNS hemangioblastomas in the supratentorial compartment (21 tumors [1%]), cerebellum (865 [45%]), brainstem (129 [7%]), spinal cord (689 [36%]), cauda equina (212 [11%]), and nerve roots (5 [0.3%]; follow-up 15,819 hemangioblastoma-years). Increased tumor burden was associated with partial deletions in the *VHL* gene ($p = 0.005$) and male sex ($p = 0.002$). Hemangioblastoma

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Disclosure

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development (median 0.3 new tumors/year) was associated with younger age ($p < 0.0001$) and more tumors at study entrance ($p < 0.0001$). While 1278 hemangioblastomas (51%) did not grow, 1227 hemangioblastomas (49%) grew in a saltatory (886 [72%]), linear (76 [6%]), or exponential (264 [22%]) pattern. Faster tumor growth was associated with male sex ($p = 0.001$), symptomatic tumors ($p < 0.0001$), and tumors associated with cysts ($p < 0.0001$). Location-dependent tumor size was the primary predictor of eventual symptom formation (159 symptomatic tumors [6.3%]; area under the curve > 0.9).

Conclusions—Central nervous system hemangioblastoma burden in VHL is associated with partial germline deletions and male sex. Unpredictable growth of hemangioblastomas compromises assessment of nonsurgical therapies. The judicious treatment of symptom-producing hemangioblastomas, while avoiding unnecessary treatment of asymptomatic tumors that may not progress, can provide clinical stability. Clinical trial registration no.: NCT00005902 (ClinicalTrials.gov).

Keywords

central nervous system; hemangioblastoma; natural history; von Hippel-Lindau disease; oncology

Germline mutations of the von Hippel-Lindau (VHL) disease gene on chromosome 3 underlie the pathogenesis of this neoplastic disorder. Transmitted in an autosomal dominant manner, VHL disease can result in the development of tumors and cysts of the viscera and nervous system.[16] The most common neoplastic manifestations of VHL are CNS hemangioblastomas. [7,22] Prior reports estimate that multiple hemangioblastomas will develop in 60%–90% of patients with VHL disease.[5,6,10,15,17,20,21,23] While CNS hemangioblastomas are benign, they are associated with significant neurological morbidity and mortality based on their location and multiplicity.[4] Despite the frequency and devastating effects of CNS hemangioblastomas in VHL, their natural history and optimal management have not been defined.

To determine the natural history of CNS hemangioblastomas, to gain insight into factors affecting tumor development and/or progression, and to improve tumor management, patients with VHL disease and associated hemangioblastomas were prospectively evaluated using clinical, imaging, and genetic analyses. Specifically, analyses were performed to determine the biological properties of CNS hemangioblastomas, as well as to identify factors associated with tumor burden, new tumor development, and the production of symptoms requiring treatment.

Methods

Patients

This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is NCT00005902. Patients with at least one hemangioblastoma visible on MRI provided written informed consent and were enrolled in an institutional review board–approved protocol to determine the natural history of VHL-associated hemangioblastomas (accrual ceiling 250 participants). Patients were enrolled from November 2001 to October 2005. All patients had genetic and/or clinical confirmation of VHL.[12,19]

Germline Genotype Analysis

Analysis of *VHL* mutation was performed on samples of peripheral blood from the study participant or at least one family member to determine germline genotype, as described previously.[26]

Study Evaluation

Clinical Evaluation—Patients were evaluated at 6-month intervals. At each visit, detailed neurological examinations were performed and Karnofsky Performance Scale (KPS) scores were determined. Abdominal imaging and patient records were used to document the presence of visceral lesions.

Imaging Evaluation—Craniospinal high-resolution (1-mm slice thickness) FLAIR and T1- and T2-weighted MRI (with and without contrast) was performed at each clinical evaluation.

Hemangioblastoma Characteristics

To accurately assess tumor distribution, development, and growth over time, patients and/or tumors with less than 2 years of follow-up were excluded from analysis. Data analysis for patients and/or tumors treated with systemic chemotherapy, stereotactic radiosurgery, or craniospinal radiation was terminated on initiation of those therapies.[2,25]

Postcontrast T1-weighted, spoiled gradient recalled, and T2-weighted MRI sequences were acquired at clinic visits and analyzed. Hemangioblastoma and associated cyst (if present) volumes were calculated using a modified ellipsoid formula at each visit.[14] Peritumoral cysts were assessed using T2-weighted (hyperintensity) MRI. Intratumoral cysts were evaluated using T1-weighted (hypointensity within enhancing tumor) postcontrast MRI. Volume assessment values were initially assessed serially by a single observer and confirmed by at least one other observer. Patterns of tumor growth were classified as saltatory (exhibiting periods of growth and growth quiescence), linear, or exponential. Tumors that did not progress in size were classified as stable.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and hemangioblastoma features. To examine the effect of factors, such as age and sex, on tumor growth rate, a linear mixed model (MIXED procedure, SAS Institute Inc.) with the patient as random effect was used since most patients had more than 1 tumor. All tumors in the study had at least 2 years of follow-up and 4 data points.

Tumor growth pattern was determined with mathematical characterization. “No growth” was defined as the difference in tumor size ≤7.5 mm^3/year between baseline and the last visit divided by the years of follow-up. “Saltatory growth” was defined as the total number of days at zero-growing intervals divided by the total number of days of follow-up for the tumor (≥25%), where the zerogrowing interval was defined as the interval with 0 difference between tumor size at adjacent time points. A tumor was defined as having “linear growth” if the R^2 (R_1^2) from the regression of tumor size (dependent variable) on the visit date

(independent variable) was ≥0.85 and greater than or equal to the R^2 (R_2^2) from the regression of log-transformed tumor size (dependent variable) on the visit date. A tumor was defined as having "exponential growth" if R_2^2 was ≥0.85 and > R_1^2.

A general linear model (GLM procedure, SAS Institute Inc.) was applied to examine the association of patient total number of tumors with age (categorized as 12–20, 21–30, 31–40, 41–50, or > 50 years), sex, years of follow-up, and mutation genotype. A general linear model was also applied to determine the association of newly developed tumor per year with age (categorized), sex, number of tumors at study entrance, and mutation genotype. Pedigree effect was examined using a mixed model (MIXED procedure). Since most patients had more than 1 tumor and the tumors from the same patient were not independent, a general linear mixed model with subject as the random effect (MIXED procedure) was used to assess the association of tumor growth rate with age, sex, tumor location, cyst-linked tumor type (4 levels, including linked to intratumoral cyst, linked to peritumoral cyst, linked to both cysts, and linked to none), and tumor symptom type (that is, asymptomatic or symptomatic tumor). A p value of 0.1 was used as a model selection criterion for the above association analysis.

To examine the effect of factors on a patient's total number of tumors and number of newly developed tumors per year, a general linear model was performed since pedigree effect was not significant. Receiver operating characteristic (ROC) curve analysis using a generalized mixed model (GLIMMIX procedure) and a logistic regression model (LOGISTIC procedure, both SAS Institute Inc.) was applied to evaluate tumor volume for the prediction of symptomatic tumors. Discrimination was assessed using the area under the ROC curve (AUC). Survival analysis was performed using growth as the event of interest, defined as the difference in tumor volume > 7.5 mm^3 between the last and first evaluation, and not growing as censored. The timing of events was determined using the time the tumor was detectable on imaging (12 mm^3) to a time in which growth was > 7.5 mm^3.

Quantitative outcome measures were logarithmically transformed because their distributions had a long right tail. For any fixed factor with more than 2 levels in which significance was found, Tukey-Kramer multiple pairwise comparisons were performed. A p value of 0.01 was used as the significance level to adjust for multiple tests, and a p value of 0.1 was used as the covariate selection. For statistical analyses, SAS software version 9.2 was used (SAS Institute Inc.).

Results

Patient Characteristics

Two hundred fifty patients with VHL disease (119 males, 131 females) were enrolled in the study. The mean age at study entrance was 38.5 ± 12.3 years (range 12.3–66.1 years). Two hundred twenty-five patients (90%) had tumors as well as more than 2 years of follow-up and were used for analysis (Table 1). The mean follow-up was 6.9 ± 1.6 years (range 2.1–9.0 years). During the study, 16 patients died (mean age 41.9 ± 10.9 years, range 17.7–56.3 years) from renal cell carcinoma (2 patients), CNS hemangioblastoma progression (4 patients), stroke (1 patient), pneumonia (1 patient), and unknown causes (8 patients).

Twenty-five patients (10%) had less than 2 years of evaluation as a result of death (7 patients), study withdrawal (5 patients), or loss to follow-up (13 patients).

Hemangioblastoma Features

Hemangioblastoma Burden—At study entrance, the 225 patients harbored 1921 craniospinal hemangioblastomas (mean 8.5 ± 7.0 tumors/patient, median 7 tumors/patient, range 1–33 tumors/patient) located in the supratentorial compartment (21 tumors [1%]), brainstem (129 [7%]), cerebellum (865 [45%]), spinal cord (689 [36%]), cauda equina (212 [11%]), and nerve roots (5 [0.3%]; Table 1). The mean total tumor volume per patient upon study entrance was 562.8 ± 1306.6 mm^3 (median 182.5 mm^3, range 12–11,919.9 mm^3).

At the last evaluation, patients harbored 2336 craniospinal hemangioblastomas (mean 10.4 ± 7.8 tumors/patient, median 8 tumors/patient). Hemangioblastomas were found in the supratentorial compartment (21 tumors [1%]), brainstem (132 tumors [6%]), cerebellum (1049 tumors [45%]), spinal cord (867 tumors [37%]), cauda equina (261 tumors [11%]), and nerve roots (6 tumors [0.3%]). The mean total craniospinal hemangioblastoma volume per patient was 1618.4 ± 3734.7 mm^3 (median 369.1 mm^3, range 0–28,304.5 mm^3). Total tumor follow-up was 15,819 hemangioblastoma-years.

New Hemangioblastoma Development—One hundred sixty-two patients (72%) exhibited new CNS hemangioblastomas during the study. Consistent with the overall anatomical distribution of tumors, new hemangioblastomas developed in the supratentorial compartment (4 [0.7%]), cerebellum (291 [50%]), brainstem (16 [3%]), spinal cord (217 [37%]), cauda equina (54 [9%]), or nerve roots (2 [0.3%]). Over the study duration, a mean of 0.4 ± 0.4 new tumors/year/patient developed (median 0.3 tumors).

Hemangioblastoma Growth—Twelve hundred seventy-eight hemangioblastomas (51% of tumors evaluated) remained stable and 1227 (49%) grew during the study. Progression was observed in 25% of tumors followed up for 1.5–5.0 years and in 50% of tumors followed up for 5.6–8.9 years, depending on tumor location (Fig. 1). Patterns of growth varied and were categorized as saltatory (886 tumors [72%]), linear (76 [6%]), or exponential (264 [22%]; Fig. 2). The median growth rate was 3.7 mm^3/year (range 0.8–2331.9 mm^3/year) for tumors growing in a saltatory pattern, 23.8 mm^3/year (range 0.8–1245.4 mm^3/year) in a linear pattern, and 79.2 mm^3/year (range 1.8– 6216.6 mm^3/year) in an exponential pattern ($p < 0.0001$ for all pairwise comparisons).

While the various patterns of growth were represented among the different anatomical regions, hemangioblastomas grew at significantly different rates depending on their anatomical region. Hemangioblastomas located in the brainstem (median 3.1 mm^3/year) and cerebellum (median 1.2 mm^3/year) grew significantly faster than those arising in the spinal cord (median 0.3 mm^3/per year) or cauda equina (median 0 mm^3/year; $p < 0.0001$).

Hemangioblastoma-Associated Cysts—During the study, 295 hemangioblastomas developed cysts. Two hundred forty-seven tumors (9.9% of total 2505) developed peritumoral cysts, 37 (1.5%) developed intratumoral cysts, and 11 (0.4%) developed both types of cyst. Five cysts arose in the supratentorial compartment (1.7%), 190 in the

cerebellum (64.4%), 32 in the brainstem (10.8%), 67 in the spinal cord (22.7%), and 1 in a nerve root (0.3%).

Tumors associated with cysts demonstrated increased lesion volume, growth rate, and production of symptoms. For instance, there were 100 symptomatic cerebellar tumors (8.6%) among 1156 cerebellar hemangioblastomas, and 60 were associated with peritumoral cysts, as compared with 89 (8.4%) of the 1056 cerebellar hemangioblastomas without symptoms. The ratio of the median growth rate of peritumoral cysts to the tumor growth rate for symptomatic cerebellar hemangioblastomas was 22:1, and the ratio of the median volume of the peritumoral cyst compared with tumor was 10:1.

Hemangioblastoma Symptom Association—While 2346 hemangioblastomas were asymptomatic (93.6%) at the final evaluation, 159 hemangioblastomas (6.3%) in 75 patients produced symptoms and required treatment. Neurological symptoms and signs were caused by mass effect related to hemangioblastoma and/or cyst size in their specific anatomical location (Table 2). Fourteen of the hemangioblastomas (8.8%) that became symptomatic were not present on imaging at study entrance.

Clinical Progression

The KPS score remained unchanged in 136 patients (60%), improved in 32 (14%; all associated with resection of symptom-producing hemangioblastomas), and worsened in 57 (25%). Declines in KPS scores during the study were a result of disease progression (45 patients [20% of all patients]), postoperative morbidity (10 patients [4%]), or unknown reasons (2 patients [1%]).

Analysis of Factors Associated With Tumor Behavior

Tumor Burden—Factors associated with an increased tumor burden included male sex ($p = 0.002$; mean 11.5 tumors/male patient vs 9.2 tumors/female patient; median 9 vs 7, respectively), longer follow-up ($p = 0.007$), and genotype ($p = 0.002$; Table 3). Specifically, patients harboring partial germline deletions (60 patients [27%]) had more tumors than patients with missense mutations (86 patients [38%]; $p = 0.005$).

New Tumor Development—Sex and genotype had no effect on the development of new tumors (Table 3). Patients with a greater tumor burden at study entrance demonstrated more tumors over the course of the study ($p < 0.0001$). Age had a significant ($p < 0.0001$) effect on tumor development. Patients 12–20 years of age developed more tumors per year than older groups.

Tumor Growth—Tumors grew faster in males than in females ($p = 0.001$; Table 3). The effects of tumor growth rate on the presence and type of symptoms varied with location ($p < 0.0001$). For each anatomical compartment, the symptom-producing tumors grew faster than the asymptomatic ones ($p < 0.0001$). Symptom-producing tumors in the spine grew significantly slower than those in the cerebellum ($p = 0.0007$). Asymptomatic tumors in the spine and cauda equina (no significant difference between these 2 regions, $p = 1.0$) grew significantly ($p < 0.0001$) slower than those in the brainstem and cerebellum (no significant

difference between these 2 regions, p = 0.7). For each anatomical compartment, tumors associated with a cystic component grew substantially faster than tumors not associated with cysts (p < 0.0001). For the cerebellar compartment, symptomatic tumors associated with intratumoral cysts grew faster than those associated with peritumoral cysts (p < 0.0001).

Cyst Growth—All types of cerebellar cysts (peritumoral, intratumoral, or combination of the two) grew at greater rates in younger patients (p = 0.01; Table 3). Peritumoral cysts grew faster in symptomatic (p < 0.0001) than in asymptomatic hemangioblastomas.

Factors That Predict Symptom Formation—Receiver operating characteristic analysis demonstrated that thresholds of location-dependent tumor size predict symptom formation (AUC of 0.99, 0.94, and 0.97 for brainstem, cerebellum, and spine, respectively). When specificity was set to at least 90%, cerebellar hemangioblastomas reaching a diameter of 5.6 mm, brainstem hemangioblastomas reaching a diameter of 4.0 mm, and spinal cord hemangioblastomas reaching a diameter of 4.5 mm would be diagnosed as symptomatic with a sensitivity of 78% (specificity 96%), 53% (specificity 92%), and 78% (specificity 95%), respectively.

Discussion

Previous Reports

Clinical studies have been used to develop successful paradigms for the treatment of VHL-associated visceral tumors (renal cell carcinoma, pancreatic neuroendocrine tumors, and pheochromocytomas)[11,27,28] and endolymphatic sac tumors.[3,18] Previous reports defining the natural history of VHL-associated hemangioblastomas have been inconclusive because of their retrospective analyses, inadequate numbers of patients, and limited follow-up.[1,17,24,29] Given these limitations, the natural history of CNS hemangioblastomas, the timing for removing VHL-associated CNS hemangioblastomas, and the role of radiosurgery and/or chemotherapy are unknown. To better understand features that can be used to guide management of CNS hemangioblastomas in VHL, we performed a long-term, prospective natural history study in a large cohort of patients.

Biological and Clinical Implications

Tumor Burden and New Tumor Development—Male sex was associated with increased CNS hemangioblastoma burden and growth rate, which may indicate that male hormonal influences affect the development and growth of CNS hemangioblastomas. This effect of sex on tumor development is consistent with previous findings that pregnancy did not impact hemangioblastoma development or progression in VHL patients of childbearing years.[34]

New hemangioblastomas developed in most patients (72%). An increased rate of tumor development was associated with tumor burden at study entrance and younger age. These findings suggest that patients with more tumors at any point in time may be predisposed to additional tumors over a lifetime. Moreover, tumors developed in younger patients at a faster rate than in older patients. This finding indicates that CNS hemangioblastoma

development in VHL may be affected by biological features related to developmental processes, hormonal factors, other systemic factors, and/or proteasomal processing.

Patients with partial germline deletions had an increased tumor burden as compared with the patients with missense mutations. Recent observations indicate that protein produced by missense germline alterations in neoplasia and metabolic syndromes, including VHL,[33] can maintain intrinsic function.[13,32] Further, the severity of disease burden and tumor development in patients with familial neoplasia syndromes may be the result of the rapid degradation of functional mutant protein via proteasome control pathways[32] and/or an age-related decline in proteasome function of mutated tumor suppressor protein.[9] These findings suggest that residual VHL protein (tumor suppressor) function associated with a germline missense mutation may underlie reduced disease severity.

Growth of Tumors—Consistent with prior retrospective studies,[1,29] variable patterns of tumor growth were observed. While approximately half (51%) of all CNS hemangioblastomas remained stable in size during long-term follow-up, 49% grew. The most common pattern of growth was saltatory (72% of growing tumors), followed by exponential (22%) and linear (6%). Because most tumors remain stable or grow in a saltatory pattern (characterized by prolonged periods, often years, of quiescence), extended periods of follow-up (probably 5 or more years) are necessary to accurately assess the efficacy of nonsurgical therapies, such as chemotherapy and radiation therapy, and tumor stability. Previously, we analyzed CNS hemangioblastomas treated with stereotactic radiosurgery in a cohort of patients with VHL (40 hemangioblastomas in 20 patients).[2] At nearly 6 years after stereotactic radiosurgery, no progression occurred in 33% of tumors, similar to the natural history of (untreated) CNS hemangioblastoma progression in the current study (25%).

Clinical Progression—Previous reports have indicated that patients with VHL have a shortened lifespan because of complications related to renal cell carcinoma and CNS hemangioblastomas.[30] Similarly, our study indicates that 25% of mortality was the result of VHL-associated tumor progression. Specifically, progression of CNS hemangioblastomas was the leading cause of VHL-associated mortality, followed by renal cell carcinoma–related disease. These findings differ from those in a number of previous reports that describe renal cell carcinoma as the leading cause of VHL-associated mortality[4,17] and may reflect the universal occurrence of VHL-associated hemangioblastomas in the current study population.

The mainstay of therapy for sporadic and VHL-associated CNS hemangioblastomas is resection. Surgery can be safely performed in most patients. Better patient function in the current study was the result of resection of symptomatic CNS hemangioblastomas. These findings are similar to those in previous studies demonstrating symptom stability or improvement in most patients after resection of hemangioblastomas.[8,31] Together, these results underscore the lasting clinical stability provided in most patients by the judicious treatment of symptom-producing hemangioblastomas and the avoidance of unnecessary therapies for asymptomatic tumors that may not progress.

Conclusions

Consistent with prior retrospective studies,[1,29] signs and symptoms of hemangioblastomas are dictated by tumor location, associated edema, and cyst formation and propagation (Table 2).[8] However, absolute size of the lesion did not dictate the symptoms for tumors in all locations, and neither did the rate of growth. Although a threshold size was used as the primary factor in the ROC modeling to predict eventual symptom formation, the likely time to symptom formation for individual lesions remains undefined because of the saltatory growth pattern exhibited by many tumors. These findings support the onset of symptoms associated with a particular CNS hemangioblastoma as the indication for surgery.

Abbreviations used in this paper

AUC	area under the ROC curve
KPS	Karnofsky Performance Scale
ROC	receiver operating characteristic
VHL	von Hippel-Lindau

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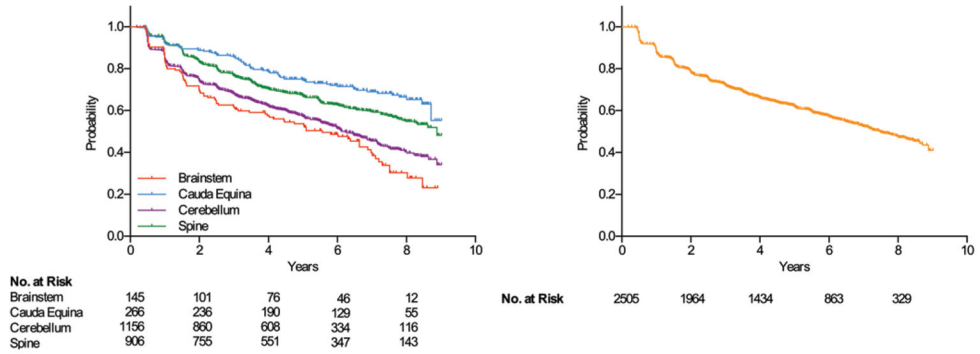

Fig. 1.

Kaplan-Meier analysis of hemangioblastoma progression over an 8-year period in patients with VHL disease. **Left:** Fifty percent of (nongrowing) hemangioblastomas located in the brainstem progressed in 5.6 years. Twenty-five percent of hemangioblastomas located in the cauda equina progressed in 5.0 years. Fifty percent of hemangioblastomas located in the cerebellum progressed in 6.2 years. Fifty percent of hemangioblastomas located in the spine progressed in 8.9 years. **Right:** Twenty-five percent of hemangioblastomas at all tumor locations progressed in 2.5 years and 50% in 7.5 years. No. at risk = tumors at risk for growing. The numbers of tumors at risk refer to the years on the x-axis under which they align.

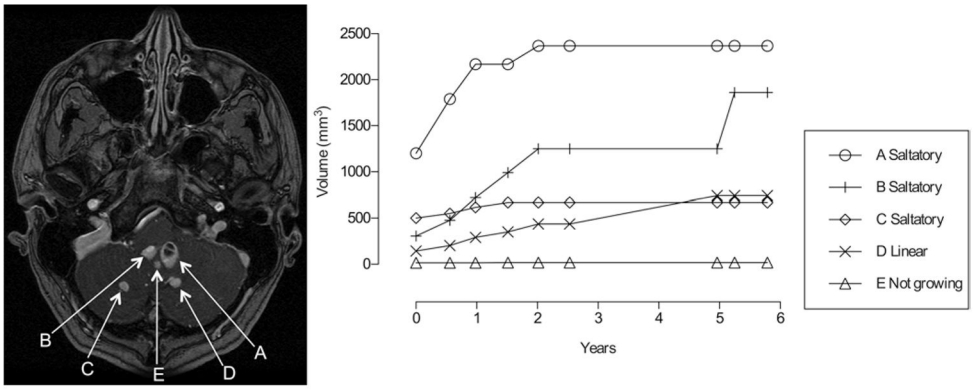

Fig. 2.

Characteristic patterns of growth associated with CNS hemangioblastomas in patients with VHL disease. **Left:** Axial contrast-enhanced MR image of the cerebellum in a patient showing 5 tumors (A–E) that demonstrated 3 growth patterns. **Right:** Tumor growth patterns, including saltatory (A–C), linear (D), and stable (E).

TABLE 1

Lesions associated with VHL disease in 225 patients at study entrance

Lesion	No. of Patients (%)
nervous system	
craniospinal hemangioblastoma	
supratentorial	23 (10.2)
cerebellum	197 (87.6)
brainstem	94 (41.8)
spinal cord	193 (85.8)
cauda equina	139 (61.8)
nerve root	5 (2.2)
retinal hemangioblastoma	118 (52.4)
endolymphatic sac tumor	29 (12.9)
visceral lesions	
renal cell carcinoma	131 (58.2)
renal cyst	144 (64.0)
pancreatic neuroendocrine tumor	75 (33.3)
pancreatic cyst	130 (57.8)
pheochromocytoma	47 (20.9)
reproductive adnexal organ cystadenoma	71 (31.6)

TABLE 2

Symptoms based on anatomical location of 159 tumors*

Lesion Location	Frequency of Symptomatic Lesions (%)
brainstem	
headache	10 (83.3)
singultus	8 (66.7)
nausea/vomiting	6 (50.0)
dysphagia	5 (41.7)
cough	3 (25.0)
paresthesia	3 (25.0)
cauda equina	
urinary/bowel abnormalities	5 (100.0)
pain	5 (100.0)
paresthesia	4 (80.0)
headache	2 (40.0)
cerebellum	
headache	77 (77.0)
gait ataxia	57 (57.0)
nausea/vomiting	19 (19.0)
vertigo	18 (18.0)
speech difficulties	15 (15.0)
dysmetria	11 (11.0)
nerve root	
cruciate paralysis	1 (3.3)
paresthesia	28 (73.7)
pain	24 (63.2)
gait ataxia	13 (34.2)
dysesthesias	9 (23.7)
urinary/bowel abnormalities	7 (18.4)
supratentorial	
vision disturbance/loss	2 (50.0)
weakness	2 (50.0)

*The symptoms listed here are the major symptoms recorded in patients who underwent resection of symptomatic tumors. Patients who underwent resections at outside institutions are not included in this analysis because of limited records.

TABLE 3

Analysis of factors associated with tumor behavior*

Outcome Measure & Factor	p Value
total tumor burden (no. of tumors; 225 patients)	
age	NS
yrs of follow-up	0.0070
sex	0.002
mutation†	0.0021
partial deletion	reference
deletion	0.0667
frameshift	0.0450
missense	0.0046
nonsense	0.2508
new tumor development (no. of tumors; 225 patients)	
sex	NS
mutation†	NS
no. of tumors at study entrance	<0.0001
age in yrs	<0.0001
12–20	reference
21–30	0.0224
31–40	0.0005
41–50	<0.0001
>50	<0.0001
tumor growth rate (mm^3/yr; 2505 tumors)	
age	NS
mutation†	NS
sex	0.0014
tumor location	<0.0001
tumor symptom type	<0.0001
tumor location × tumor symptom type	0.0001
cerebellum tumor growth rate (mm^3/yr; 1156 tumors)	
age	NS
mutation†	NS
sex	NS
cyst-linked tumor type	<0.0001
tumor symptom type	<0.0001
cyst-linked tumor type × tumor symptom type	<0.0001
cerebellum cyst growth rate (mm^3/yr; 175 cysts)	
sex	NS
mutation†	NS
age (continuous)	0.0079

Outcome Measure & Factor	p Value
tumor symptom type	<0.0001
cyst type	NS
tumor symptom type × cyst type	0.0342

* Linear or linear mixed models were performed to evaluate the association of factors with outcome measures. Age, sex, and mutation would be dropped from the model if they were not significant based on a significance level of 0.1.

NS = not significant.

† Genotype was available for 197 of the 225 patients.