

The natural history of intracranial cavernous malformations

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Literature reports on the natural history of cerebral cavernous malformations (CMs) are numerous, with considerable variability in lesion epidemiology, hemorrhage rates, and risk factors for hemorrhage. In this review, the authors performed a meta-analysis of 11 natural history studies. The overall male-to-female ratio was 1:1, and the mean age at presentation was 30.6 years. Overall, 37% of patients presented with seizures, 36% with hemorrhage, 23% with headaches, 22% with focal neurological deficits, and 10% were asymptomatic. Some patients had more than one symptom. Seizure presentation was most prevalent among supratentorial CMs, while focal neurological deficits were common in patients with infratentorial CMs. By location, CMs were in the cerebral hemispheres (66%), brainstem (18%), basal ganglia or thalamus (8%), cerebellum (6%), and other (2.5% [combined supra- and infratentorial, callosal or insular]). Overall, 19% of patients harbored multiple intracranial CMs, and 9% had radiographically apparent associated developmental venous anomalies. An overall annual hemorrhage rate of 2.4% per patient-year (range 1.6%–3.1%) was identified across 3 studies. Prior hemorrhage and female sex were risk factors for bleeding, while CM size and multiplicity did not affect hemorrhage rates. Although not impacting the hemorrhage rate itself, deep location was a risk factor for increased clinical aggressiveness. (DOI: 10.3171/2011.3.FOCUS1165)

KEY WORDS • cavernous malformation • cavernoma • hemorrhage • natural history

CAVERNOUS malformations are clusters of dilated sinusoidal channels lined by a single layer of endothelium.^{3,8,19,20,26} In contradistinction to arteriovenous malformations, these lesions do not have smooth muscle or elastin in their lining, and they are angiographically occult. Their prevalence across several reports ranges from 0.4% to 0.6% of the population.^{8,14,22,26,27} Since 1991, multiple natural history reports have surfaced in the literature, with significant dissension in regard to lesion epidemiology and particularly hemorrhage risk. Herein, we review 11 studies describing the epidemiology, clinical presentation, and natural history of these lesions in an attempt to elicit more cogent data so as to clarify hemorrhage rates and risk factors for bleeding.

Methods

A PubMed search using the terms “cavernoma,” “cavernous malformation,” “cavernous hemangioma,” “natural history,” “bleed,” and “hemorrhage” was performed. To minimize bias and to more naturally reflect the clinical course of these lesions, surgical series were excluded, leaving a total of 11 retrospective and prospec-

tive natural history studies in the English-language literature for analysis. Accounting for de novo CM development after birth, 4 retrospective studies were excluded from our analysis of CM hemorrhage rates.

Results

Epidemiology and Clinical Presentation

Epidemiological data and information on patient presentation were extracted from 10 natural history studies with a total of 837 patients (Table 1). The male-to-female ratio was 1:1 (422 males and 415 females). The mean age at presentation was 30.6 years. Across 9 studies with 775 patients providing data on clinical presentation, 37% presented with seizures, 36% with hemorrhage, 23% with headaches, and 22% with focal neurological deficits (some patients had more than one).^{2,7,8,15,17,20,23,26,31} Ten percent of patients were asymptomatic.

Across 9 series providing applicable data on cerebral CM location in 1055 patients, 803 (76%) were supratentorial, 243 (23%) were infratentorial, and 9 (1%) were both.^{2,7,8,14,17,20,23,26,31} Across 7 studies with 747 cerebral CMs providing further detailed information on lesion location, 491 lesions (66%) were located in the cerebral hemisphere (lobar), 131 (18%) in the brainstem, 61 (8.2%)

Abbreviations used in this paper: CM = cavernous malformation; DVA = developmental venous anomaly.

TABLE 1: Review of natural history studies of cerebral CMs*

Authors & Year	No. of Pts	No. of CMs	Female/Male	Mean Age (yrs)	Presentation	Location	No. w/ Multiple CMs	No. w/ DVAs	Study Design
Aiba et al., 1995†	110		52:58		62 hemorrhage; 25 seizures; 23 incidental	52 lobar; 8 BG/T; 2 callosal; 15 brainstem; 5 cerebellar			prospective
Cantu et al., 2005	133		66:67	34.3	78 hemorrhage; 64 seizure; 62 focal deficit; 57 headache; 3 incidental	73 lobar; 13 BG/T; 25 brainstem; 8 cerebellar; 9 supra-/infratentorial; 5 spinal	17	12	retrospective
Del Curling et al., 1991	32	76	15:17	37.6	3 hemorrhage; 16 seizure; 11 headache; 7 focal deficit; 6 incidental	65 supratentorial; 11 infratentorial	6		retrospective
Kim et al., 1997‡	62	108	24:38	32.2		31 lobar; 5 BG/T; 10 brainstem; 3 cerebellar	13		retrospective
Kondziolka et al., 1995	122		62:60	37.3	61 hemorrhage; 28 seizure; 18 headache	59 lobar/cerebellar; 43 brainstem; 20 BG/T	25	2	prospective
Labauge et al., 2000	40	232	19:21	33.3	19 hemorrhage; 12 seizure; 5 incidental; 4 focal deficit	176 supratentorial; 26 brainstem; 30 cerebellar			familial retrospective
Moriarity et al., 1999§	68	228	44:24	34.6	9 hemorrhage; 44 headache; 33 seizure; 31 focal deficit; 1 incidental	77 lobar; 13 BG/T; 16 brainstem; 5 cerebellar	25	13	prospective
Porter et al., 1997	173		85:88	37.5	44 hemorrhage; 62 seizure; 35 focal deficit; 11 headache; 21 incidental	96 lobar; 12 BG/T; 2 insular; 1 callosal; 52 brainstem; 10 cerebellar	31	22	prospective
Robinson et al., 1991	66	76	30:36	34.6	6 hemorrhage; 34 seizure; 30 focal deficit; 20 headache; 9 incidental	55 lobar; 4 BG/T; 8 brainstem; 9 cerebellar	7	3	prospective
Zabramski et al., 1994	31	128	18:13	25.0	16 headache; 12 seizure; 5 focal deficit; 12 incidental	107 lobar; 6 BG/T; 5 callosal; 5 brainstem; 5 cerebellar	26	2	familial retrospective

* BG/T = basal ganglia or thalamus; Pts = patients.

† Data on CM location were only provided for a subset of patients.

‡ Data on clinical presentation and hemorrhage on presentation were not provided for all patients. Data on CM location were provided for 49 lesions.

§ Data on CM location were provided for 111 lesions.

in the basal ganglia or thalamus, 45 (6.0%) in the cerebellum, 9 (1.2%) were combined supra- and infratentorial, 8 (1.1%) were in the corpus callosum, and 2 (0.27%) were in the insula.^{2,7,14,20,23,26,31} Across 7 general distribution studies with 656 patients, 125 patients (19%) harbored multiple intracranial CMs.^{7,8,14,15,20,23,26} Developmental venous anomalies were seen in 54 (9%) of 593 patients in 6 studies reporting associated vascular malformations.^{7,15,20,23,26,31} Table 2 summarizes overall epidemiological, clinical presentation, and hemorrhage rate data.

Hemorrhage

Several retrospective analyses of CM hemorrhage rates assume lesion presence since birth (that is, congenital); hemorrhage rates then would be calculated from birth. Given the known phenomenon of de novo CM formation,^{5,6,9,21,24,31} however, such studies are inaccurate and will underestimate the actual hemorrhage rates of these lesions once they are discovered. The “congenital” theory explains the extremely low annual hemorrhage in the often-cited early report by Del Curling et al.⁸ of 0.25% per patient-year or 0.1% per lesion-year.

To avoid underestimation, we reviewed the prospec-

tive natural history data in Tables 3 and 4; the latter table presents data from familial studies. Using this basis, hemorrhage rates are calculated from the onset of initial discovery of the cavernoma, not from birth. Despite the exclusion of retrospective reports, however, the data remain quite heterogeneous. Robinson et al.²⁶ reported an annual hemorrhage rate of 0.7% per lesion-year. The studies of Kondziolka et al.,¹⁵ Moriarity et al.,²⁰ and Porter et al.²³ reported annual hemorrhage rates ranging from 1.6% to 3.1% per patient-year. Across these 3 studies including a total of 363 patients followed up for 1121.5 patient-years, the overall hemorrhage rate was 2.4% per patient-year.^{15,20,23} Rates are calculated per patient-year by taking the quotient of total number of hemorrhages experienced by an individual patient and the number of years the patient is followed up. Thus, patients with multiple lesions may have higher hemorrhage rates as calculated per patient-year as opposed to per lesion-year; the latter is the quotient of number of hemorrhages per lesion and years followed. Indeed, the greatest annual hemorrhage rate of 3.1% per patient-year from the study of Moriarity et al. was for 228 lesions in 68 patients.

In addition to a variable denominator used to report hemorrhage rates, the definition of a CM hemorrhage

Natural history of intracranial CMs

TABLE 2: Summary of epidemiological, clinical presentation, and overall hemorrhage rate data*

Parameter	Value†
no. of studies reviewed	10
total no. of pts	837 (31–173)
male/female ratio	1:1 (0.5–1.6:1)
mean age at presentation (yrs)	30.6 (25–37.6)
overall clinical presentation (%)	
seizure	97
hemorrhage	36
headache	23
focal deficit	22
incidental	10
CM location (%)	
supratentorial	76
infratentorial	23
supra- & infratentorial	1
lobar	66
brainstem	18
BG/T	8
cerebellar	6
callosal	1
insular	0.2
% pts w/ multiple CMs	19 (11–37)‡
% pts w/ CM & DVA	9 (2–19)
overall annual hemorrhage rate (per pt-yr)	2.4% (1.6%–3.1%)
annual hemorrhage rate (per les-yr)	0.7%§
familial annual hemorrhage rate (per pt-yr)	5.1% (4.3%–13%)¶
familial annual hemorrhage rate (per les-yr)	0.8% (0.6%–2%)¶

* les-yr = lesion-year; pt-yr = patient-year.

† Data in parentheses represent ranges across reviewed studies.

‡ Excludes the familial study of Zabramski et al. in which 81% of patients harbored multiple CMs.

§ Only provided from the study of Robinson et al.

¶ Hemorrhage rate for patients with a family history of cerebral CM.

varied significantly across these studies. Moriarity et al.²⁰ and Robinson et al.²⁶ used a stringent definition of extral-lesional blood and accompanying symptoms. Aiba et al.² and Porter et al.²³ used more lax radiographic definitions of hemorrhage and generally relied on a clinical event. The definition of hemorrhage in the study of Kondziolka et al.¹⁵ was based solely on radiographic evidence.

Rebleed rates across these natural history studies varied widely from 0% to 22.9% per patient-year.^{2,15,20} While the study of Robinson et al.²⁶ was not adequately powered to detect the impact of prior hemorrhage on subsequent bleeding, the studies of Aiba et al.,² Kondziolka et al.,¹⁵ and Porter et al.²³ demonstrated a significantly increased risk of rehemorrhage after an initial hemorrhage. In fact, the studies of Kondziolka et al. and Aiba et al. purported prior hemorrhage as the primary risk factor for a subsequent hemorrhage, citing annual rehemorrhage rates of 4.5% and 22.9% per patient-year, respectively. In

contrast, Moriarity et al.²⁰ reported no cases of rehemorrhage in their study. Importantly, however, of 68 patients in this study, only 9 had hemorrhages, while 62 of 110 patients in the study of Aiba et al. and 61 of 122 patients in the study of Kondziolka et al. presented with hemorrhage. This intuitively demonstrates the greater power of these 2 studies to detect the clinical significance of a prior hemorrhage on subsequent bleeding, validating the maxim of prior hemorrhage increasing the risk of subsequent bleeding from a CM.

Consistent across our reviewed series, CM size and the presence of multiple lesions did not impact hemorrhage rates.^{2,15,20,23,26} Age younger than 40 years old was seen as a risk factor for hemorrhage in only 1 study.² Three of 5 reviewed natural history studies reported female sex as a risk factor for hemorrhage.^{2,20,26} This was in fact the most significant factor increasing hemorrhage rates in the study of Moriarity et al.,²⁰ with an annual bleed rate of 4.2% per patient-year for females as opposed to 0.9% per patient-year for males. This study, along with the study of Robinson et al.²⁶ that reported an increased hemorrhage risk among females, used a consistent, stringent definition of CM hemorrhage: new symptoms and new extral-lesional blood. Porter et al.²³ reported CM location as the primary factor influencing hemorrhage risk, citing a 4.1% per patient-year annual hemorrhage rate for deep lesions (deep hemispheric or brainstem). Although reported as a risk factor in some retrospective studies as well,^{7,17} all other prospective studies we evaluated did not demonstrate lesion location as a significant risk factor for hemorrhage.^{2,15,20,27} This can likely be explained in part by the definition of hemorrhage in each study. Moriarity et al. and Robinson et al. used a strict definition of extral-lesional blood and new symptoms. Kondziolka et al.¹⁵ relied on radiographic evidence alone. Porter et al.²³ allowed for changes in lesion size with new symptoms to be considered hemorrhagic events. While it is not intuitive why changing the location of a CM would increase its risk of hemorrhage, it is logical to expect more subtle, morphological changes in a CM to present symptomatically in eloquent locations. Furthermore, asymptomatic overt hemorrhage in a superficial location that would be counted radiographically in the study of Kondziolka et al. would not be accounted for in the study of Porter et al. Thus, it is reasonable to consider deep CMs as clinically more aggressive lesions owing to the sensitivity of their location to more subtle lesional changes. This is further underscored by the annual clinical event rate of 10.6% reported in the study of Porter et al. for deep lesions.

Data across prospective familial studies were generally consistent, reporting annual hemorrhage rates of 4.3%–13% per patient-year and 0.6%–2% per lesion-year.^{16,31} These ranges include asymptomatic, radiographic hemorrhage. Combining the data for 64 patients observed for 116 patient-years and 362 CMs observed for 750 lesion-years, the annual radiographic hemorrhage rate is 5.1% per patient-year and 0.8% per lesion-year.^{16,31} Emphasis should be placed on rates per lesion-year in these patients given the vast multiplicity of these lesions, making their bleeding tendency ostensibly similar to nonfamilial cases. In addition, these studies consistently demonstrated a 0.4% new lesion rate per patient-year.^{16,31}

TABLE 3: Hemorrhage rates from prospective nonfamilial natural history studies

Authors & Year	No. of Pts	No. of CMs	Hemorrhage Definition	Follow-Up (pt-yrs)*	Hemorrhage Rate (per pt-yr)*	Specific Hemorrhage Rate (per pt-yr)	Rehemorrhage Rate (per pt-yr)	Factors Impacting Hemorrhage Rate		
								Increased Risk	No Effect	
Aiba et al., 1995	110		new symptoms & perilesional or intralesional hemorrhage	196.5 hemorrhage group; 254 seizure group	reported in subgroups only	0% incidental; 0.39% seizure group	22.9% overall; 19.4% males; 25.2% females; 25.2% <40 yrs; 14.1% >40 yrs; 34% female <40 yrs	prior hemorrhage, female sex, age <40 yrs		location
Kondziolka et al., 1995	122		hemorrhage on MRI	341.6 overall; 167 non-hemorrhage group; 178 hemorrhage group	2.6%	0.6% incidental	4.5% overall	prior hemorrhage		location, sex, many CMs
Morarity et al., 1999	68	228	new symptoms & extralesional hemorrhage	352.9	3.1%	0.9% males; 4.2% females; 5.2% superficial; 3.1% deep	0%	female sex		prior hemorrhage, location, CM size
Porter et al., 1997	173		new symptoms & extralesional hemorrhage or increase in lesion size by 20%	427	1.6%	4.1% deep; 0% superficial; 4.2% event rate; 4.2%; 10.6% deep; 0% superficial		deep location, prior hemorrhage†		sex, many CMs
Robinson et al., 1991	57	66	new symptoms & extralesional hemorrhage/positive lumbar puncture	143 les-yrs	0.7%/les-yr			female sex		age, CM size

* Follow-up and hemorrhage rates in patient-years unless otherwise specified.

† Patients presenting with hemorrhage and a focal neurologic deficit had an increased risk of subsequent hemorrhage.

Natural history of intracranial CMs

TABLE 4: Prospective familial natural history studies

Authors & Year	No. of Pts	No. of CMs	Hemorrhage Definition	Yrs of Follow-Up	Hemorrhage Rate	Specific Hemorrhage Rate	New Lesion Formation (per pt-yr)
Labauge et al., 2001	33	234	hemorrhage on MRI	70 pt-yrs; 468 les-yrs	4.3%/pt-yr; 0.6%/les-yr		0.4
Zabramski et al., 1994	31	128	new symptoms & hemorrhage on MRI (may be intralesional)	46 pt yrs; 282 les-yrs	6.5%/pt-yr; 1.1%/les-yr	13%/pt-yr; 2%/les-yr*	0.4

* Includes asymptomatic hemorrhages.

Discussion

Quite consistently across most natural history studies, patients presented at a relatively young age without a sex predilection. With similar consistency across these studies—and as we reinforce, lesion distribution is generally reflective of the distribution of CNS tissue without a further biased tendency of CM localization—76% of CMs were supratentorial and 23% were infratentorial. Importantly, location does impact patient presentation. Although seizure was the most common presentation seen in our review (37% of patients) and in other studies as well, it is even more common in the subgroup of supratentorial lesions. In the study of Moriarity et al.,²⁰ 53% of patients with supratentorial lesions presented with seizures. Small hemorrhages into noneloquent supratentorial parenchyma may be silent, and thus a large number of supratentorial CMs may go undiagnosed unless a patient presents with a seizure. Reflecting the sensitivity of eloquent surrounding tissue, patients with infratentorial lesions are more likely to present with focal deficits; 64% of patients with infratentorial lesions in the study by Moriarity et al. presented with focal deficits compared with 41% of patients with supratentorial lesions. Varyingly widely across our reviewed studies (9%–59% of patients), we found that overall, 36% of patients presented with hemorrhage. Intuitively, this rate, along with the number of incidental cases, will vary with the nature of the study and institutional referral pattern, underscoring the utility of meta-analytical review. Indeed, the true distribution of CM location and mode of presentation will depend on the percentage of patients presenting

with incidental lesions as opposed to those presenting with symptoms referable to their CM.

Overall, approximately one-fifth of patients with cerebral CMs will harbor additional lesions. This rate increases significantly in familial cases to at least four-fifths of patients.³¹ Seen in primarily sporadic cases, an associated DVA was noted in 9% of cases we reviewed overall. This contrasts somewhat with primarily surgical series that cite a greater association of approximately 15%–26% of cases,^{1,4,28,30} with some citing the potential of increased CM aggressiveness when associated with these lesions.^{1,3,25,30} Even a causal relationship has been proposed^{1,3,24} and has been supported by multiple reports of de novo CM development in the presence of a DVA.^{5,6,9,24} We have seen this phenomenon in multiple cases at our institution as well (Fig. 1). Mechanisms including hemorrhagic angiogenic proliferation following microhemorrhage due to venous hypertension³ and venous outflow restriction opening pre-existing arteriovenous connections²⁹ have been proposed.

In addition to de novo CM development in the presence of a DVA, this phenomenon has been extensively noted following radiation therapy^{11,13,18,21} and in familial cases.^{16,31} We believe that the continued accumulation of evidence of de novo CM formation, particularly in cases in which a prior DVA was seen, underscores the fact that these lesions are not congenital (Fig. 2). We think that they develop in the presence of a venous anomaly in the context of venous outflow restriction and resultant hemorrhage. This proposal is supported by the study of Porter et al.,²⁴ in which all 86 patients (including familial cases) had associated venous anomalies seen at the time of sur-

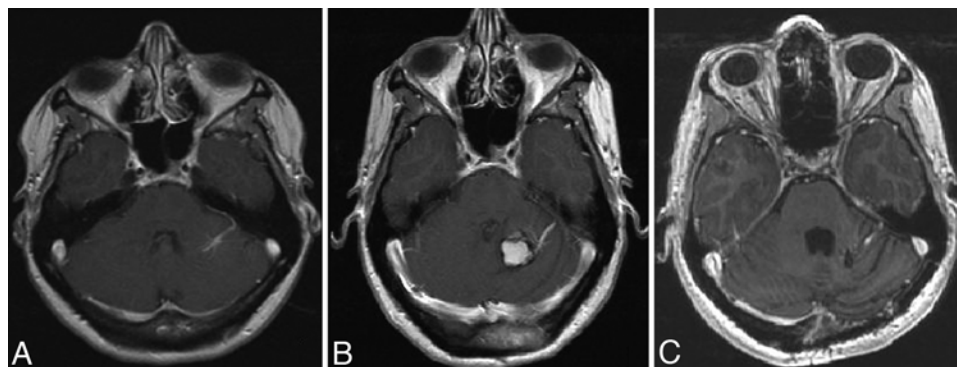


Fig. 1. Case example. This 37-year-old healthy woman presented to an outside institution with headaches. Magnetic resonance imaging only demonstrated a cerebellar developmental venous anomaly (A). Four years later, the patient presented with acute severe headache and vertigo. She underwent suboccipital decompression at an outside hospital, and postoperative MR imaging demonstrated hemorrhage from a de novo cerebellar CM (B). After transfer to our institution, the lesion was completely resected (C).

Theories for Cavernous Malformation Development

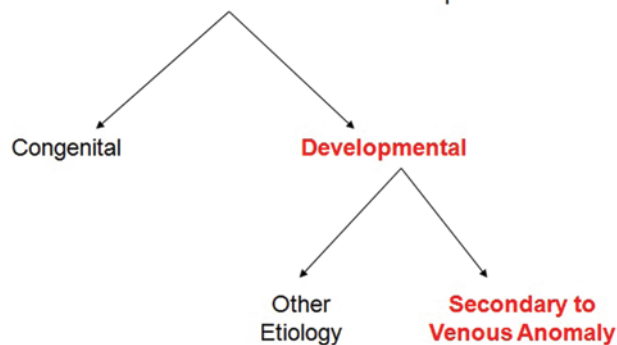


Fig. 2. Theories of CM development. Based on the senior author's extensive operative experience, the association of these lesions with a developmental venous anomaly is almost universal.

gery. Only 32% of those seen intraoperatively were seen on preoperative MR imaging, and only 14% were seen on preoperative angiographic studies, underscoring that these venous anomalies can be radiographically occult.

De novo CM development emphasizes the importance of prospective natural history data as we review in Tables 3 and 4. Frank hemorrhage from these lesions may be a result of venous congestion leading to turgor against the thin endothelial walls of the lesion and resultant rupture into the adjacent parenchyma. This mechanism is further supported by evidence that the radiographic presence of a DVA has been associated with a more aggressive clinical course.^{1,3,25,30} Notably, subarachnoid hemorrhage from cavernous malformations is rare, possibly because most are parenchymal lesions that do not proliferate into the subarachnoid space.

An overall annual hemorrhage rate of 2.4% per patient-year was seen across 3 natural history studies,^{15,20,23} with an expected, lower 0.7% annual hemorrhage rate per lesion-year reported in the study by Robinson et al.²⁶ Despite heterogeneity in defining CM hemorrhage, the 2 studies using the most stringent definition of hemorrhage (extralésional hemorrhage and new symptoms) reported the highest and lowest overall annual rates of hemorrhage (0.7% per lesion-year²⁶ and 3.1% per patient-year),²⁰ providing validity to this range and our mean hemorrhage rate. Most studies demonstrated increased hemorrhage rates after a prior hemorrhage^{2,15,23} and in females.^{2,20,27} The latter is reinforced by several reports purporting a hormonal responsiveness of CMs^{2,24,26} and by the finding of estrogen receptors on CMs.²⁴ Gazzaz et al.¹² reported a case of a 26-year-old woman who suffered 4 hemorrhages from a thalamic CM, each occurring 3 weeks after starting hormonal therapy and never recurring once hormonal treatment ceased. The finding of a possibly increased rehemorrhage risk among younger patients in the study of Aiba et al.² may also be explained by hormonal influence. Finally, several reports have suggested increased CM aggressiveness in pregnant patients.^{10,25,26} The increased venous pressure associated with pregnancy may accentuate an already compromised venous outflow in patients with CM.

Although not used in prospective studies to date, considering the first hemorrhage from a cavernoma as its genesis and considering hemorrhage rates thereafter is a con-

sideration that would likely underscore a more aggressive natural history to these lesions. In addition, it would reveal a true mean age of symptomatic presentation and would provide greater internal validity for specific extrapolation to the patient population seen by neurosurgeons and neurologists, that is, patients with symptomatic CMs.

Other factors such as CM size and multiplicity did not affect hemorrhage rates.^{2,15,20,23,26} The latter is reinforced by a mean annual hemorrhage rate of 0.8% per lesion-year (range 0.6%–2%) across familial studies in which most patients harbored multiple CMs.^{16,31} Underscored by the 10.6% annual clinical event rate for deep CMs in the study by Porter et al.,²³ lesions in eloquent locations are likely to be clinically more aggressive, although actual annual hemorrhage rates are generally not affected by lesion location.^{2,15,20,26} Importantly, there was no significant difference in the degree of recovery between hemorrhagic and nonhemorrhagic clinical events: approximately one-third of patients had resolution of symptoms, one-third improved, and one-third suffered permanent sequelae.²³

Conclusions

Cavernous malformations generally present in the younger population without a sex predilection. Supratentorial lesions most commonly present with seizures, while other modes of presentation include hemorrhage, headache, and focal neurological deficits. Lesion distribution generally reflects the distribution of CNS tissue, with the majority in the supratentorial compartment. One-fifth of patients overall will harbor multiple intracranial CMs, increasing to at least four-fifths in familial cases. Developmental venous anomalies are present radiographically in approximately one-tenth of cases overall, although they are likely to be more prevalent in aggressive lesions and may play a role in CM development. An overall annual hemorrhage rate of 2.4% per patient year was seen, with prior hemorrhage and female sex increasing the risk of subsequent hemorrhage. Cavernous malformation size, multiplicity, and location did not affect hemorrhage rates, although deep lesions were more clinically aggressive.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Gross, Lin. Analysis and interpretation of data: Day, Gross, Du. Drafting the article: Day, Gross. Critically revising the article: all authors. Study supervision: Day.

References

1. Abdulrauf SI, Kaynar MY, Awad IA: A comparison of the clinical profile of cavernous malformations with and without associated venous malformations. *Neurosurgery* 44:41–47, 1999
2. Aiba T, Tanaka R, Koike T, Kameyama S, Takeda N, Komata T: Natural history of intracranial cavernous malformations. *J Neurosurg* 83:56–59, 1995
3. Awad IA, Robinson JR Jr, Mohanty S, Estes ML: Mixed vas-

Natural history of intracranial CMs

- cular malformations of the brain: clinical and pathogenetic considerations. **Neurosurgery** **33**:179–188, 1993
4. Bertalanffy H, Benes L, Miyazawa T, Alberti O, Siegel AM, Sure U: Cerebral cavernomas in the adult. Review of the literature and analysis of 72 surgically treated patients. **Neurosurg Rev** **25**:1–55, 2002
 5. Cakirer S: De novo formation of a cavernous malformation of the brain in the presence of a developmental venous anomaly. **Clin Radiol** **58**:251–256, 2003
 6. Campeau NG, Lane JI: De novo development of a lesion with the appearance of a cavernous malformation adjacent to an existing developmental venous anomaly. **AJNR Am J Neuroradiol** **26**:156–159, 2005
 7. Cantu C, Murillo-Bonilla L, Arauz A, Higuera J, Padilla J, Barinagarrementeria F: Predictive factors for intracerebral hemorrhage in patients with cavernous angiomas. **Neurol Res** **27**:314–318, 2005
 8. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE: An analysis of the natural history of cavernous angiomas. **J Neurosurg** **75**:702–708, 1991
 9. Detwiler PW, Porter RW, Zabramski JM, Spetzler RF: De novo formation of a central nervous system cavernous malformation: implications for predicting risk of hemorrhage. Case report and review of the literature. **J Neurosurg** **87**:629–632, 1997
 10. Flemming KD, Goodman BP, Meyer FB: Successful brainstem cavernous malformation resection after repeated hemorrhages during pregnancy. **Surg Neurol** **60**:545–548, 2003
 11. Gaensler EH, Dillon WP, Edwards MS, Larson DA, Rosenau W, Wilson CB: Radiation-induced telangiectasia in the brain simulates cryptic vascular malformations at MR imaging. **Radiology** **193**:629–636, 1994
 12. Gazzaz M, Sichez J, Capelle L, Fohanno D: [Recurrent bleeding of thalamic cavernous angioma under hormonal treatment. A case report.] **Neurochirurgie** **45**:413–416, 1999 (Fr)
 13. Heckl S, Aschoff A, Kunze S: Radiation-induced cavernous hemangiomas of the brain: a late effect predominantly in children. **Cancer** **94**:3285–3291, 2002
 14. Kim DS, Park YG, Choi JU, Chung SS, Lee KC: An analysis of the natural history of cavernous malformations. **Surg Neurol** **48**:9–18, 1997
 15. Kondziolka D, Lunsford LD, Kestle JR: The natural history of cerebral cavernous malformations. **J Neurosurg** **83**:820–824, 1995
 16. Labauge P, Brunereau L, Laberge S, Houtteville JP: Prospective follow-up of 33 asymptomatic patients with familial cerebral cavernous malformations. **Neurology** **57**:1825–1828, 2001
 17. Labauge P, Brunereau L, Lévy C, Laberge S, Houtteville JP: The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients. **Neuroradiology** **42**:327–332, 2000
 18. Larson JJ, Ball WS, Bove KE, Crone KR, Tew JM Jr: Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children. **J Neurosurg** **88**:51–56, 1998
 19. McCormick WF, Hardman JM, Boulter TR: Vascular malformations (“angiomas”) of the brain, with special reference to those occurring in the posterior fossa. **J Neurosurg** **28**:241–251, 1968
 20. Moriarity JL, Wetzel M, Clatterbuck RE, Javedan S, Shepard JM, Hoenig-Rigamonti K, et al: The natural history of cavernous malformations: a prospective study of 68 patients. **Neurosurgery** **44**:1166–1173, 1999
 21. Nimjee SM, Powers CJ, Bulsara KR: Review of the literature on de novo formation of cavernous malformations of the central nervous system after radiation therapy. **Neurosurg Focus** **21**(1):e4, 2006
 22. Otten P, Pizzolato GP, Rilliet B, Berney J: [131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,535 autopsies.] **Neurochirurgie** **35**:82–83, 128–131, 1989 (Fr)
 23. Porter PJ, Willinsky RA, Harper W, Wallace MC: Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. **J Neurosurg** **87**:190–197, 1997
 24. Porter RW, Detwiler PW, Spetzler RF, Lawton MT, Baskin JJ, Derksen PT, et al: Cavernous malformations of the brainstem: experience with 100 patients. **J Neurosurg** **90**:50–58, 1999
 25. Pozzati E, Acciarri N, Tognetti F, Marliani F, Giangaspero F: Growth, subsequent bleeding, and de novo appearance of cerebral cavernous angiomas. **Neurosurgery** **38**:662–670, 1996
 26. Robinson JR, Awad IA, Little JR: Natural history of the cavernous angioma. **J Neurosurg** **75**:709–714, 1991
 27. Sarwar M, McCormick WF: Intracerebral venous angioma. Case report and review. **Arch Neurol** **35**:323–325, 1978
 28. Symon L, Jackowski A, Bills D: Surgical treatment of pontomedullary cavernomas. **Br J Neurosurg** **5**:339–347, 1991
 29. Wilson CB: Cryptic vascular malformations. **Clin Neurosurg** **38**:49–84, 1992
 30. Wurm G, Schnizer M, Fellner FA: Cerebral cavernous malformations associated with venous anomalies: surgical considerations. **Neurosurgery** **57** (1 Suppl):42–58, 2005
 31. Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, et al: The natural history of familial cavernous malformations: results of an ongoing study. **J Neurosurg** **80**:422–432, 1994

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