Symptomatic Cavernous Malformation Presenting with Seizure without Hemorrhage: Analysis of Factors Influencing Clinical Presentation

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■ BACKGROUND: **Supratentorial cavernous malformations (CMs) can be epileptogenic lesions. However, little is known about clinical comorbidities, medication use, and radiologic features that predict a first seizure presentation without associated CM hemorrhage.**

■ METHODS: **We queried a prospective registry of consecutive patients with CM established in January 2015. Data regarding clinical presentation, comorbid conditions, daily medication use, and radiologic CM characteristics were collected. Univariate and multivariate regression analysis was performed assessing variables for presentation with seizure without hemorrhage with *P* values, odds ratios, and 95% confidence intervals reported.**

■ RESULTS: **Of 202 patients, 58.4% were women, and the average age at diagnosis was 43.7 ± 16.5 years. Of the patients, 59.4% were symptomatic. In 40.6%, the CM was an incidental finding. Of the 30 patients who presented with a first-time seizure without concomitant hemorrhage, the mean age at diagnosis was 38.4 ± 14.6 years, and 56.7% were women. Compared with incidental CM, patients with seizure without hemorrhage were younger, had a cortically based, supratentorial lesion, and were less likely to have chronic inflammatory disease or to use aspirin, vitamin D, or statin. Compared with other supratentorial lesions, patients with seizure without hemorrhage more commonly had a temporal lobe CM.**

■ CONCLUSIONS: **These prospective data provide possible clues to radiologic factors, clinical comorbidities, and medication influences on seizure presentation in patients with CM. Further multicenter studies would be helpful to determine if disease-modifying agents in addition to epileptic medications or surgery might be helpful.**

INTRODUCTION

Cavernous malformations (CMs) are vascular malformations formed by endothelial-lined caverns containing blood of different ages without intervening brain parenchyma. Unlike normal endothelial cells, the cells lining the caverns of a CM have incomplete or dysfunctional tight junctions. These pathologic features favor leakage of blood products in the parenchyma surrounding the lesion. This phenomenon is responsible for the characteristic perilesional hemosiderin rim and has been linked to the epileptogenic nature of these lesions.[1]

Several studies have focused on patients with CMs presenting with seizures.[2-9] However, in these studies, patients with seizures with or without hemorrhage were included together. Moreover, patients with long-standing epilepsy from a CM were considered together with those presenting with a single seizure, causing data to conflict on the age at onset of symptoms. There is little information available on the clinical and radiologic characteristics associated with clinical presentation in a homogeneous population of patients who suffer a first seizure from a CM without concomitant hemorrhage. In this study, we analyzed clinical and radiologic factors associated with a clinical presentation of seizure without concomitant hemorrhage in a large prospective, contemporary registry of consecutive patients.

Key words
- Cavernoma
- Cavernous malformation
- Clinical presentation
- Seizure

Abbreviations and Acronyms
CM: Cavernous malformation
DVA: Developmental venous anomaly
MRI: Magnetic resonance imaging

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MATERIALS AND METHODS

Patient Selection

Institutional review board approval was obtained for this study. A prospective CM registry was established in January 2015. Adult patients (18 years of age and older) with cerebral and spinal cord CMs were asked to participate in the study, and only patients who consented were included. For the purpose of this study, we included only patients with CMs of the brain.

Clinical Data Collection

Through personal interviews, a chart review, and an introductory questionnaire, we collected demographic information and information about sporadic versus familial form, comorbid conditions, and medications used at the time of presentation. Specific medications of interest collected included vitamin D, multivitamin, fish oil, aspirin, any antithrombotic (antiplatelet agent or anticoagulant) drug, statins, nonsteroidal anti-inflammatory drugs, and serotonin reuptake inhibitors. Statins, nonsteroidal anti-inflammatory drugs, and vitamin D were chosen because of preclinical evidence of potential benefit in the literature.[10,11] Serotonin reuptake inhibitors and fish oil were chosen because of their association with an increased risk of bleeding. Aspirin and antithrombotic drugs were included because prior studies showed a lower incidence of bleeding,[12-14] and we wondered if the same effect was true for presentation with seizure.

Patients were classified into 4 categories based on the initial clinical presentation: seizure without hemorrhage, focal neurologic deficit without hemorrhage, intracerebral hemorrhage (presenting with focal neurologic deficit or seizure), and incidental finding. Initial clinical presentation refers to the symptoms that led the patients to seek medical attention initially and therefore led to the diagnosis of CM. For clinical hemorrhage, we used the standard definition reported by Al-Shahi Salman et al.[15] (i.e., a clinical event related both to the de novo appearance of symptoms and to radiologic, pathologic, or surgical evidence of blood in the cerebrospinal fluid).

Radiologic Data Collection

All patients underwent magnetic resonance imaging (MRI) either at our institution or elsewhere to diagnose the CM. The MRI scans were evaluated by the interpreting neuroradiologist and independently by one of the authors (K. D. F.). The CM size was measured on the T2 sequence, and the presence of a developmental venous anomaly (DVA) was evaluated. The Zabramski et al. classification[16] was used.

The number of CMs was assessed on hemosiderin-sensitive sequences (susceptibility-weighted imaging or gradient recall echo imaging when available). CMs were considered sporadic form if there was a single lesion or multiple lesions clustering around a DVA. The site of the cerebral CM was divided into supratentorial-cortical, supratentorial-subcortical, infratentorial-brainstem, infratentorial-cerebellum, and other. The cortical localization was divided into frontal, temporal, parietal, and occipital, and the temporal site was further subdivided into mesial temporal (i.e., amygdala, hippocampus, uncus, dentate gyrus, parahippocampal gyrus) and another temporal for those not in the mesial temporal lobe.

Data Analysis

Descriptive statistics (frequencies, percentages, means, medians, SDs, and ranges) are reported. Associations of categorical variables were assessed using the χ^2 or Fisher exact test. Wilcoxon rank-sum tests were assessed for continuous variables. Univariate and multivariate logistic regression models were assessed, where the odds ratios and 95% confidence intervals were calculated. Multivariate logistic regression models were done based on factors that were significant from the univariate analysis. We also did a subset analysis that analyzed the differences between those patients presenting with seizures without hemorrhage compared with incidental CM. A second subset analysis was performed evaluating the differences between those patients presenting with seizures without hemorrhage and those patients presenting with hemorrhage. Statistical analysis was done using JMP (SAS Institute Inc., Cary, North Carolina, USA) software. Two-sided P values <0.05 were considered statistically significant.

Data Statement

All relevant data have been shared and published in this article. Patient-identifying data are confidential.

RESULTS

As of October 30, 2018, 202 patients with cerebral CMs were enrolled in the cohort. The mean age at diagnosis of the entire population was 43.7 ± 16.5 years, and 58.4% were women. Overall, 30 patients (14.8%) presented with seizure without concomitant hemorrhage, and 75 patients (37.1%) presented with intracerebral hemorrhage; 13 patients (6.5%) had a focal neurologic deficit without hemorrhage. CMs were found incidentally during radiologic evaluation for unrelated issues in 82 patients (40.6%). One patient each presented with a movement disorder (0.5%) and hydrocephalus (0.5%) (Table 1). Radiographically, there were a total of 125 supratentorial lesions. Of these, 79 were cortically based, including 39 frontal (42.4%), 37 temporal (40.2%), 12 parietal (13.0%), and 4 occipital (4.3%).

In the 30 patients who presented with a first-time seizure without concomitant hemorrhage, the mean age at diagnosis was 38.4 ± 14.6 years, and 56.7% were women. All 30 patients presenting with seizure without concomitant hemorrhage had a supratentorial, cortically based CM. The most common location was the temporal lobe (n = 19), followed by a frontal lobe location (n = 8), parietal location (n = 2), and occipital location (n = 1) (Figure 1). Of the 19 CMs in the temporal lobe in these patients, 6 were located in the mesial aspect of the temporal lobe. When compared with other supratentorial lesions, patients presenting with seizure without hemorrhage were more likely to have a CM in a temporal, cortical location and be a Zabramski type 2 lesion (Table 2). Of all supratentorial, cortical lesions (n = 79), 30 (38.0%) presented with seizure. Of those with supratentorial temporal lobe CM, 51.3% (19/37) presented with seizure.

When compared with patients with incidental lesions, patient presenting with seizure without concomitant hemorrhage were younger (mean age, 46.5 years incidental vs. 38.4 years seizure; $P = 0.0221$) and less likely to have a chronic inflammatory disease (6.7% vs. 39.0%, respectively; $P = 0.0009$). Patients without symptoms were more commonly taking statin (25.6% vs. 6.7%; $P = 0.03$),

Table 1. Absolute Number and Percentage of the Initial Clinical Presentation in this Cohort (N = 202)

Initial Clinical Presentation	Number of Patients (%)
Incidentally finding	82 (40.6)
Hemorrhage	75 (37.1)
Seizure without concomitant hemorrhage	30 (14.8)
Focal neurologic deficit without hemorrhage	13 (6.5)
Movement disorder	1 (0.5)
Hydrocephalus	1 (0.5)

vitamin D supplementation (36.6% vs. 16.7%; P = 0.044), and daily aspirin (34.1% vs. 6.7%; P = 0.0034), respectively. Radiologically, patients with seizure without hemorrhage were more likely to have a supratentorial (100.0% vs. 76.8%; P = 0.0031), cortically based lesion (100.0% vs. 47.6%) than patients with incidental CM. The comparison between patients with seizures without concomitant hemorrhage and those with incidental lesions is summarized in Table 3. Accounting for factors such as age, chronic inflammatory disease, aspirin use, vitamin D supplementation, and statin use in a multivariate model, chronic inflammation and aspirin remained significant.

When compared with those patients presenting with hemorrhage, patients with seizures without concomitant hemorrhage more commonly had supratentorial cortical lesions and Zabramski type 2 lesions. Table 4 summarizes a comparison between these 2 groups of patients.

DISCUSSION

In a modern cohort of patients with CMs, we found that patients presenting with seizures without concomitant hemorrhage are younger and more likely to have cortical CMs compared with incidental CMs. When compared with other supratentorial lesions, those with seizure without hemorrhage are more likely to have a temporal lobe CM. Compared with incidental CM, patients with seizure without hemorrhage were less likely to have concomitant chronic inflammatory disease or use daily aspirin, statin, or vitamin D supplementation. Patients with hemorrhage as the initial presentation, as expected, are more likely (when compared with those with seizures without hemorrhage) to have CMs located in deep structures such as the basal ganglia and the brainstem.

In this cohort of patients over 18 years of age, the average age of presentation was 38.4 years, younger than those with an incidentally found CM. It is possible that some CMs form and are unstable with hemosiderin leakage resulting in seizures, whereas others form and stabilize because of unclear factors and therefore are found at a later age.

Many studies have shown seizures to be precipitated by cortically based CMs; however, it is unclear whether the temporal lobe is more epileptogenic in patients with CM.[1] Our data support the temporal location as the location with the highest risk for seizures. More than 50% of the patients with a temporal lobe, cortical lesion were likely to present with seizure compared with 38.0% of all supratentorial, cortical lesions. Our data suggest a lower rate of patients with seizure presentation than some prior reports[17]; however, referral bias may be the reason. Although some studies have shown multiple lesions or the familial form to present more commonly with seizure,[1] we did not find this to be true in our cohort.

Our group previously found that chronic inflammatory disorders increased the risk of sporadic CM formation compared with DVA control subjects.[18] Animal data also support a role for inflammatory disease in increasing lesion burden and disease severity.[19] One might think, therefore, that these same inflammatory diseases increase the risk for presentation with seizure or hemorrhage. However, we found the opposite to be true. Patients with incidental disease were more likely to have a chronic inflammatory disease than those presenting with seizure without hemorrhage. Interestingly, patients with chronic inflammatory disease were more likely than those without to

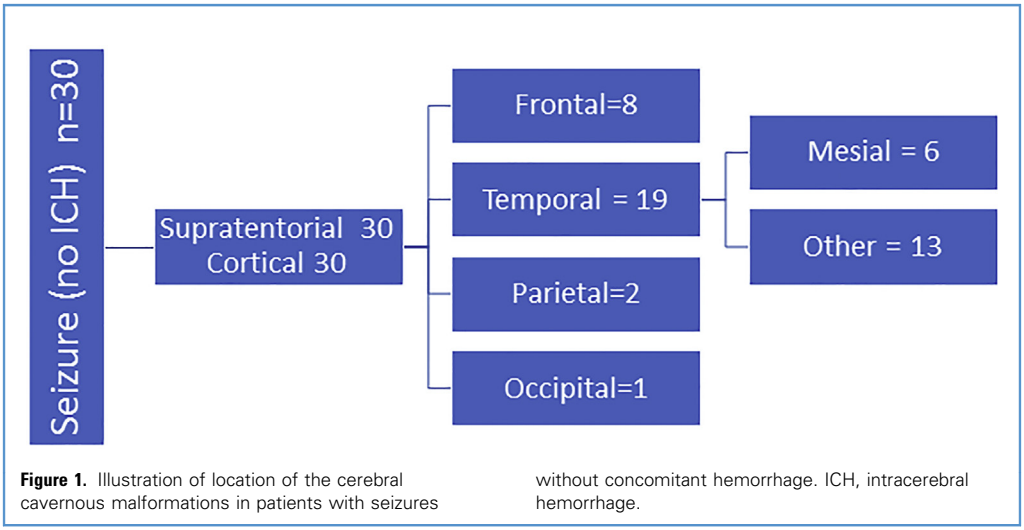

Figure 1. Illustration of location of the cerebral cavernous malformations in patients with seizures without concomitant hemorrhage. ICH, intracerebral hemorrhage.

Table 2. Comparison of Supratentorial Lesions

Characteristic	Present with Seizure without ICH (n = 30)	Present Incidental or with ICH (n = 95)	*P* Value (Significance at <0.05)
Mean age ± SD (years)	38.4 ± 14.6	43.9 ± 16.4	0.1049
Cortical location	30 (100.0)	49 (51.0)	<0.0001*
Side (right)	20 (66.7)	46 (48.4)	0.2115
Temporal lobe versus other	19 (63.3)	18 (29.0)	0.0017*
Zabramski type 2 versus other	19 (79.7) (6 with missing data)	47 (54.6) (9 with missing data)	0.0302*
Size on T2 (median and range; mm)	10 (6.1–30.9)	11.25 (1–34.7)	0.6724

Values are number of patients (%) or as otherwise indicated.
ICH, intracerebral hemorrhage.
**P* value <0.05.

Table 3. Comparison of Patients Presenting with Seizure Compared with Patients Presenting with an Incidental Cavernous Malformation

Characteristic	Present with Seizure without ICH (n = 30)	Incidental (n = 82)	*P* Value (significance at <0.05)	Odds Ratio (95% CI)
Demographics				
Mean age at diagnosis ± SD (years)	38.4 ± 14.6	46.5 ± 17.0	0.021*	For each year, 0.97 (0.94–0.99)
Sex (female)	17 (56.7)	50 (61.0)	0.68	0.84 (0.36–1.95)
Familial form	10 (33.3)	15 (18.3)	0.09	2.23 (0.87–5.74)
Multiple lesions	11 (36.7)	22 (26.8)	0.31	1.58 (0.65–3.84)
Comorbid conditions				
Chronic inflammatory disease	2 (6.67)	32 (39.0)	0.0009*	0.11 (0.025–0.50)
Neoplastic disease	4 (13.8)	21 (25.6)	0.30	0.46 (0.14–1.49)
Medications				
Any antithrombotic drug	3 (10.0)	31 (37.8)	0.0049*	0.18 (0.051–0.65)
Aspirin	2 (6.7)	28 (34.1)	0.0034*	0.14 (0.03–0.62)
NSAIDs	13 (43.3)	39 (47.6)	0.69	0.84 (0.36–1.96)
Vitamin D	5 (16.7)	30 (36.6)	0.044*	0.35 (0.12–1.00)
Fish oil	7 (23.3)	16 (19.5)	0.66	1.26 (0.04–3.14)
Estrogen (women n = 67)	1/17 (5.9)	7/50 (14.0)	0.67	0.38 (0.04–3.37)
Any statin	2 (6.7)	21 (25.6)	0.034*	0.21 (0.046–0.95)
SSRI†	3 (10.0)	10 (12.2)	1.0000	0.8 (0.20–3.13)
MRI findings				
Location supratentorial	30 (100.0)	63 (76.8)	0.0031*	
Location cortical	30 (100.0)	30 (47.6)	<0.0001*	
Zabramski type 2	18 (78.3)	53 (72.6)	0.14	1.43 (0.47–4.36)
Presence of DVA	5 (25.0) (10 with missing data)	29 (42.0) (17 with missing data)	0.17	0.46 (0.15–1.40)

Values are number of patients (%) or as otherwise indicated.
CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; SSRI, serotonin reuptake inhibitor; MRI, magnetic resonance imaging; DVA, developmental venous anomaly; ICH, intracerebral hemorrhage.
**P* value <0.05.

Table 4. Comparison of Patients Presenting with Seizure without Hemorrhage and Patients Presenting with Hemorrhage

Characteristic	Present with Seizure without Hemorrhage (n = 30)	Present with Hemorrhage (n = 75)	*P* Value	Odds Ratio (95% CI)
Demographics				
Age at diagnosis (years)	38.4 ± 14.6	42 +/- 16.6	0.30	For each 1 year, 0.98 (0.96–1.01)
Sex (female)	17 (56.7)	42 (56.0)	0.95	1.03 (0.44–2.41)
Familial form	10 (33.3)	13 (17.33)	0.073	2.38 (0.91–6.27)
Multiple lesions	11 (36.7)	19 (25.33)	0.24	1.71 (0.69–4.23)
Comorbidities				
Chronic inflammatory disease	2 (6.7)	17 (22.7)	0.054	0.24 (0.05–1.13)
Neoplastic disease	4 (13.8)	12 (16.0)	1.0	0.84 (0.25–2.85)
Medications				
Any blood thinner	3 (10.0)	6 (8.0)	0.71	1.28 (0.30–5.48)
Aspirin	2 (6.7)	5 (86.7)	1.00	1 (0.18–5.46)
NSAIDs	13 (43.3)	18 (24.0)	0.049*	2.42 (0.99–5.93)
Vitamin D	5 (16.7)	17 (22.7)	0.49	0.68 (0.23–2.05)
Fish oil	7 (23.3)	12 (16.0)	0.38	1.5978 (0.56–4.55)
Estrogen (women only; n = 59)	1 (5.9)	11 (26.2)	0.15	0.18 (0.02–1.49)
Statin	2 (6.7)	9 (12.0)	0.73	0.524 (0.11–2.58)
SSRI	3 (10.0)	5 (6.7)	0.35	1.56 (0.35–6.96)
MRI findings				
Location supratentorial	30 (100.0)	29 (38.7)	<0.0001*	46.0 (85.94–356.23)
Location cortical	30 (100.0)	18 (24.3)	<0.001	
Zabramski type 2 versus other type	17 (77.3)	2 (3.1)	<0.0001*	
Location temporal versus other	17 (60.7)	4 (21.0)	0.0073*	5.80 (1.52–22.10)

Values are number of patients (%) or as otherwise indicated.
CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; SSRI, serotonin reuptake inhibitor; MRI, magnetic resonance imaging.
**P* value <0.05.

take vitamin D supplementation (50.0% vs. 23.1%, respectively; P = 0.0047). In vitro and animal model data suggest a role for vitamin D in restoring endothelial dysfunction in CM disease.[10] Therefore, we think vitamin D supplementation, rather than the influence of the chronic inflammatory disease, might be important in seizure presentation. This is supported by the fact that more people taking vitamin D supplementation were asymptomatic. It is also possible that various medications used for the inflammatory disease (not collected) influence CM presentation.[19,20]

Several clinical studies have shown a lower hemorrhage rate in patients with CM taking antithrombotic drugs.[12-14] Theoretically, in the sporadic form of CM, antithrombotic drugs might reduce thrombosis in associated DVA radicles preventing venous outflow and therefore increasing hemorrhage risk. Interestingly, we found that aspirin or any antithrombotic drug to be more common in the asymptomatic group than the seizure group, raising the possibility that the same mechanism previously described plays a role in seizure presentation, perhaps related to chronic leak of hemosiderin into the surrounding tissue. Although this could be a spurious finding (because patients with incidental disease were older and older people are more likely to require aspirin), it deserves further study. In a multivariate analysis, adjusting for age, aspirin remained significant. We also found that patients on daily aspirin were more likely to be on a statin (53.3% of patients on aspirin also were on statin compared with only 8.5% on statin alone; P < 0.0001). Statins may play a theoretic role in reducing leakiness of endothelial cells in CM disease.[21] These findings may suggest a role for disease-modifying agents along with antiseizure medications in patients not undergoing surgery. However, we think that early surgery should be considered in patients with a cortically based, surgically accessible lesion, especially if the patient is poorly tolerant of or not responding to antiseizure medications.

Limitations of the Study

Despite the prospective data collection, our study is limited by tertiary referral bias, which could result in a higher number of symptomatic lesions. Ascertainment bias—because of errors in electronic health records or recall bias by patients—can influence comorbidities and medication use. We reviewed medical records but verified medical comorbidities and medication use with patients through interviews and questionnaires to reduce this bias. We were unable to determine the frequency and compliant use of medications stated by patients, which might particularly influence medications or supplements used. Nevertheless, to our knowledge, this is the only prospective study to focus on a specific and homogeneous group of patients with a first seizure from a CM in absence of hemorrhage. As such, it provides valuable information in terms of demographics, lesion location and characteristics, comorbidities, and medication use in a focused population.

CONCLUSIONS

Patients who present with a first seizure from a CM in absence of concomitant hemorrhage are younger and more likely to have a cortically based CM compared with those patients with incidental CM. Of supratentorial lesions, patients presenting with seizure without hemorrhage are more likely to have a CM located in the temporal lobe. The potential role of select medications influencing clinical presentation and modifying disease activity beyond antiseizure medications and/or surgery deserves further scrutiny.

REFERENCES

1. Rosenow F, Alonso-Vanegas MA, Baumgartner C, et al. Cavernoma-related epilepsy: review and recommendations for management—report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2013;54:2025-2035.
2. Al-Shahi Salman R, Hall JM, Horne MA, et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurol*. 2012;11:217-224.
3. Flemming KD, Link MJ, Christianson TJ, Brown RD Jr. Prospective hemorrhage risk of intracerebral cavernous malformations. *Neurology*. 2012;78:632-636.
4. Horne MA, Flemming KD, Su IC, et al. Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data. *Lancet Neurol*. 2016;15:166-173.
5. Kondziolka D, Lunsford LD, Kestle JR. The natural history of cerebral cavernous malformations. *J Neurosurg*. 1995;83:820-824.
6. Labauge P, Brunereau L, Levy C, Laberge S, Houtteville JP. The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients. *Neuroradiology*. 2000;42:327-332.
7. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg*. 1997;87:190-197.
8. Rigamonti D, Hadley MN, Drayer BP, et al. Cerebral cavernous malformations. Incidence and familial occurrence. *N Engl J Med*. 1988;319:343-347.
9. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. *J Neurosurg*. 1991;75:709-714.
10. Gibson CC, Zhu W, Davis CT, et al. Strategy for identifying repurposed drugs for the treatment of cerebral cavernous malformation. *Circulation*. 2015;131:289-299.
11. Shenkar R, Peiper A, Pardo H, et al. Rho kinase inhibition blunts lesion development and hemorrhage in murine models of aggressive Pdcd10/Ccm3 disease. *Stroke*. 2019;50:738-744.
12. Bervini D, Jaeggi C, Mordasini P, Schucht P, Raabe A. Antithrombotic medication and bleeding risk in patients with cerebral cavernous malformations: a cohort study. *J Neurosurg*. 2018:1-9.
13. Flemming KD, Link MJ, Christianson TJ, Brown RD Jr. Use of antithrombotic agents in patients with intracerebral cavernous malformations. *J Neurosurg*. 2013;118:43-46.
14. Schneble HM, Soumare A, Herve D, et al. Antithrombotic therapy and bleeding risk in a prospective cohort study of patients with cerebral cavernous malformations. *Stroke*. 2012;43:3196-3199.
15. Al-Shahi Salman R, Berg MJ, Morrison L, Awad IA, Angioma Alliance Scientific Advisory Board. Hemorrhage from cavernous malformations of the brain: definition and reporting standards. Angioma Alliance Scientific Advisory Board. *Stroke*. 2008;39:3222-3230.
16. Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familial cavernous malformations: results of an ongoing study. *J Neurosurg*. 1994;80:422-432.
17. Menzler K, Chen X, Thiel P, et al. Epileptogenicity of cavernomas depends on (archi-) cortical localization. *Neurosurgery*. 2010;67:918-924.
18. Kumar S, Lanzino G, Brinjikji W, Hocquard KW, Flemming KD. Infratentorial developmental venous abnormalities and inflammation increase odds of sporadic cavernous malformation. *J Stroke Cerebrovasc Dis*. 2019;28:1662-1667.
19. Retta SF, Glading AJ. Oxidative stress and inflammation in cerebral cavernous malformation disease pathogenesis: two sides of the same coin. *Int J Biochem Cell Biol*. 2016;81:254-270.
20. Chohan MO, Marchio S, Morrison LA, et al. Emerging pharmacologic targets in cerebral cavernous malformation and potential strategies to alter the natural history of a difficult disease: a review. *JAMA Neurol*. 2018;4:429-500.
21. Polster SP, Stadnik A, Akers AL, et al. Atorvastatin Treatment of Cavernous Angiomas with Symptomatic Hemorrhage Exploratory Proof of Concept (AT CASH EPOC) trial. *Neurosurgery*. 2019;84:954-964.

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