Cavernous Malformation Hemorrhagic Presentation at Diagnosis Associated with Low 25-Hydroxy-Vitamin D Level

Kelly D. Flemming^a Shivram Kumar^a Robert D. Brown Jr^a Ravinder J. Singh^c
Kevin Whitehead^d Lauren McCreath^d Giuseppe Lanzino^b

^aDepartment of Neurology, Mayo Clinic, Rochester, MN, USA; ^bDepartment of Neurosurgery, Mayo Clinic, Rochester, MN, USA; ^cDepartment of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; ^dDepartment of Cardiovascular Medicine, University of Utah, Salt Lake City, UT, USA

Keywords

Cavernous malformation · Hemorrhage · Cavernoma · Cavernous · Angioma · Vitamin D · 25-Hydroxy-vitamin D

Abstract

Background: Cavernous malformations (CM) are angiographically occult vascular malformations that may be incidental or present with intracerebral or spinal hemorrhage, seizures, or nonhemorrhagic focal neurologic deficit (FND). Recently in vitro data have suggested vitamin D may play a role in stabilizing CCM2 endothelial cells. Little is known about the effect of vitamin D in human CM disease. **Methods:** Beginning in 2015, consecutive patients at our institution with radiologically confirmed CM were recruited to participate in a prospective clinical registry as well as 25-hydroxy-vitamin D study. A structured interview, survey, and examination were performed at baseline. Medical records and magnetic resonance imaging studies were reviewed and data collected included comorbid conditions, medication use, and location of CM. Standard definition of clinical hemorrhage, FND, and seizures was used. Univariate and multivariate logistic regression models were used, and OR, 95% CIs, and likelihood-ratio *p* values were calculated to de-

termine the influence of the 25-hydroxy-vitamin D level on clinical presentation with hemorrhage. **Results:** Of 213 patients enrolled in the clinical registry between January 2015 and October 2018, 70 participated in the vitamin D study (median age: 38.3 years; 51.4% female). Of the 70 participants, 30 (42.9%) presented with hemorrhage. 25-Hydroxy-vitamin D levels were performed within 1 year of symptoms in 64.1% of patients. Patients presenting with hemorrhage had a lower 25-hydroxy-vitamin D level compared to those presenting with seizure without hemorrhage, FND, or as an incidental finding (median 25.5 ng/mL; range 11–59 hemorrhage vs. median 31.0; range 14–60, no hemorrhage; *p* = 0.04). After adjusting for age, month of blood draw, and body mass index, 25-hydroxy-vitamin D remained a significant predictor of hemorrhagic presentation. Brainstem location also predicted hemorrhage at presentation. **Conclusion:** Low 25-hydroxy-vitamin D level was more common in patients with CM presenting with hemorrhage. This study supports the potential role of modifiable factor in the initial clinical presentation of CM. Further study is needed to determine the role of vitamin D on prospective hemorrhage risk and whether supplementation may be beneficial.

© 2020 S. Karger AG, Basel

Background

Cavernous malformations (CM) are low flow vascular malformations that occur in the brain, spinal cord, and rarely the dura. Pathologically, CM consist of endothelial lined caverns lacking appropriately formed tight junctions [1]. The vascular leak due to poorly formed tight junctions leads to the clinical consequences of the disease. Patients may come to medical attention due to intracerebral or spinal hemorrhage, seizure, focal neurologic deficit (FND) without overt hemorrhage, or as an incidental finding.

Recently, vitamin D has been shown to play a role in CM endothelial leakiness in animal and in vitro models [2]. Only one study has assessed the influence of 25-hydroxy-vitamin D level on the clinical course of patients with CM [3]. In that study, lower 25-hydroxy-vitamin D was found in CM patients with “chronically aggressive disease” defined as one of the following: early age at symptom onset, 2 or more symptomatic hemorrhages, or high lesion burden. In that study, low 25-hydroxy-vitamin D did not correlate with hemorrhage alone, although small numbers and 25-hydroxy-vitamin D levels drawn months to years after presentation may account for such findings.

We aimed to assess the influence of 25-hydroxy-vitamin D level on initial clinical presentation with hemorrhage in patients with CM of the brain and spinal cord.

Methods

Patient Selection

IRB and institutional approval was obtained. Adult patients (18 years and older) with CM of the brain or spinal cord were recruited to participate in a cavernous malformation clinical and radiologic registry in addition to participating in a vitamin D study. Some data from the clinical registry have been presented elsewhere [4, 5]. Patients who consented to the vitamin D study were included. Patients were excluded if they could not consent or consented, but did not complete the study (i.e., undergo the blood draw).

Clinical Data Collection

Demographic data, medical conditions, medications at diagnosis, and type of presentation were collected from in-person interviews, medical record review, and an initial questionnaire. Patients were presumed to have the familial form of CM if they had a family history, CCM gene mutation, or multiple lesions without DVA. We defined “clinical presentation” as the first time a patient presented to medical attention and was diagnosed with a CM. As per standard guidelines [6], clinical hemorrhage was defined as a clinical event involving both symptoms (headache, seizure, impaired consciousness, new/worsened FND referable to the anatomic location of the CM) and radiological, pathological, surgical, or CSF

evidence of hemorrhage. Nonhemorrhagic FND was defined as a new or worsened FND referable to the anatomic location of the CM but without obvious evidence of hemorrhage [6]. Patients were classified by hemorrhage status: hemorrhagic (with either FND or seizure) or nonhemorrhagic with seizures, FND, or incidental.

Radiologic Data Collected

The first magnetic resonance imaging performed diagnosing the CM was reviewed by a staff neuroradiologist in addition to the lead author (K.D.F.). The magnetic resonance imaging was reviewed to determine if acute hemorrhage was present. The number of CM was recorded based on hemosiderin-sensitive sequences (susceptibility weighted imaging [SWI], gradient recalled echo) when available or on T2 if SWI and gradient recalled echo were not available. The locations of the cerebral CM were divided into supratentorial-cortical, supratentorial-subcortical, infratentorial-brainstem, infratentorial-cerebellum, and other.

Physical Data Collected

Height, weight, and BMI data were collected as obesity can influence vitamin D level.

Laboratory Data Collected

Blood was collected to assess the 25-hydroxy-vitamin D level. Twenty millilitre of blood was collected in 4 standard serum separator tubes from each patient. Specimens were allowed to clot at 4°C for 30–60 min and then spun at 1,000 rcf for 10 min in a swinging bucket centrifuge. Serum was then collected from each tube and aliquoted into approximately 12 sterile and endotoxin-free Eppendorf tubes (~1 mL per tube) until all serum had been aliquoted. Eppendorf tubes were snap-frozen and stored at –80 °C. Containers were then batch shipped to Associated Regional and University Pathologists laboratories (Salt Lake City, UT, USA). The researcher assessing 25-hydroxy-vitamin D levels and recording them was blinded to the clinical information.

Data Analysis

Descriptive statistics including means, SDs, and frequencies were utilized for patient characteristics and presenting symptoms. Univariate and multivariate logistic regression models were used assess 25-hydroxy-vitamin D levels and hemorrhagic CM presentation versus other presentation, and we report the OR, 95% CIs, and likelihood-ratio *p* values with statistical significance set at a *p* value of <0.05. JMP Pro software version 14.1.0 (SAS Institute Inc. Cary, NC, USA) was used for analysis.

Results

Of 213 patients consented to participate in a longitudinal survey, 80 patients consented for the vitamin D study between January 2015 and October 2018, but only 70 completed the blood draw and thus were included in this study (Fig. 1). Demographic data, comorbid conditions, concomitant medication use, radiologic data, and laboratory data are reported in Table 1. The median age of pa-

Fig. 1. Study screening and enrollment.

tients at diagnosis was 38.3 years (range 5.75–70.5) and 51.4% were female. The majority of patients were white (87.1%) and about 1/5 (20.3%) of patients had the familial form of CM. Of these, 10 had a family history of CM and 6 were genotyped (2 *CCM1*; 4 *CCM2*). The remainder were presumed based on imaging findings. During the same time frame, 143 additional patients consented to be involved in the clinical cavernous malformation registry, but not the vitamin D study. Patients participating in the vitamin D part of the study differed from those not participating in the vitamin D study in that they were slightly younger (38.3 vs. 45.5 years; $p = 0.044$). There were no differences in clinical comorbidities, medication use, proportion of those presenting with hemorrhage, and brainstem location (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000507789).

At first presentation and diagnosis of the CM, the CM was felt to be an incidental finding in 26 (37.2%) of patients. Thirty (42.9%) patients presented with hemorrhage, 5 (7.1%) with FND-non-hemorrhagic, 7 (10.0%) with seizure (without hemorrhage), and 1 (1.4%) with hydrocephalus and 1 (1.4%) with a movement disorder. Sev-

enteen patients were taking vitamin D supplementation, but only 12 knew the dose. The median dose was 2,000 international units daily (range 200–8,000).

CM were located in the supratentorial-cortical location 25 (35.7%), supratentorial-subcortical 18 (25.8%), infratentorial-brainstem 21 (30.0%), infratentorial-cerebellum 1 (1.4%), spinal cord 4 (5.7%), and intraventricular 1 (1.4%). Patients with a brainstem location CM had a higher odds of presenting with hemorrhage (OR 5.67; 95% CI 1.84–17.45).

The 25-hydroxy-vitamin D level was drawn within 1 year of symptom onset in 43 (61.4%) patients (median: 0.38 years; range 0–28 years; Table 2). The 25-hydroxy-vitamin D levels drawn in the spring/summer were similar to those drawn in the fall/winter (31.6 vs. 29.7 ng/mL; $p = 0.57$). The 25-hydroxy-vitamin D level was lower in patients presenting with hemorrhage compared to those not presenting with hemorrhage (median 25; range 11–59 ng/mL hemorrhage vs. median 31; range 14–60; no hemorrhage, $p = 0.038$; Fig. 2). For each unit increase in 25-OH-vitamin D, the odds of presentation with hemorrhage were 5% lower (OR 0.95; 95% CI 0.91–0.99). There was no relationship of 25-hydroxy-vitamin D level and seizure without hemorrhage (29.8 ± 4.3 vs. 30.8 ± 1.4 ng/mL; $p = 0.83$) or any related clinical presentation (seizure, FND, hemorrhage) versus incidental finding (28.8 ± 1.7 vs. 33.3 ± 2.2 ng/mL; $p = 0.13$). After controlling for age, BMI, and month of biomarker draw (October–March vs. April–September), 25-hydroxy-vitamin D level remained significant (Table 3).

Patients with a chronic inflammatory disease not only had a higher median 25-hydroxy-vitamin D level (35.2 vs. 28.2 ng/mL; $p = 0.02$; online suppl. Table 2) but also reported higher use of vitamin D supplementation (53.0 vs. 22.9%; $p = 0.03$). There were no other associations of 25-hydroxy-vitamin D level and other comorbidities or medications, except those reporting use of vitamin D supplementation (mean: 40 ng/mL; range 18–60 reported vitamin D supplementation versus 26 ng/mL; range 11–56 no supplementation; $p \leq 0.001$).

Discussion

In a large, prospective cohort of people with a CM, we report a higher likelihood of initial presentation with hemorrhage in patients with low 25-hydroxy-vitamin D levels (<30 ng/mL). While vitamin D is one potential influence on hemorrhage risk, it remains unknown if there are differential influences on the familial versus sporadic

Table 1. Patient characteristics in those with and without clinical hemorrhage at presentation

	All patients	Presentation with hemorrhage	Presentation without hemorrhage	<i>p</i> value	OR (95% CI)
Number, <i>n</i> (%)	70	30 (42.9)	40 (57.1)		
Demographic information					
Age, years at diagnosis, median (range)	38.3 (5.75–70.5)	36.1 (17.7–70.5)	44.5 (5.75–63.4)	0.30	0.98 (0.95–1.02)
Gender, female, <i>n</i> (%)	36 (51.4)	16 (53.3)	20 (50.0)	0.78	1.14 (0.44–2.95)
Race (white), <i>n</i> (%)	61 (87.1)	27 (90.0)	34 (87.2)	0.72	1.32 (0.29–6.04)
Familial form, <i>n</i> (%)	14 (20.3)	5 (16.7)	9 (22.5)	0.51	0.67 (0.20–2.25)
Medical history, <i>n</i> (%)					
Presentation between October–March and April–September ¹	25/39 (64.1)	16/27 (59.2)	9/12 (75.0)	0.34	0.48 (0.11–2.20)
Chronic inflammatory disease	23 (32.9)	8 (26.7)	15 (37.5)	0.34	0.61 (0.22–1.70)
Inflammatory bowel disease	3 (4.9)	0	3 (7.5)	0.27	–
Medication use at presentation					
Propranolol	0	0	0	No data	No data
Supplemental vitamin D, <i>n</i> (%)	17 (32.7)	5 (16.7)	12 (30.0)	0.20	0.47 (0.14–1.51)
Statin, <i>n</i> (%)	10 (14.5)	4 (13.3)	6 (15.0)	0.84	0.87 (0.22–3.41)
Radiologic information					
Brainstem location, <i>n</i> (%)	21 (30.0)	15 (50.0)	6 (15.0)	0.0016	5.67 (1.84–17.45)
Associated DVA, <i>n</i> (%)	16 (27.1)	6 (24.0)	10 (29.4)	0.70	0.79 (0.24–2.62)
Missing data	11	5	6		

¹ Only patients with known month of onset of symptoms included in this calculation.

DVA, developmental venous anomaly.

Table 2. Laboratory data in patients with and without hemorrhage at presentation

Clinical and laboratory data	All patients	Present with hemorrhage	Present without hemorrhage	<i>p</i> value	OR (95% CI)
BMI, kg/m ² , median (range)	26.8 (16.7–48.4)	29.8 (17.8–45.6)	26.0 (16.7–48.4)	0.85	1.00 (0.94–1.07)
Biomarker drawn within 1 year of presentation, <i>n</i> (%)	43 (61.4)	20 (66.7)	23 (57.5)	0.44	1.48 (0.55–3.96)
Biomarker drawn October–March, <i>n</i> (%)	39 (55.7)	17 (56.7)	22 (55.0)	0.89	1.07 (0.41–2.78)
25-Hydroxy-vitamin D level, ng/mL, median (range)	29.0 (11–60)	25.5 (11–59)	31.0 (14–60)	0.038	0.95 (0.90–0.99)

BMI, body mass index.

form and whether supplementation could alter the future course of disease after presentation.

Ideal 25-hydroxy-vitamin D levels for skeletal health have varied across medical societies and foundations with some suggesting a level >20 ng/mL as ideal and others suggesting >30 ng/mL [7, 8]. There is no known ideal value for vascular health. The ideal value being above 30 ng/mL correlates closely with the median value of those CM patients who did not present with hemorrhage (31 ng/mL).

The mechanism of the role of vitamin D role in CM has been debated. There may be an effect on inhibiting transforming growth factor beta signaling as well as in-

hibition of RHOA [2, 9]. Prior studies have shown that when RhoA is activated, there is increased endothelial leakiness, and when it is inhibited, there is less CM leakiness or disease activity. Vitamin D is also an inhibitor of TLR4 [10, 11], which has been recently proposed as a mechanism in CCM formation [12] and some have proposed that vitamin D may act as an antioxidant [13].

In an in vitro study by Gibson et al. [2], vitamin D3 was found to restore structural abnormalities in human endothelial cells deficient in CCM2. In a clinical study by Girard et al. [3], 43 CM patients underwent labora-

Fig. 2. 25-Hydroxy-vitamin D levels in cavernous malformation patients with and without hemorrhage at presentation.

Table 3. Multivariate analysis of presentation with hemorrhage adjusted for age, BMI, and month of lab draw

Variable	OR	95% CI	<i>p</i> value
Age, years	0.99	0.95–1.02	0.43
Lab drawn between October and March	0.88	0.81–0.92	0.81
BMI, kg/m ²	1.00	0.93–1.07	0.96
25-Hydroxy-vitamin D level	0.95	0.91–1.00	0.049

BMI, body mass index.

tory testing to assess 25-hydroxy-vitamin D, approximately half of whom were familial form. Patients were stratified into “acute” and “chronic” aggressiveness. Acute aggressiveness was defined as lesional growth or symptomatic hemorrhage within the prior year or new lesion formation in the prior year in familial cases. Chronic aggressiveness was defined as any one of the following: symptom onset prior to age 18, >25 lesions on SWI, history of 2 or more confirmed clinical hemorrhages, or >5 T2 lesions >4 mm in size. The authors found lower 25-hydroxy-vitamin D levels in chronically aggressive disease, but only when considering the combined chronic aggressiveness outcome, not just hemorrhage alone. This study was the first to report on clinical vitamin D and CM patients but may have suffered from Type II error because of small sample size and timing of the vitamin D sample to the time of symptoms. Specifically, the average age at diagnosis compared to the average age at blood draw was nearly 10 years different. Our study remains small but has 70 patients, 61.4% of whom

had the biomarker drawn within 1 year of diagnosis strengthening the correlation of the level and symptomatology.

Since it is known that vitamin D levels can vary seasonally [14], one might expect a seasonal variation in hemorrhagic presentation with CM. Our group previously reported a higher likelihood of hemorrhagic presentation during fall and winter months (October–March) in our retrospective CM cohort supporting this theory [15]. However, we did not see a seasonal variation in the current, prospective cohort. We feel this is because the number of people on vitamin D supplementation during the time frame of the prospective cohort (2015–present) is likely higher than during our previously reported cohort of patients who were diagnosed between 1989 and 1999. Between 1999 and 2012, the use of vitamin D supplementation and fish oil increased in the US adult population [16].

Our group has previously reported that chronic inflammatory illnesses increase the risk of sporadic CM formation compared to DVA controls [17]. In addition, others have suggested inflammation as a trigger for CM lesion genesis [12, 13, 18]. We did not see that chronic inflammatory disease increased the likelihood of presenting to medical attention with hemorrhage, however. This may be because patients with chronic inflammatory disease reported higher likelihood of vitamin D supplementation than those without chronic inflammatory disease. The 25-hydroxy-vitamin D levels were also higher in patients with chronic inflammatory disease.

Our study has limitations. It is not a population-based study, but a prospective cohort from a large academic Institution. In any academic center, there is tertiary referral bias. Specifically, our institution may see more patients with symptomatic brainstem CM due to the nature of our surgical practice. Ascertainment of comorbidities and medications is subject to recall bias by patients. For example, medications such as supplements may be used intermittently and may not be included in a patient’s medication list, whereas daily medications may be more accurately recalled by patients, recorded in the medical record and collected. We tried to reduce this bias by thorough medical record review in addition to patient surveys. Doses of medications and supplements were not always available or readily recalled by patients. Data on vitamin D are limited by small numbers, and nearly 40% of patients had their levels assessed >1 year after clinical diagnosis. Initially, we limited the study to only those patients diagnosed within 6 months to improve correlation with symptomatology, but due to slow recruitment, expanded the study to any patient

with CM. Thus, 64.1% of 25-hydroxy-vitamin D levels were drawn within 1 year of initial diagnosis. Despite these limitations, our study is, to our knowledge, the largest CM registry with systematic assessment of the impact of 25-hydroxy-vitamin D levels on CM presentation. As such it provides novel data on evolution of clinical symptoms and factors associated with hemorrhagic presentation.

In conclusion, vitamin D may be a potential disease-modifying agent. More data are needed to assess whether low 25-hydroxy-vitamin D predicts prospective hemorrhage risk after initial presentation and whether supplementation modifies risk. We are collecting ongoing prospective data in these same patients. However, given the readily available, over-the-counter vitamin D supplementation with limited side effects, such studies might prove difficult. Large cohorts of recently diagnosed CM patients might be helpful. In addition, as future clinical trials assessing medications for hemorrhage prevention in patients with CM evolve [19], a 2×2 factorial design might aid in answering the question whether supplementation is beneficial.

Acknowledgment

The authors thank Lea Dacy, Mayo Clinic Department of Neurology, for proofreading and formatting of the manuscript.

References

- 1 Revencu N, Vikkula M. Cerebral cavernous malformation: new molecular and clinical insights. *J Med Genet*. 2006 Sep;43(9):716–21.
- 2 Gibson CC, Zhu W, Davis CT, Bowman-Kirigin JA, Chan AC, Ling J, et al. Strategy for identifying repurposed drugs for the treatment of cerebral cavernous malformation. *Circulation*. 2015 Jan;131(3):289–99.
- 3 Girard R, Khanna O, Shenkar R, Zhang L, Wu M, Jesselson M, et al. Peripheral plasma vitamin D and non-HDL cholesterol reflect the severity of cerebral cavernous malformation disease. *Biomarkers Med*. 2016;10(3):255–64.
- 4 Agosti E, Flemming KD, Lanzino G. Symptomatic Cavernous Malformation Presenting with Seizure without Hemorrhage: Analysis of Factors Influencing Clinical Presentation. *World Neurosurg*. 2019 Sep;129:e387–92.
- 5 Flemming KD, Kumar S, Brown RD, Lanzino G. Predictors of Initial Presentation with Hemorrhage in Patients with Cavernous Malformations. *World Neurosurg*. 2020 Jan;133:e767–73.
- 6 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. *Stroke*. 2008 Dec;39(12):3222–30.
- 7 Vieth R. What is the optimal vitamin D status for health? *Prog Biophys Mol Biol*. 2006 Sep;92(1):26–32.
- 8 American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults. Recommendations abstracted from the American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and Their Consequences. *J Am Geriatr Soc*. 2014 Jan;62(1):147–52.
- 9 Gibson CC, Whitehead KJ, Li D. The role of Vitamin D in Endothelial Cells with CCM2. 2013.
- 10 Murillo G, Nagpal V, Tiwari N, Benya RV, Mehta RG. Actions of vitamin D are mediated by the TLR4 pathway in inflammation-induced colon cancer. *J Steroid Biochem Mol Biol*. 2010 Jul;121(1-2):403–7.
- 11 Qian L, Wang H, Wu F, Li M, Chen W, Lv L. Vitamin D3 alters Toll-like receptor 4 signaling in monocytes of pregnant women at risk for preeclampsia. *Int J Clin Exp Med*. 2015 Oct;8(10):18041–9.
- 12 Tang AT, Choi JP, Kotzin JJ, Yang Y, Hong CC, Hobson N, et al. Endothelial TLR4 and the microbiome drive cerebral cavernous malformations. *Nature*. 2017 May;545(7654):305–10.
- 13 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 Dec;81 Pt B:254–70.
- 14 Kasahara AK, Singh RJ, Noymer A. Vitamin D (25OHD) Serum Seasonality in the United States. *PLoS One*. 2013 Jun;8(6):e65785.
- 15 Flemming KD, Brown RD, Link MJ. Seasonal variation in hemorrhage and focal neurologic deficit due to intracerebral cavernous malformations. *J Clin Neurosci*. 2015 Jun;22(6):969–71.
- 16 Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in Dietary Supplement Use Among US Adults From 1999–2012. *JAMA*. 2016 Oct;316(14):1464–74.

Statement of Ethics

The Mayo Clinic Institutional Review Board reviewed and approved this study, finding it in compliance with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki. Only patients providing written consent were included in the study.

Disclosure Statement

Dr. Kelly D. Flemming reports research funding from the National Institute of Neurological Disorders and Stroke. Dr. Shivram Kumar, Dr. Robert D. Brown Jr, and Ms. Lauren McCreath report no disclosures. Dr. Ravinder J. Singh reports research funding from the National Center for Advancing Translational Sciences. Dr. Kevin Whitehead reports research funding from a VA Merit Award. Dr. Giuseppe Lanzino reports research funding from the National Institute of Neurological Disorders and Stroke; Cersys, Inc.; Covidien; and Sequent Medical, Inc.

Funding Sources

This publication (or project) was supported by Grant Number UL1 TR002377 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The sponsor had no role in the preparation of this manuscript.

- 17 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 Jun;28(6):1662–7.
- 18 Choquet H, Pawlikowska L, Nelson J, McCulloch CE, Akers A, Baca B, et al.; Brain Vascular Malformation Consortium (BVMC) Study. Polymorphisms in inflammatory and immune response genes associated with cerebral cavernous malformation type 1 severity. *Cerebrovasc Dis*. 2014;38(6):433–40.
- 19 Chohan MO, Marchio S, Morrison LA, Sidman RL, Cavenee WK, Dejana E, 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*. 2019 Apr; 76(4):492–500.