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ABSTRACT

BACKGROUND AND PURPOSE: The etiology of sporadic cavernous malformations is not well-understood. However, recent evidence suggests that they may arise from a developmental venous anomaly. The goal of this study was to evaluate the prevalence of developmental venous anomalies associated with sporadic cavernous malformations using 7T MR imaging.

MATERIALS AND METHODS: We retrospectively identified patients with a sporadic cavernous malformation imaged with 7T MR imaging between August 2019 and July 2022. Two raters determined whether a developmental venous anomaly was associated with each malformation.

RESULTS: The study included 59 patients with a total of 61 cavernous malformations. Of the sixty-one, 44 (72%) had an associated developmental venous anomaly. An associated anomaly was most common for cavernous malformations in the brainstem (88%) compared with the cerebral hemispheres or cerebellum (60%–67%).

CONCLUSIONS: By means of high-quality 7T imaging, most patients with a sporadic cavernous malformation were found to have an associated developmental venous anomaly. These findings support the hypothesis that cavernous malformations may arise secondary to hemodynamic abnormalities.

ABBREVIATIONS: CM = cavernous malformation; DVA = developmental venous anomaly; VM = venous malformation

Cavernous malformations (CMs) are vascular malformations identified in <1% of the population that may occur in sporadic or familial forms.[1] Sporadic CMs most commonly occur as a single lesion, and multiple CMs are more commonly found in patients with familial multiple CM syndrome.[1,2] Familial CMs are thought to arise secondary to mutations in 1 of 3 known cerebral CM genes that lead to increased vascular permeability. The etiology of sporadic CMs is less well-understood, but recent studies have helped elucidate implicated somatic gene mutations. Sporadic CMs require either 2 somatic CM gene mutations in the same cell or a single gain-of-function mutation in the gene mitogen activated protein kinase 3 (*MAP3K3*). Mutations of the gene phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) have also been implicated in sporadic CM genesis and symptomatic disease.[3] An analysis in a limited number of patients demonstrated *PIK3CA* mutations in adjacent developmental venous anomalies (DVAs), suggesting that sporadic CMs may be derived from cells of the DVA.[3]

DVAs may be visualized on postcontrast T1WI as well as T2*-WI, which are sensitive to heme products based on the susceptibility effects. In large cohorts, approximately 20%–40% of sporadic CMs will have a DVA detected on gradient-echo MR imaging, bringing into question the theory that the CM arises from a DVA in every sporadic CM.[4] More recently, however, SWI has been developed and has improved detection of venous structures. SWI combines phase and magnitude information to create images that are sensitive to local susceptibility changes. On the basis of higher signal and improved spatial resolution, SWI is more sensitive than standard T2* gradient-echo sequences for the detection of heme products, including those associated with CMs.[5,6] SWI also allows improved depiction of venous structures, including DVAs.

In addition to the choice of imaging sequences, higher MR imaging field strength may provide improved detection of lesions such as DVAs. Specifically, high-field imaging (>3T) has become more prevalent during the past several years, with human 7T imaging available at many academic institutions. High-field (7T) MR imaging provides improved signal relative to 3T and 1.5T and may support improved spatial resolution. Prior studies have

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From the Departments of Radiology (P.M.C., J.J.P., G.L.), Neurosurgery (G.L.), and Neurology (K.D.F.), Mayo Clinic, Rochester, Minnesota.

Please address correspondence to Petrice M. Cogswell MD, PhD, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: Cogswell.petrice@mayo.edu

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Frequency of CMs and associated DVAs by location[a]

	Cerebral	Basal Ganglia	Brainstem	Cerebellum	Total
All CMs	36	5	17	3	61
Associated DVA	24 (67%)	3 (60%)	15 (88%)	2 (67%)	44 (72%)
Solitary CM	31	5	16	3	55
Associated DVA	20 (65%)	3 (60%)	14 (88%)	2 (67%)	39 (71%)
Clustered CM	5	0	1	0	6
Associated DVA	4 (80%)	0	1 (100%)	0	5 (83%)

[a] A cluster of CMs in a single region was considered a single CM incidence.

shown the potential benefits of high-field-strength imaging for detection of DVAs associated with CMs.[7-9] With improved imaging technology, a higher number of sporadic CMs have been found to be associated with a DVA, and a 2017 study by Dammann et al[7] suggested that all sporadic CMs are associated with a venous malformation (VM), either a typical VM (DVA) or an atypical VM (dilated draining vein or asymmetric venous structure). The purpose of this study was to test the hypothesis that most sporadic CMs are associated with a DVA when evaluated using SWI and postcontrast T1WI at 7T.

MATERIALS AND METHODS

Patients

This study included patients with sporadic CMs and no prior intracranial intervention who underwent 7T brain MR imaging between August 2019 and July 2022 and had research authorization. Patients with presumed familial CMs, as identified by familial history, numerous widespread CMs on brain MR imaging and/or genetics were excluded. Patients with multiple CMs in 1 location (clustered CMs) were included. The clinical presentation in each patient was recorded from medical records as per standard guidelines.[10]

Imaging

All subjects underwent 7T MR imaging using a standardized protocol that included T2 FSE, SWI, and MPRAGE performed before and after IV gadolinium contrast administration. The T2 FSE parameters were the following: TR/TE = 5790/56 ms, flip angle = 150°, FOV = 171 × 200 mm, matrix = 784 × 504, and section thickness = 2 mm. The SWI parameters were the following: TR/TE = 22/15 ms, flip angle = 15°, FOV = 165 × 200 mm, matrix = 640 × 480, and section thickness = 1.2 mm. The MPRAGE parameters were the following: TR/TE = 2240/3.05 ms, TI = 1050 ms, flip angle = 7°, FOV = 224 × 224 mm, matrix = 320 × 320 mm, and section thickness = 0.7 mm. In 2 patients no postcontrast imaging was performed.

Image Review

First, 1 rater (P.M.C.) identified all CMs using the SWI, T2 FSE, and precontrast MPRAGE sequences. The SWI was used to detect foci of susceptibility, and the T2 FSE and MPRAGE, to verify the presence of a discrete lesion compatible with a CM. Punctate foci of susceptibility, which were too small to characterize on T2 FSE (1–2 mm), were not included. The CM number, location, and size were evaluated. Location was specified as cerebral white matter (frontal, parietal, temporal, or occipital), basal ganglia, brainstem, or cerebellum. For patients with multiple CMs, the distribution was characterized as a multifocal solitary CM (a single CM in one of the above regions) or clustered (multiple CMs in a single region). The CM size was measured as the greatest transverse dimension on the T2 FSE sequence; in patients with multiple CMs, the largest one in each region was measured.

Next, 2 readers (P.M.C. and J.J.P.) reviewed each case to evaluate the presence or absence of a DVA in association with each CM or cluster of CMs using SWI and postcontrast MPRAGE sequences. An associated DVA was defined as a venous structure with a branching pattern (caput medusa) that terminated near the margin or immediately adjacent to the CM. If a DVA was present, it was characterized as having deep-versus-superficial venous drainage. The 2 readers independently reviewed a subset of 12 cases to evaluate for the presence or absence of a DVA; this subset was used to determine interrater agreement. The remaining cases were reviewed in consensus. Image review was performed using the multiplanar reformatting tool in Visage Imaging (Version 7.1; https://visageimaging.com/).

Statistical Analyses

Interrater agreement for the presence or absence of a DVA was evaluated use the κ statistic. Descriptive statistics were used to summarize CM and DVA characteristics.

RESULTS

The study included 59 patients with a mean age of 47 (SD, 15) years at the time of imaging; 27 (46%) were women. The initial clinical presentation was intracranial hemorrhage in 25 (42.4%) patients, seizure (no hemorrhage) in 8 (13.5%), and focal neurologic deficit without hemorrhage in 5 (8.5%), and 21 (35.6%) patients presented with incidental findings. The 7T MR imaging was completed an average of 34.8 months after the initial diagnostic MR imaging.

The prevalence of CMs and associated DVAs is presented in the Table. Of the 59 patients, 51 (86%) had a single CM, and 8 (14%) had >1. Of the 8 cases with multiple CMs, 6 had multiple CMs that were clustered in 1 region. The other 2 patients had single CMs in 2 different brain regions: 1 patient had a CM in the pons and another CM in the parietal cortex; a different patient had a CM in the temporal cortex and another CM in the caudate head. Therefore, there were 55 solitary CMs in 53 patients, and 6 CM clusters in 6 patients. CMs were most frequently located in the cerebral white matter (36/61, 59%) and brainstem (17/61, 29%), with only a few found in the basal ganglia or cerebellum (Table). The average CM size on the T2 FSE sequence was 16 (SD, 8) mm, with a range of 4–33 mm.

Of the 55 solitary CMs, 39 (71%) had an associated DVA (Fig 1). Of the 6 CM clusters, 5 (83%) had an associated DVA (Fig 2). Overall, CMs in the brainstem were more likely to have an associated DVA (88%) than CMs in the cerebellum (67%), cerebral white matter (65%), and basal ganglia (60%). Of the 44 DVAs present, more than half, 25 (56%) had deep venous drainage (Fig 3).

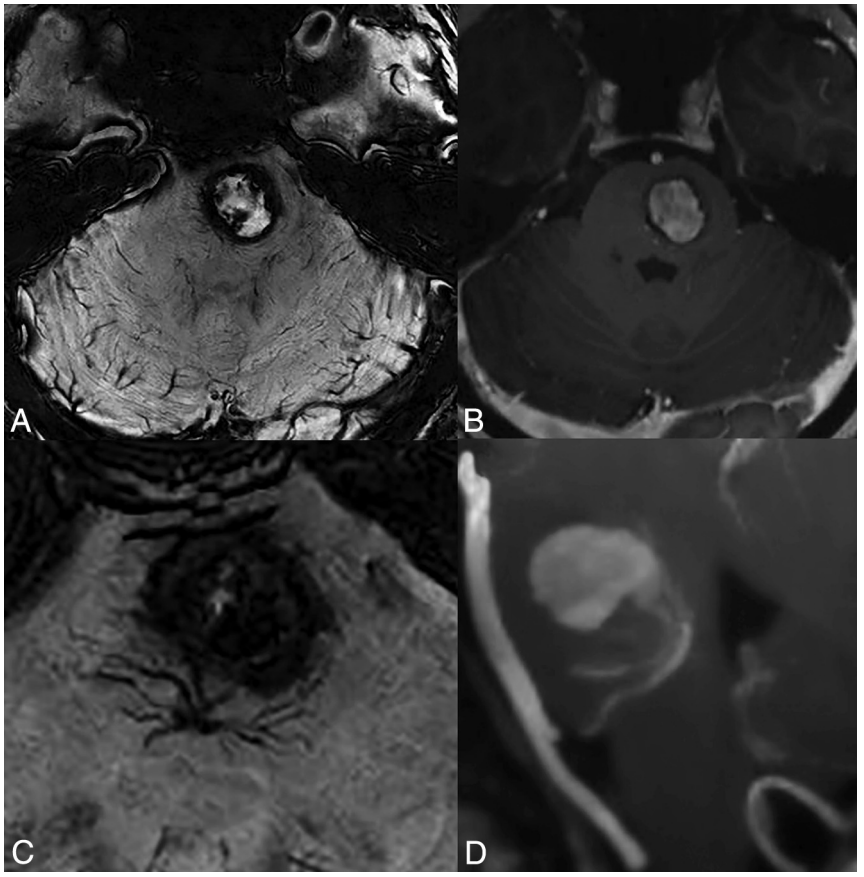

FIG 1. Representative CM with an associated DVA. Axial SWI (*A* and *C*) and postgadolinium MPRAGE (*B* and *D*) of a CM in the left aspect of the pons (*A* and *B*). Magnified axial-section SWI just inferior to the CM shows the caput medusa of the DVA (*C*). Sagittal MIP of a postgadolinium MPRAGE shows the DVA abutting the CM (*D*).

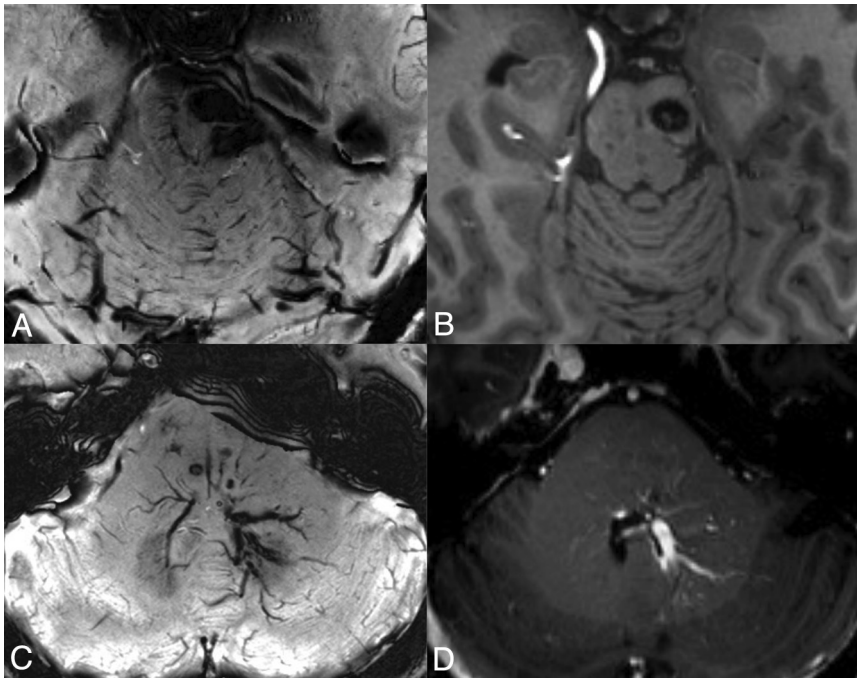

FIG 2. Representative example of clustered CMs with an associated DVA. Axial SWI (*A* and *C*) and pre- and postgadolinium MPRAGE (*B* and *D*) of adjacent slices show a dominant left cerebral peduncle CM (*A* and *B*) and a DVA with additional small CMs (*C* and *D*).

The 2 raters agreed on the presence or absence of a DVA in 11/12 (92%) CM locations with a κ statistic of 0.82 (near perfect agreement). On consensus review, it was determined that the 1 case in which the raters disagreed did have a DVA.

DISCUSSION

We found that most, but not all, sporadic CMs are associated with a DVA when evaluated on 7T MR imaging. The frequency of a DVA varied with location, with CMs in the brainstem being most likely to have an associated DVA.

Compared with the prior literature, we must consider the criteria and the imaging technique used to determine the presence or absence of a CM-associated VM. In this study, we focused on the prevalence of a DVA associated with CMs because DVAs have a well-defined and recognized appearance (caput medusa) leading to a definitive assessment of their presence or absence. The percentage of sporadic CMs with an associated DVA/typical VM in this study (72%) was greater than that found in some prior studies, including a study based on 1.5 and 3T imaging with T2* gradient recalled-echo or SWI sequences (8/18, 44%)[4] and a 7T study with the use of SWI (7/20, 35%),[8] though less than that reported at 7T by Dammann et al,[7] in 2017 (11/13, 85%). A limited body of literature exists on the association of DVAs and CMs as studied with high-field MR imaging. This work adds to the literature by validating the results of prior work in a larger sample size, which supports generalizability of these findings.

Prior studies have considered the presence of a DVA as well as atypical VMs when concluding that all sporadic CMs are associated with a VM. Because atypical VMs are not well-defined structures that can be reliably differentiated from normal variations in the vasculature, we did not report their prevalence in this study.

It has been proposed that changes in the DVA angioarchitecture cause local venous hypertension that contributes to recurrent microhemorrhages and CM formation,[11] in part on the basis of a comparison of imaging features

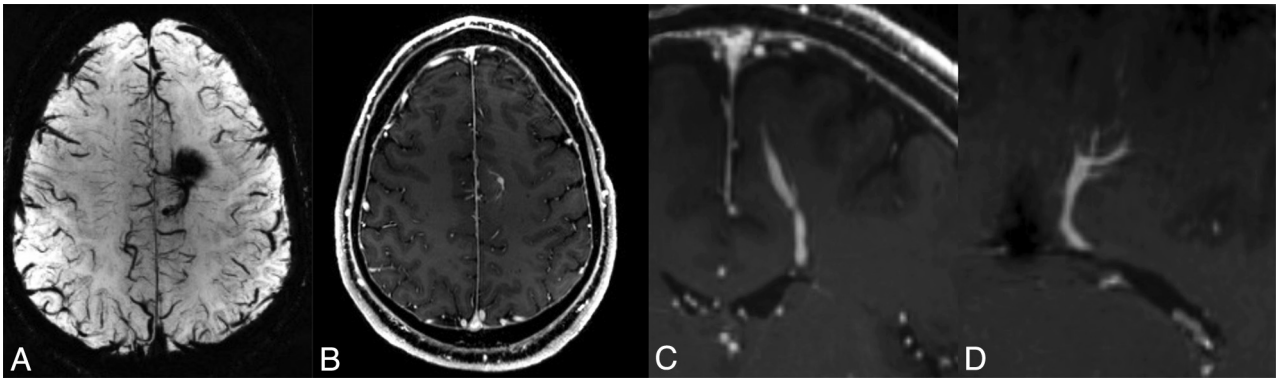

FIG 3. Sample of a left frontal CM (*A*, SWI) with an associated DVA (*B*, postcontrast MPRAGE) that has both superficial (*C*) and deep (*D*) venous drainage.

of DVAs with-versus-without an associated CM.[12,13] Another study of a large number of patients with DVAs showed that the percentage of DVAs with an associated CM increases with age, further supporting CMs being acquired lesions.[14] Our findings support the hypothesis that sporadic CMs may arise secondary to hemodynamic abnormalities in association with a DVA. Although a DVA was not visualized in association with all CMs, it is possible that there were regional venous/outflow abnormalities not visible on high-quality MR imaging or that the DVA could not be differentiated from normal vasculature.

There are limitations to this study. Evaluation of the frequency of DVAs with CMs in the basal ganglia and cerebellum was limited in this analysis due to low numbers of CMs in those regions. Some patients in our cohort were referred to our institution on the basis of an indeterminant interpretation of imaging findings elsewhere; therefore, our sample may be biased toward inclusion of cases without an obvious DVA. Finally, this is a single-center study. Future evaluation in a multicenter study with a larger sample size would provide additional support for these findings.

CONCLUSIONS

We found that when using high-quality 7T imaging, most (72%) patients with a sporadic CM had an associated DVA. These findings support the hypothesis that sporadic CMs may arise secondary to hemodynamic abnormalities.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

REFERENCES

1. Zabramski JM, Wascher TM, Spetzler RF, et al. **The natural history of familial cavernous malformations: results of an ongoing study.** *J Neurosurg* 1994;80:422–32 CrossRef Medline
2. Kattapong VJ, Hart BL, Davis LE. **Familial cerebral cavernous angiomas: clinical and radiologic studies.** *Neurology* 1995;45:492–97 CrossRef Medline
3. Snellings DA, Girard R, Lightle R, et al. **Developmental venous anomalies are a genetic primer for cerebral cavernous malformations.** *Nat Cardiovasc Res* 2022;1:246–52 CrossRef Medline
4. Petersen TA, Morrison LA, Schrader RM, et al. **Familial versus sporadic cavernous malformations: differences in developmental venous anomaly association and lesion phenotype.** *AJNR Am J Neuroradiol* 2010;31:377–82 CrossRef Medline
5. de Champfleur NM, Langlois C, Ankenbrandt WJ, et al. **Magnetic resonance imaging evaluation of cerebral cavernous malformations with susceptibility-weighted imaging.** *Neurosurgery* 2011;68:641–47; discussion 647–48 CrossRef Medline
6. Sparacia G, Speciale C, Banco A, et al. **Accuracy of SWI sequences compared to T2*-weighted gradient echo sequences in the detection of cerebral cavernous malformations in the familial form**. *Neuroradiol J* 2016;29:326–35 CrossRef Medline
7. Dammann P, Wrede K, Zhu Y, et al. **Correlation of the venous angioarchitecture of multiple cerebral cavernous malformations with familial or sporadic disease: a susceptibility-weighted imaging study with 7-Tesla MRI.** *J Neurosurg* 2017;126:570–77 CrossRef Medline
8. Dammann P, Wrede KH, Maderwald S, et al. **The venous angioarchitecture of sporadic cerebral cavernous malformations: a susceptibility weighted imaging study at 7 T MRI.** *J Neurol Neurosurg Psychiatry* 2013;84:194–200 CrossRef Medline
9. Frischer JM, Göd S, Gruber A, et al. **Susceptibility-weighted imaging at 7 T: improved diagnosis of cerebral cavernous malformations and associated developmental venous anomalies**. *Neuroimage Clin* 2012;1:116–20 CrossRef Medline
10. Al-Shahi Salman R, Berg MJ, Morrison L, et al; Angioma Alliance Scientific Advisory Board. **Hemorrhage from cavernous malformations of the brain.** *Stroke* 2008;39:3222–30 CrossRef Medline
11. Perrini P, Lanzino G. **The association of venous developmental anomalies and cavernous malformations: pathophysiological, diagnostic, and surgical considerations.** *Neurosurg Focus* 2006;21:e5 CrossRef Medline
12. Hong YJ, Chung TS, Suh SH, et al. **The angioarchitectural factors of the cerebral developmental venous anomaly; can they be the causes of concurrent sporadic cavernous malformation?** *Neuroradiology* 2010;52:883–91 CrossRef Medline
13. Sharma A, Zipfel GJ, Hildebolt C, et al. **Hemodynamic effects of developmental venous anomalies with and without cavernous malformations.** *AJNR Am J Neuroradiol* 2013;34:1746–51 CrossRef Medline
14. Brinjikji W, El-Masri AE, Wald JT, et al. **Prevalence of cerebral cavernous malformations associated with developmental venous anomalies increases with age.** *Childs Nerv Syst* 2017;33:1539–43 CrossRef Medline