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Familial versus Sporadic Cavernous Malformations: Differences in Developmental Venous Anomaly Association and Lesion Phenotype

ORIGINAL RESEARCH

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BACKGROUND AND PURPOSE: CCMs are commonly associated with DVAs, but the incidence of association in familial CCM is unknown. The presence of a DVA significantly complicates surgical management of a CCM because of the risk of compromised venous drainage. In this investigation, we compared the incidence of a DVA in the presence of a CCM in sporadic and familial CCM cases comprising predominantly familial CCM with the Southwestern US common Hispanic mutation (or *Q455X* mutation) of *CCM1*.

MATERIALS AND METHODS: Retrospective review was performed of 112 patients identified with CCM. MR imaging review included the presence or absence of a DVA and number, location, size, and signal-intensity characteristics of CCMs. Record review included patient and family history and documented genetic mutations. Statistical analysis was performed by using the Fisher exact and 2-sample *t* tests.

RESULTS: Eighty-one cases were familial, 18 were sporadic, and 13 were indeterminate. There were a total of 2212 CCMs: 2176, 21, and 15 in the familial, sporadic, and indeterminate groups, respectively. There was a close association of CCM and DVA (an apparent combined vascular lesion) in 8 of 18 (44%) sporadic cases and only 1 possible such association in the familial cases. The difference was highly statistically significant ($P < .0001$).

CONCLUSIONS: Familial CCMs are unlikely to be associated with DVAs, and sporadic CCMs have a high rate of association with DVA. This difference in imaging features of familial and sporadic CCMs suggests the possibility of a different developmental mechanism.

ABBREVIATIONS: CCM = cerebral cavernous malformation; DVA = developmental venous anomaly; FLAIR = fluid-attenuated inversion recovery; FSE = fast spin-echo; GR = gradient recall; SE = spin-echo; SWI = susceptibility-weighted imaging

BRAIN

ORIGINAL RESEARCH

CCMs and DVAs are both low-flow vascular malformations of the brain. Considered separately, they have a very different histologic character and clinical impact.[1] Although usually classified as a type of vascular malformation, DVAs may represent an anatomic variation of venous drainage, in which several small veins join and drain to a larger vein forming the familiar medusa or spoked wheel pattern on imaging studies.[2] As an isolated finding, a DVA usually has little significance other than the risk of venous infarct if the draining vein is compromised. Conversely, CCMs are discrete well-circumscribed lesions comprising sinusoidal spaces lined by a single layer of endothelium and separated by a collagenous matrix devoid of elastin, smooth muscle, or other vascular wall elements. The MR imaging appearance reflects blood products of varying stages, sometimes associated with edema in acute hemorrhage. Clinically, patients with CCMs typically present with seizures, headache, hemorrhage, or focal neurologic deficits related to lesion size and location. Because CCMs are low-flow lesions, patients usually do not require emergent medical management, though death can occur suddenly from hemorrhage in the central nervous system.

Combined lesions are well known,[3] including a DVA immediately associated with ≥1 CCM, and management may be different. Specifically, there is a risk of venous infarct if the draining vein of a DVA is occluded. If resection of a CCM is being considered, most neurosurgeons, therefore, consider it important to recognize these combined lesions to avoid venous infarction.[3-7]

CCMs occur in both sporadic and familial forms. Patients with familial CCMs typically have multiple malformations, with a correspondingly higher risk of complications.[8-10] Familial CCMs have been linked to 3 specific CCM genes, with the *CCM1* (*KRIT1*) Hispanic mutation (or the *Q455X* mutation), the most common in the Southwestern United States. Northern New Mexico has a dense population of patients with familial *CCM1*, which has been traced back to early Spanish settlers.[10] A genetic founder effect is likely to explain this high density of patients within New Mexico and surrounding states.[11] This group of patients shares Hispanic-American her-

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itage, extensive family histories of the disease, and multiple CCM lesions per patient.

CCMs are reported in the literature to have an association with DVA at a rate of 14%–30%.[12-17] When acute hemorrhage is observed with a DVA, it is likely to be associated with a CCM.[18] Other authors have suggested a low association of familial CCM with DVA, but there is a paucity of data in the literature to substantiate these observations in a large population.[12,18,19] The purpose of this study was to investigate the prevalence of DVAs in a large population of patients with a predominance of familial CCMs compared with patients with sporadic CCM of the brain, to provide a better understanding for implications for clinical management and to support further investigations regarding pathophysiology.

Materials and Methods

This retrospective review of case records was approved by an institutional review board. Patients with CCM were identified by searching through our hospital data bases. A data base with patient information removed was created by using age; sex; CCM lesion number, size, and location; the presence of a DVA; imaging characteristics of blood products; gadolinium enhancement if used; gradient sequences; SWI; *CCM1* DNA testing; and CCM family history based on chart-review information. CCM diagnosis was made during a routine MR imaging reading on the basis of typical findings on clinical scans. Patients were identified as familial cases of CCM if there were ≥3 CCM lesions or ≥1 CCM with a family history of CCM and/or confirmed *CCM1* testing. Those for whom there was inadequate information to determine a familial or sporadic form were considered an indeterminate group. Patients with a history of cranial radiation were excluded.

Typical MR imaging sequences used in most cases included sagittal T1, axial dual-echo long TR (intermediate and T2), axial fluid-attenuated inversion recovery, axial T2 GR, and axial or coronal T1. Because this was a retrospective review, certain sequences were not available for lesion identification and measurements in all cases. MR imaging was performed on a 1.5T magnet in 88 patients and on a 3T magnet in 24. Nearly all 1.5T scans were performed by using routine SE T2, not FSE. (This technique is used in our institution in part because of the high prevalence of familial CCM in our patient population; FSE T2 is much less sensitive to susceptibility effects.) The 3T scans were obtained with FSE T2 and GR T2. GR was used in 94 patients, and gadolinium contrast was used in 61. SWI was used in 26 patients and was reviewed in conjunction with other sequences. However, because of the increased sensitivity of SWI[20,21] and because so many patients did not undergo SWI, we did not count CCM lesions seen only on SWI for our analysis. We relied on T2 GR images whenever available for identifying and counting CCMs.

Because of the "blooming" from susceptibility effects on T2 GR, for the size of CCMs, we measured the greatest dimension of a lesion on SE T2 sequences unless the lesion was visible only on GR. The lesions visible only on GR were typically small, only 1 or 2 mm, and 1 mm was the minimum size that we recorded. More than 1 scan was available for some patients. In these cases, we used the most recent scans for evaluating lesions, or we combined information if different sequences were used. For example, if an earlier scan included T2 GR but a later scan did not, we used information from both scans for lesions that appeared stable. For new or apparently changed lesions, we used only the most recent available scan.

DVAs were identified on the basis of information from all sequences; postgadolinium images and SWI were considered the most reliable for demonstration of DVAs. For purposes of this study, we were interested in DVAs found close to 1 or more CCMs, which is the association commonly reported in previous literature.[3,12,14-16] The presence of a DVA remote from any CCM was noted but was not considered part of the analysis.

A comparison was made of familial and sporadic CCMs to determine if the presence of a DVA was statistically significant by using a Fisher exact test. Numbers and sizes of CCM lesions per patient were calculated. CCM size in the sporadic and familial groups was compared by using 2-sample *t* tests and Mann-Whitney-Wilcoxon tests (the latter to account for numerous outliers in the data); analysis was performed for familial and sporadic groups regarding mean, median, minimum, and maximum size per patient. A further CCM size comparison was made in the sporadic group between CCMs with DVAs and those without DVAs. Statistical analyses were done by using SAS software, Version 9.2.

Results

There were 112 patients with CCMs, 50 males and 62 females, ranging from 1 to 86 years of age. Of the 112 patients, 81 were classified as familial (35 male, 46 female; mean age, 33 years; range, 1–78 years); 18, as sporadic (8 male, 10 female; mean age, 37.6 years; range, 1–86 years); and 13, as indeterminate (7 male, 6 female; mean age, 37.9 years; range, 2–79 years). There were a total of 2212 malformations: 2176 familial, 21 sporadic, and 15 indeterminate. In the familial group, there were 3 patients with 168, 316, and 405 lesions each; this finding explains much of the difference between the mean lesion number of 26.9 and the median of 7. Although lesion counting was performed with 2 observers, these very large numbers are subject to counting error. The sporadic group had a mean of 1.2 lesions per patient with a median of 1. Two patients, both in the familial group, also had a spinal cord CCM; these spinal cord CCMs were not included in the above brain CCM count or in the following analysis of brain lesions.

The comparison of CCM size between familial and sporadic groups revealed significant differences between mean ($P < .001$), median ($P < .0001$), and minimum ($P < .0001$) values by using the Mann-Whitney-Wilcoxon test; *t* test *P* values were only slightly larger and all were also highly significant. No significant difference was observed for maximum size between the 2 groups (Mann-Whitney-Wilcoxon, $P = .08$). Minimum and mean size differences were due to the numerous small lesions present in many familial cases. In a further analysis for the sporadic group, CCM mean, median, minimum, and maximum lesion size were compared for those with a DVA in close proximity to those without; exact Mann-Whitney-Wilcoxon $P = .012$ for all 4 tests. The small sample size limits the significance of this finding.

In the 18 patients determined to have sporadic CCM, 8 (44%) had a DVA closely associated with ≥1 CCM (Fig 1). In the 81 patients with familial CCM, 1 DVA was found in possible association with a CCM. In addition, 2 patients (1 familial and 1 sporadic CCM case) had a single DVA remote from any CCM. We considered these unrelated to the CCM and in the same category as having no DVA present. Two patients with familial CCMs had an apparent prominent vein near a CCM, but without the typical branching pattern of a DVA.

The Fisher exact test showed a significant difference, $P <$ .0001, between the 2 populations with respect to the presence

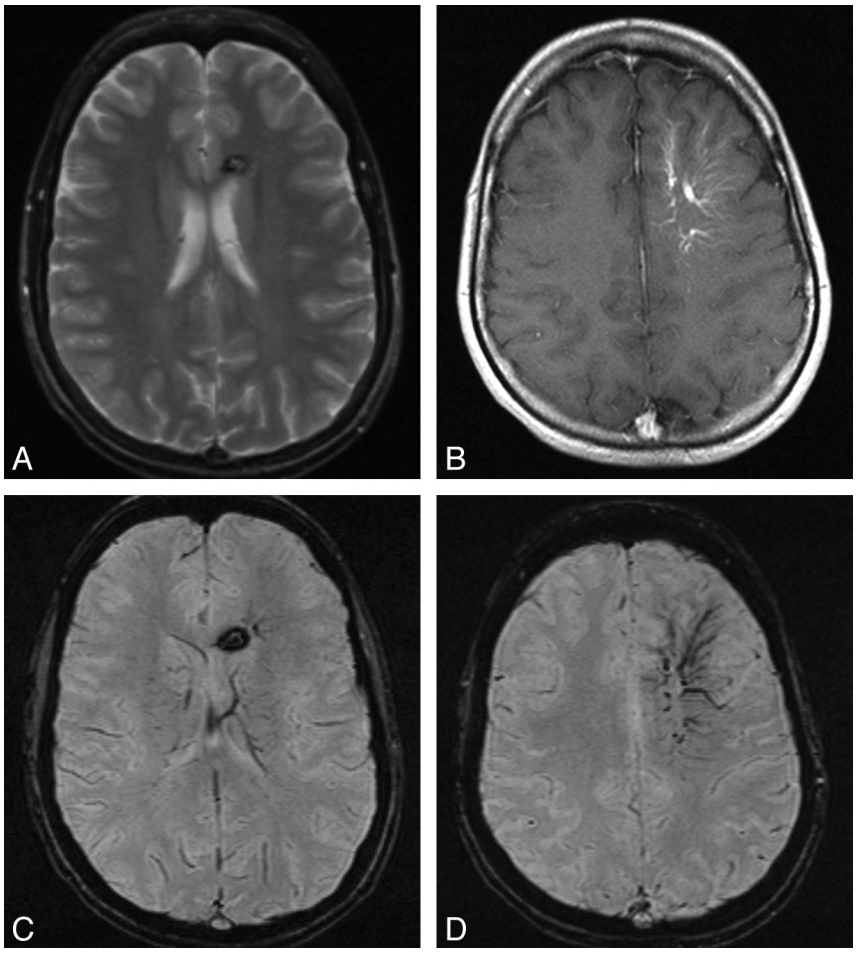

Fig 1. Sporadic CCM with a very large DVA. *A,* Axial T2 SE of a 26-year-old woman shows a CCM near the left lateral ventricle. *B,* Postgadolinium T1 shows a large DVA involving much of the left frontal lobe. *C* and *D,* SWI demonstrates very clearly the CCM and DVA without gadolinium administration.

or absence of combined DVA/CCM lesions. A more conservative analysis of only those patients who had gadolinium contrast and/or SWI (54 familial and 16 sporadic, 70 total patients), in whom there was the greatest confidence in identifying a DVA, still showed $P < .0001$. We also performed an analysis assuming that indeterminate cases were all sporadic, which is highly unlikely. Nevertheless, this worst-case scenario, which would maximize the number of sporadic cases, still produced $P < .0001$, which is highly significant.

Discussion

The findings from this study are clear: Sporadic and familial CCM groups differ with respect to their association with DVA. In the literature, while there has been limited observation and speculation on the differences,[12,19] adequate data were not previously available to answer this question with statistical confidence. Abdulrauf et al[12] studied 55 patients with CCMs and found a family history of CCM in 7 of 42 patients without a DVA and no family history in the 13 patients with both CCMs and DVAs. The difference did not achieve statistical significance ($P = .13$), and the authors suggested that a larger series might substantiate the difference in populations. Guclu et al[19] reported that in a family of 4, 2 subjects had a CCM and were gene-positive and another had a DVA and was gene-negative. The findings we present here are based on a much larger group of familial CCMs. In our large group, we found a statistical difference, $P < .0001$, for a conservative analysis. Of the >2100 lesions in 81 patients with familial CCMs, only 1 patient had a possible DVA close to ≥1 CCM. Among the 18 patients with sporadic CCM, nearly half had lesions closely associated with a DVA.

Why does this difference occur? It is possible that some sporadic cases codevelop with a DVA as mixed lesions. However, only 1 of the familial lesions may have manifested this pattern. Awad et al[3] have discussed possible pathogenetic mechanisms for mixed malformations in further detail. One possible explanation is that some sporadic CCMs result from a pre-existing DVA. Several case reports or small series have described cases in which ≥1 CCM were observed to appear or grow along 1 branch or radicle of a DVA.[22-26] It has been hypothesized that stenosis along 1 of the feeding branches of a DVA may lead to diapedesis of blood cells, followed by development of a CCM.[27] One of the sporadic cases in our study may illustrate another example of this process of a DVA followed by a CCM (Fig 2). A teenaged Hispanic boy had a large DVA in the right temporal lobe, with only a very subtle small focus of possible blood along 1 edge of the DVA on initial MR imaging. Two years later, a subsequent MR imaging study showed a typical appearance of a solitary CCM in the same location. Gene testing was negative for the *KRIT1* mutation.

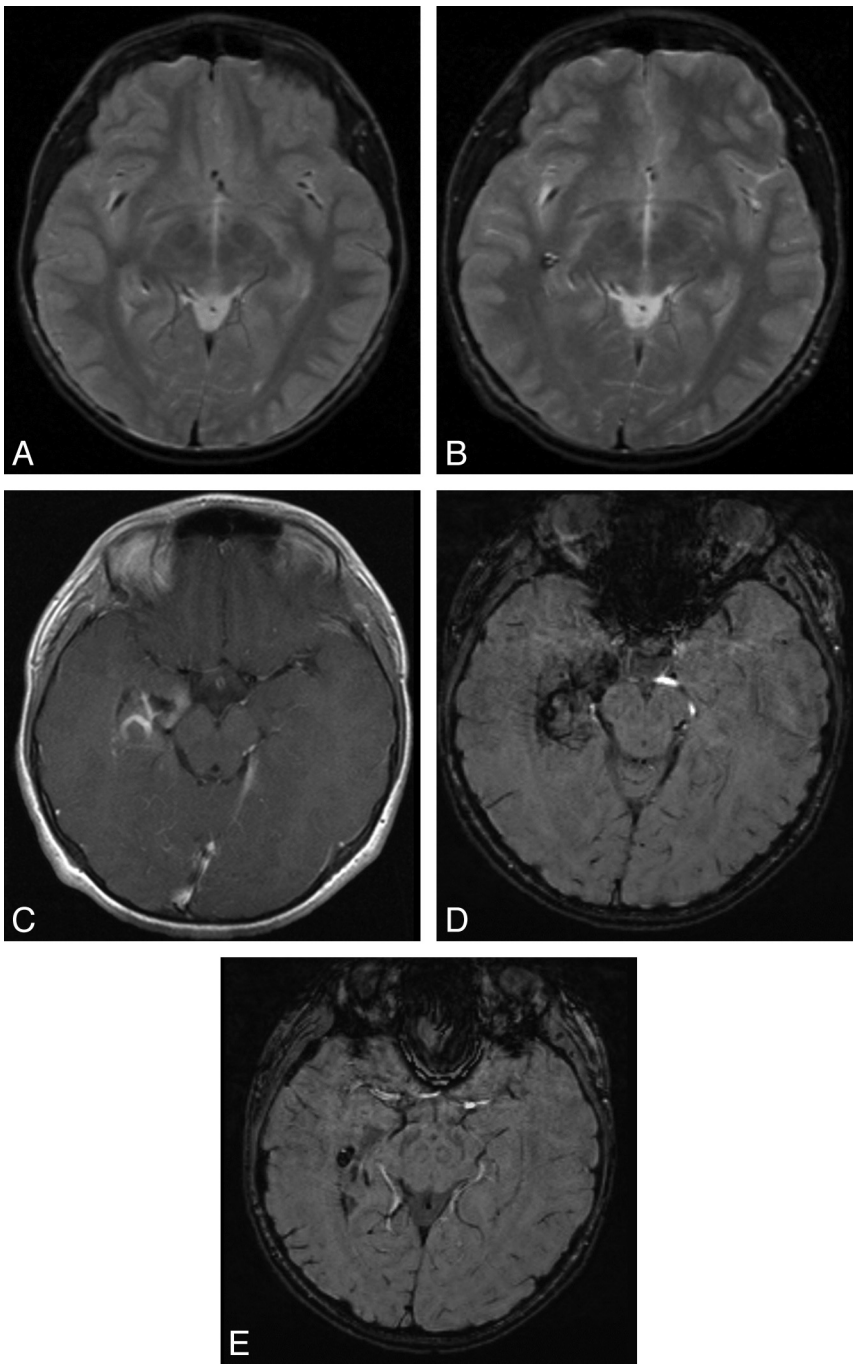

Fig 2. DVA with a sporadic CCM, which enlarged with time. *A*, Initial T2 SE of a 14-year-old boy shows only a small subtle focus of low signal intensity. *B*, Repeat MR imaging 2 years later shows a more typical reticulated or popcorn-like appearance of a CCM. *C*, The associated DVA is best seen at a slightly lower level (T1 postgadolinium). *D* and *E*, The DVA and CCM are clearly demonstrated on SWI on the second study.

The hypothesis that sporadic CCM may result from a DVA is consistent with the significant difference between the 2 groups that we studied, but the evidence is still limited.

The association of a DVA with a CCM in the sporadic cases studied was even higher (44%) than the roughly 20%–30% reported in the literature. There are several possible reasons. Particularly with a relatively small sample size, the difference may simply be due to chance. Since ending this retrospective study, though, our experience has continued to show a similar or higher association of a DVA with a solitary CCM (4 of the next 7 sporadic CCM cases had an associated DVA, for a combined frequency to date of 12 of 25 cases or 48%). Improved detection of DVAs with advances in imaging technology may be 1 explanation. The use of 3T MR imaging and of SWI, in some cases, may have further improved the definition of vascular lesions. Another possibility is that previous reports regarding the frequency of combined CCM/DVA lesions were based on a mixed population, including some familial cases. On the basis of our findings, familial cases would be expected to dilute the positive cases and thus lower the percentage.

This study is limited by its retrospective nature. Clinical information from charts was limited, and 13 cases had to be

classified as indeterminate for this reason and were excluded from most comparative analyses. However, we were confident in the classification of the remaining 99 cases. It is possible that ≥1 of the small foci of low T2 signal intensity in patients with many lesions, especially those seen only on GR, could by chance have represented other lesions, such as capillary telangiectasia, but the conclusions would not be altered by a few such lesions out of hundreds. The numerous small GR-only lesions were seen in patients who also had larger classic CCMs and are consistent with prior pathology experience confirming small CCMs along with large ones. Imaging techniques were not uniform across the group. The actual number of CCM lesions may be undercounted in some cases, especially in those for whom gradient imaging was not available. For more accuracy and consistency in studying changes in CCM size and number with time, prospective studies with consistent techniques, including gradient T2 sequences and especially SWI, are necessary.

Despite these limitations, the fundamental conclusion regarding the lack of association of DVA in the familial CCM population is highly statistically significant. There was 1 case of a possible DVA in a patient with multiple CCMs; however, the characteristic medusa pattern was not observed and the finding may well be a variant of a draining vein. Additionally, that patient had >70 CCMs, with the highest attenuation in the area of the DVA, suggesting it would be difficult to determine the CCM/DVA causal relationship; and there remains the possibility of an incidental case of a DVA formation in the presence of familial CCMs, especially in a series this large. However, our statistical analysis was performed assuming that this case was an example of a true association of DVA and CCM. Even so, the analysis showed that familial CCMs are usually not associated with DVAs.

DVA can occur on a congenital basis in the familial CCM groups and in the general population, suggesting that later acquisition of a CCM secondary to a DVA might be possible in familial cases. Because of the implications of a concomitant DVA for surgical management, due to risk of venous infarct, we continue to evaluate presurgical CCM candidates with gadolinium for a possible DVA. The detection of combined lesions in familial cases is, nevertheless, expected to be very low. Note that on clinical MR imaging studies, DVAs are relatively common findings, most of which are incidental. We do not recommend repeat MR imaging for following a DVA without an associated CCM unless new symptoms appear. Longitudinal research studies to better determine the natural history of the DVA-CCM relationship would help clarify more of the biology of these vascular entities.

Elucidation of the pathogenesis and pathobiology of familial CCM may lead to improved patient management and informed decision making. Examples include concerns related to pregnancy and type of delivery, surgical complications, hypertension management, bleeding disorders, anticoagulation management, and control of seizures and pain. Understanding the role of SWI in the detection of DVA/CCM may eliminate the need for gadolinium and reduce scanning time; in the pediatric population, this change would reduce or eliminate the need for sedation in some patients.

With widespread use of MR imaging, the diagnosis of CCM is made on the basis of characteristic appearance, and pathologic confirmation is rare. For example, some patients who undergo cranial radiation therapy develop lesions on MR imaging with an appearance typical of cavernous malformations.[24,28-30] With radiation, there is also the possibility of endothelial damage, stenosis, and diapedesis of blood cells. In familial CCM, presumably the genetic mutations lead to altered biologic factors that result in CCM formation; the pathogenesis is under investigation.[31] Also, the marked increase in the total number of CCM lesions in familial cases compared with sporadic ones supports a different mechanism of angiogenesis. It is likely that cavernous malformations, as identified on MR imaging, are an end result of several possible initiating causes of vascular change: DVA, perhaps with stenosis in 1 branch; radiation; and genetic factors such as the *KRIT1* and other known mutations. Understanding the factors involved in CCM promotion and growth may be important in prognosis and perhaps treatment.

Conclusions

Our study found a difference between sporadic and familial cases of CCMs with respect to DVAs: In sporadic cases of CCM, nearly half are associated with an immediately adjacent DVA, but in familial cases, there is near absence of associated DVAs.

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