Infratentorial Developmental Venous Abnormalities and Inflammation Increase Odds of Sporadic Cavernous Malformation

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Goal: Sporadic brain cavernous malformations commonly correlate with developmental venous anomalies; however, developmental venous anomalies may exist without cavernous malformations. Infratentorial location and specific angioarchitectural features of the developmental venous anomaly increase the odds of a concomitant malformation. Animal data also suggest chronic inflammatory disease, oxidative stress, and angiogenesis promote cavernous malformation development. We sought to determine potential clinical and radiologic factors promoting development of sporadic cavernous malformations. *Methods:* One hundred and forty-five patients with sporadic, nonradiation-induced brain cavernous malformations (63 with radiologic-apparent and 82 with radiologic-occult developmental venous anomalies) were compared to developmental venous anomaly controls without associated malformation. Data collection included demographic information, comorbidities, medications at diagnosis, and location of the developmental venous anomaly and/or malformation. Logistic regression with likelihood ratios, odds ratios and 95% confidence intervals were calculated comparing malformation cases with controls. A similar analysis compared malformations with radiologic-apparent anomalies to controls. *Results:* Compared to controls, cases were more likely to have had a major infectious illness (10.3% versus 2.3%; $P = .0003$ and/or chronic inflammatory disease (31.7% versus 21.3%; $P = .0184$) prior to diagnostic magnetic resonance imaging. Infratentorial location was more common in cavernous malformation cases (31.7% versus 15.7% controls; $P \leq .0001$) with similar findings in cavernous malformation with radiologic-apparent developmental venous anomalies versus controls. *Conclusions:* Infratentorial developmental venous anomalies location, major infectious illness, and chronic inflammatory disorders increase the odds of sporadic cavernous malformation formation. Inflammation may promote local thrombosis of developmental venous anomalies, trigger angiogenic response through increased vascular permeability, or promote cavernous malformation through Toll-like receptor 4.

Key Words: Cavernous malformation—chronic inflammation—developmental venous anomaly—cavernoma—case-control

Introduction

Cavernous malformations (CMs) are angiographically occult vascular malformations that may form in the brain or spinal cord. Pathologically they consist of endothelial-lined caverns lacking normally formed endothelial tight junctions.[1]

CM may be acquired and sporadic or familial. In the sporadic form, patients typically have a single CM lesion with an associated developmental venous anomaly (DVA). In approximately 10%-30% of CM patients, the DVA is visible on standard magnetic resonance imaging (MRI) sequences.[2] However, surgical series and 7-T MRI

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Table 1. *Chronic inflammatory diseases included in study*

Chronic inflammatory disease (present prior to diagnosis of DVA or CM)	
Neurologic	• Multiple sclerosis • Vasculitis • Chronic encephalitis • Neurosarcoidosis
Pulmonary	• COPD • Chronic bronchitis • Asthma • Asbestosis, silicosis
Rheumatologic	• Systemic lupus erythematosus • Sjögren's syndrome • Vasculitis • Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Myositis Sarcoidosis
Gastrointestinal	• Gingivitis • Gastritis • Barrett's esophagitis • Inflammatory bowel disease • Celiac disease • Chronic cholangitis (primary sclerosing cholangitis) • Primary biliary cirrhosis • Chronic cholecystitis • Chronic hepatitis • Chronic pancreatitis • Chronic sclerosing sialadenitis
Endocrine	• Hashimoto's thyroiditis • Grave's disease • Type 1 diabetes mellitus
Genitourinary	• Pelvic inflammatory disease • Lichen sclerosus
Bone	• Osteomyelitis (chronic)
Infectious	• AIDS • Schistosomiasis • Human papilloma virus infection • Lyme disease

data suggest that every sporadic brain CM has an associated DVA.[3-5]

Current opinion is that the DVA causes the CM to form sometime during life,[2] and there are well-documented cases of CMs developing adjacent to previously known DVAs.[6,7] Some have hypothesized that the DVA causes venous hypertension, and red-cell diapedesis occurs in the local tissue with resultant angiogenic response.[2,6,8-10] Others hypothesize that local hypoxia due to venous hypertension triggers angiogenesis.[11] It is not clear why some patients with DVA develop coexistent cavernous malformations while others do not. Proposed radiologic risk factors include infratentorial location, stenosis of the dominant collecting vein, venous outflow obstruction, tortuosity of the collecting vein, and the multiplicity of medullary veins.[2,8,12-14] Less data are available on clinical factors that also may play a role.

Animal models based on the familial form of CM demonstrate that factors other than the abnormal gene are necessary for lesion development. Hypothesized factors include oxidative stress, inflammation, and abnormal angiogenesis.[15] There are no animal models of the sporadic type of CM. We hypothesize that the inflammation or modifiers of inflammation may influence patients with DVA to develop concomitant CM.

We aimed to determine whether acute and chronic inflammatory conditions, select medication use, and lesion location are more common in patients with sporadic, brain CM versus DVA controls without concomitant CM in a case-control design.

Methods

CM Patient Selection

An IRB-approved ongoing prospective registry of consecutive patients with CM seen at our institution has been kept since 2015. All patients or their authorized representatives provided written consent for the use of their medical information for research purposes. Since familial CMs are not associated with DVAs, we excluded patients with familial CMs. We further excluded those CMs felt to be caused by radiation and those located in the spinal cord. Because all sporadic brain CMs presumptively have an associated DVA,[3,5] we felt all cases could be compared to a control group of patients with DVA alone. We designated those with a radiologic DVA visible on standard sequences as "CM with radiologic apparent DVA" and those who had a presumptive DVA, but it was not radiologically apparent on standard imaging as "CM with radiologic occult DVA." We did a secondary analysis of those with CM with apparent radiologic DVA versus DVA controls as well.

DVA Patient Selection

Approximately 300 consecutive patients seen at Mayo Clinic with a radiologic diagnosis of DVA, but no evidence of CM was reviewed.

Clinical Data

Clinical data collected included age at first diagnostic MRI demonstrating the DVA or CM, sex, history of an infectious illness requiring hospitalization prior to diagnostic MRI, tobacco use (current, past, and never), and chronic inflammatory diseases diagnosed prior to the MRI (Table 1).[16-20] We also assessed chronic use of antiplatelet agents, anticoagulants, statins, and vitamin D prior to the diagnostic MRI.

Table 2. *Comparison of sporadic brain CM (with radiologic visible and radiologic occult DVA) versus DVA controls*

	Sporadic brain CM cases = 145	DVA controls = 300	*P* value	Odds ratio
Age at diagnosis (years)	Median: 43.2(5.75-81.4)	Median: 43.9(15.6-86.9)	.3436	—
Sex (female)	88 (60.7%)	160 (53.3%)	.1437	1.35 (.90-2.02)
Radiologic apparent DVA	63 (43.4%)	300 (100%)	<.0001*	—
Radiologic apparent infratentorial DVA	25 (17.2%)	47 (15.7%)	.6064	1.15 (.67-1.96)
Infratentorial Location	46 (31.7%)	47 (15.7%)	<.0001*	2.56 (1.6-4.10)
Major Infectious Illness	15 (10.3%)	7 (2.3%)	.0003	4.8 (1.92-12.1)
Chronic inflammatory disease	46 (31.7%)	64 (21.3%)	.0184*	1.75 (1.11-2.73)
Use of Aspirin	25 (17.2%)	60 (20.0%)	.6194	.87 (.52-1.47)
Use of Statin	19 (13.1%)	52 (17.3%)	.3633	.77 (.43-1.36)
Use of Vitamin D	41 (28.3%)	94 (31.3%)	.6119	1.12 (.71-1.76)
Anticoagulant	3 (2.1%)	22 (7.3%)	.0407	.27 (.4-1.10)
Use of antiplatelet or anticoagulant	26 (17.9%)	73 (24.3%)	.1169	.67 (.4-1.10)
Current or past tobacco	36 (24.8%)	106 (35.3%)	.0197*	.59 (.38-.92)

*$P < 0.05$.

Radiologic Data

We reviewed the initial diagnostic MRI in patients with CM and recorded the location of the CM (infratentorial versus supratentorial) and presence of a visible or radiologically apparent DVA. In the group of patients with DVA alone, we recorded the location (infratentorial versus supratentorial) and reason for MRI.

Data Analysis

This was a case-control study. Descriptive statistics, including means, standard deviations, and frequencies, were utilized for patient characteristics and presenting symptoms. Univariate and multivariate logistic regression models were used, and we report the odds ratio, 95% confidence intervals, and likelihood ratio *P* values.

Results

We identified 145 CM cases (63 with apparent radiologic DVA and 82 with occult radiologic DVA) and 300 DVA controls. Indication for DVA control group MRI included neoplastic evaluation (26.7%), seizure (9.7%), headache (17.3%), dizziness/ataxia/vertigo (7.3%), acquired brain disorder (10.7%), degenerative brain disorders or encephalopathy (6.3%), neurologic symptoms/exam signs (13.0%), and noncancer systemic evaluation (9.0%).

Clinical and radiologic information is presented in Table 2. The average age at diagnosis was similar in cases and controls (43.2 versus 43.9 years, $P = .3436$). There was a nonsignificant predominance of females in the cases versus controls (60.7% versus 53.5%, $P = .1437$). Cases were more likely than controls to have had a major infectious illness (10.3% versus 2.3%; .0003) or chronic inflammatory disease (31.7% versus 21.3%; $P = .0184$) prior to the diagnosis. Cases were less likely to have current or prior tobacco exposure (24.8% versus 35.3%; $P = .0197$). Fewer cases than controls were on anticoagulation prior to diagnosis (2.1% versus 7.3%; $P = .0407$), but there was no significant difference between cases and controls in use of aspirin, statin, or vitamin-D supplementation prior to the

Table 3. *Comparison of sporadic brain CM with radiologic apparent DVA versus DVA controls*

	Sporadic CM with radiologic apparent DVA Cases = 63	DVA controls = 300	*P* value	Odds ratio
Age at diagnosis	39.4 (18-71.8)	43.7 (15.6-86.9)	.3580	
Sex (Female)	43 (68.2%)	160 (53.3%)	.0318*	1.88 (1.06-3.34)
Number with radiologic apparent infratentorial DVA	25 (39.7%)	47 (15.7%)	<.0001*	3.54 (1.96-6.41)
Major Infectious Illness	5 (7.9%)	7 (2.3%)	.0333*	3.6 (1.11-11.8)
Chronic inflammatory disease	20 (31.7%)	64 (21.3%)	.0636	1.75 (.96-3.2-)
Use of Aspirin	7 (11.1%)	60 (20.0%)	.1239	.52 (.22-1.19)
Use of statin	7 (11.1)	52 (17.3%)	.2631	.62 (.27-1.43)
Use of vitamin D	19 (30.2%)	94 (31.3%)	.4586	1.26 (.68-2.33)
Anticoagulant	1 (1.58%)	22 (7.3%)	.1272	.21 (.03-1.57)
Use of any blood thinner	9 (14.3%)	73 (24.3%)	.0811	.51 (.24-1.08)
Current or past tobacco	12 (19.0%)	106 (35.3%)	.0104*	.41 (.21-.81)

*$P < 0.05$.

Table 4. *Types of inflammatory diseases in cases (with radiologic apparent and occult DVA) versus DVA controls***

	Sporadic brain cases of CM (n = 145)	DVA controls (N = 300)	*P* value
Neurology	1 (.7%) Multiple sclerosis[1]	20 (6.7%) Multiple sclerosis[17] Vasculitis[2] Neurosarcoid[1]	.0236*
Gastrointestinal	10 (6.9%) Inflammatory bowel disease[7] Barrett's esophagus[1] Autoimmune hepatitis[2]	4 (1.3%) Inflammatory bowel disease[3] Celiac disease[1]	.0027*
Rheumatology	6 (4.1%) Sjögren's[2] Lupus[1] Rheumatoid arthritis[2] Connective tissue disease[1]	19 (6.3%) Psoriatic[3] Sjogrens[4] Myositis[1] Antiphospholipid antibody syndrome[2] Lupus[4] Vasculitis[2] Rheumatoid arthritis[2] Connective tissue disorder[1]	.05096
Endocrine	13 (9.0%) Type 1 diabetes[1] Hashimotos thyroiditis[11] Graves[2]	8 (2.7%) Type 1 diabetes[3] Hashimoto's thyroiditis[4] Graves disease[1]	.0031*
Pulmonary	19(13.1%) COPD[2] Asthma[17]	17 (5.7%) COPD[8] Asthma[9]	.0065*
Infectious	5 (3.4%) Lyme disease[3] Herpes simplex infection[1] Severe, recurrent otitis media[1]	0 (0)	.0032*
Genitourinary	1 (.7%) Interstitial nephritis[1]	0	—
Multiple	11 (7.6%)	4 (1.3%)	.0010*

*$P < 0.05$.
**Some patients had multiple inflammatory conditions and thus were added to each category they fit into. However, no patient was included twice in the same category.

diagnosis. Cases were more likely than controls to be infratentorial (31.7 % versus 15.7%; $P < .0001$). When controlling for age and sex, multivariate logistic regression revealed that infratentorial location, radiologic apparent infratentorial DVA, major infectious illness, and chronic inflammatory disease remained significant predictors of CM compared to DVA controls.

We performed similar analysis on CM patients with radiologic apparent DVA on standard sequences versus DVA controls (Table 3). Univariate factors associated with both a CM and DVA include female sex (68.2% versus 53.3%; $P = .0318$), infratentorial DVA location (39.7% versus 15.7%; $P < .0001$), and major infectious illness (7.9% versus 2.3%; $P = .0333$). Chronic inflammatory disease was notably more common in the CM group (31.7% versus 21.3%; $P = .0636$). Past or current or tobacco use was higher in the control group (35.3% versus 19.0%; $P = .0104$). There was no significant difference in cases and controls in age at presentation, use of aspirin, anticoagulation, statin, or vitamin D.

We further evaluated the types of chronic inflammatory diseases in both CM cases (radiologic apparent and occult DVA) and DVA controls (Table 4). There were more DVA controls than cases with neurologic inflammatory disease (6.7% versus .7%; $P = .0236$) and more cases than controls with gastrointestinal (6.9% versus 1.3%; $P = .0027$), pulmonary (13.1% versus 5.7%; $P = .0065$), endocrine (9.0% versus 2.7%; $P = .0031$), infectious (3.4% versus 0; $P = .0032$), genitourinary (0.7% versus 0), and multiple (7.6% versus 1.3%; $P = .0010$) inflammatory diseases.

Discussion

It is known that patients with DVA may develop CM, but the factors leading to CM formation from a pre-existing DVA are a matter of speculation. While some have suggested the location and venous angioarchitecture may play a role,[2,8,12-14,21] potential concomitant clinical factors are largely unknown. Here, for the first time, we report a higher incidence of pre-existing inflammatory conditions in patients with sporadic CMs than in an age-matched DVA control group without CM. This suggests that acute and chronic inflammatory conditions also play a role in pathogenesis of sporadic CM.

We found that patients with a previous history of major infectious illness had a nearly 5-fold increased risk of developing a CM, and a patient with a chronic inflammatory disorder was nearly twice as likely to develop a CM. Three theories might help explain this potential relationship: inflammation-enhanced vascular permeability, the role of Toll-like receptor 4 (TLR4), and the potential for inflammation to increase risk of venous thrombosis within a DVA.

One theory of why patients with DVA develop CM is that red-cell diapedesis results in local microhemorrhage and subsequent triggering of an angiogenic response. There are further theories that DVAs with draining vein stenosis and/or those with venous hypertension proven on perfusion imaging[8,14,21] are more likely to have a concomitant CM because the venous hypertension increases local angiogenesis through either local hypoxia or red-cell diapedesis.[14,21] Inflammation also increases the permeability of the endothelium,[22] and perhaps this mechanism accelerates the red-cell diapedesis.

Another potential mechanism linking inflammation and CM formation is TLR4. Recently, TLR-4 has been implicated in the pathogenesis of CMs.[23] TLR4 responds to bacterial lipopolysaccharide and induces a downstream inflammatory response. Chronic obstructive pulmonary disease patients are often colonized by respiratory bacteria, and these patients may have chronic stimulation of TLR4.[24] TLR4 may also be activated in asthma.[25] We found that cases were more likely to have respiratory chronic inflammatory disease, which is a potential correlation. However, tobacco smoking also increases TLR4, and we saw that controls had a higher likelihood of being a past or current smoker. However, we believe this finding is due to imaging-indication bias (see limitations below).

A third theory suggests that inflammation increases the risk of venous thrombosis in a prone DVA, which may lead to additional venous hypertension and subsequent angiogenic response. The combination of the initial angioarchitecture may predispose to thrombosis under certain conditions.

Infratentorial DVA location increased the risk of a concomitant CM 2.6 times. Several prior studies have also suggested infratentorial DVA location as a risk factor for CM development.[12] The reason is not clear but may correlate with the size and tortuosity of DVA in this location.

We found that controls were more likely to have a history of current or past tobacco use and neurologic inflammatory disease. We believe this is due to bias. DVAs are typically identified on contrasted MRI scans, but not all patients undergoing MRI receive contrast. Approximately one quarter of the patients in the control group underwent brain imaging with contrast for cancer or cancer screening, which may explain the preponderance of tobacco users in the control group. In addition, neurologic inflammatory disease is detectable only with contrast and thus may be a confounder rather than correlation.

In univariate analysis, use of anticoagulation reduced the odds of a patient having a concomitant DVA. Theoretically, one might wonder if anticoagulants and/or antiplatelet agents reduce the risk of thrombosis of a DVA with associated venous hypertension or stasis and, consequently, reduce the risk of CM formation or reduce symptoms from an existing CM. This complements other studies suggesting use of antithrombotics is not associated with increased bleeding in CM and, in fact, lowers the risk.[26,27] This is exploratory, and the numbers were small. We found no difference in the use of statin, aspirin, or vitamin D amongst cases and controls.

There are many limitations to our study. The ideal study would identify all patients with DVA and follow them prospectively. However, that type of study would be costly, would take many years to complete, and would enroll an unrealistically high number of patients; thus, we performed a case-control study. Based on surgical and 7-T MRI studies, we assumed all sporadic CM have a DVA, but our control group had a radiologically identified DVA on standard sequences. Because of this potential limitation, we opted to perform analyses of the entire group and also separately in those CM with radiologic apparent DVA to verify our findings. Because patients with chronic inflammation may be treated with immunosuppressants that may have an effect on pathogenesis, we attempted to collect data on immunosuppressant use. However, the data for the control group relied on chart review alone whereas the CM group had been interviewed. Thus, we felt the data may be biased due to ascertainment. Our study may be further biased by the population undergoing clinically indicated MRIs in the control group, tertiary care-referral bias, and ascertainment bias (chart review of concomitant illnesses). However, this is unlikely as the demographics of the controls reflect those individuals diagnosed with incidental DVAs.

In conclusion, we found infratentorial location, major infectious illness, and chronic inflammatory disorders increase the odds of a cavernous malformation formation in the sporadic form. Inflammation may increase risk of local thrombosis of the DVA, trigger an angiogenic response, or act through TLR4 to promote CM formation.

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