Patients with cranial dural arteriovenous fistulas may benefit from expanded hypercoagulability and cancer screening

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OBJECTIVE Cranial dural arteriovenous fistulas (DAVFs) have been associated with dural sinus occlusion, and previous reports have suggested the association of hypercoagulability with some cases. But the prevalence of a hypercoagulable state has not been systematically analyzed in conjunction with laboratory markers and clinical manifestations, including history of thromboembolism or systemic malignancy. The authors hypothesize that laboratory or clinical evidence of a hypercoagulable state, including cancer, is commonly identifiable in consecutively identified patients with DAVFs, with implications for clinical management.

METHODS The retrospective cohort study included all patients older than 17 years with cranial DAVFs diagnosed at University of Chicago Medicine during a 6-year period, whose medical records and imaging results were reviewed for objective laboratory or clinical evidence of a hypercoagulable state, including malignancy. Each case was analyzed for implications on clinical management. Data were analyzed in relation to a systematic review of the literature on this association.

RESULTS Fifteen (88%) of 17 cases of DAVFs had laboratory (n = 8) or clinical evidence of a hypercoagulable state (thromboembolism [n = 8] or cancer [n = 6]). This hypercoagulability or cancer impacted clinical care in all 15 cases.

CONCLUSIONS An underlying hypercoagulable state manifested by laboratory testing or clinically, including cancer, is staggeringly common. It is important to recognize this association, along with its impact on the management of the DAVFs and systemic diseases.

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KEY WORDS dural arteriovenous fistula; coagulation; hypercoagulable condition; cancer; oncology; vascular disorders

DURAL arteriovenous fistulas (DAVFs), also known as malformations or shunts, have long been believed to arise in the setting of dural sinus thrombosis and venous hypertension.^{1,5,7,13,14,17,34,40} DAVFs have also been reported in the setting of postoperative sinus manipulation, head trauma, and less frequently in the setting of meningiomas.^{4,8,12,18,30}

Several reports have identified hypercoagulable states in patients with DAVFs, including prothrombotic genes, or

acquired hypercoagulopathy associated with malignancy, pregnancy, or infection.^{23,25,30,36} However, the prevalence of such states could not be gleaned from case reports, and reported series often included inconsistent case selection, and variable and often limited hypercoagulability surveys.^{14,23,25,35} Recent evidence-based guidelines for the clinical management of DAVFs did not consider or address an association with a hypercoagulable state.²⁹ We hypothesize that hypercoagulable factors are common in

ABBREVIATIONS DAVF = dural arteriovenous fistula; DSA = digital subtraction angiography; DVT = deep vein thrombosis; MRA = MR angiography; MRV = MR venography; PE = pulmonary embolism.

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FIG. 1. Axial T1-weighted postcontrast MR image (A), axial FLAIR MR image (B), and anteroposterior projection of the left vertebral digital subtraction angiogram (C) from a 68-year-old man with a DAVF draining with retrograde Galenic leptomeningeal venous drainage, who presented with congestive venous encephalopathy including cognitive, gait, and midbrain (gaze) signs and symptoms (Case 2, Table 1). The MRI revealed prominent deep veins and FLAIR abnormalities in the deep cerebral hemisphere and midbrain from congestive venous encephalopathy. Angiography revealed a major arterial supply from the dorsal meningeal branch of the vertebral artery. The lesion was successfully obliterated with transarterial embolization. Laboratory tests identified a previously unsuspected heterozygous factor V mutation and antiphospholipid antibody and elicited a history of lower extremity DVT. The patient is receiving lifelong therapeutic anticoagulation treatment, with no recurrent sequelae during 5 years of follow-up after verified DAVF occlusion, regression of venous encephalopathy, and complete neurological recovery.

consecutive cases of cranial DAVFs, and that they impact clinical management.

Methods

This study was approved by the local IRB, which waived the need for patient consent in this study.

Patient Selection and Clinical Features

The retrospective cohort study identified all patients (> 17 years of age) diagnosed with cranial DAVFs at our institution during a 6-year period (January 2010 to December of 2016), based on screening of management case logs, ICD-9 diagnosis code 447.0, or key word survey (“dural” and “arteriovenous”) in radiology reports. The diagnosis of DAVF was confirmed by review of digital subtraction angiography (DSA) or MRI, MR angiography (MRA), and MR venography (MRV). Figure 1 shows an illustrative case. Patient demographics including age at diagnosis, sex, smoking status, and comorbidities were reviewed. Clinical and imaging features of the DAVF were noted, including referral source, symptoms at presentation, and Borden class.⁵

Hypercoagulability

There was no standardized policy of screening for hypercoagulability during the period of the study. However, because of our awareness of previous case reports and reported associations, there was a low threshold of assessing for a hypercoagulable state. At the time of presenting to the neurovascular team, the patient’s clinical history was assessed for any evidence of known hypercoagulability and the laboratory workup was ordered in conjunction with the clinical care of the DAVF at first visit. Clinical evidence was specifically sought from the clinical record, including any history of prior venous thromboembolic events and/or the presence of malignancy. Thromboembolic events included a history of deep vein thrombosis

(DVT), pulmonary embolism (PE), or dural sinus thrombosis at any time prior to or in conjunction with a diagnosis of DAVF. Thromboembolic events were adjudicated by confirmatory imaging evidence (lower extremity Doppler ultrasonography, CT or venous angiography, or MRI/MRA/MRV). The medical oncology team adjudicated the cancer diagnosis.

Laboratory markers of a venous hypercoagulable state, when assessed, included the following test panel according to established clinical protocols at our institution:^{10,22} 1) prothrombin gene mutation G20210A; 2) antiphospholipid antibodies including 1 or more of the following: lupus anticoagulant, anticardiolipin, antibeta 2 glycoprotein 1, and antiphosphatidylserine antibodies; 3) abnormal homocysteine level; 4) protein C deficiency; 5) protein S deficiency; 6) APC resistance/factor V Leiden mutation; 7) elevated factor VIII; and 8) antithrombin III.

Smoking status or history of tobacco products was also reviewed. However, smoking alone was not considered a criterion for hypercoagulability.

Systematic Literature Review

A systematic literature review was completed using the English electronic databases MEDLINE and Scopus with the word search (“dural arteriovenous fistula” OR “dural arteriovenous fistulae” OR “dural arteriovenous malformation”) AND (“thrombophilia” OR “coagulation” OR “hypercoagulability”). We included all case series with more than a single case report. Papers addressing spinal DAVFs exclusively and pediatric series were excluded. Cranial cases were considered separately, whenever possible, in series that included both cranial and spinal DAVFs.

Results

Patient Characteristics

Seventeen consecutive adult patients (age > 17 years)

TABLE 1. Patient and DAVF characteristics, clinical evidence of thromboembolism or cancer, and laboratory evidence of hypercoagulable state

Case No.	Age at Presentation (yrs), Sex	Presentation (referring service)	Borden Classification	History of Smoking	Laboratory Evidence of Hypercoagulability	Clinical Thromboembolism	Malignancy	Factors Positive
1	78, M	VCE (ED)	II	Yes	Yes (elevated homocysteine)	No	No	1
2	68, M	VCE (neurology)	II	Yes	Yes (heterozygous factor V, antiphospholipid antibody)	Yes*	No	3
3	41, F	VCE (neurology)	II	No	Yes (protein S deficiency)	Yes*	No	2
4	80, M	VCE (oncology)	III	Yes	Lab tests not done	No	Lung cancer	1
5	64, M	Cranial neuropathy (ophthalmology)	I	No	Lab tests not done	No	No	0
6	51, F	Pulsatile tinnitus (primary care)	II	No	No	Yes*	No	1
7	43, M	ICH (ED)	III	Yes	No	Yes*	Thyroid cancer	2
8	58, M	VCE (ED)	II	Yes	Lab tests not done	Yes†	Nasopharyngeal cancer	2
9	54, F	VCE (neurology)	II, III (2 different DAVFs)	No	Yes (elevated factor VIII)	Yes*†	No	3
10	70, M	VCE (neurosurgery)	I, II (2 different DAVFs)	Yes	Yes (activated protein C resistance)	Yes†	No	2
11	67, M	ICH (ED)	II	Yes	Lab tests not done	No	No	0
12	63, M	ICH (neurology)	III	Yes	Lab tests not done	No	ALL	1
13	76, M	VCE (neurology)	III	Yes	Lab tests not done	No	Colon cancer	1
14	65, F	Pulsatile tinnitus (primary care)	I	Yes	Yes (antiphospholipid antibody)	No	Breast cancer	2
15	47, M	ICH (neurology)	II	No	Lab tests not done	Yes*	No	1
16	75, F	Pulsatile tinnitus (primary care)	I‡	Yes	Yes (prothrombin G20210A mutation, anticardiolipin antibody)	No	No	2
17	62, F	Cranial neuropathy (neurology)	I	Yes	Yes (protein S deficiency)	No	No	1

ALL = acute lymphoblastic leukemia; ED = emergency department; ICH = intracerebral hemorrhage; VCE = nonhemorrhagic venous congestive encephalopathy.

* History of DVT or PE.

† History of acute sinus thrombosis.

‡ Meningioma occluding venous sinus involved in DAVF.

were identified to have cranial DAVFs and were included in this study. The institution's Neurovascular Surgery and Neurointerventional Programs managed these cases. The diagnosis of DAVF was established or confirmed by DSA in 16 cases, and by MRI/MRA/MRV in 1 case that was managed palliatively because of associated malignancy.

The mean patient age at the time of diagnosis was 62 years (range 33–80 years). Eleven patients (65%) were male and 6 patients (35%) were female. Four patients presented with intracerebral hemorrhage and 8 had nonhemorrhagic cerebral venous congestive encephalopathy, and all 12 of these patients harbored retrograde leptomeningeal venous drainage (Borden Class II or III). Five patients had minor symptoms (2 with cranial neuropathy, 3 with pulsatile tinnitus), and all but 1 had a Borden Class I lesion without leptomeningeal venous drainage. Twelve (71%) of the 17 patients had a history of smoking. None of the patients had a noted history of significant head trauma or pregnancy in the year preceding DAVF diagnosis.

Prevalence of Hypercoagulability

Fifteen (88%) of the 17 patients had an associated hypercoagulable state based on clinical or laboratory criteria (Table 1). Eight patients (47%) had evidence of clinical thromboembolism (5 had prior DVT or PE, 2 had prior acute dural sinus thrombosis, and 1 had both a prior DVT and sinus thrombosis). Six patients (35%) had cancer, 5 prior to diagnosis of a DAVF, and 1 in whom malignancy was discovered soon after. Three patients were screened for cancer (2 with a PET scan and 1 with CT of the chest/abdomen/pelvis with contrast). Of those 3 patients, 1 was found to harbor colon cancer. Of 10 patients who underwent laboratory workup of hypercoagulability, 8 (80%) tested positive for a hypercoagulable marker (8 of 17, 47% in the whole series). Laboratory hypercoagulability tests were not available in 7 patients (testing was not pursued in 4 cases as they had other clinical evidence of hypercoagulability including cancer, and 3 either refused test-

TABLE 2. Prevalence of laboratory and clinical markers of hypercoagulability in cranial DAVFs in reported series and the current study

Study	No. of Patients w/ Cranial DAVFs	Patients w/ Hypercoagulability Marker*	Lab/Clinical Thromboembolisms	Prevalence of Hypercoagulability*	Prevalence of Lab/Clinical Thromboembolism
Kraus et al., 1998, 2000, 2002	23	6	6/3	26%	26%/13%
van Dijk et al., 2007†	40‡	Unknown	4/6	Unknown	10%/15%
Izumi et al., 2007	18	17	16/8	94%	89%/44%
Gerlach et al., 2008†	25	Unknown	10/7	Unknown	40%/28%
Current study§	17	15	8/8/6	88%	47%/47%/35%

* Number and prevalence of cases with laboratory and/or clinical history of thrombotic events. Hypercoagulability testing varied and often included fewer tests or clinical factors than considered in the current study. Cancer association was only sought in the current study.

† Prevalence of total number of patients with hypercoagulability could not be calculated.

‡ Authors did not separate patients into cranial and spinal DAVFs, but we opted to include the study due to its large sample size.

§ Laboratory/clinical thromboembolism/cancer.

ing or were lost to follow-up). Eight of the 17 patients in this series had more than 1 clinical or laboratory marker of hypercoagulability at the time of DAVF diagnosis, including the 2 cases with 2 distinct DAVFs. Eleven (73%) of the 15 patients with a hypercoagulable state were smokers, as well as 1 of the 2 without a hypercoagulable state.

Clinical care was influenced in all 15 cases in which a hypercoagulable state was identified. In each instance, there were special considerations on the timing and modality of DAVF treatment given the associated hypercoagulability or malignancy. In 10 cases, therapeutic anticoagulation was deployed for hypercoagulability after embolization or surgical disconnection of the DAVF. Decisions were needed in 6 patients with cancer about DAVF treatment, modality, aggressiveness, or timing vis a vis other cancer therapies (including conservative management of DAVF in a case in which palliative care was instituted for terminal cancer). Screening identified a previously undiagnosed hypercoagulable state by laboratory testing (in the absence of prior clinical history of thromboembolism or cancer) in 3 cases, and an unsuspected underlying malignancy in 1 case, all of whom required subsequent therapy for these conditions.

Systematic Literature Review

Our literature search yielded 124 publications with 7 case series, constituting 4 independent cohorts, reporting on the association of cranial DAVF and hypercoagulability (Table 2).^{14,15,19,23–25,39} One study of 40 patients by van Dijk et al.³⁹ did not differentiate spinal from cranial DAVF cases, but we opted to include it because it is a large series. The total number of patients with cranial DAVF was 106 (range 18–40 in the respective cohorts). There was no consistency among the studies on the extent of hypercoagulability workup. In the reported cohorts, the prevalence of abnormal findings suggesting a hypercoagulable state ranged from 15% to 94%. All the series of cranial DAVFs supported an association with a hypercoagulable state, but not all included a specific assessment of the prevalence of clinical thromboembolism, and none surveyed a potential association with cancer. None of the reported studies addressed the impact of hypercoagulability on clinical management.

Discussion

DAVFs are relatively rare, with a low detection rate compared with other intracranial vascular malformations.² Yet, DAVFs can lead to significant morbidity and mortality secondary to hemorrhagic events and/or encephalopathy related to leptomeningeal venous drainage.^{3,28} DAVFs are direct artery-to-venous sinus shunts within the dural leaflet that are believed to develop in adulthood, often in the setting of acquired dural sinus occlusion.^{5,6,38} DAVF development seems to differ in pediatric populations, where high-flow arteriovenous fistulas are associated with congenital venous anomalies, or failure of regression, of the developing venous system.⁹ While the etiology is still controversial and not fully understood, the genesis of these fistulas is likely multifactorial and related to poorly understood interactions of venous hypertension and venous sinus thrombosis.^{16,26,27,32}

Previous studies examined laboratory evidence of systemic hypercoagulability in patients with DAVFs.^{14,15,19,21,23–25,39} These studies included a broad variability in what coagulation factors were assessed, with several studies addressing a single or limited laboratory marker, and most of the case series did not systematically screen or report clinical manifestations of hypercoagulability. These inconsistencies would be expected to result in a reporting bias, underestimating the prevalence of hypercoagulability. None of the previous reports examined the association of malignancy, a known cause of hypercoagulability. Factor V Leiden mutation, leading to a resistance to activated protein C, was one of the most reported and studied hypercoagulability factors in DAVFs. After the study by van Dijk et al.,³⁹ 2 other case series studied this association.^{14,19} Gerlach et al. showed a variety of thrombophilic abnormalities in patients with DAVFs, including factor V Leiden and prothombin G20210A mutations.¹⁵ The second study, by Izumi et al.,¹⁹ did not assess for the presence of these mutations but did report an abnormal D-dimer level in 16 of 18 patients, with levels above those in a control cohort. In our study, we broadened the definition of hypercoagulability to also include a more comprehensive panel of laboratory tests, and malignancy or a manifestation of systemic thromboembolism.

In our series, 15 of the 17 patients were positive by 1

or more of these criteria, with the remaining 2 not manifesting clinical factors and not completing laboratory testing. Eight (47%) of the 17 cases, or 8 (80%) of 10 in which laboratory tests were done, had positive laboratory markers, and 8 (47%) of the 17 had a clinical history of thromboembolism.³⁹ Six (35%) of the 17 patients had an associated malignancy, including 1 patient who was found to harbor a malignancy after investigation regarding hypercoagulability. Eight patients had more than 1 marker of a hypercoagulable state. The prevalence of a positive laboratory test of a hypercoagulable state in the general population has been reported to range from 0.02% to 7% depending on the factor tested.¹¹ One study reported only 1 of 33 cases (3% prevalence) with a history of clinical thromboembolism among controls age- and sex-matched to DAVF cases.³⁹ All published DAVF series that examined a comparison with a control group confirmed a statistically significant greater prevalence of the respective tested parameters in DAVF cases.^{14,15,19,23–25,39} The prevalence of any type or stage of cancer is estimated at around 5% in the general population, 10% in those above 45 years of age, and 20% in those above 65 years of age (<https://www.cancer.gov/about-cancer/understanding/statistics>, <https://www.cancer.org/research/cancer-facts-statistics/survivor-facts-figures.html>, <https://www.census.gov/content/dam/Census/library/publications/2015/demo/p25-1143.pdf>). Based on the aforementioned data, the prevalence of a hypercoagulable state in patients with DAVFs is well above that of the general population in each of the categories.

A previous study³⁹ had opined against regular screening of patients with DAVFs for factor V Leiden and factor II G20210A mutations. This recommendation was attributed to the absence of these mutations in the majority of cases with DAVFs. We note that the study included both cranial and spinal DAVFs, and did not examine cranial lesions separately, nor did it consider hypercoagulable factors other than factor V Leiden and factor II G20210A. Nevertheless, this same study also documented a 5-fold greater prevalence of a history of clinical thromboembolic events among cases with DAVFs compared with age- and sex-matched controls. Based on our results, we advocate a wider workup of hypercoagulability for patients with DAVFs to include the aforementioned list of laboratory hypercoagulability markers, and a thorough review of a history of DVTs, PEs, and cancer, including potential screening for these conditions. Positive findings might influence clinical care, including the need for long-term anticoagulation. This would also influence the treatment modality for DAVFs, pursuing more aggressively a complete obliteration or disconnection of leptomeningeal venous drainage prior to therapeutic anticoagulation, as these features can predispose to catastrophic hemorrhage.³³

We cannot comment on the association of a hypercoagulable state in spinal DAVF cases, which were outside the scope of our study. Spinal DAVFs are fundamentally different pathologies, where perimedullary venous drainage causes myelopathy but rarely hemorrhage, in contrast to leptomeningeal venous drainage from cranial DAVFs. In fact, a report²¹ examining hypercoagulability in spinal DAVFs specifically did not identify a high association. Pediatric cases were also excluded from our study, as these

are believed to arise largely from congenital rather than acquired venous occlusion.^{20,31,37}

Our results should be interpreted with caution. As with other case series of DAVFs, the retrospective nature of the study along with the small sample size are major limitations. It was not possible to correlate hypercoagulable state with disease features or severity due to the sample size and missing workup on some of the patients. Not all patients had the full panel of laboratory workup, making it hard to assess the prevalence of individual hypercoagulable factors. However, one would expect that the incomplete assessment in our series (and the published literature) would actually underestimate the true prevalence of associated hypercoagulability. Another limitation of this study is that the majority of the patients referred to our neurovascular team had a symptomatic presentation. The fact that asymptomatic DAVFs are not well represented in the cohort is a limitation against generalizability of our findings to less symptomatic cases. Furthermore, the small sample size of patients did not allow us to conduct meaningful analysis on whether mode of presentation impacts the hypercoagulability association.

It is possible that hypercoagulability was an acute-phase reaction to brain hemorrhage or the DAVF itself. And laboratory or clinical evidence of hypercoagulability do not imply lifelong risk, particularly with treatment of malignancy, recovery from ICH, or treatment of the DAVF. Regardless of the causality and mechanistic link between DAVFs and hypercoagulability, the high association necessitates consideration of this phenomenon and integrating it in patient care decisions. Referral bias may have somehow selected cases to our team, with greater likelihood of hypercoagulability or malignancy. Such bias was mitigated by including all consecutive cases presenting to a specialized neurovascular team. We note that none of the cases were referred for DAVF diagnosis because of hypercoagulability as a primary problem, and only 1 case was referred through the oncology service. More likely, the higher prevalence of a hypercoagulable state in our series most likely reflects the broader definition that included clinical states, and the more comprehensive laboratory screening. During more than 2 decades of experience with hundreds of cases by the 2 senior authors, we had also failed to glean more than anecdotal associations until we embarked on the systematic study reported here.

The lack of a control group is another limitation, but the prevalence of hypercoagulability and malignancy in the general population is known, as addressed previously. By any measure, the staggeringly high rate of hypercoagulability or malignancy was clinically relevant and impacted management. Our study results, in conjunction with previous reports, support a recommendation that patients with cranial DAVFs need expanded hypercoagulability and cancer evaluation.

Conclusions

We have demonstrated a strong association of DAVFs and a hypercoagulable state, including malignancy. Thus, in the setting of a DAVF, both clinical and laboratory in-

vestigations might be required to uncover an underlying abnormality that could influence clinical management.

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Disclosures

The authors report no conflict of interest concerning the materi-

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Author Contributions

Conception and design: all authors. Acquisition of data: Awad, Polster, Zeineddine, Lee. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Awad. Study supervision: Awad.

Supplemental Information

Previous Presentations

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