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Letter to the Editor

Prevalence and Associations of Dural Arteriovenous Fistulae in Cerebral Venous Thrombosis: Analysis of ACTION-CVT

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Dear Sir:

Dural arteriovenous fistulae (DAVFs) represent approximately 10% of all intracranial vascular malformations[1] with an incidence of 0.16–1.04 per 100,000 person-years.[2,3] Prior studies identified an association between cerebral venous thrombosis (CVT) and DAVF although the direction of causality remains uncertain. In one series, 39% of DAVF patients had a CVT identified within an adjacent or downstream sinus,[4] and patients with DAVF have a higher prevalence of thrombophilia, implicating thrombosis in its pathogenesis.[5] We aimed to determine the prevalence and associated factors of DAVF in a large multicenter study of treated CVT.

The Anticoagulation in the Treatment of Cerebral Venous Thrombosis (ACTION-CVT) study was a multicenter retrospective study comparing outcomes among CVT patients treated with a vitamin K antagonist versus direct oral anticoagulants.[6] The study in-

cluded consecutive patients with acute CVT from January 1, 2015 through December 31, 2020. Patients were identified using the International Classification of Diseases (ICD)-9/10 codes, and diagnoses were confirmed by retrospective review of records and imaging studies. Institutional review board (IRB) approval was obtained at each center and informed consent was waived by IRB.

Abstracted patient variables are included in Table 1. Radiographic variables at time of presentation included venous infarction, cerebral edema, intracranial hemorrhage, and CVT location divided into cortical veins, superficial sinuses (superior sagittal, transverse, or sigmoid sinus), and deep sinuses (internal cerebral veins, straight sinus, or vein of Galen). Information about recanalization was abstracted from radiology reports of imaging obtained subsequent to the initial hospitalization for CVT and was subdivided into complete (full recanalization without residual thrombus), partial (improved opacification/flow but residual thrombus), and no recanalization (no change or worsening in opacification/flow). Characteristics of DAVF (laterality, location, timing, Borden classification, and treatment of DAVF) were retrospectively reviewed by individual sites.

Table 1. Characteristics of patients with and without dural arteriovenous fistulae

Characteristics	Total (n=1,024)	Dural arteriovenous fistula (n=19)	No dural arteriovenous fistula (n=1,005)	*P*
Demographics				
Age (yr)	44 (32–58)	55 (45–64)	44 (32–58)	0.03
Female sex	643 (62.8)	7 (36.8)	636 (63.3)	0.03
Race/ethnicity				
White	710/1,017 (69.8)	13/18 (72.2)	697/999 (69.8)	0.99
Black	160/1,017 (15.7)	3/18 (16.7)	157/999 (15.7)	0.99
Asian	39/1,017 (3.8)	0/18 (0.0)	39/999 (3.9)	0.99
Hispanic	102/1,013 (10.1)	1/19 (5.3)	101/994 (10.2)	0.71
Body mass index (kg/m^2)	28 (23.90–33.10)	28.4 (24.37–32.5)	28 (23.87–33.1)	0.78
Medical history				
Prior venous thromboembolism	121/1,024 (11.8)	3/19 (15.8)	118/1,005 (11.7)	0.48
Birth control use	235/1,006 (23.4)	2/19 (10.5)	233/987 (23.6)	0.27
Active smoking	146/1,018 (14.3)	1/18 (5.6)	145/1,000 (14.5)	0.50
Recent head trauma	89/1,023 (8.7)	1/19 (5.3)	88/1,004 (8.8)	0.99
1 or more antiphospholipid antibodies	82/839 (9.7)	0/18 (0.0)	82/821 (10.0)	0.24
Factor V leiden or prothrombin gene mutation	75/759 (9.9)	3/15 (20.0)	72/684 (10.5)	0.21
Timing				
Symptoms to diagnosis (days)	4 (1–10)	2.5 (0–21)	4 (1–10)	0.41
Symptoms to anticoagulation (days)	5 (2–12)	4.5 (2–23.5)	5 (2–12)	0.68
Presenting symptoms				
Headache	762/1,022 (74.5)	9/19 (47.4)	753/1,003 (75.1)	0.01
Isolated headache	357/1,023 (34.8)	7/19 (36.8)	350/1,004 (34.9)	0.81
Papilledema	100/957 (10.4)	1/17 (5.9)	99/940 (10.5)	0.99
Focal neurologic deficit	401/1,023 (39.1)	5/19 (26.3)	396/1,004 (39.4)	0.34
Seizure	243/1,023 (22.9)	1/19 (5.3)	242/1,004 (24.1)	0.06
Encephalopathy	209/1,023 (20.4)	4/19 (21.1)	205/1,004 (20.4)	0.99
Coma	29/1,023 (2.8)	0/19 (0.0)	29/1,004 (2.9)	0.99
Management				
Unfractionated heparin	768/1,024 (74.8)	13/19 (68.4)	753/1,005 (74.9)	0.59
Low molecular weight heparin	625/1,024 (61.0)	10/19 (52.6)	615/1,005 (61.2)	0.48
Vitamin-K antagonist first	579/1,024 (56.6)	13/19 (68.4)	566/1,005 (56.3)	0.36
Direct oral anticoagulant first	320/1,024 (31.3)	4/19 (21.1)	316/1,005 (31.4)	0.46
Oral anticoagulation duration (days)	187.5 (61–392.5)	108 (15–375)	188 (61–393)	0.48

Data are presented as median (interquartile range) or n (%).

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Clinical, imaging, and anticoagulation characteristics of patients with versus without DAVF were compared using chi-square, Fisher's exact, and rank sum tests as appropriate. Stepwise multivariable logistic regression analysis including clinical variables with $P<0.2$ in univariate analysis were used to determine factors associated with DAVF, and variables with $P<0.05$ from the stepwise regression were included in the final logistic regression to identify factors associated with DAVF. Missing data were not imputed for the initial multivariable analysis, and patients with missing data were excluded. In additional analyses, we conducted mean imputation for missing data and built multivariable binary logistic regression models to determine predictors of DAVF using the imputed values.

A total of 1,024 patients met inclusion criteria of whom 62.8% were female with median age of 44 years, and 751 (73.3%) had follow-up imaging available after hospitalization. Over a median follow-up of 284 days (interquartile range [IQR] 111–685 days), 19 patients (1.9%, 95% confidence interval [CI] 1.0%–2.7%) had DAVF. Patients with DAVF had a median age of 55 years, 36.8% were female, and 72.2% were White (Table 1). Patients with DAVF were older (median age 55 [IQR 45–64] vs. 44 [IQR 32–58], $P=0.03$), more likely to be male (63.2% vs. 36.7%, $P=0.03$), and less likely to have headache as a presenting CVT symptom (47.4% vs. 75.1%, $P=0.01$). Other clinical variables did not vary between the two groups (Table 1). Absent venous recanalization on follow-up imaging was more common among patients with DAVF compared to those without (50.0% vs. 14.9%, $P<0.01$) (Table 2), while there was no difference in CVT location or the presence of venous infarction, hemorrhage, or cerebral edema. In the stepwise binary logistic regression analysis including clinical variables with $P<0.2$ in univariate analysis (age, sex, headache, seizure, cortical vein involvement, and lack of recanalization), only cortical vein involvement ($P=0.01$) and absent venous recanalization ($P=0.01$) met the threshold for significance and in the final regression analysis both cortical vein involvement (OR 8.00, 95% CI 1.63–39.27, $P=0.01$) and absent venous recanalization on follow-up imaging (OR 6.28, 95% CI 1.60–24.68, $P=0.01$) were independently associated with detection of DAVF. In additional analyses imputing missing data, headache inversely correlated with DAVF (OR 0.31, 95% CI 0.11–0.85, $P=0.020$) and no recanalization on follow-up imaging remained a significant predictor of DAVF (OR=5.37, 95% CI 1.56–18.3, $P=0.008$).

DAVF was detected at a median of 44 days from diagnosis of CVT (IQR 0–242) (Table 3). Overall, 8 (42.1%) patients were diagnosed with DAVF within 7 days of CVT diagnosis and 11 (57.9%) were noted to have the DAVF on follow-up imaging (median 194 days). Eight fistulae were Borden type I (42.1%), five were Borden type II (26.3%), and six were Borden type III (31.5%). The majority of patients (n=15, 78.9%) underwent surgical or endovascular treatment of the DAVF.

In this international multicenter cohort of 1,024 patients diagnosed with CVT, 19 (1.9%) DAVF were identified including 11

Table 2. Imaging characteristics of patients with and without dural arteriovenous fistulae

Characteristics	Total (n=1,024)	Dural arteriovenous fistulae (n=19)	No dural arteriovenous fistulae (n=1,005)	*P*
Venous sinus thrombosis location				
Deep vein	248/1,022 (24.3)	4/19 (21.1)	244/1,003 (24.3)	0.99
Cortical vein	30/1,022 (2.9)	2/19 (10.5)	28/1,003 (2.8)	0.11
Superficial veins	744/1,022 (72.8)	13/19 (68.4)	731/1,003 (72.9)	0.61
Superficial and deep	130/1,022 (12.7)	2/19 (10.5)	128/1,003 (12.8)	0.99
Associated imaging findings				
Venous infarct	273/1,020 (23.2)	6/18 (33.3)	267/1,002 (26.6)	0.59
Edema	318/1,020 (31.2)	7/18 (38.9)	311/1,002 (31.0)	0.45
Hemorrhage	389/1,019 (38.2)	6/18 (33.3)	383/1,001 (38.3)	0.81
Timing of follow-up imaging				
Time to recanalization imaging (days)	180 (93–300)	194 (101–545)	180 (92.5–300)	0.39
Follow-up imaging modality				
Computed tomography	253/751 (33.7)	4/13 (30.8)	249/738 (33.7)	0.99
Magnetic resonance	572/751 (76.2)	7/13 (53.8)	565/738 (76.6)	0.09
Conventional angiogram	31/751 (4.1)	5/13 (38.5)	26/738 (3.5)	<0.01
Recanalization				
No recanalization	114/730 (15.6)	7/14 (50.0)	107/716 (14.9)	<0.01

Data are presented as median (interquartile range) or n (%).

Table 3. Characteristics of dural arteriovenous fistulae identified in cerebral venous thrombosis patients

No.	Imaging modality	Days from presentation to fistula diagnosis	Fistula location	Borden classification	Treatment
1	MR	0	Posterior fossa	1	Yes
2	CT	0	Right transverse	2	Yes
3	CT	0	Superior sagittal sinus	2	Yes
4	CT	0	Left tentorial draining into torcula	1	Yes
5	CT	0	Right transverse sinus	2	Yes
6	MR	0	Right sigmoid sinus	3	Yes
7	MR	1	Right transverse and sigmoid sinuses	2	Yes
8	DSA	4	Left transverse and sigmoid sinuses	3	Yes
9	MR	28	Right transverse sinus	1	Yes
10	MR	44	Left transverse sinus and cortical veins	2	Yes
11	MR	100	Left transverse sinus	1	No
12	DSA	101	Right transverse sinus	1	No
13	CT	174	Left sigmoid	1	Yes
14	CT	194	Posterior fossa	3	Yes
15	MR	290	Right and left transverse sinuses and deep venous system, intracranial cortical draining veins	3	Yes
16	DSA	333	Right tentorial	3	Yes
17	DSA	492	Left transverse and sigmoid sinuses	1	No
18	MR	660	Posterior fossa	3	Yes
19	DSA	688	Posterior right frontal lobe	1	No

MR, magnetic resonance; CT, computed tomography; DSA, digital subtraction angiography.

that were not recognized during initial hospitalization for CVT. Cortical vein thrombosis and absent recanalization on follow-up imaging were independently associated with DAVF.

Our findings are in keeping with prior studies on this subject demonstrating a higher prevalence of DAVF among patients with CVT as compared to the reported incidence rate of DAVF in population-based studies.[2,3] In an International Cerebral Venous Thrombosis Consortium study, DAVF was detected in 2.4% of CVT patients and was associated with male gender, chronic CVT, and older age.[7] Several pathophysiological events have been proposed to underly the *de novo* formation of DAVF after CVT including neovascularization secondary to venous hypertension caused by CVT[8] or enlargement of pre-existing shunts between meningeal arteries and dural venous sinuses. The observation that venous hypertension appears to play a role in DAVF formation offers an explanation as to why absent CVT recanalization is a risk factor of DAVT. Cortical vein thrombosis has not been associated with DAVF in prior studies, but has previously been described in 17%–61% of patients with CVT,[9,10] and involvement of cortical veins is associated with higher prevalence of venous infarction/hemorrhage and worse outcomes.[10]

Despite the strengths of a large international multicenter cohort, our study has several limitations. Limited information regarding characteristics of DAVFs was available, restricting our ability to comment on clinical symptoms suggestive of DAVF or the decision to treat or observe the DAVF. Furthermore, ACTION-CVT did not capture all lab values of systemic hypercoagulability (such as d-dimer) and given the known association between hypercoagulability and DAVF, this reflects an area of potential future study. Follow-up imaging was not systematically obtained for all patients (performed in 751/1,024 [73.9%] within the cohort), different sites had variable imaging practices, and the indication for choosing the imaging modality was not reported. Only 4% of patients underwent digital subtraction angiography (DSA) in our study (which may result in under-recognition as it is the gold standard for detection of DAVF) and it is likely that those that underwent DSA did so due to concern for DAVF on initial imaging. Finally, the direction of causality between DAVF and CVT remains uncertain given the possibility of a DAVF being missed on initial imaging, and it is possible that in some cases that the presence of a DAVF was the reason for lack of venous recanalization and not the result of lack of recanalization of a CVT.

In this large multicenter study of patients with CVT, cortical vein thrombosis and lack of venous recanalization at follow-up were independently associated with DAVF. The present study reinforces the association between CVT and DAVF as both con-

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comitant diagnoses as well as the potential for DAVF formation after CVT identification.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

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