The Significance of Venous Outflow Obstruction in Dural Arteriovenous Fistulas

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BACKGROUND AND OBJECTIVES: The association between venous outflow obstruction (VOO) and cranial dural arteriovenous fistulas (DAVF) is well established; however, its impact on the natural history remains unclear. This article aims to characterize its clinical significance and further describe the natural history of DAVF.

METHODS: A retrospective cohort study was performed at a tertiary neurosurgical center. Cohort characteristics were described with a focus on patients with VOO. Annualized event rates and risk factors for hemorrhage and nonhemorrhagic neurological events (NHNE) were also investigated.

RESULTS: The cohort consisted of 108 patients, 74 of which had follow-up greater than 1 month including 24 low-grade (Cognard I-IIa) fistulas (21.7 lesion-years) and 50 high-grade (Cognard IIb-V) fistulas (60 lesion-years). 18 patients with concurrent VOO were identified; most (83.3%) were high-grade DAVF and had obstruction of the direct draining sinus. Annualized rates of hemorrhage and NHNE for high-grade DAVF were 4.6% and 10.6%, respectively. Those high-grade lesions presenting with hemorrhage had a 10.9% annual rate of recurrent hemorrhage, while those presenting with NHNE had a 22.3% annual rate of subsequent NHNE. Fifteen high-grade DAVF with VOO (15.7 lesion-years) had annualized hemorrhage and NHNE rates of 6.4% and 31.9%, respectively. High radiological grade, an aggressive index presentation, and the presence of VOO were the predictors of hemorrhage and NHNE ($P < .05$).

CONCLUSION: This study reports a novel association between VOO and a more aggressive clinical course. DAVF with high-grade angiographic features, an aggressive index presentation, or VOO should be considered for early treatment.

KEY WORDS: Dural arteriovenous fistula, Natural history, Venous outflow obstruction

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Cranial dural arteriovenous fistulas (DAVF) are rare cerebrovascular lesions characterized by an abnormal connection between one or more dural arteries and the cerebral venous system. DAVF account for approximately 10% of all intracranial vascular malformations, and the literature describing their natural history is limited.[1] The pathogenesis remains unclear, although their association with vascular injury, such as cerebral venous sinus thrombosis (CVST), craniotomy, and head trauma, is well established.[2-4]

ABBREVIATIONS: CCF, carotid-cavernous fistula; **CVST,** cerebral venous sinus thrombosis; **DAVF,** dural arteriovenous fistulas; **LTFU,** lost to follow-up; **NHNE,** nonhemorrhagic neurological events; **TBI,** traumatic brain injury; **VOO,** venous outflow obstruction.

A hallmark of DAVF is the heterogeneity of their presentation, vascular anatomy, and natural history. Abnormal venous drainage, either from a predisposing factor such as CVST or as a consequence of the dynamic angioarchitecture of the fistula itself, is widely accepted as playing a central role in the formation and progression of DAVF.[3,5] Subsequent venous hypertension increases the risk of hemorrhage and nonhemorrhagic neurological events (NHNE) such as seizure and nonhemorrhagic focal deficits.[6] Thus, it has been recognized for several decades that cortical venous drainage suggests a more aggressive lesion and is an important part of clinical grading systems proposed by Borden et al

and Cognard et al.[3,7-9] The pathophysiology of venous hypertension, local hypoxia, and abnormal angiogenesis that underpins this finding has been documented previously.[5,10,11] However, despite this link and the significant association between CVST and subsequent fistula formation, the impact of venous outflow obstruction on the clinical course of cranial DAVF has not been reported.

Furthermore, the rarity of DAVF and difficulties with long-term follow-up has resulted in variable reporting of the risk of hemorrhage and NHNE associated with these lesions. As such, the following study will describe a cohort of cranial DAVF with a particular focus on those patients with concurrent venous outflow obstruction (VOO) and identify factors that may predict the natural history of this uncommon pathology.

METHODS

A retrospective, observational cohort study was performed at the Royal Melbourne Hospital, a tertiary neurosurgical center with a large neurointerventional radiology service. Ethics approval was obtained from the local human research and ethics committee (*HREC 2021.120*), and a formal waiver of patient consent was granted for this study.

Patient Population

Patients 18 years and older with a cranial DAVF confirmed by catheter angiogram at the Royal Melbourne Hospital between January 1, 2011, and December 31, 2020, were eligible for inclusion. Exclusion criteria included incomplete data, unclear or mixed diagnosis (eg, lesions with substantial pial as well as dural arterial supply), or a diagnosis of carotid-cavernous fistula (CCF). The latter criterion was specified as CCF are generally recognized to be unique fistulas that differ in their presentation and clinical course from other DAVF.[12]

Study Design

International Classification of Diseases 10 clinical codes were used to identify eligible patients, and hospital records were searched to extract demographic, clinical, and radiological data. The Cognard grading system was used to dichotomize DAVF into low-grade and high-grade lesions, represented by Types I-IIa and Types IIb-V, respectively.[3] Imaging was assessed for the presence of hemorrhage, cerebral edema, and VOO. The angioarchitecture of the VOO was defined as direct, which involves the draining venous sinus immediately distal to the fistulous point (eg, ipsilateral sigmoid sinus in transverse-sigmoid DAVF), distant (eg, contralateral transverse sinus), or both direct and distant sinus obstruction. The degree of obstruction was classified as occlusion (no flow evident on angiogram) or stenosis (reduced caliber of sinus but with persistent flow). The study population was then narrowed to those patients with a follow-up period of greater than 1 month between diagnosis and several prespecified end points. These included an episode of hemorrhage or NHNE (seizures, nonhemorrhagic focal deficits, or raised intracranial pressure), successful treatment, death, loss to follow-up, and those patients under surveillance or awaiting treatment at the end of the study period. The total lesion-years (period from angiographic diagnosis to one of the above end points) exposed to a DAVF were then calculated, and subsequent analysis was performed as detailed below.

Statistical Analysis

Baseline continuous data were analyzed descriptively, and annualized event rates were calculated using the total lesion-years exposed to a DAVF during the study period. Only patients with a follow-up period greater than 1 month were included to avoid statistical skew.[13] Risk factors for hemorrhage or NHNE were assessed using the Fisher exact test for categorical variables or logistic regression for continuous variables. Given the established benign nature of low-grade DAVF, only high-grade lesions were included in the analysis of risk factors for hemorrhage or NHNE to limit confounding. The results with a P value < .05 were considered statistically significant. All analyses were conducted with *R* (v4.0.2, R Foundation for Statistical Computing).

RESULTS

Of 135 patients initially screened, 108 patients were found to meet inclusion criteria. Seventeen cases of CCF were excluded from the main cohort (further details are shown in Figure 1). Baseline data are presented in Table 1. The cohort comprised 80 high-grade and 28 low-grade DAVF with a mean age of 60 (±14.1). Most of the overall cohort were male (n = 58, 53.7%), and 22 (20.3%) patients had a previously diagnosed CVST. The most common index presentation was headache (n = 26, 24.1%), followed by tinnitus (n = 24, 22.2%) and hemorrhage (n = 23, 21.2%). The most common fistulous location was the transverse-sigmoid junction (n = 51, 47.2%), and 87 (80.6%) patients underwent successful treatment. Of those patients, 69 (79.3%) were treated endovascularly, 10 (11.5%) were treated through craniotomy, and 8 (9.2%) were treated through combined endovascular and open approaches.

Hemorrhage and NHNE

Of the 108 eligible patients, 74 had a follow-up period greater than 1 month and were included in further analysis. The 34 excluded patients consisted of 30 lesions treated within 1 month of diagnosis, 2 deaths due to significant intracranial hemorrhage on presentation, and 2 cases found in older comorbid patients who declined further investigation. Fifty high-grade DAVF were followed for a period of 66 lesion-years (median 7 months) and 24 low-grade lesions for 21.7 lesion-years (median 5.5 months). Three presentations with hemorrhage and 7 NHNE were identified during the study period. The severity of hemorrhage was variable, with 1 patient requiring craniotomy and permanent cerebrospinal fluid diversion, whereas 2 other patients had low-volume intracranial hemorrhages that were managed conservatively. NHNE comprised 3 episodes of seizure, 3 nonhemorrhagic deficits (facial numbness, transient upper limb monoparesis, and hemiparesis with dysphasia), and 1 admission for cerebral edema causing raised ICP. Overall event rates and outcomes are presented in Table 2, and a more detailed description of hemorrhage and NHNE rates in the high-grade subgroup is presented in Table 3. In high-grade (Cognard IIb-V) lesions, annual hemorrhage and NHNE rates were 4.6% and 10.6%, respectively. Those patients

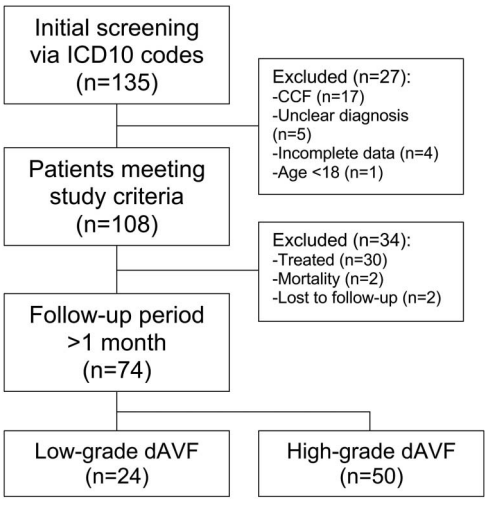

FIGURE 1. *Study design flowchart with explanations for patient exclusion included on right. CCF, carotid-cavernous fistula; DAVF, dural arteriovenous fistulas.*

with an initial hemorrhage at presentation had an annual rate of repeat hemorrhage of 10.9%. Similarly, patients with an NHNE as their index presentation had a 22.3% annual risk of subsequent NHNE. Five mortalities occurred during the study period, 4 of which were attributable to a DAVF and included 2 cases of refractory status epilepticus, aspiration pneumonia secondary to bulbar dysfunction in a Cognard V posterior fossa fistula, and a case of severe encephalopathy and Parkinsonism in the setting of venous hypertension. All deaths occurred in high-grade DAVF.

Venous Outflow Obstruction

Eighteen patients (24.3% of the cohort) had VOO at the time of diagnosis, 15 of which were high-grade DAVF with a follow-up period of 15.7 lesion-years (median of 6 months). Baseline characteristics are presented in Table 4. Of note, approximately half (55.6%) had a documented clinical history of CVST, and there was no association between VOO and aggressive index presentations. Despite this, annualized hemorrhage and NHNE rates for high-grade DAVF with VOO were 6.4% and 31.9%, respectively, higher than the general cohort. Three of the 4 mortalities attributable to DAVF occurred in patients with VOO (P = .04). Most DAVF with concurrent VOO were transverse-sigmoid sinus lesions (83.3%). By way of comparison, none of the 17 excluded CCF demonstrated VOO. Fifteen (83.3%) patients demonstrated direct VOO, and 3 (16.7%) had a direct and distant pattern (see Figure 2A and 2B). The latter group all comprised transverse-sigmoid sinus fistulas with 2 cases of bilateral transverse-sigmoid obstruction and a single case of marked VOO with occlusion of bilateral sigmoid sinuses and severe stenosis of the distal superior sagittal sinus. There were no cases of distant VOO only. Fourteen (77.8%) patients presented with complete occlusion of the draining sinus.

TABLE 1. Baseline Cohort Characteristics

Parameter	Total (%)	Low-grade (%)	High-grade (%)
Number	108	28	80
Age (SD)	60.1 (14.2)	63.8 (10.2)	58.7 (15.1)
Male	58 (53.7)	8 (28.6)	50 (62.5)
Comorbidities			
Hypertension	33 (36.3)	9 (42.9)	24 (34.3)
Smoking	28 (33.3)	5 (26.3)	23 (35.4)
Previous CVST	22 (22)	4 (16)	18 (24.7)
Previous cranial surgery	11 (11.7)	3 (4.6)	8 (11.1)
TBI	3 (3.2)	0 (0)	3 (4.2)
Index presentation			
Hemorrhage	23 (21.2)	2 (7.1)	21 (26.3)
Incidental	16 (14.8)	7 (25)	9 (11.3)
Headache	26 (24.1)	4 (14.3)	22 (27.5)
Tinnitus	24 (22.2)	15 (53.6)	9 (11.3)
Seizures	7 (6.5)	0 (0)	7 (8.6)
Focal deficit	6 (5.6)	0 (0)	6 (8.8)
Other	6 (5.6)	0 (0)	6 (7.5)
Location			
Transverse-sigmoid	51 (47.2)	21 (75)	30 (37.5)
Superior sagittal sinus	15 (13.8)	0	15 (18.8)
Posterior fossa	17 (15.7)	3 (10.7)	14 (17.5)
Anterior fossa	7 (6.4)	4 (14.3)	3 (3.8)
Tentorial	9 (8.3)	0	9 (11.3)
Other	9 (8.3)	0	9 (11.3)

CVST, cerebral venous sinus thrombosis; TBI, traumatic brain injury.

Prognostic Factors

A number of risk factors were assessed for association with hemorrhage and NHNE, and these are presented in Tables 2 and 3. High-grade DAVF (P = .03), an aggressive index presentation (P = .01), and the presence of VOO (P = .04) were statistically significant. Aggressive index presentation (P < .01) and VOO (P = .04) were both independent predictors of mortality.

TABLE 2. Outcome Data for Patients With a Follow-up Period Greater than 1 Month

Outcome	Total	Low-grade	High-grade
Followed >1 month	74	24	50
Median follow-up in months (IQR)	6.5 (3.5-15.5)	5.5 (3.5-15.5)	7 (3.5-18)
Total lesion-years	87.7	21.7	66
End point			
Treated	44	15	29
Ongoing	12	5[a]	7[b]
Hemorrhage	3	0	3
NHNE	7	0	7
Death (unrelated)	1	0	1
LTFU	7	4	3

LTFU, lost to follow-up; NHNE, nonhemorrhagic neurological event.
[a]One patient awaiting treatment and 4 under surveillance.
[b]Three patients declined treatment, 2 partially treated with persistent high-grade features, and 2 with no viable treatment options.

Although all deaths in the cohort occurred in patients with high-grade DAVF, this association was not statistically significant (P = .29). Additional characteristics of age, sex, active cigarette smoking, and hypertension were not significant.

DISCUSSION

High radiological grade, an aggressive index presentation, and the presence of VOO are identified as predictors of hemorrhage and NHNE, the latter of which is a novel finding. The cohort's mean age of 60 years and the slight male predominance in the high-grade DAVF subgroup are consistent with previous literature.[2,6,7] No events were recorded in low-grade DAVF.

DAVF with cortical venous drainage have been recognized for several decades as carrying an increased risk of hemorrhage and NHNE.[3,7,14] Van Dijk et al[14] reported hemorrhage and NHNE rates of 8.1% and 6.9% in a small cohort of patients with persistent cortical venous reflux. In the largest series to date, Gross et al[15] found annualized hemorrhage rates of 4.5%–6% and NHNE rates of 3.4%–9.1% across 207 lesion-years of the high-grade DAVF follow-up. As such, the annual rates of 4.6% and 10.6% for hemorrhage and NHNE presented in this study are concordant. The risk posed by an aggressive index presentation is variably reported. In Gross et al,[15] those presenting with hemorrhage had a 46.2% annualized risk of subsequent hemorrhage (8 lesion-years) and those with NHNE had a 23.1% risk of subsequent NHNE (74 lesions-years). Studies by Soderman et al and Strom et al described the rates of recurrent hemorrhage of 7.4% (40.4 lesion-years) and 19% (25.3 lesion-years), respectively.[16,17] Existing data on the risk of NHNE are limited. As detailed above, this article reports a 10.9% annual risk of re-hemorrhage and a 22.3% risk of repeat NHNE. The inconsistency in reported hemorrhage rates (7.4%-46.2%) in this specific subgroup is likely attributable to small cohorts with limited follow-up periods, largely due to expeditious treatment of DAVF that present with hemorrhage.

In our cohort, high-grade DAVF, aggressive index presentation, and VOO were statistically significant predictors of hemorrhage and NHNE. Furthermore, the latter 2 predictors were also associated with mortality. High radiological grade was not a significant predictor, despite all deaths occurring in high-grade DAVF. This finding is likely explained by small numbers of low-grade DAVF (n = 24) in the cohort, which limited statistical comparison between high-grade and low-grade lesions. The authors' decision to exclude the clinically distinct diagnosis of CCF, most of which are low-grade lesions, partially explains this low number. In addition, low-grade DAVF are more likely to remain asymptomatic and thus undiagnosed. Aside from the aforementioned variables, limited data exist describing the risk factors

TABLE 3. Annualized Rates of Hemorrhage and NHNE for High-Grade DAVF Delineated by Risk Factors

Risk factor	n =	Lesion-years	Hemorrhage	NHNE	Overall event rate	P value[a]
Benign presentation	30	34.1	2.9%	2.9%	5.8%	—[b]
Aggressive presentation	20	31.9	6.3%	18.8%	25.1%	.01
Hemorrhage	5	9.2	10.9%	10.9%	21.8%	.26
NHNE	15	22.4	4.5%	22.3%	26.8%	**.04**
Venous outflow obstruction	15	15.7	6.4%	31.9%	38.3%	**.04**

NHNE, nonhemorrhagic neurological events.
[a]Bolded P values indicate statistically significant results.
[b]Data included for comparison, and no statistical analysis of association was undertaken.

TABLE 4. Description of 18 Patients With Concurrent Venous Outflow Obstruction

Characteristic	Frequency
Age (SD)	57.1 (15.9)
Male	6 (33.3%)
Cognard grade	
Low-grade (I-IIa)	3 (16.7%)
High-grade (IIb-V)	15 (83.3%)
Previous CVST	10 (55.6%)
Aggressive index presentation	3[a] (16.7%)
Fistula location	
Transverse-sigmoid junction	15 (83.3%)
Superior sagittal sinus	2 (11.1%)
Tentorial	1 (5.6%)
Site of VOO	
Direct sinus only	15 (83.3%)
Both direct and distant sinuses	3 (16.7%)
Distant sinus only	0
Complete occlusion	14 (77.8%)
End point	
Hemorrhage	1 (5.6%)
NHNE	5[b] (27.8%)
Treated	8 (44.4%)
Ongoing	4 (22.2%)
Mortality	3[c] (16.7%)

CVST, cerebral venous sinus thrombosis; NHNE, nonhemorrhagic neurological event; VOO, venous outflow obstruction.
[a]Two nonhemorrhagic neurological events (Parkinsonism and seizure) and 1 hemorrhage.
[b]Two seizures, 2 nonhemorrhagic focal deficits, and 1 case of venous hypertension resulting in refractory intracranial hypertension.
[c]Two refractory status epilepticus and 1 progressive Parkinsonism and encephalopathy.

predicting a more aggressive clinical course in DAVF. Recent publication of the baseline characteristics of the Consortium for Dural Arteriovenous Fistula Outcomes Research cohort emphasizes the importance of largescale collaborative databases to aid accurate investigation of this uncommon pathology.[18]

The presence of VOO was found to independently predict mortality as well as hemorrhage and NHNE, with the annual events rates of 6.4% and 31.9%, respectively. To the best of authors' knowledge, this is a novel finding that adds to our understanding of DAVF pathophysiology. This association is consistent with the current understanding of venous hypertension as a key driver of vascular remodeling, cerebral edema, and locally altered brain tissue metabolism with subsequent clinical sequelae.[4,19,20] Early work by Lawton et al identified the association between venous hypertension and DAVF formation in experimental rat models, with subsequent corroboration by several other groups.[5,10] Furthermore, the expression of hypoxia-inducible factor-1 has been demonstrated to directly vary in proportion to the degree of venous hypertension in experimental models.[5,21] These findings support the cyclical mechanism originally posited by Lawton et al[10] by which raised intracranial venous pressure induces abnormal angiogenesis with consequent increases in arteriovenous shunting, venous hypertension, and further fistula expansion. These data not only underpin the link between venous sinus thrombosis and DAVF formation but may also provide a pathophysiological basis for the clinical association identified in this study between VOO and poor outcome.[22] Shin et al[9] examined the venous architecture of high-grade DAVF and reported an association between the uncommon finding of an isolated sinus (occluded both proximal and distal to the fistulous point) and aggressive clinical course; however, this finding was not replicated in patients with direct VOO (distal occlusion of the draining sinus only). A single case of DAVF draining to an isolated venous sinus was identified in our cohort. Most (83.3%) patients demonstrated direct VOO only, and 77.8% had complete occlusion of the draining sinus. In contrast to the even distribution of the overall cohort and the male predominance in the high-grade DAVF subgroup, 66.7% of patients with VOO were female. It is difficult to draw conclusions from these data, given the small sample size; however, this may reflect the higher rate of CVST observed in female populations.[22] Although not a focus of our study, 17 patients with CCF were identified and none demonstrated VOO. These data support the clinical differences between CCF and other DAVF as well as recent hypotheses on CCF having a distinct pathogenesis that involves microarterial injury in the cavernous sinus rather than venous injury or thrombosis that is central to the formation of extracavernous DAVF.[23]

VOO is a dynamic process, particularly in patients with an underlying thrombophilia causing recurrent thrombosis and recanalization with associated hemodynamic changes through the DAVF and adjacent brain.[20] Progressive stenosis and eventually occlusion can occur, and this subset of patients poses unique challenges. Although anticoagulation is effective for thrombotic occlusions of the venous sinuses, fixed outflow obstructions are more difficult and can result in complex arterial and venous fistula anatomy with limited treatment options. To the best of the authors' knowledge, there are no data available on the effectiveness or safety of anticoagulation in the treatment of cranial DAVF with VOO. A limited number of studies describe the use of anticoagulation in patients with spinal DAVF who experience reversible postoperative neurological deterioration, presumably due to venous thrombosis.[24,25] However, similar studies in cranial DAVF are lacking and represent an area for future investigation. Endovascular management may include stenting, balloon-assisted embolization in select cases, or, if alternate drainage pathways are available, sacrifice of the sinus.[26-28] Surgical management of

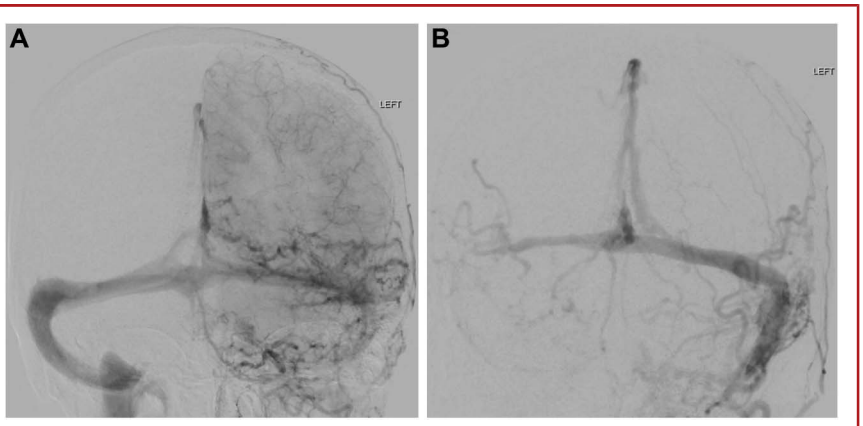

FIGURE 2. *Digital subtraction angiogram of external carotid artery (anteroposterior view) of 2 patients with transverse sinus dural arteriovenous fistulas demonstrating* **A**, *direct draining sinus occlusion only and* **B**, *direct and distant sinus occlusion.*

DAVF with VOO may be associated with significant morbidity because of the hypervascularity of adjacent tissues and the technical difficulties associated with high-flow venous bypass.[29,30] Hence, the recognition of VOO as a significant predictor of morbidity and mortality should prompt clinicians to consider early treatment to prevent progression of the VOO beyond the scope of intervention and to avoid the substantial risks of hemorrhage and NHNE.

Limitations

The authors acknowledge several limitations of our study. The retrospective design and relatively small numbers limit statistical analysis. It should be recognized that early treatment of clinically aggressive DAVF is a standard practice in most institutions, and this impairs the ability to assess the natural history of this subgroup. Gross et al noted that most existing data are derived from patient cohorts comprised untreated, partially treated, and "untreatable" lesions with the potential for altered vascular architecture and hemodynamics after intervention.[14] Most high-grade lesion-years derived in this study were from patients awaiting treatment or those who had declined intervention and were under long-term surveillance. Two partially treated patients were included in our cohort because of persistent high-grade radiological features. Although this problem makes the natural history studies difficult, such cohorts are what clinicians are faced with practically. As such, carefully considered data describing their characteristics and possible natural history remain an important adjunct to clinical decision-making.

CONCLUSION

VOO is a recognized driver of the formation and progression of cranial DAVF. Novel data reported in this study extend our understanding of the pathophysiology and natural history of DAVF by identifying an association between VOO and a more aggressive clinical course. In addition to VOO, high-grade angiographic features and an aggressive index presentation were associated with increased risk of hemorrhage and NHNE. The significance of VOO warrants further investigation to improve our understanding of the natural history of DAVF and guide patient care.

Ethics Approval

This study was approved by the Melbourne Health Human Research and Ethics Committee (HREC) on May 20, 2021, under the Protocol No. *HREC 2021.120*.

Publication & Presentation History

Data in this study were presented in an oral presentation with published abstract in conference proceedings at the Stroke Society of Australasia annual meeting on October 14, 2021, in Perth, Western Australia. Neither this manuscript nor any data included in it have been published previously.

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