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Original Article

Ischemic Stroke in Patients With Intracranial Dural Arteriovenous Fistulas

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Background/Purpose: Intracranial dural arteriovenous fistulas (DAVFs) can be complicated by ischemic stroke. This study investigated the frequency and determinants of ischemic stroke in patients with intracranial DAVF.

Methods: We conducted a retrospective study of consecutive patients with intracranial DAVF. Patients with pure hemorrhagic stroke or without available brain imaging for clarifying stroke type were excluded. DAVF was diagnosed by cerebral catheter angiography. Cognard classification and location of DAVFs were ascertained. The clinical characteristics, outcome, and radiographic findings were recorded. Factors associated with occurrence of ischemic stroke in the patients with DAVFs were determined.

Results: A total of 134 patients were enrolled. Six patients (4.5%) had ischemic stroke (mean age: 53.8 ± 13.4 years) and 128 patients were free from stroke (mean age: 55.4 ± 15.2 years). Men accounted for 83% in the ischemic stroke group and 34% in the non-stroke group. Chemosis, exophthalmos and tinnitus were more frequent in the non-stroke group, whereas seizure and mental decline were more frequent in the ischemic stroke group. DAVF was associated with highest risk of ischemic stroke at locations other than the cavernous sinus or large sinuses. Ischemic stroke also correlated with types of DAVF involving cortical venous drainage, including type IIb (18%), III (15%), and IV (100%). No patient with DAVF type I and IIa had ischemic stroke. The rate of ischemic stroke in patients with concomitant DAVF and cerebral sinus thrombosis was higher than in DAVF patients without cerebral sinus thrombosis. Venous infarct was the major subtype of ischemic stroke in five DAVF patients. Endovascular therapy was the most common choice in both groups, and fewer patients in the ischemic stroke group did not receive any treatment for DAVFs.

Conclusion: Location and type of DAVF were two important factors related to the occurrence of ischemic stroke in DAVF patients.

Key Words: cerebral sinus thrombosis, dural arteriovenous fistula, ischemic stroke, venous infarct

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Intracranial dural arteriovenous fistulas (DAVFs) are abnormal arteriovenous shunts between dural arterial feeders and dural venous drainage channels. DAVFs comprise 10–15% of all intracranial vascular malformations.[1–3] The clinical presentation of DAVF is highly variable, and includes pulsatile tinnitus, chemosis of the eyes, exophthalmos, double vision, seizure, cognitive decline, and stroke.[2,4,5] These manifestations are usually related to the location and drainage pattern of the DAVF.[4,6] Stroke is an uncommon but severe manifestation. There have been many articles that have discussed the frequency and determinants of intracranial hemorrhage associated with DAVF,[1,2,4–10] but there have been no large case series to delineate the relationship between ischemic stroke and intracranial DAVF. Prompt and adequate treatment of DAVF patients at high risk for ischemic stroke might prevent stroke. Also, effective treatment of DAVFs in stroke patients can prevent stroke recurrence. Therefore, identification and treatment of high-risk DAVF patients might offer clinical benefit. The aims of this study were to assess the frequency, predictors, and neuroimaging characteristics of DAVF-related ischemic stroke.

Materials and Methods

A total of 158 consecutive patients diagnosed with DAVF and admitted to the National Taiwan University Hospital, Taipei, Taiwan, from January 1995 to December 2007 were retrospectively reviewed. The diagnosis of DAVF in each patient was based on cerebral catheter angiography. Four patients who developed stroke after endovascular treatment for DAVF were excluded.

The medical records of each patient were reviewed by two of the authors (S.J Yeh and L.K. Tsai) and the data were abstracted systematically. The details of clinical and radiological manifestations, risk factors, and outcome were recorded. Angiographic findings were reviewed for the location, drainage pattern, and possible cerebral sinus thrombosis (CST) of DAVFs. The angiographic features of CST were defined as abrupt cessation and stasis of contrast medium.[6]

The drainage patterns of DAVFs were classified according to the Cognard classification method as follows: type I, located in the main sinus without reflux; type II, located in the main sinus with reflux into the sinus (IIa), cortical veins (IIb), or both (IIa + b); type III, with direct cortical venous drainage without venous ectasia; type IV, with direct cortical venous drainage with venous ectasia; and type V, with spinal venous drainage.[8] The locations of DAVFs were divided into three groups, as previously reported,[11] including cavernous sinus (Figure 1), large cerebral sinus (Figure 2), and other locations. Large sinuses included transverse, sigmoid, and superior sagittal sinuses. The drainage sites of DAVFs other than large sinuses and cavernous sinuses were defined as other locations. In cavernous sinus DAVF, direct carotid–cavernous fistula was excluded because it is not a transdural fistula.[4]

The diagnosis of ischemic stroke was based on clinical manifestation and neuroimaging findings. Acute stroke was defined as acute onset of a focal neurological deficit that persisted for > 24 hours. The diagnosis of acute ischemic stroke requires diffusion restriction on brain magnetic resonance imaging (MRI). Venous infarct is a special kind of infarct other than arterial infarct in patients with DAVF. The definition of venous infarct on brain MRI is based on hypointensity on apparent diffusion coefficient (ADC) mapping, and the infarct region not corresponding to an arterial territory.[11] Hyperintensity on diffusion-weighted imaging without decrease of ADC value is consistent with T2 shine-through effect, which can be attributed to vasogenic edema instead of venous infarct.[11] Follow-up brain images were also reviewed for negative mass effect at the infarct region. Infarct with hemorrhagic transformation was included in the ischemic stroke group. Seizure with Todd's paralysis was excluded from stroke by clinical manifestations of seizure.

Student *t* test for age and Fisher exact test for categorical variables were used to assess the statistical difference between the ischemic stroke and

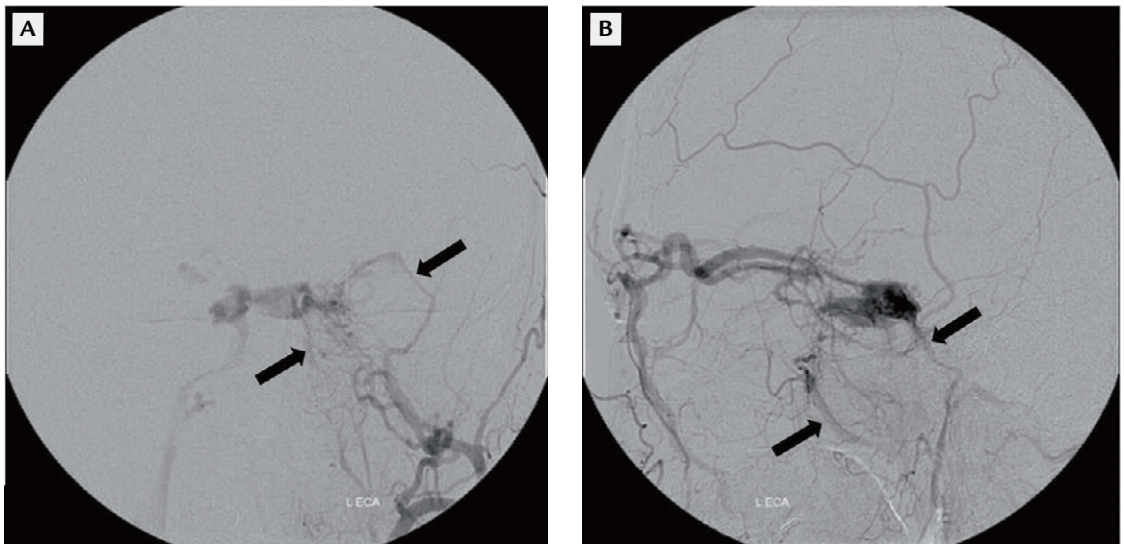

Figure 1. Type I dural arteriovenous fistulas (black arrows) at the left cavernous sinus with drainage to bilateral superior ophthalmic veins. Angiography of the left external carotid artery injection showed early opacification of the left and right cavernous sinuses through the intercavernous communication (A), with subsequent drainage into bilateral superior ophthalmic veins (B).

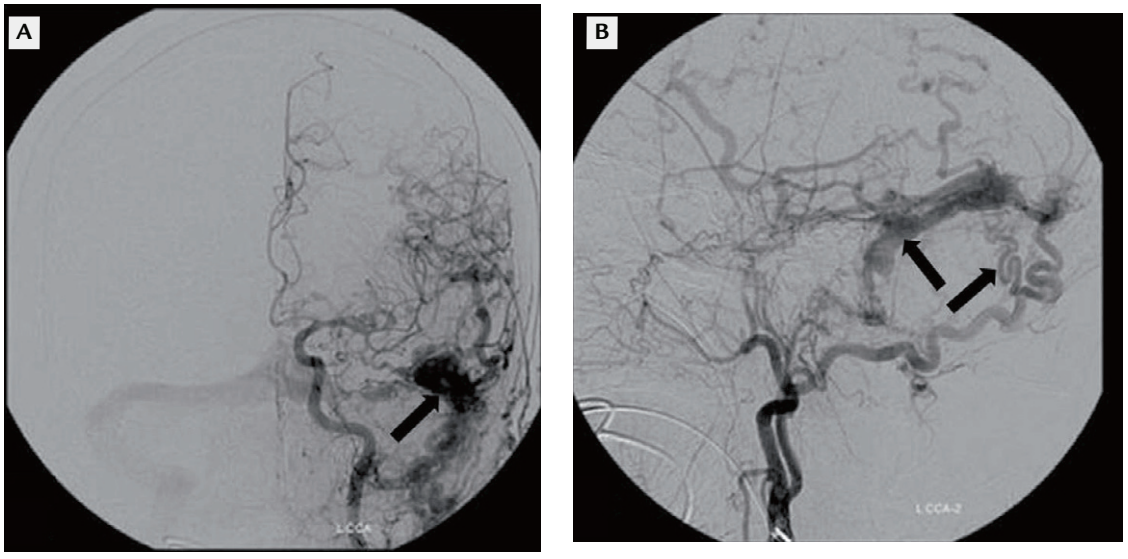

Figure 2. Type IIa + b dural arteriovenous fistulas at the left transverse sigmoid sinus. The anterior–posterior (A) and lateral (B) views of angiography from the left external carotid artery injection showed dural arteriovenous fistulas (black arrows) at the left transverse sigmoid sinus, supplied by multiple feeding arteries from the left external carotid artery, with retrograde drainage to many tortuous cortical veins and right transverse sinus.

non-stroke groups. Multiple logistic regression analysis was not performed due to the very small sample size of ischemic stroke patients. Results were considered significant if the p value was < 0.05. The SPSS 12.0 software package (SPSS, Chicago, IL, USA) was used for statistical analyses.

Results

Clinical characteristics of DAVF patients with or without ischemic stroke

Among the 154 patients, 19 (12.3%) who had pure hemorrhagic stroke were excluded from

Table 1. Clinical characteristics of dural arteriovenous fistula patients with or without ischemic stroke[a]

	Without stroke ($n=128$)	With IS ($n=6$)	p
Age (yr)	55.4 ± 15.2	53.8 ± 13.4	0.811
Male sex	44 (34)	5 (83)	0.025
Clinical presentations			
Tinnitus	69 (54)	0 (0)	0.012
Exophthalmos	46 (36)	0 (0)	0.095
Chemosis	51 (40)	0 (0)	0.044
Headache	32 (25)	1 (17)	1.000
Conscious changes	1 (1)	0 (0)	1.000
Seizure	7 (6)	2 (33)	0.052
Cognitive decline	4 (3)	1 (17)	0.208

[a]*Data are presented as mean ± standard deviation or n (%). IS = ischemic stroke.*

analysis because this study focused on ischemic stroke. The brain MRI film of another patient was not available for clarifying stroke subtype, therefore, that patient was not enrolled into the analysis. The remaining 134 patients were divided into two groups: with ischemic stroke and without stroke. Of the 134 patients, the average age was 55.3 ± 15.1 years, and 85 (63.4%) were female. Six patients had ischemic stroke (mean age: 53.8 ± 13.4 years). The clinical characteristics are listed in Table 1. In the group of patients with ischemic stroke, male patients accounted for 83.3%. On the contrary, in the group without stroke, only 34.4% of patients were male. No patient in the ischemic stroke group presented with tinnitus, eye chemosis, or exophthalmos, whereas in the non-stroke group, a considerable number of patients presented with these symptoms (54%, 40%, and 36%, respectively). Seizure (6% *vs.* 33%, $p=0.052$) and cognitive decline (3% *vs.* 17%, $p=0.208$) were more frequent in patients with ischemic stroke, but without statistical significance. There were no significant differences in the frequency of headache or change in consciousness between the two groups.

The type of DAVF also was found to influence the risk of ischemic stroke (Table 2). There was no ischemic stroke in patients with type I and type IIa DAVF. Ischemic stroke occurred in patients with type IIb (18%), III (15%), and IV (100%) DAVF. Comparison of the occurrence of ischemic stroke in DAVFs without cortical venous drainage (type I and IIa) and with cortical venous drainage (type IIb, IIa + b, III, IV, and V) showed that there was a significant difference between the two groups (0% *vs.* 12%, $p=0.003$).

With regard to location of DAVF (Table 2), patients with cavernous sinus DAVF had no ischemic stroke; this contrasted with moderate frequency of ischemic stroke in patients with DAVF in large sinuses (2%, $p=0.665$), and significantly higher frequency of ischemic stroke in patients with DAVF in other locations (16%, $p=0.003$).

Imaging findings of DAVF-related ischemic stroke

Among the six patients with infarction, five had findings that were compatible with venous infarction on brain imaging. The infarct region in the final patient with ischemic stroke was at the basal ganglia and might have been an arterial infarction. The most characteristic imaging finding of venous infarction was hypointensity on the ADC map of MRI, which indicated cytotoxic edema. The infarct region also did not follow an arterial territory. Other associated features included abnormal vascular enhancement, infarct with petechial hemorrhage, and vasogenic edema. Four of the infarction patients had CST. Patients with CST had higher risk of ischemic stroke than those without (10% *vs.* 3%, $p=0.136$).

Table 2. Angiographic characters of dural arteriovenous fistulas in the two groups with and without ischemic stroke[a]

	Without stroke ($n=128$)	With IS ($n=6$)	p
Type of DAVF			
I	58 (45)	0 (0)	0.036
IIa	24 (19)	0 (0)	0.591
IIb	9 (7)	2 (33)	0.077
IIa+b	18 (14)	0 (0)	1.000
III	17 (13)	3 (50)	0.043
IV	0 (0)	1 (17)	0.045
V	2 (2)	0 (0)	1.000
Type of DAVF (grouping)			
I+IIa	82 (64)	0 (0)	0.003
IIb+IIa+b+III+IV+V	46 (36)	6 (100)	
Location of DAVF			
Cavernous sinus	56 (44)	0 (0)	0.04
Large sinuses[b]	46 (36)	1 (17)	0.665
Other locations[c]	26 (20)	5 (83)	0.003
CST			
With CST	28 (22)	3 (9.7)	0.136
Without CST	100 (78)	3 (2.9)	

[a]Data are presented as n (%); [b]transverse sinus, sigmoid sinus, and superior sagittal sinus; [c]all locations other than cavernous sinus and large sinuses. IS=ischemic stroke; DAVF=dural arteriovenous fistula; CST=cerebral sinus thrombosis.

Table 3. Treatment modalities between the two groups of dural arteriovenous fistula patients with and without ischemic stroke[a]

	Without stroke ($n=128$)	With IS ($n=6$)	p
Endovascular therapy	85 (66)	4 (67)	1.000
Operation	1 (1)	0 (0)	1.000
Gamma-knife	4 (3)	1 (17)	0.208
Without treatment of DAVF	38 (30)	1 (17)	0.671

[a]Data are presented as n (%). IS=ischemic stroke; DAVF=dural arteriovenous fistula.

Treatment and outcome

The treatment modalities in these patients are listed in Table 3. The most frequently used treatment for DAVF in this series was endovascular treatment, which was used in 66.4% of patients in the non-stroke group and 66.7% in the ischemic stroke group. One patient in the ischemic stroke group and four in the non-stroke group were treated with gamma knife therapy. Surgical procedures were performed in one non-stroke patient, but none were performed in ischemic stroke patients. There was no interventional treatment in 30% of patients in the non-stroke group and 17% in the ischemic stroke group ($p=0.67$).

Of the six ischemic stroke patients with DAVF, three had a good functional outcome (modified Rankin scale 0 or 1), and three had an unfavorable outcome (modified Rankin scale ≥2). The outcome was not significantly related to cerebral venous thrombosis, or DAVF type, location or treatment.

Discussion

This was a retrospective study to examine the factors related to occurrence of ischemic stroke in DAVF patients. This was the first study to focus

on ischemic stroke in DAVF patients. Our major findings were that DAVF types that involved cortical venous drainage and DAVFs at other locations had a significant influence on the occurrence of ischemic stroke in DAVF patients.

DAVFs at other locations are associated with intracranial hemorrhage or aggressive manifestations,[4,6,10] and it also correlated with occurrence of ischemic stroke in our study. DAVFs at large sinuses were associated with less risk of ischemic stroke than at other locations. The venous outflow capacity of DAVFs at large sinuses was larger than at other locations, and venous stagnation was the major mechanism of DAVF-related ischemic stroke.[12] The venous stagnation in DAVFs at large sinuses is less severe than that at other locations, so DAVFs at large sinuses are associated with less risk of ischemic stroke. However, patients with large sinus DAVF were not free from ischemic stroke, which might be because of rare spontaneous regression and high flow.[13] Cavernous sinus DAVF is known to have the most benign course.[1,6,13,14] In the present study, patients with exophthalmos or eye chemosis were all shown to have cavernous sinus DAVF and they were all free from ischemic stroke. The reasons for this might be early detection of DAVF by eye symptoms, benign venous drainage pattern, and higher percentage of spontaneous regression.[13]

Type of DAVF is an independent predictor of aggressive manifestations,[4,6,8,9] and it also played an independent role in the occurrence of ischemic stroke in our study. It was particularly interesting that the rate of ischemic stroke in type IIa + b DAVF was lower than that in type IIb. Partial venous reflux into a large sinus in type IIa + b might have contributed to relieving some of the venous pressure, therefore, the rate of ischemic stroke was lower than in type IIb. The rate of ischemic stroke in type IV was much higher than in type III, which further confirmed the dangerous sign of venous ectasia.[15]

CST was also a borderline predictor of ischemic stroke in DAVF patients, which is compatible with the previous study of Tsai et al.[6] CST can result in venous hypertension and infarction.[16] CST and DAVF are considered to have a causal relationship with each other.[14] CST could result in opening of dural arteriovenous shunts, which might become DAVFs. In addition, the abnormal high flow of DAVF might damage the venous wall, which could result in CST.

Male sex is known to be a risk factor for aggressive manifestation in DAVF patients.[6] In the present study, there was also a significant trend that male DAVF patients were more susceptible to ischemic stroke than their female counterparts. This partly reflected the different location distribution of DAVF: 49% of DAVFs in female patients and 29% in male patients were located at the cavernous sinus, which was associated with the lowest risk of ischemic stroke.

The imaging characteristics of ischemic stroke in patients with DAVF differed from those in patients with arterial stroke. In this study, five of the six infarct patients had venous infarction that was secondary to venous hypertension. Venous hypertension decreases cerebral blood flow, which causes tissue damage and cytotoxic edema.[11,12] This presents as hypointensity on ADC maps and is defined as venous infarct. The rising venous pressure also disrupts the blood–brain barrier, which increases net capillary filtration and leads to the development of vasogenic edema.[11] In the single patient with infarct at the basal ganglia, infarction might have been secondary to his hypertension, which resulted in arterial thrombosis. This suggests that intracranial DAVF should be considered as an important differential diagnosis in patients with ischemic stroke and imaging findings compatible with venous infarct. For suspected cases, carotid duplex study is a valid modality before performing angiography to check for the possibility of DAVF by a decreased resistivity index of the external carotid artery < 0.72.[17]

The main treatment modality in this series was endovascular treatment, which is less invasive than traditional surgery. The ratios of patients without interventional treatment did not differ significantly between the ischemic stroke and non-stroke groups. In the ischemic stroke group, the only patient who did not receive treatment for DAVFs

had arterial stroke rather than venous infarct. In other words, all of the DAVF patients with venous infarct received treatment for DAVFs. As for the ratios of favorable outcome, there was no significant difference between the non-stroke and ischemic stroke groups, which indicated that the initial presentation of non-stroke symptoms might not be a guarantee of a good outcome in DAVF patients.

There were some limitations in our study. First, although, to the best of our knowledge, this was the largest case series to date, the number of patients was still small, which might have affected the statistical power of the study. Second, this was a hospital-based study, therefore, some asymptomatic DAVF patients might not have been included. However, the diagnosis of DAVF depends on angiography, therefore, it is impossible to screen for DAVF in the general population. Third, this study was retrospective, and the symptoms were only obtained from medical records, which might have been underestimated if patients did not report their symptoms. However, in our hospital, patients who were suspected or confirmed to have DAVF were routinely asked about symptoms of DAVF. Therefore, the possibility of underestimation could have been low.

In conclusion, our study showed that the risk of ischemic stroke in DAVF patients is associated with the location and type of DAVF. When patients present with ischemic stroke with imaging characteristics of venous infarct, the possibility of DAVF should not be neglected. Conventional angiography is mandatory for these patients because DAVF is a treatable etiology of stroke.

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