Prevalence of Thrombophilia in Dural Arteriovenous Fistula Patients with and without Cerebral Venous Sinus Thrombosis

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Background: *Thrombophilia could be one of the causes of venous thromboembolism at the unusual sites such as cerebral venous sinus thrombosis (CVST). In addition, it is generally accepted that CVST is one of the etiologies of dural arteriovenous fistulas (DAVFs).*
Objective: *The present study aimed to examine the prevalence of CVST in DAVF patients and to identify the associations between thrombophilia and DAVFs.*
Material and Method: *This is a cross sectional pilot study included 30 patients with DAVFs. All patients underwent cerebral angiography and were examined for thrombophilic factors potentially relevant to venous sinus thrombosis. The prevalence of thrombophilic abnormalities were compared between patients with and without CVST.*
Results: *CVST was diagnosed in 21 out of 30 patients (70%) patients with DAVFs. There are 11 out of 30 patients (36.7%) who had low protein S level. Six out of 28 patients (21.4%) had low antithrombin III level. Four patients (13.3%) had positive lupus anticoagulant. There was no patient with low level of protein C or positive anticardiolipin antibodies. There was no statistical difference in the prevalence of thrombophilic abnormalities between the patients with and without CVST.*
Conclusion: *This pilot study reported the prevalence of CVST in DAVFs in Thai population. It provides the information that DAVFs seemed to correlate with thrombophilia, whether the patients had CVST or not.*

Keywords: *Thrombophilia, Dural arteriovenous fistulas, Cerebral venous sinus thrombosis, Cerebral angiography*

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Intracranial dural arteriovenous fistulas (DAVFs) are abnormal shunts localized to the intracranial dura mater. They account for 10 to 15% of all intracranial arteriovenousmal formations[1,2]. While there is abundant evidence among current literatures regarding the treatment of DAVFs, the pathogenesis of DAVFs remains inconclusive. Nonetheless, it is generally accepted that cerebral venous sinus thrombosis (CVST) plays an important role as one of the etiologies of DAVFs[2-5]. In addition, Tsai et al reported a high frequency of sinus thrombosis (39%) among DAVF patients[6].

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Thrombophilia, a predisposition to develop blood clot, is among the causes of venous thromboembolism at the unusual sites such as CVST, which can be either hereditary or acquired. The common hereditary and acquired thrombophilia in Asian population included antithrombin III, protein C, or protein S deficiency, and antiphospholipid antibody syndrome, respectively. Currently, the association between thrombophilia and DAVFs is still unknown. Previously, there is no prior data regarding the prevalence of CVST in patients diagnosed with DAVFs. Furthermore, neither the prevalence of thrombophilia in DAVF patients nor the type of hypercoagulable defects found in patients with and without CVST have been formerly studied. Therefore, we conducted a pilot study to examine the prevalence of CVST in DAVF patients and to identify the associations between thrombophilia and DAVFs.

To the best of our knowledge, this is the first study reporting the prevalence of thrombophilia in DAVF patients including those with CVST and without CVST.

Material and Method

Patients

This is a cross sectional study. All adult DAVF patients diagnosed by digital subtraction cerebral angiography at Siriraj Hospital from July 2011 to January 2015 were recruited to the study. All related information was prospectively collected. The inclusion criteria was adult (age ≥18 years) DAVF patients with or without CVST diagnosed by cerebral angiography (Fig. 1). The exclusion criteria were previous history of head trauma or cranial surgery, recent extracranial thromboembolic events such as deep vein thrombosis, diseases or conditions that can affect the thrombophilic testing such as liver disease, anticoagulant treatment, or pregnancy.

Methods

All patients underwent cerebral angiography with special attention directed to establish the evidence of CVST. The diagnosis of CVST was made by two neurointerventionists whose experience was more than 5 years and who were blinded to the result of thrombophilic testing. Kappa statistic was used to evaluate the agreement in angiographic interpretation of CVST between the two neurointerventionists. The diagnosis of CVST was then separate to cavernous sinus and non-cavernous sinus thrombosis. The diagnosis of CVST was based on the following criteria:

Non-cavernous sinus thrombosis was diagnosed if there was any evidence of the followings: total occlusion, filling defect, outlet occlusion, or isolated sinus.

Cavernous sinus thrombosis was diagnosed if less than half of the common outlets were seen (less than 4 outlets). Common outlets of the cavernous sinus included the followings: ophthalmic venous drainage (superior ophthalmic vein or inferior ophthalmic vein), sphenoparietal sinus, pterygoid venous plexus, intercavernous sinus, pericarotid venous plexus, superior petrosal sinus, inferior petrosal sinus, and meningeal vein.

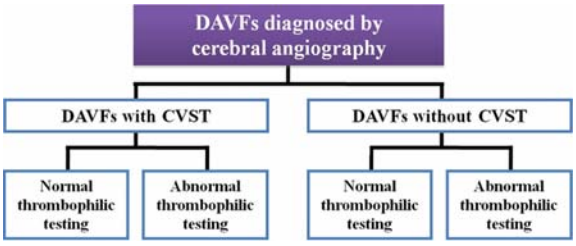

Fig. 1 The schematic design of the study.

Blood was collected for complete blood count, activated partial thromboplastin time, prothrombin time, antithrombin, protein C and protein S activities, anticardiolipin IgG and IgM, anti-β_2 glycoprotein 1 IgG and IgM and lupus anticoagulants in all patients prior to the performance of cerebral angiography. The specimens were sent to the hospital's central laboratory and were processed according to the standard methods.

The data was analyzed with SPSS program (PASW statistics 18.0). A *p*-value less than 0.05 was considered statistically significant. The prevalence of thrombophilic abnormalities were compared between the two groups (patients with CVST and without CVST) using the Chi-square test. Other categorical variables and continuous variables were compared using Chi-square test and T-test, respectively. The study was approved from Institutional Ethics Committee.

Results

Of the 30 patients, 11 were men and 19 were women. The mean age at diagnosis was 51.4±12.85 years (Table 1). There were no sex and age differences with regard to the presence and absence of CVST (Table 2).

The locations of DAVFs were at cavernous sinus in 10 patients (33.3%) and at non-cavernous sinus locations in 20 patients (66.7%). Non-cavernous sinus locations were further divided into transverse-sigmoid junction in 10 patients (33.3%), superior sagittal sinus in 4 patients (13.3%), torcular herophili in 2 patients

Table 1. Characteristics of 30 patients

Characteristics	Value
Age, mean ± SD (years)	54.1±12.85
Sex, n (%)	
Male	11 (36.7)
Female	19 (63.3)
Location, n (%)	
Cavernous sinus	10 (33.3)
Transverse-sigmoid sinus	10 (33.3)
Superior sagittal sinus	4 (13.3)
Torcularherophili	2 (6.7)
Others	4 (13.3)
CVST, n (%)	
Present	21 (70)
Absent	9 (30)

(6.7%). The rest of the locations were tentorial sinus, falx, posterior condylar vein, and lateral condylar vein with a single patient at each site. The most frequent locations of DAVFs were cavernous sinus and transverse-sigmoid junction, followed by superior sagittal sinus (Fig. 2).

CVST was diagnosed in 21 (70%) patients. Eleven out of 21 non-cavernous sinus-DAVF patients had CVST (52%), while all cavernous sinus-DAVF patients had CVST (100%).

Moderate agreement in CVST angiographic interpretation between the two neurointerventionists with Kappa of 0.46 was observed.

Thrombophilic test results

Eleven out of 30 patients (36.7%) had low protein S activity. Six out of 28 patients (21.4%) had low antithrombin activity. Four out of 30 patients (13.3%) had positive lupus anticoagulant. However, there was no patient with low protein C activity or positive neither anticardiolipin antibodies nor anti-β_2 glycoprotein 1.

The prevalence of thrombophilic abnormalities defined as at least one positive thrombophilic testing in patients with and without CVST were compared using Chi-square test. Interestingly, the prevalence of thrombophilia was not significantly difference between the two groups (p = 0.417) (Table 3). In addition, the type of thrombophilic abnormalities found in patients with and without CVST was not statically different between the two groups (Table 4). Two patients had incomplete blood test (no data of antithrombin activity) and were excluded from the comparison analysis.

Discussion

The locations of DAVFs in the present study

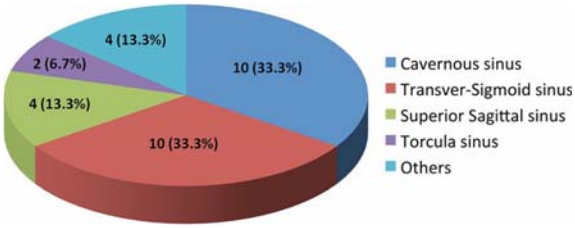

Fig. 2 Locations of DAVF.

Table 2. Comparison of age and sex among DAVF patients with CVST and without CVST

Characteristics	DAVF with CVST	DAVF without CVST	*p*-value
Age, mean ± SD (years)	54.43±14.99	53.3±5.98	0.77
Female sex (%)	61.9	66.7	1

Table 3. Comparison of thrombophilic abnormalities in DAVF patients with CVST and without CVST

Thrombophilic testing results	DAVF with CVST	DAVF without CVST	*p*-value
Abnormal, n (%)	11 (57.9)	7 (77.8)	0.417
Normal, n (%)	8 (42.1)	2 (22.2)	
Total	19	9	

Table 4. Comparison ofthe prevalence of protein S deficiency, antithrombin deficiency, and positive lupus anticoagulant in DAVF patient with CVST and without CVST

Hematologic abnormalities	DAVF with CVST (Total n = 21)	DAVF without CVST (Total n = 9)	Total	*p*-value
Protein S deficiency, n (%)	7 (33.3)	4 (44.4)	11 (36.7)	0.687
Antithrombin deficiency, n (%)	4 (19)	2 (22.2)	6 (20)	1.000
Positive lupus anticoagulant, n (%)	2 (9.5)	2 (22.2)	4 (13.3)	0.563
Low protein C activity, n (%)	0 (0)	0 (0)	0 (0)	
positive anticardiolipin antibodies, n (%)	0 (0)	0 (0)	0 (0)	
Positive anti-β_2 glycoprotein 1, n (%)	0 (0)	0 (0)	0 (0)	

were similar to previous reports[2,6] that the most frequent locations were cavernous sinus, transverse-sigmoid sinus, and superior sagittal sinus.

CVST was diagnosed in 21 (70%) patients with DAVFs. This finding is in harmony with a previous report[6] that the prevalence of CVST in DAVFs was high, especially in our series. However, the definition of CVST is different among prior studies. Therefore, the results should be interpreted with caution. Previously, Satomi et al[7] reported that cavernous sinus location was preferentially related to CVST compared to other locations. In addition, all 10 patients with cavernous sinus DAVFs in our study also had CVST. This may suggest that cavernous DAVFs have tendency to develop CVST at some degree.

As shown in previous reports, thrombophilia was related to DAVFs[8,9]. Considering the cause of thrombophilia associated with DAVFs in this study, low protein S activity was the most frequent abnormalities followed by low antithrombin activity and positive lupus anticoagulant. The prevalence of low protein S activity was as high as a third of all patients and was much higher than that found in healthy subjects[10,11]. To the best of our knowledge, this is the first study to demonstrate the high prevalence of thrombophilia in patients diagnosed with DAVFs. On the basis of current evidence, the formation of DAVFs seems to strongly correlate with thrombophilia. Thus, it could serve as a warning sign that, when dealing with patients diagnosed with DAVFs, clinicians should be aware of the association between thrombophilia and DAVFs. In addition, screening for thrombophilia may be useful in patients diagnosed with DAVFs in order to identify the patients who might be at high risk to develop CVST in the future. Hence, the appropriate treatment and monitoring could be planned in advance for such high risk patients who are also at increased risk to develop venous thromboembolism at other locations. The prevalence of thrombophilic abnormalities in patients with and without CVST were not statistical different. Moreover, patients without CVST had tendency to have an abnormal blood test compared to those with CVST (77.8% versus 57.9%). We hypothesized that patients who did not have CVST detected at the time of cerebral angiography might already have thrombus resolved before or after the time of blood sampling. Furthermore, given that the sample size was rather small in this pilot study and that our study did not have adequate power to detect the difference of thrombophilia between the two groups, a future research with larger sample size needs to be conducted to validate current findings and our hypothesis.

Conclusion

The prevalence of thrombophilic abnormalities in Thai DAVF patients was high. Clinicians should be aware of the association between thrombophilia and DAVFs. Further study is required to determine the usefulness of thrombophilia screening in patients diagnosed with DAVFs.

What is already known from this topic?

The incidence of CVST in Thai population was high. However, there is no prior data regarding the prevalence of CVST in patients diagnosed with DAVFs. There is also no study concerning either the prevalence of thrombophilia in DAVF patients or the hypercoagulable defects found in patients with and without CVST.

What this study adds?

This pilot study reported the prevalence of CVST in DAVFs in Thai population. It provides the information that DAVFs seemed to correlate with thrombophilia, whether the patients had CVST or not.

Potential conflicts of interest

None.

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ความชุกของภาวะ thrombophilia ในผู้ป่วยโรค duralarteriovenous fistula เปรียบเทียบระหว่างกลุ่มที่มีและไม่มี cerebral venous sinus thrombosis

สุชลิต ธรรมชาติถาวร, ทวีศักดิ์ เอื้อบุญญาวัฒน์, บุณฑริกา สุวรรณวิบูลย์, เอกวุฒิ จันแก้ว, ประจักษ์ ศรีรพีพัฒน์

วัตถุประสงค์: *ภาวะ Thrombophilia สามารถทำให้เกิด venous thrombosis รวมถึง cerebral venous sinus thrombosis (CVST) ได้การศึกษาก่อนหน้านี้พบว่า CVST มีความสำคัญต่อกระบวนการเกิดโรค duralarteriovenous fistula (DAVFs) คณะผู้นิพนธ์จึงได้ศึกษาถึงความชุกของภาวะ Thrombophilia ในผู้ป่วย DAVFs เพื่อหาความสัมพันธ์ระหว่างภาวะ thrombophilia กับการเกิดโรค DAVFs และเปรียบเทียบความชุกของภาวะ thrombophilia ระหว่างผู้ป่วย DAVFs ที่มีและไม่มี CVST*

วัสดุและวิธีการ: *ผู้ป่วย 30 คนที่ได้รับการวินิจฉัยว่าเป็นโรค DAVFs โดย digital subtraction angiography จะได้รับการตรวจเลือดเพื่อหาภาวะ thrombophilia โดยการส่งตรวจ complete blood count, prothrombin time, activated partial thromboplastin time, antithrombin, protein C และ protein S activities, anticardiolipin IgG และ IgM, anti-β_2 glycoprotein 1 IgG และ lupus anticoagulant*

ผลการศึกษา: *จากผู้ป่วย DAVFs 30 ราย พบผู้ป่วยที่มี protein S activity ต่ำผิดปกติ 11 คน (ร้อยละ 36.7) ผู้ป่วยที่มี antithrombin activity ต่ำผิดปกติ 6 คน (ร้อยละ 21.4) และผู้ป่วยที่มี lupus anticoagulant ผลเป็นบวก 4 คน (ร้อยละ 13.3) โดยไม่พบผู้ป่วยที่มี protein C activity ต่ำผิดปกติหรือผู้ป่วยที่มี antiphospholipid antibodies ผิดปกติเมื่อเปรียบเทียบความชุกของผู้ที่มีผลการตรวจ thrombophilia ผิดปกติ (มีความผิดปกติของผลเลือดอย่างน้อย 1 ชนิด) ในกลุ่มผู้ป่วย DAVFs ที่มี CVST กับกลุ่มที่ไม่มี CVST พบว่าไม่มีความแตกต่างของความผิดปกติของผลเลือดอย่างมีนัยสำคัญทางสถิติ*

สรุป: *จากการศึกษานี้พบว่ามีความชุกของภาวะ thrombophilia มากในผู้ป่วย DAVFs แพทย์ที่ทำการรักษาคนไข้กลุ่มนี้ ควรคิดถึงว่าผู้ป่วยอาจมีภาวะนี้ร่วมด้วยเสมอ และคณะผู้นิพนธ์คิดว่ามีความจำเป็นอย่างยิ่งที่จะต้องมีการวิจัย เพิ่มเติมต่อไปเพื่อศึกษาประโยชน์ของการตรวจหาภาวะ thrombophilia ในผู้ป่วย DAVFs ที่อาจเป็นประโยชน์ในการวางแผนการรักษาผู้ป่วยกลุ่มนี้ในอนาคต*