Indian J Hematol Blood Transfus (July-Sept 2022) 38(3):522–528
https://doi.org/10.1007/s12288-021-01480-3

ORIGINAL ARTICLE

Comprehensive Thrombophilia Evaluation in Cerebral Venous Thrombosis: A Single Center Cross Sectional Study

Rajiv Kumar[1] · Pulikottil Wilson Vinny[2] · Vishnu G. Nair[3] · Rajesh Jakku[3]

Received: 31 August 2020 / Accepted: 6 August 2021 / Published online: 14 August 2021

Abstract In patients with Cerebral Venous Thrombosis (CVT), inherited and acquired thrombophilic conditions have been studied either individually or as subset of a comprehensive evaluation. None of the studies have included a comprehensive evaluation of all the known associations. The associations for various conditions have been found to differ significantly between the Indian and the Western population. We defined a Comprehensive Thrombophilia panel (inherited and acquired) comprising of 13 thrombophilic conditions to include all the relevant known associations in CVT. All patients in this cross-sectional study were evaluated as per the defined protocol during the three-year study period. We evaluated 42 patients of CVT for presence of inherited and acquired thrombophilic conditions. The mean age of the study population was 38.4 yrs. An inherited or an acquired thrombophilic condition was diagnosed in 76% patients. Hyperhomocysteinemia and raised factor VIII levels were the most common conditions, seen in 38% and 35.7% patients respectively. MTHFR mutation was seen in 21% patients. Protein S deficiency was seen in 7% patients. Factor V Leiden and JAK2 positive MPN were seen in 2.3% cases. We did not detect any patients with Protein C deficiency, APLA syndrome, anti-thrombin deficiency, PG20210A mutation or PNH. PAI-1 polymorphism was not included in the protocol as its role is controversial and it has not been established in Indian studies. There is an urgent need for Comprehensive Thrombophilia testing in a larger population of CVT patients to better delineate the spectrum of associated thrombophilic conditions. Such a study is bound to impact therapy and prognosis of CVT.

Keywords CVT · Thrombophilia · MTHFR · fVIII · Hyperhomocysteinemia

Introduction

Cerebral Venous Thrombosis (CVT) is a rare manifestation of Venous Thrombosis (VT) and accounts for < 1% of all strokes [1]. The most common risk factor identified for CVT throughout the world is a prothrombotic condition [2]. The prevalence of an underlying thrombophilic condition in patients with CVT has been found to be different in different population groups. The ISCVT cohort found a prothrombotic condition in 34% patients, with a genetic prothrombotic condition in 22% patients [3]. The largest study from India by Pai et al. found a prothrombotic condition in only 18% patients [4]. Pai et al. had however studied only 04 prothrombotic markers in their study. Narayan et al. has reported an inherited thrombophilia in 26.5% in the Nizam's venous stoke registry [5]. Narayan et al. studied 05 thrombophilic conditions in their study. Similarly, most of the Indian studies have limited the thrombophilia evaluation to a few of the known factors and are not comprehensive. A large meta-analysis (including 23 cohort and 33 case control studies) showed that the thrombophilia factors studied were short of a comprehensive evaluation, leaving out many of the known factors in the individual studies. The meta-analysis had to leave out many of the factors due to inadequate data [1]. The cost of

✉ Pulikottil Wilson Vinny
vinnywilson@gmail.com

[1] Department of Medicine & Clinical Hematology, INHS Asvini, Mumbai, India

[2] Department of Medicine & Neurology, INHS Asvini, R C Church, Colaba, Mumbai 400005, India

[3] Internal Medicine, INHS Asvini, Mumbai, India

a comprehensive evaluation is a limiting factor in resource limited settings. The picture of the spectrum of underlying thrombophilic conditions in CVT and extent of the role played by individual thrombophilic conditions is conspicuously incomplete. Newer thrombophilic conditions like JAK2 positive Myeloproliferative Neoplasms (MPN), Paroxysmal Nocturnal Hemoglobinuria (PNH) and Anti Phospholipid Antibody (APLA) syndrome, the role of anticoagulation and its duration in CVT is being revisited. Patients of CVT with APLA syndrome, PNH and JAK2-positive MPNs are candidates for long term anticoagulation due to the persistence of the prothrombotic milieu. CVT also differs significantly from venous thrombosis in other vascular beds. The physiology of an erect posture affecting the incidence and pathophysiology of Deep Vein Thrombosis (DVT) in the lower limbs is possibly not applicable to CVT. Furthermore, the risk of recurrence in CVT patients is significantly smaller in comparison to patients with deep vein thrombosis (DVT) [6]. It is likely that the spectrum of thrombophilic conditions predisposing to a CVT is different from the more common DVT of lower limbs. We undertook a one-time Comprehensive Thrombophilia Evaluation of 13 Thrombophilic conditions on peripheral blood sample in patients of CVT presenting to our tertiary care hospital.

Patient and Methods

This was a cross sectional study conducted at a tertiary care teaching hospital over a period of 3 years from Feb 2017 to Feb 2020. The aim of the study was to study the prevalence of thrombophilic conditions in Indian patients with CVT. The objective of the study was to study the spectrum of thrombophilic conditions as per a defined comprehensive thrombophilia panel consisting of 13 parameters in patients with CVT. All consecutive patients newly diagnosed as CVT or being followed up for an old CVT underwent a one-time Comprehensive Thrombophilia Evaluation on peripheral blood sample as per standard institutional protocol. The patients met following inclusion and exclusion criteria.

Inclusion Criteria

1. All patients presenting to our tertiary care center with radiologically demonstrated CVT. Diagnosis of CVT was based on Contrast Enhanced Computed Tomography (CT) Scan of Head and/or Magnetic Resonance (MR) Venography of Brain.
2. Patients who are off anticoagulation for two months prior to recruitment.

Exclusion Criteria

Patients with conditions defined to have a prothrombotic mileu and/or established provoked CVT were excluded. These included:

1. Patients of cancer related CVT
2. Patient with pregnancy/puerperium related CVT
3. Patients with CVT related to local causes like neurosurgical interventions, trauma, para infectious CVT, etc.
4. Patients currently on anticoagulation for any reason or who were receiving hormonal pills/therapy.

The details of the comprehensive thrombophilia evaluation protocol done in all patients is given in Table 1. Patient's demographic data, provoking factors, clinical presentation, radiological findings, duration of anticoagulation, neurological outcomes, etc., were collected as per the protocol mentioned in Table 2. A database was created and analysed in Microsoft Excel (MS excel). Numerical variables are summarised as mean and median and nominal variables are presented as percentages.

Results

54 consecutive patients of CVT were studies. However, 12 patients were excluded from the study as per the exclusion criteria. A total of 42 cases were included during the study period. The mean age of the patient population was 38.4 yrs. There were 35 males (83%) and 7 females (16%). The median follow-up duration was 39.5 months. Headache was the most common presenting symptom (85.7%) followed by seizures (38%) and limb paresis (21.4%) (Table 2). Papilledema was observed in 23.8% patients. Transverse Sinus was involved most frequently (57.1%) followed by Superior Sagittal Sinus (50%) and Sigmoid Sinus (50%) (Table 2). The median time to testing for thrombophilia from the onset of CVT was 9 months. An inherited or an acquired thrombophilic condition was diagnosed in 32/42 patients (76%) (Table 1). Hyperhomocysteinemia was the commonest inherited thrombophilic condition of the study population (38%), followed by Factor VIII levels of $> 150\%$ (35.7%) and MTHFR (C677T/A1298C) mutation (21%). In 17% patients, both MTHFR mutation and hyperhomocysteinemia were observed. Protein S deficiency was detected in 7% patients. Factor V Leiden mutation (heterozygous) and JAK2 positive Essential Thrombocythemia were seen in only one patient (2.3%) each. The patient with JAK2 positive Essential Thrombocythemia was put-on long-term anticoagulation. No cases of APLA were detected in the study. Protein C deficiency, Anti thrombin deficiency,

Table 1 Comprehensive thrombophilia evaluation protocol and distribution in our cohort

Srl No	Thrombophilic condition	Method of detection used	Prevalence (n)
	Inherited thrombophilic conditions		
1	Raised Serum Homocysteine levels	Chemi luminscence microparticle immunoassay	38% (16)
2	Factor VIII levels (> 150%)	Photo optical/ Electromechanical clot detection	35.7% (15)
3	MTHFR Mutation (C677T/A1298C)	Real Time PCR	21% (09)
4	Factor V Leiden mutation	Real Time PCR	2.3% (01)
5	Protein S deficiency	Photo optical/Electromechanical clot detection	7% (03)
6	Protein C deficiency	Chromogenic assay	NIL
7	Anti-Thrombin deficiency	Photo optical clot detection/ Chromogenic assay	NIL
8	Prothrombin gene mutation (PG20210A)	Real Time PCR	NIL
	Acquired thrombophilic conditions		
9	JAK2 mutation V617F	Qualitative PCR	2.3% (01)
10	JAK2 Exon 12 mutation	PCR, Fragment analysis	NIL
11	PNH by flow cytomtery[13]	Flow cytometry (CD14,24,55,59, FLAER)	NIL
12	Lupus anticoagulant	dRVVT, Partial Thromboplastin Time Lupus Anticoagulant (PTT- LA)	NIL
13	Anti- ß2 Glycoprotein-1 IgM antibody	ELISA	NIL

Prothrombin gene mutation (PG20210A) or PNH were conspicuously absent in our study population. 01 patient died of CVT during the study period. He had prior history of recurrent arterial thrombosis involving the ulnar and radial artery for which he was not on long term anticoagulation. In 7% patients, a past history of a VTE or arterial thrombosis was observed. In 4.7% patients, recurrent arterial/venous thrombotic events (non-CVT) were noted during follow up post CVT. There was no recurrence of CVT in any patient with a median follow up of 39.5 months.

Table 2 Demographic and clinical characteristics of the patients

Characteristics	Patients: n (%)
Age- Yr	
Mean	38.45 +/− 10.29
Range	18–60
Sex	
Male	35/42 (83.33)
Female	7/42 (16.66)
Neurological deficit	
Papilledema	10/42 (23.8)
Vision loss	01/42 (2.38)
Monoparesis	03/42 (7.14)
Hemiparesis	05/42 (11.9)
Precipitating factors	
HAA	13/42 (30.95)
Pregnancy	01/42 (2.38)
Fever	01/42 (2.38)
Dehydration	02/42 (4.76)
DKA	01/42 (2.38)
Location of thrombus on MRI	
Superior Sagittal Sinus	21/42 (50)
Sigmoid sinus	21/42 (50)
Transverse Sinus	24/42 (57.14)
Cortical veins	05/42 (11.9)
Straight Sinus	02/42 (4.76)

HAA high altitude area, *DKA* diabetic ketoacidosis

Discussion

Francesco Dentali et al. in their systematic review of Natural history of CVT did not study the thrombophilia status of the patients and its effects thereof [7]. There is, however, a growing evidence to suggest the association of CVT with underlying thrombophilic conditions [2–6].

The knowledge of an underlying prothrombotic condition and its testing has traditionally been considered to affect the therapeutic decisions only in conditions like purpura fulminans, APLA syndrome, pregnancy with venous thrombosis, age < 40 yrs, and strong family history of venous thrombosis [8]. However, the current guidelines on CVT recommend consideration for long term anticoagulation in patients with severe thrombophilia including protein C, protein S and antithrombin deficiency, homozygous prothrombin G20210A or factor V Leiden, antiphospholipid antibodies or combined abnormalities [9].

The thrombophilic states with the maximum data on their association with CVT are factor V Leiden mutation, PG20210A mutation and hyperhomocysteinemia [10, 11].

Most studies on CVT in the Indian patients have focused on certain subsets of thrombophilia [4]. A comprehensive thrombophilia evaluation in CVT comprising of all the known thrombophilic conditions is conspicuously lacking in all these studies. As a result, the true picture of the spectrum of the underlying thrombophilic conditions in CVT is unknown. We defined a Comprehensive Thrombophilia protocol to include 13 known thrombophilic conditions in CVT at our institution. We instituted it as the standard of care for all newly diagnosed and old patients of CVT attending our hospital.

In our study, Hyperhomocysteinemia, raised factor VIII levels and MTHFR mutation emerged as the most commonly associated conditions. Hyperhomocysteinemia has been suggested to increase the risk of CVT by fourfold. This may be even higher with patients on OCPs [12]. While hyperhomocysteinemia is independently associated with an increased risk of thrombosis, pharmacological strategies that effectively lower plasma homocysteine levels do not reduce the risk of thrombotic vascular events [13]. Also, the causal effect of hyperhomocysteinemia in vascular thrombotic conditions is still unclear. While three meta-analysis have demonstrated a modest association of homocysteine levels with venous thrombosis, some studies have refuted any link between raised homocysteine levels and venous thrombosis [14–17]. In view of the confounding variables that are likely to affect serum homocysteine levels, interpretation of causal association between raised homocysteine levels and CVT warrants caution. The various other causes of a raised homocysteine level need to be kept in mind [18]. Cantu et al. in their case control study found a higher frequency of MTHFR mutation in patients with CVT (22% versus 10%), but it was not statistically significant [19]. Thermolabile MTHFR mutation is a known cause of hyperhomocysteinemia, however, its lack of association with CVT is intriguing and needs to be studied in larger population of CVT patients. Pai et al. study did not study MTHFR mutation or hyperhomocysteinemia in their cohort.

PG20210A mutation has been described as the second most common hereditary thrombophilia after the factor V Leiden mutation in patients with venous thrombosis [1]. PG20210A mutations along with OCP use has been associated with increased risk of CVT [6]. Also, one study suggested that there is an increased risk of recurrence of CVT in pediatric CVT patients with PG20210A mutations. However, in our study no patient was found to have this mutation. The prevalence of PG20210A mutations in the Indian population has been found to be very low as compared to the western population [8]. Pai et al. did not study PG20210A mutation as it was considered possibly non-existent in the Indian population [4]. The utility of this test needs to be assessed in larger population studies in the Indian context. Similarly, factor V Leiden (FVL) has been associated with CVT in the western studies [1, 10]. While Indian studies have found a weaker association between factor V Leiden (FVL) and CVT, we found factor V Leiden mutation in 2.3% patients [4]. Garewal et al. have reported a prevalence of FVL in of 10.9% CVT patients of *Punjabi Indian* origin [20]. However, Pawar et al. found no association of FVL with DVT and Strokes but observed a 20.6% prevalence with Budd Chiari Syndrome [21]. Similarly, a higher prevalence of FVL and absence of PG20210A mutations have been reported in *Tunisian* population with CVT [22]. The genetic heterogeneity due to different ethnic profiles in Indian population and the thrombotic propensity of different thrombophilic conditions in different vascular beds could account for these differences. This aspect needs to be studied in larger studies.

APLA is also a common risk factor for CVT and is seen in 6–17% patients [6]. However, in our study we didn't find any case of APLA. This could be due to the skewed male to female ratio in our study. CVT is 3 times more common in women and 6 times in those women who are taking OCPs [6]. Also, we conducted only LAC and anti-beta-2 glycoprotein-1 antibody in our panel for APLA. It is possible that a few patients with anti-cardiolipin (aCL) may have been missed in our study. It has also been suggested that different thrombophilic conditions may predispose to thrombosis in different vascular beds and APLA has been most strongly associated with placental thrombosis [11]. A systematic review on CVT and a large study on CVT from India did not report on APLA [1, 4].

Protein S deficiency in CVT has been reported variably in the Indian context with studies showing the prevalence ranging from 4.8% in the largest CVT data from India to 12.3% seen in the venous stroke registry from southern India to 70% in a study from Northern India [5, 23]. In our study we found a very low incidence of Protein S deficiency which is commensurate with the study of Pai et al. Higher protein S deficiency data from some centres also needs to consider the low levels seen during the acute thrombotic stage or while the patient is on anticoagulants, which may sometimes be overlooked. Pai et al. had reported Protein C as the most common inherited disorder in CVT. However, we did not find any patient of Protein C deficiency in our patient cohort. This could be due to the relatively small sample size of our study. It is very important to consider the median time to thrombophilia work up as testing in a steady state while the patient is off anticoagulants and in the absence of other confounders is likely to give the best information. In our study the median time to thrombophilia workup post the index CVT event was 9 months.

Table 3 Suggested timing of comprehensive thrombophilia assessment panel in CVT

Option 1: 8–12 weeks after stopping anti coagulation/ VKAs (Preferred option)	Remarks
Protein C levels	1. Cost effective
Protein S (Free) levels	2. Single point analysis
Antithrombin levels	3. Helps prognostication and counselling of patients
Factor VIII levels (> 150%)	4. May indicate the requirement of extended anticoagulation in select patient groups as per the current guidelines
Factor V Leiden/APCR	
MTHFR mutation (C677T/A1298C)	
PG20210A mutation	
JAK2 V617F/Exon 12 mutation	
PNH by flow cytometry/FLAER	
APLA: LAC & Anti ß2 GP1 IgM/IgG/IgA	
Serum Homocysteine levels	
OPTION 2	
AT DIAGNOSIS	
Factor V Leiden/APCR	Not affected by the acute thrombotic state
MTHFR mutation (C677T/A1298C)	
PG20210A mutation	
JAK2 V617F/Exon 12 mutation	
PNH by flow cytometry/FLAER	
APLA: Anti beta-2 GP1 IgM/IgG/IgA	
AT 8–12 Weeks After Stopping Anticoagulation	
Protein C levels	Likely to be affected by the acute thrombotic state or the use of VKAs
Protein S (Free) levels	
Antithrombin levels	
Factor VIII	
Lupus anticoagulant	
Serum Homocysteine levels	

PNH has also been associated with venous thrombosis at unusual sites and CVT may reveal an underlying PNH in 30% cases. 2–8% patients of PNH may develop CVT [24]. However, we did not detect any such case in our study, possibly due to the rarity of this disorder and small sample size of our study. Increased factor VIII levels have been associated with 15–18 times increased risk of CVT and has been reported to be raised in 25–80% of patients [25, 26]. We found high factor VIII levels in 35.7% patients. However, being an acute phase reactant, the exact role of raised factor VIII is difficult to analyze and will require large studies to confirm its pathogenic role and implications for therapy. In view of the very high levels reported in the few studies, it is imperative that factor VIII levels be included in the thrombophilia workup of all CVT patients, after due precautions. Increased factor VIII levels are currently not an indication for long term anticoagulation, however, it is imperative that these patients be followed up closely to look for recurrence.

JAK2 positive MPNs, although a rare cause of CVT, have not been assessed in most of the larger studies and may be important to be assessed in all patients of CVT as it has a higher risk of recurrence and may be an indication for long term anticoagulation. We detected 01 patient (2.3%) with JAK2V617F positive essential thrombocythemia (ET). JAK2V617F mutation may be present even in the absence of an overt MPN which may be diagnosed on follow up. JAK2 V617F mutation has been reported in 1.1% to 6.6% of CVT patients [27–29].

The role of Plasminogen Activator Inhibitor—1(PAI-1) polymorphism has been found to have a controversial role in venous thrombosis. Prabhudesai et al., in their study on 156 Indian CVT patients found PAI -1 genotypic frequencies in 18.6% for 4G/4G, 49.4% for 4G/5G and 32% for 5G/5G. The frequency of 4G/4G phenotype was high but not statistically significant [30]. Hence, we did not include it in our protocol.

Thrombophilia testing is routinely advised by the Neurologists in CVT patients. The cost of 'panel-testing' is

much lower than when the tests are conducted individually or in small variable groups at various time point of the course of CVT. Thrombophilia panel testing done at a point in time during the course of CVT where it is unlikely to be affected by variables like acute thrombosis or VKAs holds multiple benefits. Besides the cheaper cost factor, such one point "panel testing" is likely to prognosticate the chances of CVT recurrence which further has a bearing on its treatment. A suggested schema for thrombophilia testing in CVT is as given in Table 3. Despite large retrospective data on thrombophilia in CVT, there is still a lot of controversy on the prevalence of various disorders in individual patient populations and its impact on therapy and prognosis. Hence, there is an urgent need of systematic studies incorporating standardized comprehensive testing protocol in all patients with CVT. The complex interplay of inherited and acquired thrombophilic conditions, predisposing factors and transient precipitating events, leading to the final outcome of CVT needs to be better defined in larger studies especially in the Indian context.

The limitations of our study include a small sample size and the skewed male to female ratio due to the type of clientele presenting to our hospital.

Conclusion

The data on the prevalence of inherited and acquired thrombophilic conditions in CVT is very variable and is also affected by the population being studied. The data from other countries is significantly different from Indian population, especially with respect to factor V Leiden mutation and PG20210A mutation. The high prevalence of hyperhomocysteinemia, factor VIII levels and MTHFR mutation seen in our study needs to be further studied in a larger CVT population to better delineate the underlying mechanisms contributing to thrombosis. While estimating its true prevalence, the effects of subclinical B12 deficiency in a largely vegetarian Indian population with a propensity to cause high homocysteine levels in the general population has to be borne in mind. The debate on the relevance of thrombophilia evaluation in CVT is ongoing. We propose that thrombophilia evaluation in CVT should either be comprehensive, as suggested by us, or should not be done at all. Institutional protocols for investigating CVT should be developed accordingly. Limited thrombophilia testing in all the large studies and meta-analysis so far has failed to deliver clear guidelines on CVT management. This study also emphasizes, especially for the non-Hematology community of physicians/neurologists to avoid thrombophilia testing during certain phases of the disease/therapy and suggests a guideline for the same.

Funding No financial support was received from any source for this study.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical Approval Ethical clearance was obtained for the study.

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