

Prevalence of Inherited Procoagulant States in Cerebral Venous Thrombosis and its Correlation with Severity and Outcome

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Abstract

Background Cerebral venous thrombosis (CVT) is one of the important causes of stroke in young adults. It is caused by complete or partial thrombotic occlusion of the cerebral venous sinuses or cortical veins. There are many risk factors associated with this condition, out of which common ones are oral contraceptives use, genetic, or acquired thrombophilias, infections, malignancy, pregnancy, and puerperium. We aimed to study the prevalence of inherited procoagulant states in patients with CVT and correlate these states with the severity and outcome.

Materials and Methods It was a prospective observational study of 2 years duration in which 75 patients, 18 to 50 years old, with confirmed CVT were included. The baseline data, imaging findings were recorded for all the patients. After 3 months of the onset of CVT, anticoagulants were stopped and a procoagulant test was done for all patients. Severity was assessed by Glasgow Coma Score (GCS) at the onset of illness. Functional assessments were done using the modified Rankin Scale (mRS) at presentation, at 7 days, 6 weeks, and 3 months.

Results In the present study, any procoagulant state was seen in 9 out of 75 patients with CVT that accounted for 12% of the total population. There was no significant correlation between the presence of procoagulant states and severity of illness as assessed by GCS at presentation. The presence of any thrombophilia did not affect the final outcome at 7 days, 6 weeks or 3 months ($p = 0.532$, $p = 0.944$ and $p = 0.965$ respectively) as assessed by modified Rankin Scale (mRS).

Conclusion Inherited procoagulant states are an important risk factor for CVT. The presence of an inherited procoagulant state does not have any correlation with the disease severity and outcome.

Keywords

- ▶ cerebral venous thrombosis
- ▶ procoagulant state
- ▶ thrombophilia

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Introduction

Cerebral venous thrombosis (CVT) is one of the important causes of stroke. It is the treatable cause of stroke and accounts for 0.5% of all strokes.¹ Amongst the various causes of stroke in the young, CVT is an important cause.² It has an incidence of 0.22 to 1.32 cases per lac per year.³ It is caused by thrombotic occlusion of the venous sinuses in the brain. Cerebral venous sinus occlusion may be partial or complete. It may involve the smaller feeding cortical veins that drain into cerebral sinuses (cortical vein thrombosis).

Cerebral venous thrombosis may be unprovoked (no underlying cause) or provoked (identifiable etiology). Certain risk factors may coexist with CVT in a patient.⁴ The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)⁵ revealed that ~85% of adult patients have one or more identifiable risk factors. The most common risk factor in the ISCVT study was oral contraceptive pill use followed by the prothrombotic states, which may be genetic or acquired, with genetic prothrombotic states being commoner than the acquired prothrombotic states. Other common risk factors included pregnancy, puerperium, malignancy, head trauma, infections such as sinusitis, drugs (oral contraceptives, steroids, cytotoxic drugs), dehydration, high altitude, and inflammatory conditions such as Behçet's disease, systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD).⁵ Risk factors specific to females are more important in the younger age group, whereas malignancy is commoner in the elderly patients.⁶

Thrombophilic states are detected in more than 22% of patients with CVT.⁵ These states are classified into mild and severe forms. The mild forms include heterozygous factor V Leiden mutation and prothrombin G20210A gene mutation. The severe ones are protein C deficiency, antithrombin deficiency, protein S deficiency, prothrombin G20210A gene mutation, homozygous factor V Leiden mutation, antiphospholipid antibodies, and a combination of these abnormalities. The commonest among the inherited thrombophilias are the factor V Leiden mutation and prothrombin G20210A gene mutation that account for nearly 50 to 60% of cases and have been vastly studied in CVT.^{7,8}

In hereditary prothrombotic states, the therapeutic decision regarding administering long-term anticoagulation often needs to be individualized.⁹⁻¹² This decision needs to be taken after a thorough evaluation and discussion of the risk of recurrence of thrombosis and the risk associated with long-term anticoagulation. If a hereditary hypercoagulable state is detected, the screening of other family members may be recommended. There have been only a few studies and limited data on the prevalence of these procoagulant states in CVT in the Indian population^{13,14} and the implications of these procoagulant states on the subsequent morbidity and mortality.

The purpose of this study was to assess the prevalence of cerebral venous sinus thrombosis at a tertiary care center and assess its correlation with severity and outcome using GCS and modified Rankin Scale (mRS) as a measure.

Materials and Methods

It was a prospective observational study of 2 years duration in which 75 patients, 18 to 50 years old, with confirmed CVT (on MRI and MRV or CT venography), attending the department of neurology OPD/emergency at a tertiary care hospital, were included after prior consent. Patients with an immunocompromised state, systemic illness, and pregnant and lactating female patients were excluded from the study. Baseline data were recorded for each patient including a detailed history and clinical findings at presentation. All patients underwent neuroimaging and received standard care after confirmation of diagnosis. After 3 months of onset, these patients underwent procoagulant testing after stopping oral anticoagulant drugs for 2 weeks. The procoagulant tests included heterogeneous factor V Leiden mutation, prothrombin G20210A gene mutation, antithrombin III levels, protein C and protein S levels, homozygous factor V Leiden mutation, and prothrombin G20210A gene mutation.

Functional assessments were done using the modified Rankin scale (mRS) at presentation, at 7 days, 6 weeks, and 3 months.

Statistical Analysis

Continuous variables are presented in form of mean \pm standard deviation (SD). The categorical variables are expressed as proportions. Chi-square/Fisher's exact test was used to study the association between proportions. Multiple linear/logistic regressions were performed to see the impact of a group of variables on a dependent variable. *P*-value equal to or less than 0.05 was considered statistically significant. SPSS version 16.0 or higher was used to analyze the data.

Results

Seventy-five patients were included in this study. The baseline data are given in **Table 1**.

The mean age of the patients was 30.68 years. The study included 40 (53.3%) male patients and 35 (46.7%) female patients. The onset of CVT was acute (< 48 hours) in 22 (29.3%) patients, subacute (48 hours–7 days) in 48 (64%) patients, and chronic (>7 days) in 5 (6.7%) patients. The most common mode of presentation was subacute. Amongst the clinical features at presentation, the headache was the most common feature found in 56 (74.7%) patients, followed by seizures in 37 (49.3%) patients. Hemiparesis and altered sensorium were seen in 34 (45.3%) patients each. The most common examination finding was papilledema seen in 60 (80%) patients. Focal neurological deficits were common in the study group with hemiparesis occurring in 34 patients. However, cranial nerve involvement was seen in only three (4%) patients (facial palsy in two and pupil involving complete third nerve palsy in one).

In investigations, the mean hemoglobin was 12.4 g/dL. Total leucocyte counts ranged from 4800 to 21000/mm³. The renal functions (blood urea nitrogen and creatinine) of nearly all patients were normal and only three patients had acute kidney injury that resolved subsequently. Liver

Table 1 Baseline data of study patients

| | Variables | | No of patients (total no = 75) | Percentage (%) |
|----|-----------------------|-------------------------|-----------------------------------|----------------|
| 1. | Sex | Male | 40 | 53.3 |
| | | Female | 35 | 46.7 |
| 2. | Onset | Chronic | 5 | 6.7 |
| | | Acute | 22 | 29.3 |
| | | Subacute | 48 | 64 |
| 3. | Presenting Complaints | Headache | 56 | 74.7 |
| | | Seizures | 37 | 49.3 |
| | | Hemiparesis | 34 | 45.3 |
| 4. | Examination findings | Papilledema | 60 | 80 |
| | | Hemiparesis | 34 | 45.3 |
| | | Cranial nerve palsy | 3 | 4 |
| 5. | Neuroimaging findings | Bleed | 17 | 22.7 |
| | | Hemorrhagic infarct | 35 | 46.7 |
| | | Infarct | 11 | 14.7 |
| 6. | Affected sinuses | Superior sagittal sinus | 44 | 58.7 |
| | | Transverse sinus | 35 | 46.7 |
| | | Straight Sinus | 16 | 24 |
| | | Internal jugular vein | 10 | 13 |
| | | Cortical veins | 6 | 8 |
| | | Deep veins | 8 | 11 |

function tests were normal in all patients. The mean random blood sugar was 93.3 mg/dL and none of the patients had hypoglycemia or hyperglycemia needing intervention.

The diagnostic modality was MRI and MRV in all patients except in 6 out of 75 patients (8%) who underwent CT venography for documentation of thrombosed cerebral veins/sinuses. The most common parenchymal lesion on MRI was hemorrhagic infarct not respecting arterial boundaries (46.7%). Other findings included bleed in 22.7%, infarct in 14.7%, and normal brain parenchyma in 16% of patients.

The most common sinus involved was superior sagittal sinus that was seen in 44 (58.7%) patients. Other sinuses involved in decreasing order included transverse sinus in 35 (46.7%), sigmoid sinus in 18 (24%), an internal jugular vein in 10 (13%), deep veins in 8 (11%), and cortical veins in 6 (8%) patients. Multiple sinus involvement was seen in 44 (58.7%) patients of which ≥ 2 were involved in 33 (44%) patients and 11 (15%) patients had ≥ 3 sinuses involved. The most common combination amongst these was superior sagittal sinus, transverse sinus, and sigmoid sinus thrombosis.

The prevalence of inherited thrombophilia in CVST: In the present study, any procoagulant state was seen in 9 out of 75 patients with CVST, which accounted for 12% of the study population. Out of these 9 patients, 5 were males and 4 were females. Among the procoagulant states studied, protein C was seen most frequently (4 out of 75, 5.3%), followed by

protein S (4%), antithrombin III (2.7%), and heterogeneous factor V Leiden (1.3%).

None of the patients had prothrombin G20 210A gene mutation and homozygous factor V Leiden mutation. More than one state was seen in one patient who had two states present (Proteins C and S; **Table 2**).

Correlation of inherited thrombophilic states with the severity and outcome in CVST: Overall, the GCS ranged from 6 to 13. Six (8%) patients had a GCS < 7 , 84.3% of the patients had a GCS between 8 and 12, and 2.7% had a GCS of ≥ 13 . The mean GCS was 9.3. All patients with poor GCS had either deep venous thrombosis or multiple sinus thrombosis with hemorrhagic infarcts or bleeding. There was no significant correlation between the presence of procoagulant states and poor GCS at presentation. Mean GCS in patients with any procoagulant state was 9.32 ± 1.51 and in patients with normal thrombophilic profile was 9.22 ± 2.33 ($p = 0.868$).

There was no significant correlation between the extent of MRI parenchymal involvement and the presence of procoagulant states ($p = 0.229$). None of the patients with infarct on imaging had any procoagulant state and out of nine patients with normal brain parenchyma on MRI, three had thrombophilia. There was no significant association between the number of sinuses involved and the presence of thrombophilia ($p = 0.807$).

The mean mRS was 3.2 (range: 1–5), 2.4 (range: 1–4), and 1.9 (range: 1–3) at 7 days, 6 weeks, and 3 months,

Table 2 Prevalence of various procoagulant states

| Procoagulant state | No. of patients |
|---|----------------------------------|
| Protein C | 4 |
| Protein S | 3 |
| Antithrombin III | 2 |
| Heterogenous factor V Leiden | 0 |
| Prothrombin G20 210A gene mutation | 0 |
| Homozygous factor V Leiden | 0 |
| >1 procoagulant state | 1 (both protein C and protein S) |
| Total patients with thrombophilic state | 9 |

respectively. Also, 62% of patients had become nearly independent for their activities of daily living (mRS: 1–3) by 7 days, 89% by 6 weeks, and 93.3% by the end of 3 months. The presence of any thrombophilia did not affect the final outcome at 7 days, 6 weeks, or 3 months ($p=0.532$, $p=0.944$ and $p=0.965$ respectively) as measured by mRS (–Table 3). At 7 days, the mean mRS was 3.19 ± 1.07 when thrombophilia was present and was 3.0 ± 0.93 when none of the thrombophilic states were present ($p=0.637$). At 6 weeks, the mean mRS was 2.25 ± 0.71 when the thrombophilia was present and was 2.38 ± 0.71 when none of the thrombophilic states were present ($p=0.623$). At 3 months, the mean mRS was 1.88 ± 0.83 when the thrombophilia was

present and was 1.94 ± 0.77 when none of the thrombophilic states were present ($p=0.831$).

No significant correlation was found between the presence of a procoagulant state and sex. The chi-square statistic with Yates correction was 0.0457 and the p -value was 0.8308. Five (6.7%) patients died in the study. Most of the deaths occurred in the first week of onset. There was no significant correlation in the frequency of deaths and the presence of procoagulant states ($p=0.579$).

Discussion

This was a prospective study done on 75 patients of CVST aged 18 to 50 years, presenting to a tertiary care center. CVST occurs most commonly in middle age and is rare in the elderly or in children. The present study cohort was younger with a mean age of 30.68 years. CVST commonly affects both sexes equally. However, the sex distribution varies considerably across various cohorts.^{13,14} In our study, there was a slight non-significant female preponderance. The presence of non-significant female preponderance in the present study may be due to the fact that females who were pregnant or were lactating were excluded. The most common mode of onset of CVT was subacute in our study, which is consistent with the previous studies.^{5,13,14} Headache is one of the commonest presenting features in CVT and has been reported in close to 90% of cases.^{15–17} In this study, headache occurred in 74.7% of the study population followed by seizures, hemiparesis, and altered sensorium in decreasing

Table 3 Correlation of thrombophilic states with outcome assessed by mRS at 7 days, 6 weeks, and 3 months

| mRS at 07 days | Thrombophilia | | Total | Pearson Chi-square | p -Value |
|-----------------|---------------|---------|-------|--------------------|------------|
| | Absent | Present | | | |
| 1 | 3 | 0 | 3 | 4.120 ^a | 0.532 |
| 2 | 12 | 3 | 15 | | |
| 3 | 28 | 2 | 30 | | |
| 4 | 13 | 3 | 16 | | |
| 5 | 7 | 0 | 7 | | |
| 6 | 1 | 0 | 1 | | |
| Total | 64 | 8 | 72 | | |
| mRS at 06 weeks | | | | | |
| 1 | 7 | 1 | 8 | .382 ^a | 0.944 |
| 2 | 26 | 4 | 30 | | |
| 3 | 29 | 3 | 32 | | |
| 4 | 1 | 0 | 1 | | |
| Total | 63 | 8 | 71 | | |
| mRS at 3 months | | | | | |
| 1 | 21 | 3 | 24 | .071 ^a | 0.965 |
| 2 | 26 | 3 | 29 | | |
| 3 | 17 | 2 | 19 | | |
| Total | 64 | 8 | 72 | | |

order of frequency. Papilledema was the most common examination finding. Others are focal neurological deficit, cranial nerve palsies.

The diagnostic modality was MRI and MRV in the majority of the patients.¹⁸⁻²⁰ The most common parenchymal lesion on MRI was hemorrhagic infarct not respecting arterial boundaries occurring in 46.7% of patients which is similar to other major studies.^{5,20} The superior sagittal sinus is the most frequently affected sinus (in 62%), followed by transverse sinus (~45%). Sigmoid sinus involvement occurs rarely in isolation. Thrombosis of the deep veins is present in ~18%.^{5,13,14} In the present study, the most common sinus involved was superior sagittal sinus (seen in 58.7% of patients). Other sinuses involved in the decreasing order of frequency included transverse sinus (46.7%), sigmoid sinus (24%), internal jugular vein (13%), deep veins (11%), and cortical veins (8%) which is similar to other major studies.^{5,13,14}

Thrombophilic states predispose an individual to venous thrombosis more than arterial thrombosis, especially when another event contributes.²¹⁻²⁴ In CVST, the prevalence varies across western and Indian literature. In the ISCVT, any thrombophilia, whether genetic or acquired, was seen in 34.1% of patients, out of which 22.4% of cases accounted for inherited thrombophilia.⁵ Amongst the Indian studies, the prevalence of inherited thrombophilic states was found to be 18% in one major study and 12% in the other study.^{13,14} In our study, any procoagulant state was seen in 9 out of 75 patients with CVST, which accounted for 12% of the total population, and among the procoagulant states studied, protein C was seen most frequently (4 out of 75, 5.3%), followed by protein S (4%), antithrombin III (2.7%), and heterogeneous factor V Leiden (1.3%). None of the patients had prothrombin *G20 210A* gene mutation or homozygous factor V Leiden mutation.

In the present study, there was no significant correlation between the presence of procoagulant states and poor GCS at presentation. There was also no significant correlation between the mode of MRI parenchymal involvement and the presence of procoagulant states ($p = 0.229$). No significant correlation was found between the presence of procoagulant states and sex ($p = 0.8308$). Also, 62% of patients had become nearly independent for their activities of daily living (mRS: 1-3) by 7 days, 89% by 6 weeks, and 93.3% by the end of 3 months, which is comparable to previous studies.²⁵⁻²⁷ However, the presence of thrombophilia did not affect the functional outcome as assessed by mRS. In our study, five (6.7%) patients died in the study. Most of the deaths occurred in the first week of onset. There was no significant correlation between the frequency of deaths and the presence of procoagulant states ($p = 0.579$). The risk factors associated with death were male sex, poor GCS at onset, and multiple sinus involvement.

Conclusion

The results of this study showed that CVST commonly affects both sexes equally with a slight female preponderance and most commonly occurs at young-to-middle age.

The most common mode of onset was subacute followed by acute, and the least common was chronic. The most common presentation was with headache followed by seizures, hemiparesis, and delirium. Papilledema and hemiparesis were frequently present, and cranial nerve deficits and sensory abnormalities were rare. In most of the patients, diagnosis of CVST was confirmed with an MRI and MRV.

Any inherited thrombophilia was seen in 12% of the patients, of which protein C was seen most frequently followed by protein S, antithrombin, and heterogeneous factor V Leiden. Prothrombin *G20 210A* gene mutation and homozygous factor V Leiden were not seen in any patient. More than one state was seen in only one patient (Proteins C and S).

The presence of inherited thrombophilia studied was not related to sinus involvement, parenchymal involvement, and did not affect the short- or long-term outcome when measured by mRS. The mortality was 6.7% and the presence of inherited thrombophilia did not affect the mortality in CVST.

The study had certain limitations that included small sample size and the sample taken from a tertiary care center may not be a true representation of the disease in the population. Also, the procoagulant states that were present or absent were not repeated, and because false-positive/negative results are known, these may have falsely increased or decreased the prevalence of these states.

Conflict of Interest

None declared.

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