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# Clinical associations, biological risk factors and outcomes of cerebral venous sinus thrombosis

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## Abstract

**Objective:** Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease affecting young adults. The majority of the patients are female. The aim of this study is to assess the clinical associations, risk factors and outcomes of the patients with CVST.

**Methods:** The data of 75 patients with CVST admitted to our hospital between 2006 and 2016 were reviewed. Demographic and clinical features and the thrombophilic risk factors of the patients were recorded. The localizations of the thrombi were determined and modified Rankin score at the time of onset and discharge were calculated.

**Results:** The majority of our patients (78.7%) were female. Median age was 35 years (16–76). The most common symptom was headache (86.7%). In 82.6% of our patients, inherited or acquired risk factors for thrombosis were detected. Transverse sinus was the most common site of thrombosis followed by sigmoid and superior sagittal sinuses. Two thirds of the patients had involvement of multiple sinuses. The patients with the involvement of sagittal sinus had better disability at the time of admittance ($p = 0.013$) while the number of involved sinuses was correlated worse disability ($p = 0.015$). The neurologic states in the majority of the patients were improved by the end of the hospitalization period ($p = 0.001$). There was no significant difference in disability score at discharge between men and women ($p = 0.080$). No patient with CVST died in the hospitalization period.

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**Conclusions:** This study is one of the largest cohort studies on CVST in our region. The results of the study disclosed that CVST had wide range of clinical manifestations and non-specific symptoms at the beginning. For that reason, in especially high risk groups for thrombosis, the diagnosis of CVST should be kept in mind.

**Keywords**
Cerebral venous sinus thrombosis, risk factors, outcome

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## Introduction

Cerebral venous sinus thrombosis (CVST) is a rare form of cerebrovascular disease that most often affects young adults. Although magnetic resonance imaging (MRI) has made CVST easier to diagnose, its detection may be challenging because of its multiple and non-specific symptoms. The estimated incidence of CVST is 3–4 cases per million population, although the true incidence is still not known. Recognized risk factors for CVST include pregnancy, recent childbirth, oral contraceptive (OC) drug use, prothrombotic states and disorders of coagulation; consequently, the majority of patients with CVST are female. The clinical course of CVST is highly variable. Recent improvements in treatment and earlier diagnosis have resulted in better outcomes for patients.[1–4] The aim of this study was to assess the clinical associations, biologic risk factors and short-term outcomes of patients with CVST.

## Patients and methods

We reviewed the medical records of all patients diagnosed with CVST between 2006 and 2016 in our hospital. We identified 75 patients for inclusion in this retrospective study. In all patients, cranial computerized tomography (CT), MRI and magnetic resonance venography (MRV) were performed within 72 hours of symptom onset. The diagnosis of CVST was based on MRI and MRV findings in all patients. We recorded the demographic and clinical characteristics of each patient, including the presence of known risk factors for CVST such as pregnancy, recent childbirth, OC drug use, connective tissue disease and Behçet's disease.[2] Complete blood count, blood biochemistry, coagulation profile, prothrombin time, activated partial thromboplastin time, and serum homocysteine and vitamin B12 concentrations were also identified. Each patient was assessed for genetic thrombophilic risk factors such as factor V Leiden, prothrombin G20210A gene mutation and methylene-tetrahydrofolate reductase (MTHFR) mutation using light cycler real-time polymerase chain reactions. All patients were also assessed for deficiency of protein C, protein S and antithrombin III. We recorded the site of thrombosis and the score on the modified Rankin Scale (mRS) to determine the severity of disability at the time of symptom onset and hospital discharge. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Ankara Training and Research Hospital (approval date February 04, 2015; reference number 0581).

### *Statistical analysis*

Statistical Packages for the Social Sciences (version 20.0; SPSS Inc., Chicago, IL, USA) software was used for all analyses.

Categorical and continuous data were compared using the chi-squared (or Fisher's exact test if required by sample size) and Student's t-test, respectively. Bivariate correlation analyses for categorical and continuous data were performed by Spearman's and Pearson's correlation analysis, respectively. The Kruskal–Wallis and Kolmogorov–Smirnov tests were used to make comparisons between related samples. A $P$ value $<0.05$ was considered to be statistically significant.

**Table 1.** Clinical presentations of patients with cerebral venous sinus thrombosis.

| Symptoms and signs | n | % |
|---|---|---|
| Headache | 65 | 86.7 |
| Vomiting | 19 | 25.3 |
| Visual disturbances | 19 | 25.3 |
| Focal neurologic deficit | 17 | 22.7 |
| Seizure | 9 | 12.0 |
| Papilledema | 27 | 36.0 |
| Cranial involvement | 19 | 25.3 |
| Impaired consciousness | 8 | 10.7 |

## Results

Fifty-nine (78.7%) of the patients were female, and 16 (21.3%) were male. The median age of the cohort was 35 years (range 16–76 years), and there was no significant difference in the median age of men and women. The most common symptom was headache in 65 patients, (86.7%) and the most common clinical sign was papilledema (27 patients, 36.0%; Table 1).

Disease onset was acute in 52 patients (69.3%), but was subacute or chronic in 18 (24.0%) and five (6.7%) patients, respectively; there was no difference in speed of onset between men and women. The main characteristics, and inherited and acquired risk factors for thrombosis, are presented in Table 2. Inherited or acquired risk factors for thrombosis were detected in 62 patients (82.6%), the remaining 13 (17.4%) had no identifiable risk factors for CVST. Four of the female patients (6.8%) were pregnant and 16 (27.1%) had recently given birth. Six women (10.2%) had been taking OC drugs. Female sex-specific risk factors (pregnancy, recent childbirth and OC usage) were associated with CVST in 44.1% of women. Five patients had Behçet's disease (6.7%), three had a history of previous venous thrombosis (4.0%) and three of malignancy (4.0%), and three had incurrent infection (4.0%). Other acquired risk factors for CVST identified were hyperhomocysteinaemia in 24 patients (32.0%) and vitamin B12 deficiency in 14 (18.7%). We detected inherited risk factors in 48 patients (64.0%). Factor V Leiden, prothrombin G20210A gene, MTHFR mutation, or deficiencies of protein C, protein S or antithrombin III, were detected in 13, 12, 28, 11, 15 and five patients, respectively (corresponding to 17.3%, 13.3%, 37.3%, 14.7%, 20% and 6.7% of the total cohort, respectively). In one patient (1.3%), prothrombin G20210A gene mutation was the sole risk factor for thrombosis and no other acquired or inherited risk factors were found. Likewise, factor V Leiden mutation was the sole risk factor in two patients (2.6%) and MTHFR mutation was the sole risk factor in four patients (5.3%). There was no significant difference in the incidence of hyperhomocysteinemia, vitamin B12 deficiency or indeed any of the inherited or acquired risk factors for CVST between men and women (Table 2).

On hospitalization, haemorrhagic and non-haemorrhagic infarcts were identified on imaging in nine patients (12.0%) and 16 patients (21.3%), respectively; there were no specific imaging findings in the remaining 50 patients (66.7%). The transverse sinus was the most common site of thrombosis, followed by the sigmoid and superior sagittal sinuses, but in 50 patients (66.7%) multiple sinuses were thrombosed (Table 3).

**Table 2.** Presence of risk factors for thrombosis in patients with cerebral venous sinus thrombosis.

| | Female n = 59 | % 78.7 | Male n = 16 | % 21.3 | Total n = 75 | % | *P* |
|---|---|---|---|---|---|---|---|
| Age mean years, (min-max) | 37 (18–76) | | 34 (16–66) | | 35 (16–76) | | 0.271 |
| Acquired risk factors | | | | | | | |
| Pregnancy/recent childbirth | 20 | 33.9 | | | | | |
| OC usage | 6 | 10.2 | | | | | |
| Previous venous thrombosis | 2 | 3.4 | 1 | 6.2 | 3 | 4.0 | 0.605 |
| Malignancy | 2 | 3.4 | 1 | 6.2 | 3 | 4.0 | 0.605 |
| Infection | 2 | 3.4 | 1 | 6.2 | 3 | 4.0 | 0.605 |
| Behçet's disease | 3 | 5.1 | 2 | 12.5 | 5 | 6.7 | 0.292 |
| Hyperhomocysteinemia | 17 | 28.8 | 7 | 43.8 | 24 | 32.0 | 0.256 |
| Vitamin B12 deficiency | 10 | 16.9 | 4 | 25.0 | 14 | 18.7 | 0.464 |
| Inherited risk factors | | | | | | | |
| Factor V Leiden mutation | 10 | 16.7 | 3 | 18.0 | 13 | 17.3 | 0.493 |
| Prothrombin G20210A mutation | 8 | 13.5 | 2 | 12.5 | 10 | 13.3 | 0.449 |
| Methylene tetrahydrofolate reductase mutation | 23 | 38.9 | 5 | 31.3 | 28 | 37.3 | 0.640 |
| Protein C deficiency | 9 | 15.2 | 2 | 12.5 | 11 | 14.7 | 0.782 |
| Protein S deficiency | 14 | 23.7 | 1 | 6.3 | 15 | 20.0 | 0.121 |

(Normal serum homocysteine concentration is $<15\,\mu$mol/L, normal serum vitamin B12 concentration is $>150$ ng/L; OC, oral contraceptive drug).

**Table 3.** Location of sinus thrombosis in patients with cerebral venous sinus thrombosis.

| Sinuses | Female n = 59 | % | Male n = 16 | % | Total n = 75 | % | *P* |
|---|---|---|---|---|---|---|---|
| Transverse | 52 | 88.1 | 13 | 81.3 | 65 | 86.7 | 0.472 |
| Sigmoid | 38 | 64.4 | 10 | 62.5 | 48 | 64.0 | 0.888 |
| Superior sagittal | 15 | 25.4 | 7 | 43.8 | 22 | 29.3 | 0.153 |
| Inferior sagittal | 3 | 0.5 | 1 | 6.3 | 4 | 5.3 | 0.854 |
| Rectus | 3 | 0.5 | 1 | 6.3 | 4 | 5.3 | 0.854 |
| Cavernous | | | 1 | 6.3 | 1 | 1.3 | |
| Transverse + sigmoid + superior sagittal + rectus | 1 | 1.7 | 1 | 6.3 | 2 | 2.6 | |
| Transverse + sigmoid + superior sagittal | 11 | 18.6 | 1 | 6.3 | 12 | 16.0 | |
| Transverse + sigmoid | 26 | 44.0 | 6 | 37.5 | 32 | 42.0 | |
| Transverse + superior sagittal | 2 | 3.4 | 1 | 6.3 | 3 | 4.0 | |
| Sigmoid + superior sagittal | | | 1 | 6.3 | 1 | 1.3 | |

There was no significant difference in the site of thrombosis between men and women ($P > 0.05$). The internal jugular vein and cerebral cortical veins were involved in 26 patients (34.7%) and four patients (5.3%), respectively.

Glasgow coma scale (GCS) and mRS were used to assess conscious level and

**Table 4.** Score on the modified Rankin Scale at hospital admission and discharge.

| Score on modified Rankin Scale | On hospital admission | | At the time of hospital discharge | |
|---|---|---|---|---|
| | n = 75 | % | n = 75 | % |
| 0 | 9 | 12.0 | 50 | 66.6 |
| 1 | 47 | 62.6 | 21 | 28.0 |
| 2 | 9 | 12.0 | 3 | 4.0 |
| 3 | 5 | 6.7 | 1 | 1.4 |
| 4 | 3 | 4.0 | 0 | 0.0 |
| 5 | 2 | 2.7 | 0 | 0.0 |
| Total | 75 | 100 | 75 | 100 |

disability. The median GCS of the patients was 15 (range 11–15). The mRS score was documented on hospital admission and discharge. Patients with sagittal sinus involvement had significantly lower disability mRS score at hospitalization ($P = 0.013$, Pearson chi-square), while the number of involved sinuses was correlated with higher admission mRS score ($P = 0.015$, Pearson correlation). Neurologic state improved significantly in most patients by the time of discharge ($P = 0.001$ Kolmogorov-Smirnov test). There was no significant difference in disability score at discharge between men and women ($P > 0.05$, Pearson chi-square). None of the patients died during hospitalization or in the follow-up period (Table 4).

## Discussion

CVST is an unpredictable disease with a wide range of clinical presentations, pathophysiologic risk factors and variable sinus involvement. It is well recognized that CVST is most common in young adults, especially women, and indeed our cohort had a median age of 35 years (range 16–76 years) and 78.7% were female.[5,6]

Headache is the most common early presenting symptom described in the literature.[1,2,7] In our cohort headache was seen in 86.7% of patients. Papilledema was the most frequent physical sign in our cohort, identified in about one-third of patients. Nonetheless, our cohort exhibited some important differences when compared with cases already published in the literature. It has been reported that dizziness, nausea and visual disturbances are common symptoms of CVST, and that focal neurologic deficits, including focal seizures, cranial nerve palsies and impaired consciousness, are present in 30%–50% of cases.[8–10] All these symptoms and signs were substantially less common in our cohort.

Patients diagnosed with CVST should be investigated for inherited and acquired thrombophilic risk factors. In our cohort, about 44% of our female patients had female sex-specific risk factors for thrombosis such as pregnancy, recent childbirth or OC drug use, which are judged to explain the preponderance of CVST in women.[11–13] About 82% of our patients with CVST had at least one risk factor related to thrombosis, but it is important to recognize that 18% did not. The diagnosis of CVST should be born in mind when assessing relatively young patients with sudden onset headache, even if there are no hereditary and/or acquired risk factors.

Behçet's disease is reportedly a rare risk factor for CVST,[14,15] but 6.7% of our patients had been diagnosed with Behçet's disease. This could be explained by the relatively high prevalence of Behçet's disease

in regions surrounding the old silk trading routes in the Middle East and Central Asia. We also found that a significant proportion of our patients with CVST had hyperhomocysteinaemia and vitamin B12 deficiency, a finding compatible with previous reports of an association between hyperhomocysteinaemia and stroke.[16–18] The homocysteine-lowering effects of vitamin B12, vitamin B6 and folate have been extensively described in the literature.[18,19] Vitamin B12 and folate supplements, and acetylsalicylic acid, may be administered to reduce the serum concentration of homocysteine and thereby reduce the risk of CVST and stroke.

We identified an inherited hypercoagulable state in about two-thirds of our patients with CVST: the most common was MTHFR mutation in about 40%, followed by factor V Leiden and prothrombin G20210A gene mutation. The proportion of MTHFR mutation in our cohort is one of the highest reported.[20–22] There have been conflicting reports of the most common site of thrombosis, but the transverse and superior sagittal sinuses appear to be the most frequently involved.[1,2,23] Our finding that transverse sinus was most often affected chimes with the published literature, but it was notable that the majority of our patients had multiple sinus involvement. Although CVST predominately affected women due to the preponderance of sex-specific risk factors, the clinical manifestations, other risk factors and site of thrombosis did not differ between our male and female patients.

At disease onset, disability scores are reportedly lower in those patients with sagittal sinus involvement, and those with multiple sinus involvement are more disabled.[4,6,7] Although CVST is potentially life threatening, neurologic outcomes can be improved with appropriate treatment. Acute disease management includes anticoagulation with heparin and supportive treatment. Supportive therapy includes hydration, anticonvulsants, antibiotics and neurologic interventions to reduce intracranial pressure. There is a body of evidence that anticoagulation therapy is beneficial for the majority of patients; however, poor outcomes may be seen in 9%–13% of patients despite anticoagulation. In these patients, thrombolytic therapy or invasive therapeutic procedures such as direct catheter chemical thrombolysis or direct mechanical thrombectomy may be considered.[24–26] In our cohort, all the patients who were anticoagulated showed clinical improvement, and none required surgical intervention.

We found that CVST had wide range of clinical manifestations and non-specific symptoms at onset. Consequently, the differential diagnosis of CVST should be always be born in mind in patients with sudden onset headache, especially in those at high risk of thrombosis. Ours was one of the largest cohort studies of CVST in our region, but its main limitations were nonetheless a relatively small number of patients and its retrospective design. Prospective clinical studies with larger cohorts are needed to further improve our understanding of CVST.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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