Clinical features, risk factors, and outcome of cerebral venous thrombosis in Tehran, Iran

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ABSTRACT

Introduction: Despite increasing the use of magnetic resonance imaging (MRI), cerebral venous sinus thrombosis (CVST) has remained an under-diagnosed condition. In this study, characteristics and frequency of various risk factors of CVST patients in a tertiary referral hospital were closely assessed. Methods: Patients with an unequivocal diagnosis of CVST confirmed by MRI and magnetic resonance venography during 6 years of the study were included. All data from the onset of symptoms regarding clinical signs and symptoms, hospital admission, seasonal distribution, medical and drug history, thrombophilic profile, D-dimer, neuroimaging, cerebrospinal fluid findings, mortality, and outcome were collected and closely analyzed. Result: A total of 53 patients with female to male ratio of 3.07 and mean age of 33.7 years were included in the study. Headache and papilledema were the most frequent clinical features (44 and 36 patients, respectively). An underlying disease (diagnosed previously or after admission) was the most common identified risk factor for CVST in both females and males (21 patients). A total of 15 women used the oral contraceptive pill (OCP) where 12 of them had simultaneously other predisposing factors. Overall, 19 patients (36%) had more than one contributing factor. D-dimer had a sensitivity of 71.4% in CVST patients. The mortality of patients in this study was 3.7% (n = 2). Focal neurologic deficit and multicranial nerve palsy were associated with poor outcome which defined as death, recurrence, and massive intracranial hemorrhage due to anticoagulation (P = 0.050 and 0.004, respectively). Conclusion: Unlike most of the CVST studies in which OCP was the main factor; in this study, an underlying disease was the most identified cause. Considering the high probability of multiple risk factors in CVST that was shown by this study, appropriate work up should be noted to uncover them.

Key words: Cerebral venous sinus thrombosis, etiology, oral contraceptive pill, outcome, risk factor

Introduction

Cerebral venous and sinus thrombosis (CVST) is a potentially life-threatening disorder accounting for about 0.5% among all types of strokes.10 Despite an increasing use of magnetic resonance imaging (MRI), CVST has remained an under-diagnosed condition.2,3 Although generally considered a disease with good outcome in developed countries, in under developed, and low-income countries during the hospitalization mortality rate may be up to 14%,4,5 which could be due to delay in diagnosis. On the other hand, the prevalence of CVST in Iran was reported to be 12.3 per million of the populations,6 which seems higher than western countries.7 Regarding the prevalence and higher mortality rate in the developing countries, clarification of variable risk factors of CVST with extensive assessment in these countries is necessary.

The aim of this study is to evaluate clinical characteristics including etiology, neuroimaging, and outcome of patients with CVST and address the limitations of...
previous studies such as the presence of multiple risk factors.

Methods

This study was conducted in a tertiary general referral hospital affiliated with Tehran University of Medical Sciences in Tehran, Iran, which serves many patients from all over the country. From July 2004 to September 2007, retrospective data were gathered for all patients with a diagnosis of CVST (2016 ICD-10-CM Diagnosis Code: G08) from the documents recorded in the hospital registry system. A prospective study was conducted from October 2007 to November 2010 where all patients with diagnosis of CVST were included in the study. The data included clinical signs and symptoms, from onset of symptoms, hospital admission, month of presentation, medical and drug history, laboratory results in particular hypercoagulable state factors, neuroimaging, cerebrospinal fluid (CSF) findings, and outcome of patients.

The diagnosis of CVST for all these patients was confirmed according to following imaging protocol:

Consulting with two neurologists and one radiologist, MRI/magnetic resonance venography, and/or conventional angiography were used for the confirmation of the diagnosis of CVST in all the patients. In case of any discrepancy between the clinicians regarding the diagnosis of CVST in any patient that case was excluded from the study. In the prospective phase of the study, D-dimer levels measured before the initiation of anticoagulant treatment. D-dimer was categorized as low (<0.5 mg/L), intermediate (0.6–2.0 mg/L), and high (>2.0 mg/L). Based on the delay from symptom onset to hospital admission, mode of onset was categorized as acute (<2 days), subacute (2–14 days), or chronic (>14 days).[8]

All assessed prospective patients were asked to sign a written informed consent. In case of retrospective data collection, after calling the patients or their family, permissions for data acquisition were catched. Data analysis was performed using SPSS 16 (SPSS Inc., IL, USA). Values with normal distribution were analyzed with Chi-square and t-test. Otherwise, Mann–Whitney test were used. The level of significance was set at a $P \leq 0.05$.

Results

A total of 53 patients, 13 males and 40 females were observed during this study. Of this group, 20 patients were enrolled in retrospective phase. The median age of patients was 34 years ranging 17–60.

Clinical features

Sign and symptoms of patients were depicted in Table 1. Headache was found as the most prevalent clinical feature of CVST among the patients ($n = 44$, 83%) followed by papilledema and vomiting ($n = 36$, 68%, and $n = 29$, 55%, respectively). The mode of clinical presentation was acute, sub-acute, and chronic in 14 (26.4%), 22 (41.5%), and 17 (32%) patients, respectively. Median days from the onset of symptoms to hospital admission were 11 days with the range of one to 92 days. Distribution of patients among different months of year was shown in Figure 1.

Etiology

The most frequent identified risk factor of CVST patients in this study, both females and males were the underlying disease. From 40 female patients, 40% ($n = 16$) had a predisposing condition for CVST and 37.5% ($n = 15$) had used oral contraceptive drug (OCP). Other details of underlying causes were summarized in Table 2. Four patients used OCP and simultaneously had other underlying causes including bevhct disease, hypothyroidism, pre eclampsia, and postpartum state. Moreover, 8 patients had both positive thrombophilic state and OCP consumption. Overall, 36% of patients ($n = 19$) had more than one contributing factors for CVST and 20% of them ($n = 11$) had no identifiable cause (idiopathic).

Procoagulatory factors and vasculitis conditions looked for in 32 of the patients and found abnormal results in 16 of them (50%). Protein S deficiency was the most common abnormal findings ($n = 9$, 28%). Other results contained hyperhomocysteinemia ($n = 2$), antithrombin III deficiency ($n = 2$), mutation in factor V leiden ($n = 1$), protein C deficiency ($n = 1$), and positive antiphospholipid antibodies ($n = 1$).

D-Dimer and cerebrospinal fluid analysis

From 14 patients with CVST that D-dimer was assessed in them, 10 patients showed high titer. Therefore, the sensitivity of D-dimer was 71.4%, and 4 patients represented false-negative results. Lumbar puncture had been performed in 35 patients. Nearly 80% of them had high CSF pressure (>180 mmH$_2$O). CSF analysis was normal in 31 patients (88.6%). Cell count was increased in 4 of the patients (>5 per cumm), and total protein was high (>45 mg/100 ml) in two patients. In cytology was positive in one patient who had interstitial lobular cancer of breast. No CVST patient (even with infectious causes) represented the positive culture of CSF.

Neuroimaging findings

A total of 10 patients (19%) represented supratentorial hemorrhagic infarction in initial brain computed
tomography scan. One patient had both hemispheral and cerebellar hemorrhage. The involvement of different cerebral sinuses and veins in descending order of frequency included transverse and sigmoid (20/53, 37.7%), both superior sagittal and lateral (19/53, 35.8%),
cavernous (6/53, 11.3%), bilateral transverse and sigmoid (4/53, 7.5%), isolated superior sagittal (2/53, 3.7%), and isolated straight and Galen sinuses (2/53, 3.7%).

**Outcome**
A total of 45 patients had favorable outcome that defined as improvement without any serious complication (84%). Two patients had intracranial hemorrhage (ICH) due to intravenous heparin, but finally recovered and were discharged. Death and recurrence were occurred in 2 (3.7%) and 3 (5.6%) patients, respectively. Motor and sensory focal neurological deficits and multicranial nerve palsy were associated with poor outcome that defined as death, recurrence, and ICH due to anticoagulation ($P = 0.050$ and $0.004$, respectively). The underlying disease of patients had no statistically significant association with outcome, 81% of the patients who had an accompanying disease improved versus 86% patients who did not. There was also no significant association between the outcome of the patients and the number and type of involved sinuses in Chi-square test [Table 3]. As shown in Table 3, 4 of 6 patients with cavernous sinus thrombosis were
improved ($P = 0.05$). On the other hand, one of two deaths in the study had cavernous sinus thrombosis. Therefore, we did not consider this weak statistically significant association as clinically significant.

**Discussion**

In our patients, females predominance and a female to male ratio of 3 was observed like other previous studies in developed countries.$^9,10$ The most prevalent cause of CVST was OCP in many studies in Iran.$^{11,12}$ Western countries$^{13}$ and the frequency of OCP usage among women with CVST has been reported up to 68%.$^{13}$ Unlike other studies, the most frequent risk factor of CVST in our patients was their underlying condition that was detected in 40% of patients. This was also true in women as 40% of them had a predisposing underlying state and 37.5% used OCP. The importance of attention to underlying disease in CVST patients is more emphasized because CVST was presenting feature in some of our patients (polycythemia vera and hypothyroidism) and their disease was uncovered after appropriate work up. The higher number of CVST patients in the context of a disease in this survey could be due to the setting that study has been performed. It was in a general referral hospital with different departments of internal medicine and gynecology that serves patients from all over the country.

Libourel et al. and Koopman et al. compared thrombophilic risk factors in age-matched patients with CVST and deep venous thrombosis/pulmonary thromboembolism patients (DVT/PE).$^{14,15}$ They found that there was not any difference in thrombotic profile between two groups. While OCP intake was more frequent in CVST patients, it was suggested that additional unknown risk factors should be considered to explain the different sites of embolism.$^{14}$ We suggest that the underlying disease may be one of the contributing factors in the incidence of thrombosis in different sites as DVT/PE mostly occurs in the context of immobilization and surgery.$^{15}$ These factors were not seen in this and other studies as underlying cause in CVST.$^{16}$ Although further studies with emphasize on the underlying condition between CVST and DVT/PTE patients should be performed.

The presence of multiple risk factors at the same time in patients with CVST was less considered before. In this study, 36% of patients had more than one risk factor. OCP was still a major contributing factor in women with CVST but from 15 patients who have used OCP, 12 had either simultaneous underlying condition or thrombophilia. Therefore, the effect of OCP may be enforced in the presence of other factors in developing of CVST. The importance of multiple risk factors in CVST was further discovered regarding the observation of patients over the different month of the year where it showed higher number of patients in warm months of the year which could be due to the role of dehydration in developing of CVST.

Sensitivity of D-dimer was 71.4%, and false negative results were detected in 28.5% of patients. Previously reported sensitivity of D-dimer ranged between 58%$^{17}$ and 93% in a systematic review.$^{18}$ Isolated headache, longer duration of symptoms, and limited sinus involvement may be related to false negative D-dimer results.$^{19}$ These findings show that normal levels of D-dimer could not definitely exclude the diagnosis of CVST,$^8$ because still there may be true CVST patients with negative result. However, the positive and high titer of D-dimer test could support the CVST diagnosis in suspicious cases.

CSF analysis was not performed in all of the patients, but all patients with infectious cause ($n = 7$) underwent lumbar puncture. The culture of CSF was negative in all of them. This could be due to the source of these infections which were mostly restricted to the nose and ear (in patients with mucormycosis and acute otitis media). The other reason might be the effect of infection in the induction of hypercoagulable state$^{19,20}$ which may explain CVST in the patient with hepatitis B and the patient with a history of bacterial meningitis 1 month before thrombosis.

As a limitation to this study, data were collected only from the patients referred to the general hospital. There might have been some cases of CVST patients that had minor presentations, and consequently, they were treated as an outpatient. This group could have had different etiologies. Another limitation was missing data of D-dimer and thrombophilic factors in retrospective assessments. To overcome this scenario, we conducted a prospective phase to evaluate these factors in patients. In this study, no significant association was observed.

**Table 3: Association of the type of thrombosed sinus and improvement of patients**

| Brain sinuses             | Patients (male/female) | Ratio of improvement | $P$  |
|---------------------------|------------------------|----------------------|------|
| Sagittal sinus            | 5/11                   | 15/16                | 0.33 |
| Cavernous sinus           | 2/4                    | 4/6                  | 0.05 |
| Jugular vein              | 1/12                   | 11/13                | 0.89 |
| Lateral and sigmoid vein  | 9/30                   | 35/39                | 0.32 |
| Straight and Galen vein   | 2/6                    | 8/8                  | 0.23 |

Yadegari, et al.: Cerebral venous thrombosis
between number and type of thrombosed vein or underlying conditions, and outcome. This could be related to number of enrolled patients, for example, there was 6 patients in cavernous sinus thrombosis group or may be due to potentially inadequate power of the study; however, CVST is considered a rare disease. Further studies with longer period may be needed to evaluate the relationship of underlying disease with outcome.

Conclusion

This study showed that multiple risk factors could be present in CVST. Underlying disease was the most common predisposing factor in our patients and CVST was the first presentation in some of the diseases. The outcome had no significant association with the disease of the patients.

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Conflicts of interest

There are no conflicts of interest.

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