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Cerebral Venous-Sinus Thrombosis: Risk Factors, Clinical Report, and Outcome. A Prospective Study in the North East of Iran

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ABSTRACT

Introduction: Cerebral venous-sinus thrombosis (CVST) is a life threatening condition that needs rapid diagnosis and treatment. It appears comparatively more common in Middle East and South Asia.
Objectives: To determine the demographic, clinical patterns, etiologies and prognostic factors of CVST in the North East of Iran.
Materials and Methods: All adult patients admitted with a documented diagnosis of CVST from January 2011 to March 2012 in an academic hospital in the North East of Iran, entered this prospective descriptive study. The patients' demographic characteristics, clinical presentations, laboratory and brain imaging findings, treatment options were also studied. Follow-up visits were performed at month 1, 6, and then at month 12 using modified Rankin Scale (mRS). Findings were analyzed using descriptive tests and Chi square test in SPSS software version 21.
Results: Sixty patients (13.3% men, 86.7% women) with mean age of 38.11±11.30 years were identified. Fifty one cases (85%) had a clinical picture of increased intracranial pressure. Causes included positive antiphospholipid antibodies in 3.3%, protein C, S and anti thrombin III deficiency in 5%, 1.7% and 3.3%, polycythemia in 1.7%, infections in 1.7%, postpartum in 9.6% of women, and using Oral Contraceptive Pills (OCPs) in 65.38%. We found 10% mortality rate on discharge and 11.9% within 30 days and 42.7% rate of death or dependency at month 12.
Conclusion: The findings of the study indicate that the use of OCPs was a main factor associated with CVST especially in association with inherited hypercoagulable state.

Keywords: Cerebral Veins; Thrombosis; Contraceptives Agents; Stroke

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Introduction

Cerebral venous-sinus thrombosis (CVST) is a life threatening condition that needs rapid diagnosis and treatment. Its epidemiology has altered over past years (1). Its increasing prevalence may be attributed to not only increased ease of

diagnosis by modern imaging tools such as magnetic resonance imaging (MRI), but also to the growth of underlying causes including use of Oral Contraceptive Pills (OCPs) (1,2). Several factors have been associated with CVT, but reversible factors are not common. Previous medical conditions (e.g. thrombophilia, inflammatory bowel disease), transient situations (e.g. pregnancy, dehydration, infection), special medications (e.g. oral contraceptives, substance abuse), and events such as head trauma are some predisposing factors. The symptoms and signs associated with cerebral venous thrombosis are relatively nonspecific. These include headache, papilledema, seizure, decreased level of consciousness and focal neurological deficits. CVT may be not easy to be diagnosed clinically because of its various and nonspecific manifestations and the multiple associated conditions and etiologies. Hypercoagulable state associated with puerperium as well as infectious diseases are believed to be the main etiologies in the developing country, but these are less significant in western populations. Infectious diseases are now diagnosed and treated quickly. Cerebral venous-sinus thrombosis appears comparatively more common in Middle East and South Asia (1). This study aims to state demographic, etiologic, outcome and radiological characteristics of patients with CVST in north eastern states of Iran.

Materials and Methods

The study is a prospective analysis of medical records of sixty patients with CVST, referred to an academic hospital affiliated with Mashhad University of Medical Sciences, from January 2011 to March 2012. Patients with related CVST manifestations underwent cerebral magnetic resonance imaging (MRI) and magnetic resonance venography (MRV). Patients whose presentations could be explained better by any other neurological diseases or those whose imaging revealed congenital hypoplasia of dural sinuses were excluded. Brain and paranasal sinuses MRI were performed. Also, plasma concentrations of proteins C, S, antithrombin III and antibodies such as anticardiolipin, antinuclear, anti-double-stranded DNA, and hypercoagulablity and vasculitis tests were done and the results were recorded. All patients with non-septic CVST, even those with hemorrhagic lesions, received intravenous heparin (or enoxaparin) followed by oral warfarin for a period of six months and if an important etiology of thrombophilia was found, warfarin therapy continued long-life. The patients' demographic characteristics, clinical presentations, laboratory findings, cranial imaging, and also treatment options and outcome were studied.

Follow-up visits were performed at month 1, 6, then at month 12. When a visit with the investigator was not possible, it was replaced by a telephone dialogue with a family member or the general physician. The outcome at months 1, 6 and 12 was evaluated with the modified Rankin Scale (mRS). Subjects with mRS 0 to 2 being classified as independent survivors, and patients with mRS scores 3 to 6 being classified as dependent or dead. In patients who had a phone call follow-up, the mRS score was assessed by previously validated queries. In patients who missed the 6-month evaluation but had the 1year follow-up visit, we adopted the “worst mRS” situation: we used either the mRS score at discharge, 30 days, 6 month or at 1-year follow-up, either was worst.

Statistical Analysis

Findings were analyzed using Statistical Package for Social Sciences (SPSS software version 21). The data are presented as Mean ± SD for quantitative variables, count and percent for qualitative variables. Chi square test was used to analyze qualitative results. *p-value*≤0.05 was considered statistically significant.

Results

A total of sixty subjects with mean age of 38.11±11.30 years were enrolled in the present study. Fifty-two participants (86.7%) were women and 8 (13.3%) were men. Mean length of hospital stay was 19.01±10.19 days. One patient had polycythemia. Three patients were cigarette smoker and one patient was methamphetamine addicted. One patient had the history of CVT in the past. In five patients CVT occurred after child birth (three after caesarean section delivery and two after normal vaginal delivery). One patient (1.7%) has been involved by ulcerative colitis, and 22 (36.7%) patients reported dehydration before. Sixteen (26.7%) patients were given intravenous heparin infusion and others received low molecular weight heparin. Fifty one patients (85%) received warfarin thereafter. Seven (11.7%) patients underwent decompressive hemicraniectomy. One (1.7%) patient was diagnosed as septic CVST. The most frequent clinical manifestations were headache in 60 (100%), papilledema in 51 (85%), seizure in 30 (50%), hemiparesis in 17 (28.3%), and decreased level of consciousness in 27 patients (45%). Table 1 shows the most common findings among patients with CVST. Thirty four out of fifty two women (65.38%) had used OCPs. Fifteen women (28.8%) have used OCP for duration shorter than three months and having consumed drug developed CVST.

Table 1: Common neurologic findings among patients with cerebral venous sinus thrombosis

Symptom	Number (%)
Headache	60 (100%)
Visual symptoms	40 (66.7%)
Papilledema	51 (85%)
Seizure (Focal, Generalized)	30 (50%)
Hemiparesis	17(28.3%)
Stupor	17(28.3%)
Behavioral changes	16(26.7%)
Coma	10(16.7%)
Aphasia	9(15%)
Vertigo	6(10%)
Dysarthria	5(8.3%)

Common intracranial sinuses which involved by thrombosis are presented in table 2.

Table2: The number and prevalence of cerebral sinus vein involved by thrombosis among studied patients

Cerebral Sinus-Vein	Number (%)
Superior sagittal sinus	40(66.7%)
Transverse sinus	49(81.7%)
Straight Sinus	3(5%)
Sigmoid Sinus	7(11.7%)
Cavernous Sinus	0(0%)
Deep cerebral vein	7(11.7%)

Frequency of coagulopathies and hormonal changes among studied patients has been presented in table 3.

Table 3: Frequency of coagulopathies and hormonal changes among studied patients

Laboratory Findings	Number (%)
Protein C Deficiency	3(5%)
Protein S Deficiency	1(1.7%)
Anti thrombin III Deficiency	2(3.3%)
Anti- Cardiolipin Antibody	0 (0%)
Anti- Phospholipid Antibody	2(3.3%)
Factor V Leiden Mutation	3(5%)
Lupus Anticoagulant	0 (0%)
ANA	1(1.7%)
Anti- double stranded DNA	0(0%)
Low Dose Estrogen OCP Consumption	34(56.7%)
Conjugated Estrogen Consumption	2(3.3%)

Minimum follow-up of twelve months was available for all of our patients. Recurrent thrombosis and lower extremity deep vein thrombosis (DVT) developed in one patient (1.7%). Hepatic vein thrombosis has not seen

in our patients. Poor prognostic factors at the time of hospital admission were low level of consciousness including stupor or coma (p=0.001) and intra parenchymal hemorrhage with or without subarachnoid hemorrhage in the first CT scan (p=0.005). Six (10%) patients passed away during hospitalization, one during six month and one during twelve month follow up which means an 11.9% mortality rate during 30 days, 13.8% mortality rate within one year and 42.7% rate of death or dependency at month 12.

Discussion

A number of earlier studies demonstrated increasing incidence of CVST in Iran (3-5). Such an increased incidence and prevalence, especially in young productive population prompted us to study the underlying causes of CVST in Iranian population. The present study is similar to some previous ones in terms of female dominance, clinical presentations, and the complicated sinus of CVST (3-10).

It is clear that the use of oral contraceptives is associated with an increased risk of CVT that the great majority of younger non-pregnant women with CVT have used oral contraceptives, and the risk of CVT with using the oral contraceptive by women is greater among those with a hereditary thrombophilia. The combined OCPs raise the risk of CVST, and odds ratio raise to 30.0, 79.3 and 19.5 in the existence of V Leiden factor, prothrombin mutation or hyperhomocysteinemia, respectively (2). Fifteen women (28.8%) had taken OCP for duration shorter than three months to prevent menstruation during religious ceremonies such as Hajj or Ramadan fasting, and developed CVST during the period of the drug consumption. A similar finding has been reported in other parts of Iran (11). Dehydration during Ramadan fasting and immobilization during long journey of Hajj pilgrims are the other factors in these circumstances. In present study some patients had primary antiphospholipid antibody syndrome (APLS). The role of antiphospholipid antibodies and other lupus anticoagulants in the evolution of CVST has been previously reported (12-14). Thrombophilia including deficiency of proteins C, S and antithrombin III appeared in 5%, 1.7% and 3.3% of the patients respectively.

During pregnancy and puerperium, women are at increased risk of venous thromboembolic events. Pregnancy provokes several prothrombotic alterations in the coagulation system that persists at least during puerperium. Hypercoagulability worsens after delivery because of dehydration and trauma. During the puerperium the other risk factors are infection and instrumental delivery or cesarean section, so by controlling these risk factors and avoiding volume depletion in this period we can decrease the chance of CVST (15-17).

Headache and focal neurological deficits were major sequels, which were comparable to those reported in previous studies (16-18). The findings of the study indicate that the use of OCPs was a main factor associated with CVST. Clinical presentations, involved sinuses and imaging findings of our study were similar to those of other studies.

The mortality and morbidity rates in our patients were similar to previous studies (12-16). The mortality rate was 10% during hospitalization and 11.9% after 30 days in this study, whereas that of patients with CVST in an international study on cerebral vein and dural sinus thrombosis (ISCVT) during hospitalization was 8.3 % (9).

A meta-analysis of several recent prospective series, particularly, the large ISCVT cohort, confidently established the vital and functional prognosis of patients with acute CVT, showing a 15% overall death or dependency rate (19). Long-term predictors of poor prognosis are CNS infection, cancer, deep vein thrombosis, intracranial haemorrhage, Glasgow Coma Scale score of lower than nine on entrance, mental disorder, being older than 37 years or male gender. This predictive model, resulting from the ISCVT cohort, was validated in an independent cohort (19). In the acute phase of CVST, the case-fatality was estimated approximately 4% (19). Predictors of mortality at 30 days were decreased level of consciousness, mental status disorder, and thrombosis of the deep venous system, right hemispheric bleeding, and posterior fossa lesions. The main causes of mortality were transtentorial herniation secondary to diffuse hemorrhagic lesion or disseminated brain edema. Other etiologies of acute death included status epilepticus, medical side effects, and pulmonary emboli.

Worsening after admission occurs in about 23% of patients, with deteriorating of mental status, occurrence of focal neurological deficits or headache or seizures. A new parenchymal lesion was present in one-third of patients who have been worsened. The individual prognosis is not easy to predict, but the overall vital and functional prognosis of CVT is far better than that of arterial stroke, with recovering about two-thirds of patients without any sequel.

Conclusion

The findings of the study indicate that the use of OCPs was a main factor associated with CVST especially in committed with inherited hypercoagulable state. Moreover, the results may suggest that health care policy makers should arrange a plan to warn susceptible women of the risk of CVST and inform them the preventive methods.

Conflict of Interest

No Conflict of Interest

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