

Cerebral Venous Sinus Thrombosis– Clinical Features, Predisposing and Prognostic Factors

Hossein Azin¹ and Nahid Ashjazadeh²

Abstract-

Purpose: Cerebral venous sinus thrombosis (CVST) is a disease with potentially serious consequences and usually affecting young to middle aged people. This study was designed to investigate the clinical features, and predisposing and prognostic factors of CVST in a prospective series of 61 patients.

Methods: This prospective study comprised 61 consecutive patients with confirmed diagnosis of CVST who were hospitalized in Namazi Hospital in Shiraz, south of Iran, between January 2000 and August 2003. The diagnosis was confirmed using conventional MRI or cerebral angiography.

Results: The male to female ratio was 1/3.1. The mean age of patients was 35.6 ± 12.1 years. Headache was seen in 91.8% of the patients. The most frequent risk factor was oral contraceptive consumption (62.2%). Elevation of ESR and CRP titer were seen in 37.7%, and 36.1% of patients, respectively. Involvement of superior sagittal sinus and lateral sinus was 80.3% and 41%, respectively. The final diagnosis was neurobechet in 5 patients (8.2%). The fatality rate was 14.7% and an altered consciousness was associated with poor prognosis.

Discussion: CVST presents with a wide spectrum of symptoms and signs. Headache was the most frequent symptom. Women who used OCP were especially at risk. Because of moderate to high mortality rate, patients at increased risk of death, specially comatose patients, should be closely monitored.

Key Words: Cerebral venous sinus thrombosis, Stroke, Headache

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST), first described by Ribes in 1825, is a disease with potentially serious consequences which usually affects young to

middle aged people⁽¹⁻³⁾. The incidence of CVST is unknown and is reported to be more common in developing countries⁽⁴⁾. Most reported incidences are based on autopsy studies and range from 0.1% of 12,500 consecutive autopsies to 9% of all deaths resulting from cere-

From the Departments of Neurology, ¹Rafsanjan University of Medical Sciences, Rafsanjan, and ²Shiraz University of Medical Sciences, Iran.

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Reprint requests and correspondence to: Hossein Azin, MD.
PO Box: 13185-1678, Tehran, Iran.
E-mail: swt_f@yahoo.com

brovascular causes⁽⁵⁾. All age groups can be affected. There is, however, a small preponderance in young women because of pregnancy, puerperium, and the use of oral contraceptives (OCPs)^(2,6-8). The outcome of patients with CVST may vary from complete recovery to permanent neurological deficits^(9,10). In early angiographic series, mortality still ranged between 30% and 50%, but in a number of recent series, mortality was 6-15%^(2,11,12).

There are four main clinical patterns of CVST: (1) Focal deficits associated with headache, seizures, or altered consciousness. (2) Isolated intracranial hypertension with headache, nausea, vomiting, papilledema, transient visual obscuration, and eventually sixth nerve palsy. (3) Subacute diffuse encephalopathy, characterized by a decreased level of consciousness and sometimes seizures without clearly localizing signs or recognizable features of intracranial hemorrhage (ICH). (4) Painful ophthalmoplegia caused by lesions of the third, fourth, or sixth cranial nerves, chemosis, and proptosis^(1,8).

Many factors associated with a poor prognosis have been identified, including extreme age, coma, involvement of the cerebellar veins or the deep venous system, severely raised intracranial pressure, infectious or malignant etiologies, hemorrhagic infarcts on computed tomography (CT) scan, and intercurrent complications such as uncontrolled seizures or pulmonary embolism^(2,5,6,9). Although the functional outcome from CVST is better than that of arterial stroke, the outcome of CVST remains largely unpredictable⁽⁵⁾.

The aim of this study was to investigate the clinical features, predisposing and prognostic factors of CVST in a prospective series.

SUBJECTS AND METHODS

This prospective study comprised 61 consecutive patients with proven CVST, who were hospitalized in Namazee Hospital of Shiraz University of Medical Sciences, south of Iran, between January 2000 and August 2003. The diagnosis was confirmed using magnetic resonance imaging (MRI) or conventional cerebral

angiography. The following data were obtained by a structured questionnaire: age, sex, clinical manifestations according to history and physical examination, predisposing factors, location of the thrombus, and the number, size, and location of parenchymal lesions, laboratory findings, treatment, and outcome. All of our cases were from white (Caucasian) race. Neurologic examination including evaluation of mental status, cranial nerves, motor function, sensory modalities, coordination and ophthalmoscopy. It was performed and based on a constant format by a single neurologist. Laboratory tests included: anticardiolipin antibody (ACLA), C3, C4, ANA, ESR, CRP, sickle cell prep, platelets, leukocytes, PT, PTT, and VDRL. Pathergy test was performed for all patients by pricking and scratching of forearm skin with 20-22 gauge sterile needles. An erythematous papule more than two millimeters diameter was considered as positive.

We followed the patients for 8 to 36 months by outpatient clinic visits for any signs and symptoms (headache, epileptic seizures, sensorimotor disturbances, visual disturbances, and altered consciousness), mortality and even recurrence.

The study protocol was approved by the research ethics committee of Shiraz University of Medical Sciences and an informed consent was obtained from all participants before enrollment. Descriptive statistics were performed to describe the CVST patients. For continuous variables, means and standard deviations were calculated. For categorical variables, numbers and percentages for each category were tabulated. Comparisons were made between CVST patients who died and survivors. Fisher exact test for categorical data and Student's *t*-test for continuous data were used. All significant levels reported were 2-sided, and $P < 0.05$ is considered to indicate a statistical significance. All analyses were performed using SPSS software version 11.5 for Windows.

RESULTS

Between January 2000 and August 2003, 61 CVST patients were hospitalized in Namazee Hospital of

Shiraz University of Medical Sciences. No patients were lost to follow up. Thus 61 patients, 45 women (73.8%) and 16 men (26.2%), were studied. The male to female ratio was 1/3.1. The mean age of patients was 35.6 ± 12.1 years, with a range from 13 to 75 years. The neurological symptoms and signs at admission are summarized in the Table 1. Headache was the most common presenting symptom, observed in 91.8% of the patients. The frequency of risk factors of CVST is summarized in Table 2. The most frequent risk factors of CVST were OCP consumption in women (62.2%) and hypertension (16.4%). Results of biochemical parameters are shown in Table 3. Elevations of ESR, CRP and C3 titer were most common.

In brain MRI, involvement of the superior sagittal sinus (SSS) was found in 80.3% of patients, lateral sinus (LS) in 41%, sigmoid sinus (SIG) in 6.5%, and cavernous sinus in 4.9%. In brain CT scan, normal CT was found in 30.9%, infarction in 26.2%, hemorrhage in 16.7%, empty delta sign in 14.3%, and sabarchonoid hemorrhage in 11.9%.

Eight patients (13.1%) died in acute phase in the hospital between the 1st day to the 7th day of admission (on discharge). One patient (1.6%) died during follow up period (after one year). Bilateral optic atrophy during follow-up period occurred in 4 patients; focal deficit developed in 5 patients; recurrent seizures in 2 patients; deep vein thrombosis (DVT) in 7 patients; pulmonary thromboemboli (PTE) in one patient, brain abscess in one patient; and headache in 7 patients. The final diagnosis was neurobechet in 5 patients with oral, genital, skin, ocular ulcers.

Over-all fatality rate was 14.8% (95% confidence interval, 7.4-25.3%); 13.3% (6/45) for female, and 18.7% (3/16) for male. This difference between sexes was not statistically significant. Eight patients who died had an altered consciousness. Altered consciousness was a predictor of poor prognosis ($p=0.0001$, relative risk=20.22, 95% confidence interval of RR, 5-82). The clinical and imaging findings of died cases have been shown in Table 4.

Table 1. Initial clinical presentations of CVST in 61 patients

Manifestations	Number of patients	Percent
Headache	56	91.8%
Papilledema	38	62.3%
Seizure	22	36.1%
Cranial nerve involvement	19	31.1%
Motor deficit	18	29.5%
Altered consciousness	13	21.3%
Sensory disturbance	8	13.1%
Aphasia	1	1.6%

Table 2. Predisposing factors of CVST in 61 patients

Risk factors	Number of patients	Percent
Oral contraception	28	62.2%*
Hypertension	10	16.4%
Smoking	7	11.5%
Oral ulcer	7	11.5%
Genital ulcer	6	9.5%
History of thrombosis	6	9.5%
Skin ulcer	5	8.2%
Mastoiditis	4	6.6%
Pregnancy	3	4.9%
Postpartum	3	4.9%
Otitis media	3	4.9%
Diabetes mellitus	2	3.3%
Head trauma	2	3.3%
Drugs	2	3.3%
Ocular ulcer	2	3.3%
Sinusitis	2	3.3%
Malignancy	1	1.6%

*62.2% of female

Table 3. Biochemical parameters in 61 patients with CVST

Biochemical parameters	Number of patients	Percent
ESR elevation	23	37.7%
Positive CRP	22	36.1%
C3 elevation	13	21.3%
Positive ACLA	4	6.5%
Positive pathergy test	4	6.5%
Leucocytosis	4	6.5%
Prolonged PT	3	4.9%
Prolonged PTT	2	3.3%
C4 elevation	2	3.3%
Positive ANA	2	3.3%
Thrombocytosis	2	3.3%

Table 4. Main characteristics of 9 patients who died

	Age	Sex	LOC	Site of occlusion	Risk factor	Finding of CT
1	35	F	Stupor	SSS/LS	OCP	Infarction
2	40	F	Stupor	SSS	OCP	SAH/ICH
3	28	F	Stupor	SSS	Postpartum	SAH
4	25	F	Coma	SSS	Postpartum	Delta sign
5	35	F	Stupor	SSS/SIG	Pregnant	Bil infarct
6*	45	F	Awake	SSS	Stomach CA	Normal
7	75	M	Drowsy	LS	TCC bladder	Normal
8	48	M	Stupor	SSS	-	ICH
9	50	M	Stupor	SSS/LS	-	SAH

*Died in follow-up more than one year later. TCC: transitional cell carcinoma.

DISCUSSION

In a prospective series of 61 patients seen over a 3 years period at our institution, the male to female ratio was 0.32 and the mean age was 35.6 years. In an American study, the mean age at onset was 38.5 years, and the male to female ratio was 0.64⁽¹³⁾. CVST is slightly more common in women, particularly in the age group of 20 to 35, due to pregnancy, puerperium and oral contraceptive usage⁽⁶⁾. Mean age in most larger studies was between 37 and 38 years though all ages can be affected^(8,14). In our study headache (91.8%), papilledema (62.3%) and seizures (36.1%) were the dominant clinical manifestations. In the study of Gosk-Bierska et al., the most common symptom was headache (87%) and the most common sign was papilledema (55%). Of note, 25% of patients had a normal neurologic exam at the time of diagnosis and 26.6% had seizure⁽¹⁵⁾.

CVST presents with a wide spectrum of symptoms and signs⁽¹⁶⁻¹⁸⁾. Headache is the presenting symptom in 70-90% of cases⁽¹⁸⁻²¹⁾. Focal deficits such as hemiparesis, and hemisensory disturbances, seizures, impairment of consciousness, and papilloedema occur in one-third to three-quarters of cases^(6,22-25). In this study, the most frequent risk factors were OCP consumption (62.2%) and hypertension (16.4%). In other study⁽¹⁵⁾, the most common etiology of CVST for women in this decade was oral contraception (60%). Twenty-four percent had a defined thrombophilia. For men, a specific underlying cause could not be identified in 60% of cases, and none

had a defined thrombophilia. In another study⁽¹⁹⁾, the more common risk factors were hereditary thrombophilia, pregnancy and puerperium, postoperative state, intracranial and local infections, and the use of oral contraceptives.

Pregnancy and puerperium are the most prevalent prothrombotic states leading to cerebral venous thrombosis. Likelihood of stroke to be of venous origin is greater in stroke associated with pregnancy compared to stroke unrelated to pregnancy. During pregnancy and puerperium, 27% of cerebral infarction was due to cerebral venous thrombosis⁽²³⁾.

In a study of Jeng et al., 11 of 49 strokes had C.V.T during pregnancy and puerperium⁽²⁶⁾. In our study, 6 from 61 cases occurred during pregnancy and puerperium.

Pregnancy induces several changes in coagulation system, which persists at least during early puerperium, rendering it a prothrombotic state. Hypercoagulability worsens further after delivery as a result of volume depletion and trauma. During puerperium additional risk factors include infection and instrumental delivery or Caesarean section^(20,21). CVST is more common in pregnancy-related stroke than stroke unrelated to pregnancy (39% vs. 7%)⁽²⁷⁾. Frequently, the cause of CVST is multifactorial, and in less than 20% of cases no clear risk factor is identified. Thus predisposing factors can be identified in up to 80% of patients. Numerous conditions can cause or predispose to CVST and often more than one cause will be found in an individual patient^(5,22).

The 'empty delta sign' on CT, reflecting the opacifi-

cation of collateral veins in the wall of the superior sagittal sinus after contrast injection is present in only 10-20% of cases⁽⁸⁾. CT is entirely normal in 10-20% of cases with proven CVST. In this study delta sign was seen in 14.3% of patients but normal CT scan was seen in 30.9%. It means that normal brain CT scan does not rule out CVST.

In this study, case fatality rate was 14.8% and the only factor associated with poor prognosis was altered consciousness. Case fatality rate in other series of CSVT with more 50 patients reported from 4 to 23 percent^(24,25,28,29). Main predictors of death in Canholo study⁽¹²⁾ were seizure, altered consciousness, deep CVST, hemorrhage, and posterior fossa lesions. In the study of Kalita et al., age >40 years and altered sensorium were the predictors of poor outcome⁽⁴⁾. In our study, the causes of death were not ascertained systematically. In other studies, cerebral edema, cerebral anoxia due to seizure, sudden cardiopulmonary arrest, transtentorial herniation due to hemorrhagic infarct, and septic multiorgan failure were the causes of death^(12,24,30,31) but the major cause of death was transtentorial herniation⁽²⁾.

In conclusion, CVST presents with a wide spectrum of symptoms and signs. Headache was the most frequent symptom. Women who used OCP were especially at higher risk of CVST. Because of a moderate to high mortality rate of this disease, patients at increased risk of death, especially comatose patients, should be closely monitored.

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