Clinical Profile, Risk Factors, and Outcome of Cerebral Venous Sinus Thrombosis at Tertiary Care Centre

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Abstract

Introduction: Cerebral venous sinus thrombosis (CVST) is characterized by clinical pleomorphism and pathogenic variability. Multifactorial causation of CVST and conflicting results in established literature pertaining to mortality and risk factors inspired us to study the clinical profile, risk factors, and outcome of CVST and to compare clinical profile with magnetic resonance venogram findings.

Materials and Methods: This prospective, observational, 18-month study was conducted on 64 patients of either gender, aged ≥15 years with confirmed diagnosis of CVST using magnetic resonance imaging (MRI) of brain with venogram. All patients underwent thorough vital and laboratory examination (blood and thrombophilia profile and homocysteine), and data was analyzed by analysis of variance using software R version 3.6.0.

Results: Out of 64 patients, 42 (65.6%) were males. Majority (40) were in the age group of 18-40 years (62.5%). Headache (73.4%), vomiting (57.8%), and dehydration (34.4%) were the commonly encountered symptoms. Puerperium (18.2% females), oral contraceptive usage (18.2% females), anemia (39.1%), anti-thrombin III deficiency (16.7%), protein C deficiency (16.7%), protein S deficiency (16.7%), factor V Leiden mutation (25%), and hyperhomocysteinemia (30.8%) were the common risk factors observed. Twenty-one patients (32.8%) had only superior sagittal venous sinus (SSS) involvement, 3 (4.7%) had both SSS and transverse venous sinus (TS) involvement, 21 (32.8%) had either TS alone or both TS and sigmoid venous sinus involvement (SS), and 19 (29.7%) had multiple sinus involvement (>2). There was a statistically significant difference in mean hemoglobin and total leukocyte count levels between various sites of sinuses involved (P=0.011 and P=0.003, respectively). Majority of the patients recovered (98.4%), and one patient died (1.6%).

Conclusions: CVST was more common in the third and fourth decades of life, predominantly in males with puerperium, oral contraceptive usage, anemia, and hyperhomocysteinemia being the major predisposing factors.

KeyWords: Sagittal sinus, anemia, headache, oral contraceptives
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Introduction

Cerebral venous sinus thrombosis (CVST) is considered as a distinct subgroup of cerebrovascular disease which is characterized by clinical pleomorphism and pathogenic variability. Due to its diverse presentation, CSVT is often under-diagnosed in clinical scenarios and first diagnosed only by a radiologist.[1] In India, it is a leading cause of mortality in women of childbearing age, and most of the cases occur during the post-partum period while, alcoholism is considered to be a significant risk factor in males.[2]

The outcome of CVST is highly unpredictable. It is not unusual to see dramatic recovery in deeply comatose patients as well as sudden worsening in conscious patients due to the extension of thrombosis.[3],[4] A recent research reported less than 20% mortality compared to earlier studies which reported 30-50% mortality.[3] With the advent of imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance venography (MRV), the diagnosis of CVST has improved significantly.

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In fact, after the introduction of MRV, many of the patients diagnosed with idiopathic elevated intracranial pressure (ICP) have been noted to have CVST. As the etiology of CVST is multi-factorial, it would be interesting to know whether different pathophysiological mechanisms are working at different clinical settings.[1],[4],[5] Recent review of CVST cases from Asian countries has suggested differences in the risk factor profile as well as outcome in these patients as compared to those in European countries.[6] Thus, the multi-factorial causation of CVST and conflicting results in established literature pertaining to mortality and risk factors inspired us to study the clinical profile, risk factors, and outcome of CVST and to compare the clinical profile with MRV findings.

Materials and Methods

The prospective, observational study was carried out for 18 months (Dec 2017-May 2019) in a tertiary care teaching hospital in Karad, Maharashtra, India, after approval from the institutional ethics committee.

By convenient sampling technique, 64 patients of either gender, aged ≥15 years with confirmed diagnosis of CVST through MRI of brain with venogram were recruited after obtaining a written informed consent from all of them. Patients with hypertensive hemorrhage, infarct in arterial territory, and metabolic encephalopathy were exempted from the study.

Data regarding clinical presentations, past medical history (hypertension [HTN], diabetes mellitus [DM], dyslipidemia, hematological disorder, and cancer), oral contraceptive usage, pregnancy, and alcohol consumption were recorded in a pre-structured proforma.

All patients underwent thorough physical examination. Vitals such as blood pressure (BP; average of two readings at 1-mininterval was taken), pulse rate, respiratory rate, and body temperature were checked every day during the hospital stay. Later, venous blood was collected from the antecubital area of the arm of all patients and sent for laboratory analysis such as blood profile (hemoglobin [Hb; using fully automated 3-part cell analyzer], total leukocyte count [TLC; using fully automated 3-part cell analyzer], and prothrombin time/international normalized ratio [PT/INR; using STAGO analyzer; Stago India Pvt. Ltd.]), thrombophilia comprehensive profile (lupus anticoagulant using electromechanical clot detection method, anti-thrombin III and protein-C activity using chromogenic method, protein-S activity using immunoturbidimetric method, and factor V Leiden mutation using real-time polymerase chain reaction (PCR) method. Biochemical parameters such as serum creatinine using modified JAFFE'S method, liver function tests using calorimetry, and serum quantitative homocysteine using chemiluminescent micro-particle immunoassay method were analyzed. All hematological and biochemical parameters were analyzed in EM 360 analyzer (Transasia Bio-Medicals Ltd., India). MRI of the brain with venogram was done using Siemens Avanto 1.5 Tesla (Siemens India) to confirm the diagnosis of CVST. During hospital stay, treatment in the form of unfractionated heparin (1000 units/h), low-molecular-weight heparin (0.1 mg/10 kg body weight for 10 days), mannitol, oral anticoagulants, and decompressive craniotomy was recorded. Patients' PT/INR was monitored to keep it in the therapeutic range of 2-3. Complete data of all patients was obtained during their hospital stay, and they were followed up during regular scheduled follow-up visits.

Statistical analysis

Statistical analysis was done using software R version 3.6.0. Normality of the data was determined using the Shapiro-Wilk test. Continuous variables with normal distribution were presented as mean±standard deviation and compared using one-way ANOVA analysis. Categorical variables were presented as frequencies and percentages. A P value of <0.05 was considered statistically significant at 95% confidence interval.

Results

Out of 64 patients, 42 (65.6%) were males. The mean age of all patients was 37.7±13.4 years (38.7±14 in males and 35.9±11.8 in females). Majority (40) were in the age group of 18-40 years (62.5%). Occupation-wise, 25 (38.76%) were self-employed, 19 (29.69%) were homemakers, 10 (15.63%) were students, and 9 (14.06%) were farmers. Eleven (17.9%) patients had history of HTN, 8 (12.5%) had DM, and 2 (3.1%) had deep vein thrombosis (DVT). Among the females, 4 (6.2%) had history of oral contraceptives usage and 4 (6.2%) were in the post-partum period. At the time of admission, most patients presented with headache (47; 73.4%) and dehydration (22; 34.4%). None of the patients had cerebellar dysfunction (Table 1).

Table 2 depicts the BP, Hb, and hematocrit levels of the study participants. Hb levels of most of the patients (25/64; 39.1%) were in the range of 8 to 12 g/dL. Due to financial constraints, thrombophilia profile and homocysteine levels were evaluated in 12 and 13 patients, respectively. Four out of 13 patients who were investigated for serum homocysteine had hyperhomocysteinemia (30.8%). Table 3 depicts the thrombophilia profile of study participants. MRI findings revealed that 21 (32.8%) out of 64 patients had only superior sagittal venous sinus (SSS) involvement, 3 (4.7%) had both SSS and transverse venous sinus (TS) involvement, 21 (32.8%) had either TS alone or both TS and sigmoid venous sinus (SS), and 19 (29.7%) had multiple sinus (MS) involvement (>2). TS involvement was observed in 70.3% cases either alone or with other sinuses (mostly sigmoid sinus), SSS in 60.9% cases either alone or in combination with other sinuses, and SS in 54.7% cases alone or in combination with other sinuses. Other than the involvement of the venous sinuses, 18 (28.1%) patients had internal jugular vein involvement, 3 (4.7%) had internal cerebral vein involvement, 5 (7.8%) had hemorrhagic infarct, and 2 (3.1%) had subarachnoid hemorrhage.

Table 4 depicts the average values (mean±SD) of laboratory investigations and their comparison according to the site of sinus involved. There was a statistically significant difference in the mean Hb and TLC levels between the various sites of sinuses involved (P=0.011 and P=0.003, respectively). Majority of the patients recovered, and only one patient (1.6%) died (Table 5).

Discussion

CVST is more common in the developing countries and is associated with sedentary lifestyle, dehydration, oral contraceptive usage, puerperium, and rarely infection. A total of 64 patients diagnosed with CVST by brain MRI with venogram were evaluated clinically in the present study. Most of the patients were in their third and fourth decades of life with males being predominant. Majority of the Indian studies conducted earlier have reported a female predominance as CVST is considered a traditional disease in women in tropical countries.[7],[8] With time, the pathophysiology of the disease is evolving, and CVST is reported to be more common in men. A large-cohort study conducted in south India also reported a male predominance with predominant risk factors of hyperhomocysteinemia, anemia, and alcoholism.[9] More than half of the patients in our study were less than 40 years of age (62.5%). Findings of previous studies were in favor of our study indicating that people in their third and fourth decades of life are more likely to have CVST compared to other age groups.[10] Koopman et al comparatively studied the risk factors of CVST and DVT in patients aged 15-50 years and reported that CVST is more common in younger age with a median age of 30 years.[11] A study conducted by Stolz et al showed that increasing age led to poor prognosis; however, in the present study, no significant association was seen among the different age groups of CVST patients.[12]

The clinical presentations of CVST are very much variable due to its wide range of signs and symptoms. The most common presentations (symptoms) in our study were headache (73.4%), vomiting (57.8%) and dehydration (34.4%). These findings are similar to those reported in previous studies in which headache, dehydration, seizures, altered sensorium,[13],[14] and papilledema (in some studies)[15] were the most commonly encountered presentations of CVST. Any pathology altering the Virchow's triad of thrombosis comprising endothelial injury, abnormal blood flow, and hypercoagulability can lead to thrombosis. Thrombosis of the cerebral veins may lead to focal deficits due to local effects of venous obstruction but also more generalized effects as a result of elevated ICP caused by blocking of the major sinuses. The major risk factors seen in our study were puerperium (18.2% of female population), oral contraceptive pills use (18.2% of female population), dehydration (34.4%), procoagulopathies (anti-thrombin III deficiency [2/12; 16.7%], protein C deficiency [2/12; 16.7%], protein S deficiency [2/12; 16.7%], and factor V Leiden mutation [3/12; 25%]), lymphoma (1.56%), hyperhomocysteinemia (4/13; 30.8%), leukocytosis (18.7%), and acute bacterial meningitis (1.56%). Mohapatra et al evaluated 36 patients with CVST and reported that 68% of females in their study were in puerperal period which is a predominant risk factor for CVST; however, the outcome was similar to non-pregnant females.[16] Haghighi et al analyzed cumulative data of 465 patients from published Iranian studies in a systematic manner and revealed that oral contraceptive usage is a predominant risk factor for CVST.[17] Koopman et al, Kalita et al, and Kapinder et al reported oral contraceptive usage, puerperium, and hyperhomocysteinemia as the

predisposing factors, whereas protein C deficiency, protein S deficiency, and elevated antiphospholipid and anticardiolipin antibodies were reported to be in lesser proportion.[11],[15],[18] Martinelli et al[19] conducted a case-control study in 121 CVST cases and 242 healthy controls and revealed that combined presence of oral contraceptive pills usage and hyperhomocysteinemia certainly increased the risk of CVST (OR=19.5; 95% CI: 5.7–67.3) than individual factors alone (contraceptive pills usage [OR=6.1] and hyperhomocysteinemia [OR=4]). None of these studies reported factor V Leiden mutation.[11],[15],[18],[19] Genetically inherited thrombophilia leads to 22.4% cases of CVST. The most common genetic disorder causing CVST is factor V Leiden mutation followed by the prothrombin gene mutation G20210A, whereas less common genetic factors include deficiencies of protein C, protein S, and anti-thrombin III.[20] Inherited thrombophilia along with acquired risk factors like pregnancy and puerperium, use of oral contraceptives, hyperhomocysteinemia, and antiphospholipid antibodies may increase the risk of CVST manifold.[21]

The involvement of SSS (60.9%) and TS (70.3%) was majorly seen in this study. Similar results were reported by most of the studies demonstrating that SSS is the most commonly involved sinus for thrombosis.[13],[16],[21] There was no significant difference in the clinical profile (except Hb and TLC) between radiological findings of various sinuses (involvement of various sinuses); indicating that anemia was also most commonly associated with CVST. Therefore, there was less diagnostic significance related to it. Most of the patients had involvement of the cerebral venous sinus system, risk for the development of CVST related to anatomical venous system is not significant to know a clinical profile.[18]

In the present study, almost all patients were discharged with favorable prognosis at the end of treatment except for one (1.56%) patient who died. In contrast, majority of the earlier studies reported high mortality rates.[17],[21] Also, most of the studies have reported that male sex is a poor outcome factor which was not statistically significant (OR=2.8, 95%CI: 0.93 – 9.21).[13] Mortality rate due to CVST could reduce by 13% with early diagnosis and quick initiation of appropriate treatment with anticoagulants.[22] It is one of the preventable and manageable diseases of the central nervous system, if diagnosed early and managed appropriately.

This study, however, has a limitation. The sample size of the study was very small and hence, we cannot generalize the results to the general population.

Conclusion

Cerebral venous sinus thrombosis (CVST) was more common in the third and fourth decades of life, predominantly in males. Headache and vomiting were the most common presenting complaints while dehydration, oral contraceptives usage and post-partum status were common precipitating and associated factors for the development of CVST. The transverse sinus was the most commonly involved sinus in CVST compared to other sinuses. One-third of the patients had deficiencies of protein C, protein S, and anti-thrombin III as risk factors for the development of CVST.

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Declaration of conflicting interests

There are no conflicts of interest to declare.

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Author contribution details

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Concepts	√	√
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Table 1: Clinical presentations of study participants

Clinical presentations	Frequency (n)	Percentage (%)
Symptoms		
Headache	47	73.4
Vomiting	37	57.8
Fever	7	10.9
Signs		
Cranial nerves involvement	2	3.1
Higher function affected	3	4.7
Motor weakness	5	7.8
Altered sensorium	1	1.6
Cerebellar dysfunction	0	0
Acute bacterial meningitis	1	1.6
Papilledema	4	6.3
Extensor plantar	8	12.5
Dehydration	22	34.4

Table 2: Blood pressure, hemoglobin, and hematocrit levels of study participants

Parameters		Frequency (n)	Percentage (%)	Mean±SD
SBP (mmHg)	<120	8	12.5	131.6±17.7
	120 to 140	50	78.1	
	>140	6	9.4	
DBP (mmHg)	<90	48	75.0	82±9.9
	90 to 100	14	21.9	
	>100	2	3.1	
Hb (g/dL)	<8	4	6.25	12.5±3.1
	8 to 12	25	39.06	
	>12 to 14	16	25.00	
	>14	19	29.69	
HCT (%)	<35	19	29.69	39.8±8.7
	35 to 45	28	43.75	
	>45	17	26.56	

SBP-Systolic blood pressure; DBP-Diastolic blood pressure; Hb-Hemoglobin; HCT-Hematocrit

Table 3: Thrombophilia profile of study participants

Thrombophilia profile	Frequency (n=12)	Percentage (%)
Lupus anticoagulant	1	8.3
Anti-thrombin III deficiency	2	16.7
Protein C deficiency	2	16.7
Protein S deficiency	2	16.7
Factor V Leiden mutation	3	25
Antiphospholipid antibodies	4	33.3

Due to financial constraints, thrombophilia profile was evaluated in a limited number of patients (n=12)

Table 4: Comparison of various laboratory parameters' mean among sites of cerebral venous sinus

involved

Parameters	Sites of cerebral venous sinus				P*
	SSS (n=21)	SSS and TS (n=3)	TS or TS and SS (n=21)	MS (n=19)	
SBP	133.3±17.7	136.7±20.8	134.3±20.1	125.8±14.6	0.413
DBP	82.9±10.07	83.3±5.8	81.9±9.3	80±11.5	0.831
Hb	11.1±3.1	15.2±1.6	12.4±2.8	13.8±2.8	0.011
HCT	36.3±9.9	47.6±7.8	39.4±7.9	42.9±7.2	0.035
TLC	10011.9±4048.02	20300±8870.7	10685.7±4687.6	10774.2±4699.7	0.003
PT/INR	1.66±1.5	1.30±0.1	1.2±0.1	1.2±0.2	0.311
Cr	1.36±1.7	1.2±0.4	0.92±0.2	0.89±0.2	0.421
TC	154.5±37.2	187.7±41.2	175±34.5	162.6±41.9	0.241
TG	155±35.7	126.6±29.3	147.1±47.9	160.5±67.5	0.672
HDL	38.9±6.6	36.7±2.9	37.6±9.1	40.3±7.4	0.685
LDL	100.2±42.1	94.3±34.8	97.7±32.9	101.3±35.2	0.982

Data were presented as mean±SD; *One-way analysis of variance; Cr-Creatinine; DBP-Diastolic blood pressure; Hb-Hemoglobin; HCT-Hematocrit; HDL-High-density lipoprotein; LDL-Low-density lipoprotein; MS-Multiple sinus; PT/INR-Prothrombin time/International normalized ratio; SBP-Systolic blood pressure; SSS-Superior sagittal venous sinus; SS-sigmoid venous sinus; TC-Total cholesterol; TG-Triglycerides; TLC-Total leucocyte count; TS-Transverse venous sinus

Table 5: Outcome in patients with CVST

Outcome	Frequency (n)	Percentage (%)
Cured	63	98.4
Expired	1	1.6
Total	64	100