Original Article

Critical Prognostic Factors in Cerebral Venous Sinus Thrombosis: An Observational Study

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Abstract

Background: Cerebral venous sinus thrombosis (CVST) presents with a wide variety of neurological symptoms in various combinations and has a high mortality rate of up to 50%. Recent advances in neuroimaging and therapeutic interventions have brought it down to 10%–20%. The study aims to identify critical prognostic factors associated with poor outcomes in patients with CVST. **Materials and Methods:** All cases of CVST aged >18 years from July 2015 to July 2020 who were not terminally ill and bedridden before the illness were evaluated at the entry point for various risk factors and after 30 days for outcome assessment with the modified Rankin scale (mRS). The outcome was dichotomized, applying mRS <3 as a good outcome, and analyzed with the Chi-square test or the Fischer's exact test in a bivariate analysis to identify associated variables. **Results:** A total of 149 subjects were studied. Glasgow Comma Scale (GCS) <9 (P<0.001), focal neurological deficits (P = 0.05), the presence of a mass effect (P<0.001), and the need for decompressive hemicraniectomy (P<0.001) were associated with poor outcomes. Age, gender, diagnostic delay, seizures at onset, papilledema, parenchymal lesions, deep sinus involvement, and multiple sinus thrombosis were not associated with a poor outcome. **Conclusion:** In our study, early diagnosis and treatment of CVST is associated with an overall favorable outcome even in the presence of traditional poor prognostic factors such as age, seizures at onset, deep sinus involvement, and multiple sinus involvement in the face of conventional risk factors. A large country-wide prospective study might help in elucidating the poor prognostic factors.

Keywords: Cerebral venous sinus thrombosis, CVST, outcome, prognostic factors

Introduction

Cerebral venous sinus thrombosis (CVST) was initially described in the early 19th century in French literature, but still remains a diagnostic challenge because of its varied presentation.[1] Headache, seizure, papilledema, altered sensorium, and focal deficits are the typical manifestations of the disease.[2] Headache is the presenting symptom in 70%–90% of cases.[3,4] The clinical presentation in CVST is varied, from headaches to stupors or a comatose state.[5] The largest cohort of European CVST patients (n = 624) recorded that half of those cases were associated with oral contraceptive pill (OCP) tablets, 6% were due to pregnancy, and 14% were due to puerperium.[6,7] In India, a study done at Nizam's Institute of Medical Sciences (NIMS) (n = 428) showed CSVT was associated with anemia (18.4%), hyperhomocysteinemia (18.2%), alcoholism (15.6%), OCP intake (11.4%), postpartum state (9.8%), anticardiolipin antibodies (7.2%), and protein S deficiency (12.3%). The superior sagittal sinus (72%) accompanied by the transverse sinus (70%) were the most prevalent sinuses involved. More than one sinus is involved in 30%–40% of cases.[8] In India, CVST forms a different cerebrovascular disease subgroup and is the highest cause of death in women of reproductive age.[9] In recent years, the mortality in CVST patients has come down to 10%–20%, as reported in most of the studies.[7,10,11] Regardless of the fact that most patients have a full or partial recovery, a substantial population has a poor prognosis. Hence, the purpose of the study was to analyze the outcome of CVST in the current era of modern imaging and determine the prognostic factors associated with poor outcomes.

Methods

This retrospective observational study was conducted in the department of neurology at Kasturba Medical College (KMC) Manipal, a large tertiary care hospital in southwestern Karnataka, between July 2015 and July 2020. The study protocol was approved by the Institutional Ethics Committee (ECR/146/Inst/KA/2013/9RR-19).

Inclusion criteria

The following were the inclusion criteria: (i) age >18 years; (ii) gender- both; (iii) and patients who were suspected to

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have CVST clinically and confirmed with either computerized tomography venography (CTV), magnetic resonance venography (MVR), or digital subtraction angiography (DSA).

Exclusion criteria

The exclusion criteria were: (i) age <18 years; (ii) patients who were previously bedridden; (iii) patients with both arterial and venous strokes; and (iv) patients who were terminally ill.

Data was extracted from the files of patients with suspected CVST and confirmed with CTV/MRV/DSA. The data included baseline characteristics like age, sex, type of clinical symptoms, risk factors, imaging findings, blood investigations, treatment given, and the response to treatment, along with prognostic factors such as diagnostic delay, Glasgow Coma Scale (GCS) score at admission, seizures at admission, the presence of papilledema, the presence of focal neurological deficits, the presence of parenchymal lesions, multiple sinus involvement, deep sinus involvement, the presence of mass effect, and the requirement of decompressive craniectomy.

The etiological workup for CVST was done as per the clinical suspicion by the department of neurology at our institute. All the patients were worked up with serum homocysteine, and those found to have high values were worked up with serum vitamin B12 levels during the hospital stay. Few of the patients had also undergone routine vitamin B12 level testing along with homocysteine levels. Anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and anti-phospholipid antibody (APLA) testing was done routinely for most of the patients. The thrombophilia workup was done 4 weeks after the completion of recommended anticoagulation, as per the discretion of the clinician and the financial status of the patient.

All the patients were either treated with low-molecular-weight heparin (LMWH) or unfractionated heparin (UH) as per the recommendations of the American Heart Association (AHA)/ American Stroke Association (ASA) in 2011. UH was used only when the patient had renal failure or had a possible requirement for decompressive craniectomy.

Outcomes

Follow-up information included the modified Rankin score (mRS) at 30 days after the onset of symptoms. The outcome of CVST was graded as complete recovery (mRS 0–1), partial recovery but independent (mRS = 2), partial recovery but dependent (mRS 3–5), and death (mRS = 6). mRS ≤2 was graded as a good outcome and mRS ≥3 as a poor outcome.

Statistical analysis

The statistical analysis was carried out in Statistical Package for the Social Sciences (SPSS) software version 17.0. Parametric continuous variables were presented as mean with standard deviation (SD), and nonparametric continuous variables (non-normally distributed) were expressed as medians with interquartile range (IQR). Categorical variables were expressed as proportions. Bivariate analyses were performed to identify variables associated with outcomes (good or poor outcomes based on mRS scores) using Pearson's Chi-square or Fisher's exact tests, as appropriate.

Results

A total of 149 patients diagnosed with CVST were included. There were 104 males and 45 females in the study. The overall sex ratio was skewed toward male gender, with a ratio of 2.3:1. The mean (SD) age of the group was 33.6 (11.3) years (minimum age: 18 to maximum age: 78). The median duration (IQR) of symptoms before presentation to the hospital was 7 (3–12) days. The mean GCS (SD) at admission was 13.6 (2.6), and the median GCS (IQR) at admission was 15 (13–15).

Clinical features

The most common clinical feature was headache (87.2%). It was followed by papilledema (59.7%) and seizures (51%). Aphasia was the least common clinical feature (5.4%), followed by cranial nerve deficits (CND) (7.4%). Altered sensorium was seen in 28.9%, and focal neurological deficits were seen in 37.6%. Idiopathic intracranial hypertension (IIH)-like presentation of CVST was seen in 22.8% of patients [Table 1].

The most common sinus thrombosed overall was the superior sagittal sinus (65.1%). It was followed by the right transverse sinus (43.6%) and cortical vein thrombosis (41.6%). Multiple sinus thrombosis was seen in 83.9%. Left transverse, right sigmoid, and left sigmoid sinus thromboses were seen in 34.2%, 35.6%, and 26.8%, respectively. The least common sinus thrombosed was the inferior sagittal sinus (4.0%). Deep sinus thrombosis (isolated and coexistent with superficial vein thrombosis) was seen in 16.1%. Internal jugular vein thrombosis was seen in 39.6%. Vein of Galen thrombosis was seen in 11.4%, and straight sinus thrombosis was seen in 16.8% [Table 2].

Provoked CVST was seen in 91.3% of the population, and it was unprovoked in the remaining 8.7%. The most common etiological risk factor was alcohol (38.5%). It was followed by an ANA profile (30.2%) and hyperhomocysteinemia (26.2%). Anemia was seen in 23.5%. Vitamin B12 deficiency was seen in 39.2%, and iron deficiency was seen in 90.6%. But these etiological risk factors were not evaluated in all the patients. Other tests for hypercoagulable state, such as APLA, protein

Table 1: Incidence of various clinical manifestations

Clinical feature	*n* (%)
Headache	130 (87.2)
Seizure	76 (51)
Altered sensorium	43 (28.9)
Aphasia	8 (5.4)
Papilledema	89 (59.7)
CND	11 (7.4)
FND	56 (37.6)
IIH	34 (22.8)

CND=cranial nerve deficits, FND=Focal neurological deficits, IIH=idiopathic intracranial hypertension

C and S deficiency, antithrombin III deficiency, and factor V Leiden, were found in seven patients. APLA was positive in five out of seven patients. Polycythemia was an etiological risk factor in five patients, and Janus Kinase 2 (JAK-2)–positive status was seen in two of them. OCP usage and puerperal CVST were almost equal, accounting for 7.2% each. ANA global and ANCA positivity were seen in 27% and 6.6%, respectively. Ear infection was the cause in 5.4%, and head injury was the cause in 1.3%. Prior CVST was a risk factor in 2% of the population [Table 3].

Follow-up and outcomes

A good outcome at 1 month was seen in 95.3% of the patients and a poor outcome was seen in the remaining seven patients out of 149 [Table 4].

Complete recovery (mRS 0–1) at 1 month was seen in 83.9% of the population, and partial recovery but independence (mRS 2) was seen in 11.4% of the population at 1 month. Partial recovery but dependence (mRS 3–5) was seen in seven patients at 1 month [Table 5].

Parenchymal lesions were seen in 66% and were absent in 34% of the population. The mass effect was seen in 81% and was absent in 19% of the population. Subarachnoid hemorrhage was seen in 32% and was absent in 68% of the population. The need for decompressive craniectomy occurred in 7% and did not occur in 93% of the population.

The prognostic factors associated with poor outcomes were GCS <9 at admission (P<0.001), the presence of focal neurological deficits (P=0.05), the presence of mass effect (P<0.001), and the need for decompressive craniectomy (P<0.001). Age, gender, diagnostic delay, seizures at admission, presence of papilledema, presence of parenchymal lesions, deep sinus thrombosis, and multiple sinus thrombosis were not associated with a poor prognosis [Table 6].

Discussion

This is a retrospective single-center study conducted at KMC Manipal, situated in the southwestern part of India. The mean age of the overall population was 33.6 years. The mean duration from symptom onset to presentation to the hospital was 15.96 days in our study, which was comparable to another large Indian study by Narayan *et al*. (16.1 days).[12] But in contrast, Ferro *et al*.[13] reported a mean duration of 4 days, indicating a significant diagnostic delay in identifying CVST patients in India when compared to the Western population. The most common clinical feature observed in our study was headache (87.2%), followed by papilledema (59.7%) and seizures (51%), as reported in other Indian studies, but papilledema has a higher incidence in India when compared to the Western population. The presence of a focal neurological deficit that includes monoparesis, hemiparesis, or paraparesis and the presence of altered mental status were reported in one-third of the population. IIH-like presentation, a characteristic phenotype of CVST, was seen in 22.8% of our study population, which is consistent with that reported earlier.[12,13] The most common sinus involved was the superior sagittal sinus, followed by the transverse sinus and cortical vein thrombosis. Interestingly, our study reported cortical vein thrombosis in 41.6% of the population, which was not seen in the other large prospective cohort studies that have

Table 2: Incidence of various sinuses involved

Location of thrombosis	*n* (%)
Superior sagittal sinus	97 (65.1)
Inferior sagittal sinus	6 (4)
Right transverse sinus	65 (43.6)
Left transverse sinus	51 (34.2)
Right sigmoid	53 (35.6)
Left sigmoid	40 (26.8)
Straight sinus	25 (16.8)
Vein of Galen	17 (11.4)
Deep sinus vein	24 (16.1)
Internal jugular vein	59 (39.6)
Cortical vein	62 (41.6)
Cavernous sinus	0 (0)
Multiple sinus involvement	125 (83.9)

Table 3: Incidence of various etiological risk factors

Etiological factors	Number of patients	*n*	Percentage
Hyperhomocysteinemia	39	149	26.2
APLA	5	112	4.5
Protein C and protein S	1	6	16.7
Anti-thrombin III	1	6	16.7
ANA global	30	111	27.0
ANA profile	35	116	30.2
ANCA	6	91	6.6
Polycythemia	5	144	3.5
JAK2 mutation	2	14	14.3
Factor V Leiden	-	4	-
Alcohol	55	143	38.5
B12 deficiency	31	79	39.2
Iron deficiency	29	32	90.6
Anemia	35	149	23.5
Puerperal	11	149	7.4
OCP use	11	148	7.4
Ear infection	8	149	5.4
Head injury	2	149	1.3
Prior CVT	3	149	2.0
Idiopathic	13	149	8.7

ANA=anti-nuclear antibody ANCA=anti-neutrophil cytoplasmic antibody, APLA=anti-phospholipid antibody, OCP=oral contraceptive pill

Table 4: Short term outcome at 1 month

Outcome	Number	Percentage
Good (mRS <3)	142	95.3
Poor (mRS ≥3)	7	4.7
Total	149	100.0

mRS=modified Rankin scale

reported an incidence of 3%–18%.[12,13] No cavernous sinus thrombosis was noted in our study, probably indicating better health-care management of facial, ear, and orbital infections in recent years. The incidence of multiple sinus thrombosis was found to be 83.9% in our population, indicating that it was far more common than isolated sinus thrombosis. The most common etiological risk factor identified in our study was alcohol (38.5%), which was more than double to that observed in the study of Narayan *et al*. (15.6%).[12] This probably indicates that alcohol is one of the major risk factors for CVST in India, and its incidence has risen in the Indian population, presumably due to increased awareness of its association with CVST. Genetic thrombophilia was reported in a significant number of CVST populations, amounting to around 15% in other studies.[10,12-15] But in our study, only two out of the total 149 patients had genetic thrombophilia. This is likely due to the very low number (six) of our patients being tested for genetic thrombophilia. Acquired thrombophilic conditions such as hyperhomocysteinemia were reported in 26.2% of the participants in our study. This could be related to a greater number of patients having alcohol as a risk factor in our population, as well as a significant number of our population having vitamin B12 deficiency (31 out of 79 tested, accounting for 39.2%) as an etiological risk factor. Vitamin B12 deficiency was contributory to CVST due to acquired hyperhomocysteinemia in 31 out of 39 patients tested (79.48%). Another interesting fact noticed was that vitamin B12 deficiency was found without anemia in 13.4% of our cases. This indicates that anemia need not be present in all the patients with vitamin B12 deficiency, and hence, it needs to be screened while evaluating the cause of CVST. ANA positivity was noted in 57.2% of our population, but paradoxically, this was attributed as the cause of CVST in just one patient, who was already a diagnosed case of systemic lupus erythematosus. This is likely due to most results of ANA being weak positive and patients not having clinical features of autoimmune disease. The short-term outcome of CVST at 1 month was reported to be poor (mRS >2) in 4.7% of the population in our study; this has not been reported in any major studies done so far, including Ferro *et al*.[13] (18.9% at discharge), Barboza *et al*.[16] (23.1% at 1 month), and Narayan *et al*.[12] (33.4% at 90 days). Not only that, the short-term mortality in our study was zero, whereas it was reported to be 3.4% (at 30 days),[13] 10.6% (at 90 days),[12] and 8.7% (at 30 days)[16] in other major studies. The reported incidence of malignancy causing CVST was 7.4%,[13] 2.6%,[16] 7%,[10] 2.1%,[14] and 0.9%,[12] indicating a range of 1%–7%, which, when added, would have still caused an overall good outcome in our study. The strongest predictors of poor outcome at 1 month in our population were altered mental status with a GCS <9 at admission, the presence of a mass effect on imaging, and the requirement of a decompressive craniectomy during the hospital stay. A weak predictor of poor outcome at 1 month in our population based on the *P* value was the presence of focal neurological deficits. Conventional poor prognostic factors such as higher age, male sex, diagnostic delay, seizures at onset, papilledema, parenchymal lesions, deep sinus involvement, and multiple sinus thrombosis were not associated with poor

Table 5: mRS at 1 month

Outcome	*n* (%)
MRS 0	68 (45.6)
MRS 1	57 (38.3)
MRS 2	17 (11.4)
MRS 3	2 (1.3)
MRS 4	3 (2)
MRS 5	2 (1.3)
Total	149 (100)

mRS=modified Rankin scale

Table 6: Bivariate analysis of various prognostic factors with short-term outcome

Variable	Good outcome *n* (%)	Poor outcome *n* (%)	*P*
Age categories			
≤30 years	67 (95.7)	3 (4.3)	0.8
>30 years	75 (94.9)	4 (5.1)	
Sex			
Female	44 (97.8)	1 (2.2)	0.3
Male	98 (94.2)	6 (5.8)	
Diagnostic delay			
≤7 days	87 (94.6)	5 (5.4)	0.8
>7 days	55 (96.5)	2 (3.5)	
GCS at admission			
≤9	8 (66.7)	4 (33.3)	<0.001
>9	134 (97.8)	3 (2.2)	
Seizures at admission			
Absent	71 (97.3)	2 (2.7)	0.3
Present	71 (93.4)	5 (6.6)	
Papilledema			
Absent	58 (96.7)	2 (3.3)	0.5
Present	84 (94.4)	5 (5.6)	
FND			
Absent	91 (97.8)	2 (2.2)	0.05
Present	51 (91.1)	5 (8.9)	
Parenchymal lesions			
Absent	50 (98)	1 (2)	0.3
Present	92 (93.9)	6 (6.1)	
Mass effect			
Absent	119 (99.2)	1 (0.8)	<0.001
Present	23 (79.3)	6 (20.7)	
Multiple sinus involvement			
<2	24 (100)	0 (0)	0.2
≥2	118 (94.4)	7 (5.6)	
Deep sinus involvement			
Absent	120 (96)	5 (4)	0.4
Present	22 (91.7)	2 (8.3)	
Decompressive craniectomy			
Not done	135 (97.8)	3 (2.2)	<0.001
Done	7 (63.6)	4 (36.4)	

FND=Focal neurological deficits, GCS=Glasgow Coma Scale

outcomes in our population.[13,17] Intriguingly, the diagnostic delay (>7 days) from symptom onset to diagnosis has not been shown to have any impact on the poor outcome of CVST in our population. This has also been corroborated by the fact that the mean duration from symptom onset to presentation to our hospital was reported to be 15.96 days, and 95.3% of our population had a good outcome. The probable reasons for this could be a short delay in diagnosis after reaching the hospital, the possibility of a less-severe form of CSVT in the southwestern population of Karnataka, and the possibility of severe cases succumbing to death within 7 days before reaching the hospital. The excellent prognosis noted in our study might also have been due to the smaller number of puerperal CVST cases in our population when compared to other Indian studies where puerperal CVST was the major risk factor noted.[17-20] This gives one an idea of whether the morbidity or mortality of CVST is predominantly due to puerperal CVST. Further studies with a larger sample size are required to confirm the excellent prognosis of CVST reported in our study and whether puerperal CVST has any association with morbidity or mortality.

Conclusion

This large observational study showed a trend towards a better prognosis in the southwestern part of India owing to early diagnosis and treatment. The presence of a mass effect on neuroimaging, a low GCS score, focal neurological deficits, and the requirement of decompressive craniectomy suggest a stormy course and a poor outcome. The traditional risk factors that were observed in earlier studies were found to be not so relevant in this single-center study. A large country-wise CVST registry will help in elucidating the relevant risk factors for poor outcomes in the Indian subcontinent.

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Conflicts of interest

There are no conflicts of interest.

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