A PROSPECTIVE OBSERVATIONAL STUDY OF PREDICTORS OF POOR OUTCOMES IN PATIENTS WITH CEREBRAL SINUS VENOUS THROMBOSIS AT A TERTIARY CARE CENTER IN INDIA

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ABSTRACT

Objective: The objective of this study was to evaluate the factors associated with poor outcome in cerebral sinus venous thrombosis (CSVT) patients at 3 and 6 months.

Methods: This was a prospective observational study in which CSVT patients hospitalized at a tertiary care center in Davangere, India during November 2016–October 2018 were included and followed up for 6 months. CSVT diagnosis was confirmed with imaging findings of computed tomography, magnetic resonance imaging, and magnetic resonance venography. Modified Rankin Scale score of 0–1 was considered indicative of "good outcome," while that of ≥2 indicated "poor outcome."

Results: Data of 44 patients were collected, of which 59% (n=26) were male, 68.2% of the patients belonged to the age group 25–45 years (mean age: 34.91±11.23 years). Fifteen patients (34.09%) had acute, 24 patients (54.55%) had sub-acute, and five patients (11.36%) had chronic symptom duration. At 3 months, age >45 years (p=0.008), focal seizure (p<0.001), hemiparesis (p<0.001), cerebellar signs (p<0.008), infarct (p=0.006), hemorrhage (p=0.049), edema (p=0.012) and midline shift (p=0.007), involvements of straight sinus (p=0.035), inferior sagittal sinus (p=0.007), frontal lobe (p=0.038), and Glasgow coma scale (GCS) score of 8–12 (p=0.008) were significantly associated with "poor outcome." At 6 months, patients with focal seizures (p=0.001), hemiparesis (p=0.008), hemorrhage (p=0.044), midline shift (p=0.013), involvement of parietal lobe (p=0.025), presence of hemorrhage (p=0.044), and GCS score of 8–12 (p=0.001) significantly higher rate of "poor outcome."

Conclusion: This real-world observational study identifies the clinicodemographic and neuroimaging variables significantly associated with "poor outcome" in CSVT patients.

Keywords: Disability assessment, Magnetic resonance imaging, Observational study, Outcome assessment, Venous thrombosis.

INTRODUCTION

Cerebral sinus venous thrombosis (CSVT) is an uncommon form of venous thromboembolism, which was first described in detail by Ribes in 1825 [1]. In India, the first cases were reported by Padmavati *et al.* in 1957, describing 15 cases of CSVT in puerperium in an epidemiological study evaluating the causes of hemiplegia in 44 women [2]. However, the condition still remains a diagnostic and therapeutic challenge. CSVT, with an annual incidence of 0.2–0.5/100,000 population [3], is rare as compared to arterial stroke and contributes to merely 0.5% of all strokes [4]. However, its prognosis can range from complete recovery to disability due to hemiparesis to even death [5]. Isolated intracranial hypertension and puerperal causes of CSVT have been associated with better clinical outcomes [6]. However, due to the condition being multifactorial, the predictors of long-term outcomes are not well-elucidated. The data on determining factors of the long-term prognosis are scarce from Southern India. Hence, this study was undertaken to evaluate the prognosis and outcomes in patients with CSVT from this part of the country.

METHODS

This was a prospective and observational study to evaluate the factors that predict clinical outcome in CSVT patients hospitalized at a tertiary care center in Davangere, India, during November 2016–October 2018. CSVT diagnosis was confirmed with imaging findings of computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance venography (MRV). Patients with a CSVT diagnosis but normal MRI/MRV findings were excluded from the study. A written consent form was received from each participant before their enrolment in the study. An Institutional Ethics Committee approval was received before the commencement of the study.

The patients underwent detailed physical and neurological examinations and CT imaging. Modified Rankin Scale (mRS) was applied at presentation and at 3- and 6-month follow-ups post-discharge to assess clinical outcome. An mRS score of 0–1 was considered indicative of "good outcome," while that of ≥2 indicated "poor outcome."

Statistical analyses was performed with IBM SPSS program for Windows Version 22. Categorical variables were presented as frequency and percentage. To study the association between categorical variables Chi-square test and if the cell values were small, Fisher's exact test was used. Logistic regression was used to assess the risk factors. Continuous variables were represented as mean and standard deviation. Inter-group comparison was done with unpaired t-test and within the group and comparison was done with paired t-test. To assess the relation between variables, Pearson's Correlation was applied. p<0.05 is considered as significant.

RESULTS

Demography

Data of 44 patients were collected, of which 59.09% (n=26) were male and majority (68.18%) of the patients belonged to the age group 25–45 years (mean age: 34.91±11.23 years). Twenty-four patients (54.55%) had symptom duration of <48 h (acute), 15 patients (34.09%) had symptom duration between 2 weeks and 1 month (sub-acute), and five patients (11.36%) had symptom duration of more than a month (chronic). Etiological spectrum of CSVT in this population is depicted in Table 1.

Table 1: Clinicodemographic and etiological features at presentation

Parameter	n=44, n (%)
Age (years)	
<25	6 (13.64)
25–45	30 (68.18)
>45	8 (18.18)
Gender	
Male	26 (59.09)
Female	18 (40.91)
Etiology	
Alcohol	8 (18.18)
Anemia	3 (6.82)
Dehydration	1 (2.27)
Hyperhomocysteinemia	12 (27.27)
OCP	4 (9.09)
Tubercular meningitis	2 (4.55)
Puerperium	5 (11.36)
HIV infection	1 (2.27)
Polycythemia	4 (9.09)
Protein C deficiency	1 (4.55)
Malignancy	1 (2.27)
Unknown	1 (2.27)
Glasgow Coma Scale	
≤8	0
9–12	3 (6.82)
13–15	41 (93.18)

OCP: Oral contraceptive pills, HIV: Human immunodeficiency virus

Table 2: Neuroimaging findings at presentation

|	n=44, n (%)
MRV findings	
Superior sagittal sinus	30 (68.18)
Transverse sinus	28 (63.64)
Sigmoid sinus	17 (38.64)
Torcular herophili	4 (9.09)
Straight sinus	5 (11.36)
Internal jugular vein	2 (4.55)
Cortical vein	15 (34.09)
Deep vein	2 (4.55)
MRI findings	
Infarct	15 (34.09)
Hemorrhage	15 (34.09)
Inferior sagittal sinus	2 (4.55)
Edema	16 (36.36)
Frontal lobe involvement	11 (25.00)
Parietal lobe involvement	13 (29.55)
Temporal lobe involvement	6 (13.64)
Occipital lobe involvement	2 (4.55)
Cerebellum involvement	1 (2.27)
Midline shift	1 (2.27)

MRV: Magnetic resonance venography, MRI: Magnetic resonance imaging

Clinical features and neuroimaging findings at presentation
As seen in Fig. 1, the most common symptom at presentation was headache (n=36, 81.82%), followed by generalized tonic-clonic seizures (34.09%), hemiparesis (22.73%), focal seizures (15.91%), fever (13.64%), aphasia (9.09%), and cerebellar signs (4.55%). At presentation, the mean mRS score was 2.11 (±0.90).

Outcomes at 3 months
At 3 months follow-up, mean mRS score was 0.93 (±0.79). Table 3 demonstrates the clinic-demographic, etiological, and imaging finding variables found to be significantly associated with "poor outcome" at 3 months. Patients aging >45 years had significantly higher rate of poor outcome (p=0.008) than rest of the study population, whereas gender or etiology were not associated with clinical outcome. Moreover, the clinical features of focal seizure (p<0.001), hemiparesis (p<0.001),
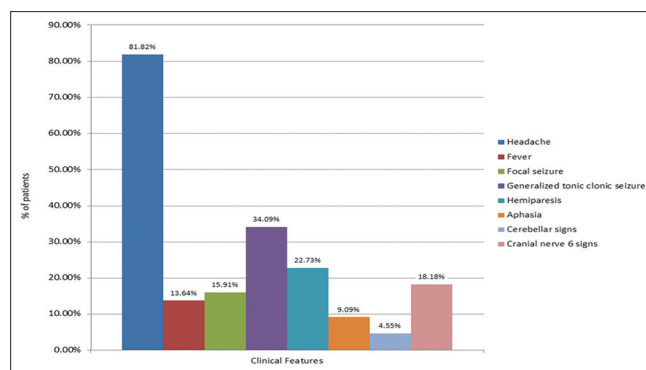
Fig. 1: Clinical features at presentation

and cerebellar signs (p<0.008) were significantly associated with poor clinical outcome. Among neuroimaging findings, the presence of infarct (p=0.006), hemorrhage (p=0.049), edema (p=0.012), and midline shift (p=0.007) significantly contributed to poor outcome. Patients with involvements of straight sinus (p=0.035), inferior sagittal sinus (p=0.007), and frontal lobe (p=0.038) had significantly higher rate of poor clinical outcome at 3 months. In terms of Glasgow coma scale, those with lower score had significantly higher rate of "poor outcome" (p=0.008).

Outcomes at 6 months
At 6 months, mean mRS score was 0.23 (±0.61). Patients with focal seizures (p=0.001) and hemiparesis (p=0.008) were shown to have significant association with "poor clinical" outcomes than those without these clinical features. The presence of hemorrhage (p=0.044), midline shift (p=0.013), involvement of parietal lobe (p=0.025), and presence of hemorrhage (p=0.044) were also significantly associated with "poor outcome" at 6 months (Table 4).

DISCUSSION

CSVT is an unusual type of stroke [7] majorly occurring in individuals of Asian [8] and Middle Eastern origin [9]. The condition is associated with an increased mortality rate, making the early identification of symptoms an important factor to improve overall outcome in these patients [10]. Hemorrhage and altered mental status have been consistently reported to be the strongest predictors of death and disability in patients with CSVT in multiple international studies [11].

Although female gender is found predominantly affected by CSVT in previously published studies, this was not the trend in our study. The possible reason for this could be infrequent use of oral contraceptive medications in the studied population, which might pose the risk of CSVT among women. In the present study, age (>45 years) was found to be a significant predictor of poor clinical outcome at 3 months. This is in line with the findings of a study by Christina *et al*. (2016), which reported that the patients with poor clinical outcome (mRS score >2) had a mean of 48.14 years, while those with an mRS score ≤2 had a mean age of 40.1 years (p=0.019). Among clinical features at presentation, seizures are associated with poor outcome in other studies as well- indicating the risk of neuronal hyperexcitability as a result of ischemic insut [15,16].

In line with the findings of the present study, hemiparesis was found to be negatively associated with clinical outcome in CSVT patients in a study by Krajíčková *et al*. [17], while the retrospective study by Karsy *et al*. did not find it to be associated with clinical outcome (p=0.95) [14]. In our study, the presence of cerebellar signs significantly predicted poor outcomes at 3 months, but not at 6 months. There are scarce data to suggest how strongly do these features correlate with clinical outcome in CSVT; hence, the current findings make this study valuable for the determination of CSVT prognosis.

Table 3: Clinicodemographic and imaging finding variables significantly associated with "Poor Outcome" at 3 months

Variables	mRS at 3 months		Total	P
	mRS (0–1) (n=34), n (%)	mRS ≥2 (n=10), n (%)		
Age (years)				
<25	6 (100.00)	0	6	0.008
25–45	25 (83.33)	5 (16.67)	30	
>45	3 (37.50)	5 (62.50)	8	
Clinical features				
Focal seizure				
Yes	1 (14.29)	6 (85.71)	7	<0.001
No	33 (89.19)	4 (10.81)	37	
Hemiparesis				
Yes	3 (30.00)	7 (70.00)	10	<0.001
No	31 (91.18)	3 (8.82)	34	
Cerebellar signs				
Yes	0	2 (100.00)	2	0.008
No	34 (80.95)	8 (19.05)	42	
MRV findings				
Straight sinus				
Yes	2 (40.00)	3 (60.00)	5	0.035
No	32 (82.05)	7 (17.95)	39	
Inferior sagittal sinus				
Yes	0	2 (100.00)	2	0.007
No	34 (80.95)	8 (19.05)	42	
MRI findings				
Infarct				
Yes	8 (53.33)	7 (46.67)	15	0.006
No	26 (89.66)	3 (10.34)	29	
Hemorrhage				
Yes	9 (60.00)	6 (40.00)	15	0.049
No	25 (86.21)	4 (13.79)	29	
Mild line shift				
Yes	0	2 (100)	2	0.007
No	34 (80.95)	8 (19.05)	42	
Edema				
Yes	9 (56.25)	7 (43.75)	16	0.012
No	25 (89.29)	3 (10.71)	28	
Frontal				
Yes	6 (54.55)	5 (45.45)	11	0.038
No	28 (84.85)	5 (15.15)	33	
GCS				
8–12	1 (25)	3 (75)	4	0.008
13–15	33 (82.5)	7 (17.5)	40	

GCS: Glasgow Coma Scale, MRV: Magnetic resonance venography, MRI: Magnetic resonance imaging, mRS: Modified Rankin Scale

Table 4: Clinicodemographic and imaging finding variables significantly associated with "poor outcome" at 6 months

Variables	mRS at 6 months		Total	p-value
	mRS (0–1) (n=42), n (%)	mRS ≥2 (n=2), n (%)		
Clinical features				
Focal seizure				
Yes	5 (71.43)	2 (28.57)	7	0.001
No	37 (100.00)	0	37	
Hemiparesis				
Yes	8 (80.00)	2 (20.00)	10	0.008
No	34 (100.00)	0	34	
MRI findings				
Hemorrhage				
Yes	13 (86.67)	2 (13.33)	15	0.044
No	29 (100.00)	0	29	
Parietal				
Yes	11 (84.62)	2 (15.38)	13	0.025
No	31 (100.00)	0	31	
Mild line shift				
Yes	2 (66.67)	1 (33.33)	03	0.013
No	40 (97.56)	1 (2.44)	41	
GCS				
8–12	1 (50)	1 (50)	02	0.001
13–15	41 (97.62)	1 (2.38)	42	

GCS: Glasgow Coma Scale, MRI: Magnetic resonance imaging, mRS: Modified Rankin Scale

Observational nature is main limitation of this study; however, given the lack of adequate data on CSVT from real world settings in Southern Indian regions, understanding of these factors would enable precise prediction of clinical outcome and facilitate overall care of patients with CSVT in routine practice.

CONCLUSION

The present study identified factors that predicted poor outcome in patients with CSVT. Mean mRS showed meaningful reduction over the follow-up period. The factors significantly contributing to poor outcome (mRS: >2) at 3 month were age >45 years, focal seizure, hemiparesis, cerebellar signs, presence of infarct, hemorrhage, and edema as well as involvements of inferior sagittal sinus and frontal lobe. While the factors associated with poor outcome at 6 months were focal seizure, hemiparesis, hemorrhage, and involvement of cortical vein and parietal lobe. These features should be identified and addressed promptly to improve the clinical outcome of this unusual type of neurological condition.

AUTHORS' CONTRIBUTIONS

Suhana S prepared the study documents, collected the study data, and conducted the study. Raval N prepared and finalized the manuscript.

CONFLICTS OF INTEREST

None.

Intracranial or subarachnoid hemorrhages have strongly been reported to be associated with poor clinical and mortality outcomes in CSVT by several studies [11,13,20]. However, in contrast to the present study, several studies have found no significant association of hemorrhage with clinical outcomes [14,18,19]. It was observed that presence of edema at presentation significantly predicted poor outcome at 3 months, but not at 6 months in our study; this is in line with the findings of an Indian study by Holay *et al.* [20]. However, few other studies have found edema to significantly contribute to poor outcome [17,21].

In the present study, patients with involvements of straight sinus and inferior sagittal sinus had significantly higher rate of poor outcome at 3 months. In previously published observational studies, the sinuses found to be significantly associated with poor clinical outcome were right lateral sinus [21], deep venous sinus [20], transverse sinus [19], sigmoid sinus [19], inferior sagittal sinus [16], and superior sagittal sinus [17]. An interesting finding of the present study is the association of involvement of cerebral lobes with clinical outcomes: At 3 months, the poor outcome was significantly predicted by the involvement of frontal lobe, while at 6 months, the involvement of parietal lobe was association with poor clinical outcome.

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