Predictors of outcome of cerebral venous sinus thrombosis at a tertiary care centre in Central India

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Abstract

Cerebral venous sinus thrombosis (CVST) is a less common cause of stroke when compared to arterial thrombosis but its clinical presentation is varied and atypical. Early diagnosis may prevent morbidity & mortality which in untreated cases has been reported as 13.8 -48%.

Materials and Methods: This prospective observational study included 40 radiologically diagnosed cases of CVST, to evaluate the predictors of outcome by using modified Rankin's Scale (mRS). The primary outcome measure was death or dependency at the end of 12 weeks.

Results: Of 40 patients, 18 cases (45.5%) had mRS 0-3 & 22(55%) had mRS >3. Mean age of the cases was 32.22 yrs with M:F= 1: 0.81. Purperium was the commonest risk factor. In univariate analysis, Age>30(p==0.10), Coma (p=0.010) and Cheyne stokes breathing (p-<0.001) were statistically significant predictors of poor outcome. On CT imaging haemorrhagic infarct & Deep venous sinus thrombosis was a significant predictor of poor outcome (p=<0.001). On multivariate analysis age>30, cerebral haemorrhage and Deep venous sinus thrombosis were the predictors of poor outcome. Rankin's score of ≤ 2 had good prognosis at 12 weeks follow up. Overall mortality was 15% at 12 weeks follow up.

Conclusion: CVST is an important cause of stroke in puerperium. Neuroimaging plays pivotal role in diagnosis. Modified Rankin's scale is a simple score system risk stratification of patients with neurodeficit. Low MRS score at hospitalization is associated with better outcome at 12 weeks.

Keywords: Cerebral venous sinus thrombosis (CVST), modified Rankin's scale (mRS) ≤ 2, good outcome.

Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon cause of stroke as compared to arterial stroke, but its clinical presentation is varied and often dramatic. It usually affects young and middle-aged patients, and more commonly women. Although recognized for more than 100 years,[1] it has only in recent years come to be diagnosed ante-mortem, frequently. This is partly due to greater awareness among physicians and neurologists, and partly to improved non-invasive imaging techniques.

Although it may present with a variety of signs and symptoms, headache is the most frequent and often the earliest manifestation.[2] Despite the improvements in its diagnosis and treatment, CVST may still cause death or permanent disability. The outcome of the patients with cerebral venous sinus thrombosis may vary from complete recovery to permanent neurological deficits as a natural course of the disease.[3] In the acute phase, it is important to identify those patients who have a poor prognosis because this may influence the therapeutic strategy and enable the treating physician to give reliable information to the patient and his/her relatives. In contemporary studies, the reported mortality rate was found to range between 8% and 14%.[4] This was in contrast to previous studies in which cause specific mortality was as high as 30% to 50%.[5]

CVST has an acute case fatality of less than 5% and almost 80% patients recover without sequelae.[4] It has been found that early diagnosis of cerebral venous thrombosis is essential because early treatment may prevent morbidity and may even be lifesaving. Reliable data on the natural history and the prognosis of CVST are scarce. Therefore, this prospective observational study was undertaken to determine the predictors of outcome in CVST.

Materials and Methods

Institutional ethics committee of Govt Medical College, Nagpur gave clearance for this study. 40 consecutive patients admitted to Govt Medical College, Nagpur, a tertiary care institute, which caters to a large population from Central India, over a period of 2 years from 1st January 2015 to 31st December 2016 with a clinical & radiologically confirmed diagnosis of Cerebral venous sinus thrombosis within 48 hours after admission were included in the study. The duration between onset of symptoms and hospitalization was less than 7 days. The last case was enrolled on 10th sept 2016 considering their duration of hospital stay & 12 weeks follow up. The patients who were enrolled in the study were evaluated for various risk factors like Ear infections, meningitis, malignancy, sickle cell disease, and hyperhomocystinemia. They were followed up throughout their hospital stay and after discharge for 12 weeks & their outcome was assessed according to modified Rankins scale.

Study design and study setting: This prospective observational study was carried out in 40 diagnosed cases of cerebral venous sinus thrombosis in the department of Medicine, Government Medical college, Nagpur, a tertiary care center in central India.

Study Population: All the cases with confirmed diagnosis of CVST based on neuro imaging i.e. CT scan head or MRI brain. CT machine used was 256 slice TCT Philip and MRI was done on 1.5 Tesla (acheiva) Philip. Patients below 12 years, arterial stroke & critically ill patients with comorbid conditions unrelated to cerebral venous sinus thrombosis were excluded from the study. Written consent was obtained from all the cases with normal level of consciousness & from legally acceptable representative (LAR) in unconscious patients. All the CT positive cases of CVST were further subjected for MRI/MRI Venography. Total duration from onset of symptoms & radiological confirmation of diagnosis was maximum 48 hrs.

Criteria for Diagnosis of CVST on CT/MRI imaging: On plain CT, demonstration of hyperdense sinus & non enhancement or typical empty delta sign on contrast CT was considered as Thrombus in cerebral venous sinuses. On MRI/MRI venography, loss of T2W flow void in sinus & noncontrast opacification and post contrast presence of infarcts in their drainage territory was suggestive of CVST. On MRI Venography non visualization of sinuses, smaller cerebral veins or cortical veins with low flow were also considered for diagnosis of CVST.[6]

Deep cerebral vein thrombosis was diagnosed when involvement of internal cerebral vein, the basal veins of Rosenthal & their tributaries resulting into unilateral or bilateral venous congestion and venous infarct in Thalami & basal ganglia was seen on neuro imaging.[6]

Demographical, clinical, laboratory, and radiological data was recorded. All investigations like complete blood count, Blood Sugar, Liver function tests, Serum Creatinine, Blood urea nitrogen, Serum electrolytes, prothombin time, activated partial thromboplastin time and International normalised ratio were done in all patients. Workup for hypercoagulable states including serum homocysteine, antithrombin III, protein C, protein S deficiency and anticardiolipin antibody, factor V leiden mutation, lupus anticoagulant, Hb electrophoresis were also performed.

A thorough clinical and neurological examination was done. Glasgow Coma scale (GCS) was used to assess the severity of neurological dysfunction. The patients were divided into 3 categories according to GCS – 0-8, 9-13 and 14-15. The functional status was assessed on a modified Rankin scale (mRS) at admission, discharge and at 12 weeks follow-up. The outcome was dichotomized as good (mRS score of 0–2) or poor (mRS score ≥3). In addition, the in-hospital mortality was recorded separately. During follow up, data regarding disability (according to modified Rankin Scale [mRS]), death, recurrent symptomatic sinus thrombosis (new symptoms with new thrombus on repeated venogram or MRI), other thrombotic events, seizures, headaches requiring bed rest or hospital admission were recorded.

The primary outcome used was death or dependency at the end of 12 weeks which was defined as mRS score >3.

Modified Rankin's scale[7,8]

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

In addition to the functional status assessement on a modified Rankin scale (mRS) at admission, discharge and at 12 weeks follow-up level of consciousness (Altered level of consciousness or coma) was assessed on Glasgow Coma scale.(GCS). GCS between 0-8 were labeled as coma while GCS between 9-13 were labeled as altered level of consciousness (excluding all secondary causes of altered consciousness like electrolytes imbalance, metabolic causes, Hypoxia, and infections).

All the cases were treated with either Inj unfractionated heparin or Inj. Low Molecular weight heparin (LMWH) followed by oral anticoagulants; Warfarin, along with supportive treatment and continuing other standard care.

Statistical Analysis

The data was analysed by the SPSS, version 14.0 (SPSS Inc). $\chi 2$ tests (or Fisher's exact test whenever appropriate) were performed to analyze the univariate

relationship between the possible prognostic factors and the outcome at 12 weeks. As the sample size was small, Fischers exact test was used for calculating the p-value. As it was likely that the different prognostic factors were mutually related, the independent effects of the prognostic factors were additionally analyzed by using multivariate logistic regression. Subsequently, all the variables with $p< 0.05$ which were identified in the univariate analysis was presented to a logistic regression model to assess their independent association. The significant prognostic factors were selected with a forward selection strategy by using the likelihood ratio statistic, with $p \leq 0.05$ as the criterion level for selection. The effect sizes were expressed as the odds ratios (OR). The OR can be interpreted as an estimation of the relative risk of a poor outcome.

Results

This prospective observational study comprises total 40 confirmed cases of cerebral Venous sinus thrombosis. Base line characteristic of these patients revealed, mean age of 31.29 $\pm$ 8.64 years. Males out numbered females marginally with a Male: Female ratio of 1:0.8.

Amongst etiological causes, puerperium was the most important cause of CVST in 27.5% cases**.** The most commonly involved venous sinus was the superior sagittal sinus in 75% cases.

Apart from the presence of sinus thrombosis, hemorrhagic infarct was seen in 55% cases on CT/MRI. There was an overlap of imaging findings. Some patients had more than one finding on imaging, eg. 15 patients had haemorrhage out of which 5 had isolated haemorrhage & 10 patients had haemorrhage with haemorrhagic infarct. Non haemorrhagic infarct was observed in 13 cases. Cerebral oedema was also observed in 19 patients along with haemorrhage and infarction.

Modified Rankins score was between 3-5 in 25(62.5%) cases & 0-2 in 15(37.5%) at the time of hospitalization**.** In univariate analysis, age >30yrs, and neurological signs like paresis, papilloedema, and coma were significantly associated with poor outcome (p=0.010,p=0.42,p=0.017, p=0.010).

No statistically significant association was found between clinical outcome and gender (p value 0.271) and other risk factors**.**

On CT/MRI, in addition to DVST, cerebral hemorrhage (p value 0.001) and cerebral oedema (p value 0.002) were associated with poor outcome, which was statistically significant. Figure 3 shows MR venography with lateral Sinus thrombosis.

Involvement of deep venous sinuses (DVST) was associated with poor outcome. 6 out of 8 i.e.87.5% cases had a poor outcome at the end of 12 weeks. (p value < 0.001). No significant association was observed between number of sinus involved and outcome. **(Table 1)**

Table 1: Baseline characteristics, imaging features, risk factors and outcome (Univariate Analysis)

Baseline Characteristics	No of Patients (%) (n=40)	Outcome		p-value
		Poor (%) (n=10)	Good (%) (n=30)	
Age				
<30 Yrs	22 (55)	2(20)	20(66.6)	0.010,
>30 Yrs	18(45)	8(80)	10(33.4)	
Gender				
Male	22 (55)	4 (40)	18 (60)	0.271
Female	18(45)	6 (60)	12 (40)	
Clinical Features				
Headache	32 (80)	6 (60)	26 (86.6)	0.068
Seizure	20 (50)	5 (50)	15 (50)	1.00,
Vomiting	17 (42.5)	4 (40)	13 (43.4)	0.853,
Paresis	17 (42.5)	7 (70)	10 (30)	0.042,
Papilloedema	13 (32.5)	8(80)	11(36.6)	0.017,
Glasgow coma score				
3 – 8 (Coma)	09 (22.5)	04 (40)	05 (16.7)	Y^2= 3.2339
9-13(Altered sensorium)	10(25)	3(30)	7(23.3)	P =0.199
14-15	21(52.5)	3(30)	18(60)	
Fever	09(22.5)	02 (20)	07 (23.3)	0.827
Dyspnea	06(15)	05(50)	01(3.3)	<0.001

Blurring Of Vision	05 (12.5)	Nil	05 (16.7)	0.168
CT/MRI lesion				
Hemorrhage	15 (37.5)	08(80)	07(23.3)	0.001
Hemorrhagic infarct	22(55)	08(80)	14(46.6)	0.067
Non-hemorrhagic infarct	13(32.5)	04(40)	09(30)	0.559
Cerebral oedema	19 (47.5)	09(90)	10(33.3)	0.002
Sinus involvement				
Superior Sagittal	30 (75)	09(90)	21(70)	0.206
Sigmoid	22 (55)	05(50)	17(56.7)	0.712
Transverse	19 (47.5)	05(50)	14(46.6)	0.855
Deep Venous Sinus Thrombosis	08 (20)	06(60)	02(6.6)	<0.001
Inferior Sagittal	03 (7.5)	Nil	03(10)	0.298
Cavernous	02 (5)	Nil	02(6.6)	0.402
Internal Jugular vein	01(2.5)	Nil	01(3.3)	0.402
No. of sinus involved				
1	12 (30)	01 (10)	11(36.7)	0.1520
2	13 (32.5)	04 (40)	09 (30)	
>2	15 (37.5)	05(50)	10(33.3)	
Risk Factors				
Puerperium	11(27.5)	02(20)	09(30)	0.540
Idiopathic	09 (22.5)	02(20)	07(23.3)	0.783
ENT Infections	07 (17.5)	02 (20)	05(16.7)	0.810
Hyper-Homocysteinemia	07(17.5)	02(20)	05(16.7)	0.810
Sickle Cell Disease	03(7.5)	01(10)	02(6.6)	1.000
Oral Contraceptive pills	01(2.5)	Nil	01(3.3)	0.559
Malignancy	01(2.5)	01(10)	Nil	0.250
Meningitis	01(2.5)	Nil	01(3.3)	0.559

On a multivariate analysis, age >30 years (p value 0.024), cerebral haemorrhage on imaging (p value 0.018) and deep cerebral venous system (p value 0.018) involvement were associated with a poor outcome at 12 weeks of follow-up. **(Table 2)**

Table 2: MRS and outcome at Discharge and at 12 Weeks

Outcome	Good Outcome mRS <3	Poor Outcome mRS ≥3
At Discharge (Mean hospital stay 10 days)	22 (55)	18 (45)
At 12 Weeks	30 (75)	10 (25)

Functional status of the cases at admission showed 15 cases (37.5%) with 0-2 mRS while 25 case (62.5%) with> 3 mRS **(Table 3)**

Table 3: Outcome at Discharge and at 12 Weeks Follow-Up by Modified Rankin's Scale

Modified Rankin Scale	Functional Status On Admission n=40	Outcome At Discharge n=40	Outcome At 12 Weeks n=35*
	No. Of Cases (%)	No. Of Cases (%)	No. Of Cases (%)
0	Nil	11 (27.5)	20 (57.14)

1	13 (32.5)	05 (12.5)	08 (22.85)
2	02 (5)	06 (15)	02 (5.71)
3	03 (7.5)	07 (17.5)	03 (8.57)
4	08 (20)	05 (12.5)	01 (2.85)
5	14 (35)	01 (2.5)	-
6 (Death)	Nil	05 (12.5)	01 (2.85)
Total	40 (100)	40 (100)	35* (100)
Death Or Dependency	25 (62.5)	18 (45)	10 (25)

* Five patients died during the hospital stay

Overall mortality was (15%) i.e. 6 out of 40 cases. Five patients died during their hospital stay and one during follow up. mRS score of >3 showed more disability & mortality**.**

In hospital mortality in 5 cases was primarily due to CVST attributed to involvement of deep cerebral vein thrombosis, cerebral edema and GCS < 8, while 1 patient died at home and exact cause could not be ascertained.

Thus 45% cases (n=18) had poor outcome (mRS >3) at the time of discharge but at the end of 12 weeks there was functional improvement and this figure was reduced to 25% (n=10) **(Table 4).**

Table 4: Multiple logistic regression analysis for factors associated with poor prognosis of CVST at 12 weeks

Variable	Adjusted Odds Ratio	95% Confidence Interval	p-value
Age >30 yrs	32.23	1.12 – 92.08	0.042, S
GCS	0.68	0.09 – 4.75	0.703, NS
Papillodema	2.34	0.11 – 49.93	0.585, NS
Cerebroedema	0.47	0.014 – 15.84	0.677, NS
Cerebral haemorrhage	23.95	1.07 – 53.67	0.045, S
DVT	6.35	1.57 – 19.13	0.028, S

P<0.5 is significant, other variables were dropped because of linearity

Discussion

CVST is a great masquerader as it can present in various forms and confuse the clinician. It manifests as a stroke with seizures confusing it with arterial strokes.

One of the greatest advances in the field of CVST is the change in outcome and prognosis of the disease throughout the years. It may be helpful in the acute stage to identify those patients who are likely to have a poor outcome, as this provides useful prognostic information for relatives and possibly influence the use of more invasive treatment. In early series of cerebral venous thrombosis (largely diagnosed by angiography) and largely related to sepsis, mortality was 30–50%. Recent studies have shown a mortality rate closer to 10%.[4]

Predisposing causes of CVST are multiple. The risk factors for venous thrombosis in general are linked classically to the Virchow triad of stasis of the blood, changes in the vessel wall, and changes in the composition of the blood.

Amongst the risk factors, purperium emerged as the commonest risk factor for CVST in the present study. A Study from south India also observed same risk factor as reported by us.[9] But the results of the western studies are different, where OC pills consumption & HRT were the commonest risk factors seen.[4,10]

Oral contraceptive use was not a major risk factor in our setting which was implicated in majority of Western female patients. This could be attributable to better obstetric facilities in West along with awareness of contraception resulting in higher number of female opting for hormonal contraceptives as compared to Indian women.

In the past, CVST was associated with a dismal prognosis and high mortality rate, reaching 30–50%.[10] The outcome of CVST has improved tremendously in the past few decades. The decreased mortality rates over the last 30 years may be the consequence of: (i) the development of brain MRI allowing an early diagnosis of benign cases of CVT, which may have remained undiagnosed before the era of MRI, and (ii) early anticoagulation even in the hemorrhagic cases.[12]

This study is one of the few studies where mRS is used as a prognostic indicator in CVST patients. mRS is usually applied to patients with arterial stroke. We found it to be a significant predictor of outcome in CVST. Patients of CVST having mRS score between 3-6 showed poor outcome in the form of death or functional dependency at 12 weeks, similar to that reported by few authors [14,17]. The period of follow up was variable from 16-36 months.

Overall mortality reported in earlier studies was 6.67%, 4.39% & 15%.[10,15] In the present study overall

mortality was noted in 15% of cases having mRS score between 3-6 which is slightly higher. High mortality may be attributed to involvement of deep cerebral vein thrombosis in 8 (20%) cases which is a risk factor for death as reported in previous literature. The deep cerebral veins (Internal cerebral veins, the basal veins of Rosenthal) & their tributaries are involved in approximately 10% of patients of CVST. It may result in unilateral or more typically bilateral venous congestion and venous infarction of the thalami and basal ganglia.[6] Involvement of deep veins has been shown to be risk factor for death & long term sequelae.[17,18] The less mortality reported in previous studies might be due to less involvement of deep cerebral veins[4,9] (< 10%).

Overall prognosis for survival and functional independence is better than it was believed. Mortality usually ranges from 4-15%.[15,16] The extent of functional recovery in survivors of CVST is better as compared to patients with arterial thrombosis in which the proportion of permanent dependent patients ranges between one third and two third of survivors which is in contrast to CVT in which an independent survival of around 80% is commonly found.

Identifying patients who are at a high risk for unfavourable outcomes may provide an opportunity for the development of novel therapeutic paradigms including thrombolysis (systemic versus endovascular) and early neurosurgical interventions.[8]

The predictors of mortality in multivariate analysis were age>30 yrs, Haemorrhagic infarcts, predisposing haemorrhagic disorders, CNS infections & Malignancy as reported in literature.[9,12,13,15]

In present study the predictors of poor outcome were age > 30, intracranial hemorrhage at the time of hospitalisation and deep cerebral venous system thrombosis. In multivariate analysis. other factors did not show statistically significant association with poor outcome, probably because of the small number of patients in our study, leading to a lack of statistical power.

Conclusion

Thus we conclude that age > 30 years, Deep venous sinus involvement, and intracerebral haemorrhage are predictors of poor outcome. Modified Rankins scale is a simple score system for categorization of clinical status of patients with neurological impairement in venous stroke also. Low mRS at hospitalization is associated with better outcome in terms of survival and functional disabilities.

Study limitation

Small sample size may be a limitation of the study and studies with larger sample size are needed to validate the findings of present study.

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