Clinical profile of cerebral venous thrombosis in a tertiary care center and utility of D-dimer in its diagnosis

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Abstract

Background & Objectives: Cerebral venous thrombosis (CVT) is a rare cause of stroke, occurring commonly in young adults. The variability in the clinical scenario from patient to patient and the lack of specificity of the presenting symptoms of CVT poses a diagnostic challenge. This study aims to analyze the clinical characteristics of patients diagnosed with CVT in comparison to the global profile and explore the diagnostic utility of D-dimer levels as a screening tool in patients with clinical features suspicious of underlying CVT. *Methods:* This was a hospital-based case-controlled study, included 50 imaging proven patients with CVT and age and sex matched healthy controls. Demographic details were collected, detailed neurological examination done at presentation and d- dimer levels were evaluated. *Results:* Among our study group a male preponderance was noted (60%) in discordance with the global pattern of CVT. Headache was the most common presenting feature and papilledema was noted in 98% of our patients. Additional clinical signs noted at presentation were nausea and vomiting (78%), seizures (28%), limb weakness (24%) and alteration in sensorium at presentation (14%). Risk factors were alcohol dependency (36%), postpartum period (12%) and anaemia (12%). Additionally the sensitivity of D-dimer was noted to be 90.74% with a specificity of 100% in predicting the disease. *Conclusion:* Our study differs from the global pattern of CVT in terms of male preponderance, higher detection of papilledema, lesser occurrence of anaemia, and a large proportion of patients with d-dimer positivity. The limitation of the study is the sample size as we cannot extrapolate our results to the population at large. However our data is in concordance with the current concept of CVT, that diagnosis is the key challenge in management.

Keywords: CVT, headache, D-dimer

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare cause of stroke, occurring commonly in young adults due to either the complete or partial occlusion of the major cerebral venous sinuses or the smaller cortical veins.[1] CVT contributes to 0.5-1% of all strokes worldwide and clinical presentation among these patients are protean.[2] They range from headaches, seizures, focal neurological deficits, altered consciousness and papilledema.[3] The venous drainage of the brain starts from the smaller cerebral veins and progressively drain into larger cerebral veins which empty into the cerebral venous sinuses and end in the internal jugular veins. Disruption in the smooth flow of blood, damage to the blood vessels or changes in the composition of the blood (Virchow's triad) lead to an imbalance between pro and anti thrombotic processes, predisposing to venous thrombosis. Obstruction of venous vessels induces increased venous pressure and reduced capillary perfusion. The venous stasis results in back pressure in the capillaries leading to vasogenic edema decrease in cerebral perfusion and tissue infarction.[2]

The variability in the clinical scenario from patient to patient and the lack of specificity of the presenting symptoms of CVT poses a diagnostic challenge as it is difficult to screen every patient

with headache for CVT by magnetic resonance imaging (MRI). Hence indirect evidence of activation of coagulation cascade like D-dimer levels have been used as a surrogate marker with variable results ranging from high diagnostic sensitivity and specificity[4] to considerable rates of false positive and negative results.[5]

Hence this study aims to analyze the clinical characteristics of patients diagnosed with CVT in comparison to the global profile and explore the diagnostic utility of D-dimer levels as a screening tool in patients with clinical features suspicious of underlying CVT.

METHODS

This study was a hospital based cross sectional case control study which included 50 imaging proven patients with CVT and age and sex matched healthy controls. The data was gathered over a period of six months from January to June 2020 in a tertiary referral centre in South India. Patients with imaging proven CVT aged more than 16 years were included in this study after taking an informed consent. Control subjects were recruited via active search between healthy volunteers accompanying patients and were age and sex matched with the cases Exclusion criteria included duration of symptoms more than three months, presence of other conditions which could potentially raise D-dimer levels including systemic infections, acute myocardial infarction, unstable angina, atrial fibrillation, pneumonia, vasculitis and superficial phlebitis.

On admission descriptive analysis of symptomology, underlying risk factors and demographic details were collected and entered into a pre structured Performa. Detailed neurological examination was done and NIH stroke scale was calculated in patients with neurological deficits. Blood was sent for D-dimer estimation and MRI brain with MR venogram was done using a 3 Tesla MRI. D-dimer values were estimated using Cobas 6000 machine which utilized a latex method of immunoturbidometric assay.

SPSS version 15.0 for windows was used for the testing of data. The confidence interval and significance level for this study as considered 95% and $p<0.05$ respectively. Verification of data's normal distribution had been conducted utilizing the "Kolmogorov–Smirnov test". Comparison of means of continuous data was done by Mann–Whitney test. Demographic aspects have been compared utilizing "chi-square test".

Receiver operating curve (ROC) analysis was also performed. To predict CVT with D-dimer levels alone we calculated sensitivity, specificity, positive and negative predictive value.

The research has been approved by the Institutional Ethical Committee of JSS Medical College [JSSMC/IEC/180820/18 NCT/ 2020-21].

RESULTS

A total of 50 patients diagnosed with CVT fulfilling the inclusion criteria were included in this study. Among these patients, 20 patients (40%) were female and 30 (60%) were male. Mean age of the patients was 31 years, with the youngest patient being 17 years old and the oldest being 55 years.

The average duration from symptom onset to presentation to the hospital was 2.4 days (SD 1.76)

Among the 50 patients, 49 had headache at presentation. Headache was described to be persistent in 48 of these patients. The most common location of headache was holocranial (74%) followed by occipital (16%) and bifrontal (10%) locations respectively. Additionally, in decreasing order of frequency, nature of headache was described to be throbbing (50%), dull aching (40%) and a sensation of heaviness of head (10%).

Additional clinical presentation was noted to be highly variable. Thirty nine patients (78%) had nausea and vomiting at symptom onset, 7 patients (14%) had alteration in sensorium, 14 patients (28%) had seizures and the semiology was of the generalized tonic-clonic convulsion (GTCS) in all. Twelve patients (24 %) had limb weakness out of whom one patient had transient symptoms lasting only for a couple of hours. One patient had only isolated dysarthria along with headache. Three patients (6%) had sensory symptoms.

It was noteworthy that 49 patients (98%) had papilledema on clinical examination, 19 patients (38%) had horizontal gaze restriction. These are summarized in Table 1.

At presentation 44 patients (88%) had a low NIHSS score while 4 patients (10%) had an intermediate score and 2 patients (4%) had a high score.

A total of 18 patients (36%) were alcohol dependent. These patients constituted 60% of all the males included in this study. Six patients (12%) included in this study were in the post partum period. These patients presented within a time range of 2 to 5 days of delivery. One of the patients had hyperglycemia, with serum

Table 1: Demographic details and clinical signs

Patient attributes (n=50)	N (%)
Age (years)	31.14 ± 9.6
Female /Male	20/30 (40% /60%)
Duration since symptom onset (days)	2.4 ± 1.8
Headache	49 (98%)
Nausea	39 (78%)
Altered sensorium	7 (14%)
Seizures	14 (28%)
Limb weakness	12 (24%)
Sensory symptoms	3 (6%)
Dysarthria	1 (2%)
Papilledema	49 (98%)
Horizontal gaze restriction	19 (38%)

glucose levels being 600mg/dl at presentation. Six patients had anemia (10%), among whom 4 were female. The minimal hemoglobin was 6.6gm/dl. Peripheral smears in 5 of these patients were microcytic hypochromic in morphology. However one patient had macrocytic morphology.

In summary, among the risk factors noted, 18 (36%) were alcohol dependent, 6 (12%) were in the postpartum period, 6 (12%) were anemic and one had hyperglycemia.

An interesting observation we made was that 9 (18 %) patients had macrocytosis with maximal values being 118 fL. All these patients were male alcoholics. Thus 50% of the alcohol dependent patients with CVT had macrocytosis, out of which one had anemia. Comparison of the sinus number, i.e. number of sinuses thrombosed as seen on MR venogram between patients with a normal MCV vs patients with a higher MCV showed that sinus number is higher in >101fL group with a t value of -1.669 and is statistically non-significant with a p value of 0.102.

The mean number of sinuses involved in these patients were 3 (SD 1.5) with maximal sinus involvement being 7. Only 2 patients in this study had involvement of the deep sinus system. The most common sinus to be involved was the superior saggital sinus in 40 (80%) patients. this was followed by transverse sinuses and left sigmoid sinus. All the patients had more than one sinus involvement. Frequencies of the various sinus involved have been listed in Table 3.

Hyperhomocysteinemia was noted in 24 (48%) patients, with a maximal value of 104 Umoles/L. Thrombophilia workup revealed an underlying prothrombotic state in 3 patients, with one testing

Table 2: Laboratory parameters

	N	Mean	Std. Deviation	Minimum	Maximum
Age (years)	50	31.2	9.6	17	55
Duration (days)	50	2.5	1.8	0	8
NIHSS	50	1.9	3.6	0	18
D-dimer (µFEU/ml)	50	1.5	1.4	0.4	8.7
Homocysteine (6-22 Umoles/L)	50	28.8	21.6	4.6	104
Hemoglobin (gm/dl) 13-17 in males 12-15 in females	50	13.6	2.8	6.6	19
MCV (83-101 fL)	50	86.9	13.8	55.7	118.5
MCH (27-32pg)	50	29.7	6.2	15.1	41.5
MCHC (33.5-35.5 gm/dl)	50	33.6	2.6	25.7	38

Table 3: Sinus involvement (number of venous sinuses affected as seen on MR venogram)

	No	Percent
Superior saggital sinus	40	80.0
Inferior saggital sinus	12	24.0
Straight sinus	4	8.0
Right transverse	14	28.0
Left transverse	16	32.0
Bilateral transverse	12	24.0
Right sigmoid sinus	11	22.0
Left sigmoid sinus	19	38.0
Bilateral sigmoid sinus	2	4.0
Right internal jugular vein	1	2.0
Left internal jugular vein	8	16.0
Internal cerebral vein	2	4.0

positive for MTHFR mutation and 2 others tested positive for factor V Leiden mutation.

Among the patients D-dimer value was noted to be abnormal (≥ 0.5μFEU/ml) in 49 patients (98%). Among these 49 patients, 35 patients had values ranging between 0.5 to 1.5, 9 patients between 1.5 to 2.5 and 5 patients >2.5μFEU/ml respectively.

Higher D-dimer value was associated with increased number of sinuses being involved (i.e number of sinuses thrombosis as noted in MRI), but this finding was not statistically significant (Figure 1).

Additional statistical analysis done showed that a d-dimer value of 1.26 was sensitive in predicting severity of CVT. (Figure 2).

Additionally D-dimer values were used to calculate sensitivity and specificity. Based on our data the sensitivity of D-dimer was noted to be 90.74% with a specificity of 100% (Table 4).

Imaging findings revealed a normal brain parenchyma in 23 patients (46%), intraparenchymal bleed in 7 (14%) patients, venous infarct in 19 (38%) patients and bleed with infarct in 1 (2%) patient. Among the patients with abnormal MRI findings, 11 (22%) patients had parenchymal lesion size >6cm. Locations most commonly involved were temporal followed by frontal, parietal and occipital respectively.

Since the mean age of CVT is 32 years,

additional subgroup analysis was done among patients aged more than 32 years to detect any difference in disease phenomenology. There were no differences noted in clinical characteristics, however comparison of the sinus (number) between the two groups showed that sinus (number) is higher in <32 group with a t value of 1.223 which was statistically non-significant with a p value of 0.228. Among the 11 patients with lesion size >6 cm, 10 were younger than 32 years, however this association was also not statistically significant (p value 0.065).

Among the 50 patients, two patients succumbed to the illness. Both patients had deep venous involvement and a poor NIHSS and GCS at admission.

DISCUSSION

CVT is a disease of the young with nearly 2/3rd of the patients being female.[1] The mean age of our patient was 31 years in keeping with global prevalence of 32 years.[1] In our study however we noted there were disproportionately more men forming 60% of the study population. Two studies done in India, one conducted in 2011[6] and the other in 2020[7] showed a female preponderance and an equal gender distribution in their studies respectively. The latter study is among the few showing an equal predisposition

Table 4: D-dimer and CVT

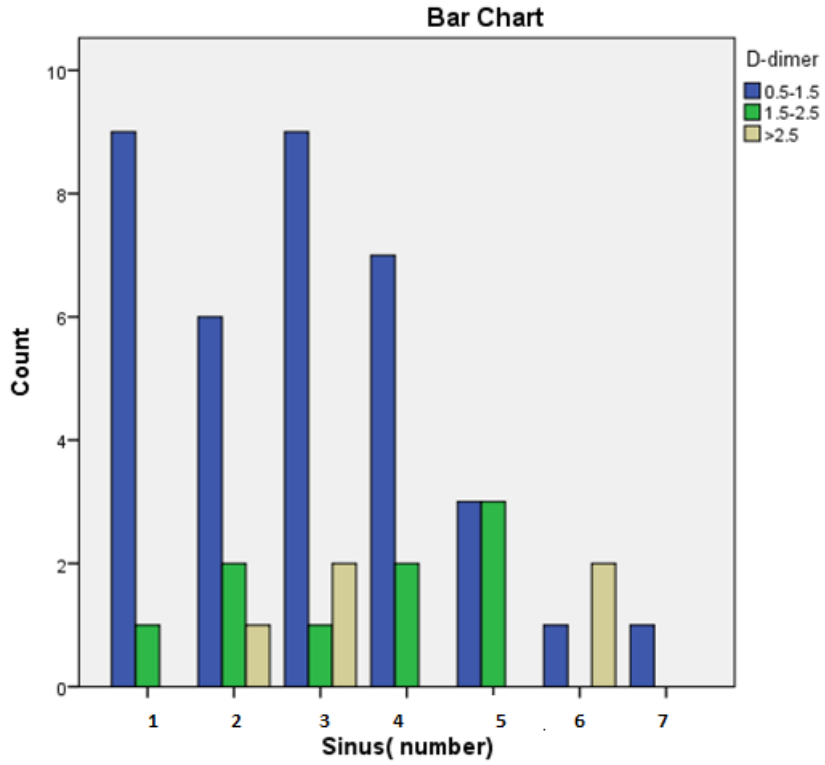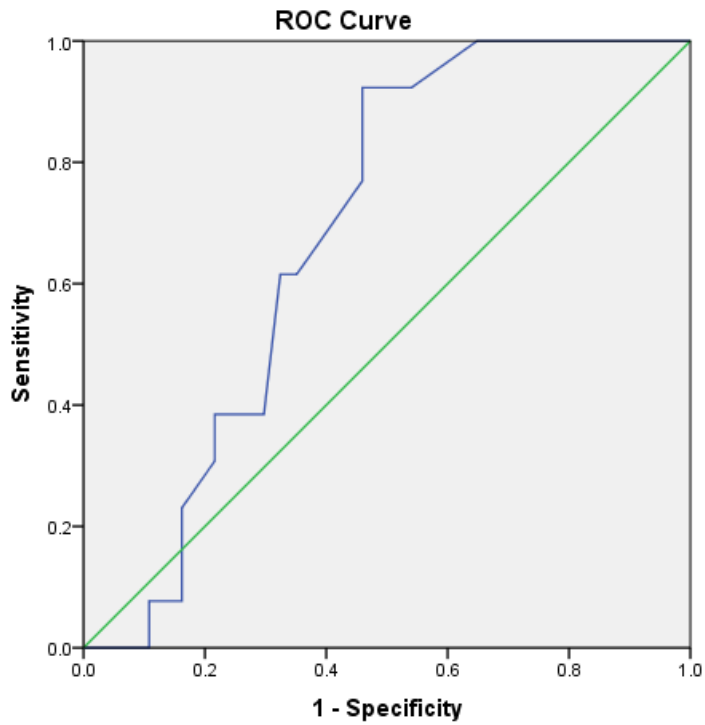|	Sensitivity	Specificity	Positive predictive value	Negative predictive value
D-dimer	90.74%	100%	100%	90.91 %

Figure 1. Correlation between d-dimer (µFEU) and number of sinus involved as viewed on MRV (p value 0.072)

Diagonal segments are produced by ties.

Figure 2. ROC curve plotted with severity as a predictor

of CVT in both genders. A reason for the male dominance in our study may be attributable to the alcohol dependence noted in them, since alcohol consumption is a risk factor for CVT.[6] Additionally this preponderance may also be secondary to a delay or inability of women to seek prompt medical attention.

Headache was the presenting clinical feature in 98 % of our patients. This was in keeping with most studies which report a range of 80-96 %.[3,7] The second common presenting symptom was nausea and vomiting seen in 78 % of the patients. This is slightly more than what was seen in a similar study conducted in India.[7] Studies have shown that patients with CVT can present with isolated headache without features of raised intracranial hypertension (ICT).[8] However in our patients features of raised ICT were present in the majority of the patients with 98% having papilledema and 38% having horizontal gaze restriction. In concordance with most studies the headache in our patients were holocranial in location and throbbing in nature.[7,9]

Fourteen patients (28%) had seizures, all of GTCS semiology. Seizures are a common neurological complication of CVT and reported incidence is around 48%.[10] CVT can be associated with status epilepticus[11] and usually the likelihood of seizures increases with parenchymal involvement.[12] This was also shown in our study as all the patients who presented with seizures had brain parenchymal involvement.

The most common neurological deficit observed in patients with CVT is motor weakness[9], however rarely sensory symptoms have also been documented.[13] Among our patients 24 % had motor weakness and 6% had sensory disturbances. Uniquely one of our patients presented with a transient weakness and when being evaluated for a TIA was detected to have a CVT. Such an atypical presentation has been reported in a case in Spain.[14]

Patients can also develop a diffuse alteration in sensorium with reported frequencies of around 21%.[7] In our study only 7 patients (14%) had an altered sensorium at presentation. While this has been usually found to be more common in elderly patients with CVT[15], this was not noted in our study.

Historically the most common risk factors associated with CVT has been anemia and the post-partum state.[9] Surprisingly, however in our study population only 6 patients (12%) had anemia. However it must be noted that this study witnessed only two deaths, one of whom had severe anemia stressing the importance of this association.

In our study 6 patients (12%) of the patients were in the post partum period. This comprised 30% of the female patients. Only one patient had undergone LSCS for an obstetric indication. All 6 had normal antenatal history. A prospective study involving 465 women found that 65% of cases had risk factors like pregnancy, puerperium, oral contraceptive pill (OCP) use, and hormonal replacement therapy, all being related with female sex hormone.[16] Our sample size is smaller in comparison and no conclusion can be drawn.

Hyperhomocysteinemia was seen in 24 (48%) of the patients. In three studies conducted in India the values noted were 12.5[7], 18.2 and 42.5[18]% respectively.

One of the main aims of this study was to assess the diagnostic utility of D-dimer in patients with CVT, 98 % of our study population had a positive value. The sensitivity was found to be 90% with a specificity of 100%. This is much higher than a similar case control study, with sensitivity and specificity of 81.2 and 62.5 % respectively.[7] Additionally the cut off value of 1.26 correlated with disease severity as evidenced by a higher NIH score and lesion size > 6 cm.[18] We explored the possibility of a prognostic association; however it was not statistically significant. A recently published study which prospectively analyzed 383 adults with CVT concluded that adding d-dimer values to a prediction model increased the likelihood of a diagnosis.[19]

Imaging findings among our patients revealed a normal brain parenchyma in 23 patients (46%), intraparenchymal bleed in 7 (14%) patients, venous infarct in 19 (38%) patients and bleed with infarct in 1 (2%) patient. Most common sinus involved was the superior sagittal sinus in 40 patients (80%) followed by the transverse and left sigmoid sinus. The MRI appearances in CVT are due to an increased amount of deoxyhemoglobin and methemoglobin in the thrombus in the acute and sub-acute forms respectively.[20] The radiological findings seen in our study correlate with similar studies done elsewhere.[3,7,9]

Two patients among the 50 succumbed to the illness. Both patients had presented in altered sensorium with a poor GCS and a poor rating on the CVT prognostic scale.[19] Moreover both patients had involvement of the deep venous system. Research has shown that patients with deep venous thrombosis are more likely to present with an alteration in sensorium and have a poor prognosis[21], which were encountered

in our patients. A multinational, prospective, observational study including 624 patients with CVT conducted over 3 years documented a 4.3% mortality rate, consistent with our data.[22]

With the exception of these two patients, the other 48 made a good recovery. All patients were managed as per standard protocols with anticoagulation, anti edema measures and anti-epileptic drugs. All patients were on follow up and doing well. This further reiterates the importance of early diagnosis and prompt initiation of treatment as prognosis in CVT is generally favorable with early treatment.[22]

The limitations of this study include a relatively small sample size making it difficult to extrapolate our results to the population at large, single center study and lack of long term follow up. Additionally since we are analyzing hospitalized patients and disease severity is likely to be higher, this could explain the increased incidence of papilledema.

In conclusion, CVT is an uncommon disease when compared to arterial strokes. However, it is disproportionately represented among the younger population with stroke. The peculiarity about this disease is that the diagnosis is not straight forward and subtle clinical signs can be missed. Our study differs from the previously reported pattern of CVT in terms of male preponderance, lesser occurrence of anemia, a subset of patients with macrocytosis and a large proportion of patients with d-dimer positivity. However our data is in concordance with the current concept of CVT that early diagnosis is the key challenge in management. Nonetheless, large multicenter studies are required to conclusively determine the diagnostic utility of d-dimer and formulate predictive algorithms.

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