Role of D- Dimer in aseptic cerebral venous sinus thrombosis

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Abstract

Introduction: Early diagnosis of cerebral venous sinus thrombosis (CVT) is essential because early treatment may prevent morbidity and may even be life-saving. Definite exclusion, however, needs advanced neuroradiologic diagnostics, which are not readily available in many hospitals. A biological marker like D-dimer can be used as a tool to help in diagnosis of CVT.
Aims: To evaluate patients with CVT with diverse clinical manifestations and assess the importance of D-dimer in the diagnosis.
Settings and Design: Prospective observational study carried out at Dept. of Neurology at a tertiary care hospital.
Methods and Material: A total of 56 patients with CVT were subjected to a detailed medical history and neurological evaluation. A MRI brain was carried out on a 1.5T scanner using T1, T2, and Diffusion weighted sequences and TOF MR venography. D-dimer was quantitatively estimated by immunoturbidimetry.
Statistical analysis used: SPSS 19 statistical software was used. Unpaired t test, ANOVA, Pearson chi square test was used to analyse different parameters. Significance level of 95% with $p<0.05$ was considered statistically significant.
Results: A total 56 patients were enrolled in this study. The mean age was 33.98 +/- 13.20 years. Female: male ratio was 2.3:1. Headache was the most common presentation (82.1%) followed by vomiting(48.2%). MRI brain showed infarct in 39(69.6%) patients, out of which 24 (42.8%) had hemorrhagic venous infarct. Most common sinus involved was superior saggital sinus (71.4%) followed by transverse (64.3%). Mean D-dimer concentration in patients with 1 vein involvement was 1.04, in 2 vein involvement it was 1.35, in 3 vein involvement it was 1.30, 1.96 in patients with 4 and 5.67 in patients with more than 6 vein involvement which was found to be significant statistically.
Conclusions: D-dimer might be not only suitable in the context of diagnosing CVT but also may be helpful in estimating severity of disease.

Keywords: D-dimer, Cerebral venous sinus thrombosis, MR venograpghy

Introduction

Thrombosis of the dural sinus and/or cerebral veins (CVT) is an uncommon form of stroke, usually affecting young individuals.[(1)] CVT is associated with a wide spectrum of clinical manifestations, ranging from isolated headache (with or without papilledema) to diffuse or focal brain edema, infarction, or haemorrhage.[(2)] Prompt diagnosis is important as there is evidence of benefit from anticoagulant therapy, and in progressive cases intrasinus thrombolytic therapy may be beneficial.[(3)] Diagnosis can be challenging and generally relies upon magnetic resonance (MR) imaging with MR venography.[(2)] In a developing country like India where MR venography is not readily accessible, a biological marker like D-dimer can be used as a tool to help in diagnosis of CVT. Different studies have shown varied results regarding utility of D-dimer in CVT.[(4,5,6,7)] Most of the previous studies are based on selected patient populations including patients with isolated headache.[(6,7)] This study was done to evaluate patients who were diagnosed CVT having diverse clinical manifestations and assess the importance of D-dimer in the diagnosis.

Subjects and Methods

Total 56 consecutive patients admitted to the Department of Neurology at a tertiary care hospital were enrolled in the study. All patients included in study were diagnosed CVT on MR venography. Patients with thromboembolic disease (deep venous thrombosis/pulmonary embolism) within the past 4 weeks, patients with known malignancy, patients with signs of disseminated intravascular coagulopathy, patients with signs of septic sinus thrombosis, and those refusing to give informed consent for study were excluded from the study. Informed consent was taken from all patients. Ethical clearance was taken from Ethical committee of the Institute.

Detail clinical history and examination was done in every patient. Routine haematological investigations were done in every patient. Imaging in form of plain CT brain and MRI brain/MR venography was performed in every patient. MRI was performed on 1.5 Tesla GE machine.

Blood sample for D–dimer analysis were taken within 24 hrs of hospitalisation before commencement of heparin in every patient. Three millilitre whole blood was taken in Sodium Citrate tube. It was mixed thoroughly by inversion. It was then centrifuged at 3600 rpm for 15 min. Supernatant was then transferred to a clean plastic tube and centrifuged again at 3600 rpm for 15 min. Finally supernatant (PPP) was then analysed quantitatively for D-dimer by

immunoturbidimetry. Cut off value was taken as 0.5 FEU/ml.

Total of thirty asymptomatic age and sex matched healthy subjects were taken as control and D dimer estimation was done in all control group subjects.

Statistical Analysis: Data was analysed using Statistical Package for the Social Sciences- SPSS 19 statistical software. Comparison of mean of continuous variable in between the two groups was done using unpaired t test and in between more than 2 group one way Analysis of variance (ANOVA) was used. Pearson chi square test was used to analyse relation in between the qualitative data of parameters. Significance level of 95% with $p<0.05$ was considered statistically significant.

Results

A total 56 patients were enrolled in this study. The mean age was 33.98 +/- 13.20 years. Thirty nine were females with female: male ratio of 2.3:1. (Table 1)

Table 1: Age group of patients with cerebral venous sinus thrombosis

Age Group (years)	Frequency	Percent
Upto 20	6	10.7
21 to 40	36	64.3
41 to 60	12	21.4
>60	2	3.6
Total	56	100.0

Headache was the most common presentation and was present in 46 (82.1%) patients followed by vomiting 28(48.2%). Non specific dull headache was present in 19(33.9%) and unilateral throbbing headache was present in 15(26.8%) patients. Altered sensorium as a presenting feature was present in 13(23.2%) patients. Seizures were present in 23(41.1%) patients. Hemiplegia/ hemiparesis was the most common focal neurological manifestation in our study i.e. in 23(41.1%) patients. (Table 2)

Table 2: Presenting symptoms of patients with cerebral venous sinus thrombosis

Symptoms		Frequency	Percent
Headache		46	82.1
Type of Headache	Generalised	25	44.6
	Unilateral	21	37.5
Character Of Headache	Dull	19	33.9
	Sharp	12	21.4
	Throbbing	15	26.8
Seizure		23	41.1
Type of seizure	Focal	6	10.7
	Generalised	17	30.4
Vomiting		27	48.2
Vertigo		8	14.3
Altered Sensorium		13	23.2
Hemiplegia		23	41.1
Sensory Disturbances		2	3.6
Speech Disturbances		4	7.1
Visual Disturbances		15	26.8
Papilloedema		20	35.7
6th Nerve Palsy		12	21.4
3rd Nerve Palsy		2	3.6

MRI brain showed infarct in 39(69.6%) patients, out of which 24(42.8%) had hemorrhagic venous infarct. Sub arachnoid haemorrhage(SAH) was present in 7(12.5%) patients.(Table 3)

Table 3: MRI Brain findings of patients with cerebral venous sinus thrombosis

MRI Brain	Frequency	Percent(%)
Normal	17	30.4
Infarct	39	69.6
Hemorrhagic Infarct	24	42.8
Non Hemorrhagic infarct	15	26.8
SAH	7	12.5
Left Side	14	25.0
Right side	14	25.0
Bilateral	11	19.6

Most common sinus involved was superior saggital sinus (71.4%) followed by transverse (64.3%) and sigmoid sinus (50.0%). Internal cerebral veins involvement was seen in 8(14.3%). Bilateral sinus involvement was seen in 11(19.6%).(Table 4)

Table 4: Venous sinus involved in the patients with cerebral venous sinus thrombosis

Sinus involved	Frequency	Percent
Internal Cerebral Vein	8	14.3
Sigmoid	28	50.0
Jugular Bulb	1	1.8
Transverse	36	64.3
Superior saggital sinus	40	71.4
Straight	15	26.8
Vein Of Galen	4	7.1

Values of D-dimer in control group ranged from 0.11 to 0.29 with the mean of 0.16+/-0.06 FEIU/ml while the values of D-dimer in cases group were in the range of 0.1 to 6.9 with the mean of 1.60 FEIU/ml. D-dimer was negative in 3 patients. Mean D-dimer concentration in patients with 1 sinus involvement was 1.04, in 2 sinus involvement it was 1.35, in 3 sinus involvement it was 1.30, 1.96 in patients with 4 sinus and 5.67 in patients with more than 6 sinus involvement. This was statistically very highly significant ($p<0.001$). Mean difference of D-dimer values was rising with the increasing number of sinus involvement in patients with CVT. In patients with 2 sinus involvement 90.0% patients had >0.5 FEIU/ml D-

dimer concentration and with 3 and more sinus involvement all 100% patients with cerebral venous sinus thrombosis had >0.5 FEIU/ml D-dimer concentration. Thus the chances of D dimer positivity increases with more number of sinus involvement i.e. two or more number of sinus involvement. (Table 5 & 6)

Table 5: Comparison of D-dimer level according to number of veins involved in patients with cerebral venous sinus thrombosis

Number of sinus involved	N	Minimum	Maximum	Mean Std. Deviation
1	16	0.3	5.4	1.04±1.33
2	11	0.1	6.7	1.35±1.86
3	15	0.5	3.5	1.30±0.88
4	11	0.4	6.9	1.96±2.19
6&7	3	5.2	6.6	5.67±0.81
Total	56	0.1	6.9	1.60±1.81

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	58.065	4	14.516	6.098	<0.001

Table 6: Relation of number of veins involved and the D- dimer levels in patients with cerebral venous sinus thrombosis

No. of sinus involved	D-DIMER		Total
	Normal	Raised (>0.5)	
1	2	14	16
	12.5%	87.5%	100.0%
2	1	10	11
	9.1%	90.9%	100.0%
3		15	15
		100.0%	100.0%
4		11	11
		100.0%	100.0%
6 & 7		3	3
		100.0%	100.0%
Total	3	53	56
	5.4%	94.6%	100.0%

Discussion

Cerebral venous thrombosis (CVT) is an infrequent variety of cerebrovascular disease with a remarkable spectrum of clinical presentations and modes of onset leading to great diagnostic difficulties. The reported incidence of CVT in the West is 3 to 4/million; whereas, in the developing countries it is reported to be 4.5/10000 obstetric admissions.[9,10] The most frequent symptom is headache, which can sometimes be isolated but is usually associated with other signs such as focal deficits, seizures, disorders of consciousness, and papilledema, which occur in highly variable combinations.[2,8] Because of this great variability, CVT is frequently clinically suspected but confirmed infrequently by neuroimaging investigations such as MRI/MR venography, which are presently considered the gold standard.[2,8] In the developing countries where a majority of the cases with CVT occur, neuroimaging is either not available or beyond the reach of most patients. It would, therefore, be of great practical interest to have a test that would be easy to perform in emergency care and would confidently rule out CVT.

D dimer is a specific degradation product of the cross-linked fibrin monomers (derived from fibrinogen) after being hydrolyzed by plasmin.[11-14] Generally, D-dimer elevation indicates secondary endogenous fibrinolysis.[11,13] However, the course of all the thrombosis is not necessarily followed by secondary endogenous fibrinolysis. Nevertheless, abnormal fibrinogen elevation in combination with d-dimer elevation can further augment and reinforce the confirmation of new thrombus formation and secondary endogenous fibrinolysis.[11-14] Hence, d-dimer and fibrinogen serve as two closely related biomarkers in stroke and other thrombotic vascular diseases.[12,15] Plasma D-dimer is a marker of endogenous fibrinolysis, being cross-linked fibrin degraded by plasmin, may be a good candidate for the diagnostic approach of CVT,[16] particularly on emergency basis, because of its well established usefulness in the diagnosis of deep venous sinus thrombosis. High D-dimer values are very sensitive markers for deep venous thrombosis and pulmonary thromboembolism whereas low values (<500 ng/mL) have a high negative predictive value.[17,18]

In our study the most common sinuses involved were superior saggital sinus and transverse sinus. Similar findings were found by Crassard I et al.[5] Our study had D-dimer positive in 53 out of 56 patients. These results are in agreement with the earlier report in which all 6 patients with CVT had positive D-dimer.[13] All patient with CVT below 2 weeks had elevated D-dimer[19] and Lalivi P H et al[6] reported elevated D-dimer in 10 out of 12 CVT patients. In a study on 8 patients with CVT. Usha K. et al[16] also had similar results. They found D-dimer positive in 20 out of 26 patients with CVT. In a study conducted by Kosinski, *et al.*, 34 out of 35 patients with CVT had high D-dimer levels giving a negative predictive value of 99.6%, specificity of 91.2%, and a positive predictive value of 55.7%.[7] It is known that in acute deep venous thrombosis of the legs, initially raised D-dimer levels may decline to normal within the first week.[18] Normal D-dimer levels in CVT patients can be seen with chronic headaches lasting for more than 3 weeks.[6,19] A negative D-Dimer assay does not confidently rule out CVT, particularly in the setting of recent isolated headache of 1-month duration.[5] A meta-analysis

showed that D-dimer is a potentially useful tool to improve the diagnostic approach to CVT patients, with a mean sensitivity of 93.9% and mean specificity of 89.7% and suggested that potential risk factors for false negative D-dimer included isolated headache, longer duration of symptoms and limited sinus involvement.[22] In our study 3(5.35%) patients had false negative D-dimer while no patient had false positive D-dimer in control group. In their study, Meng R et al had 2.5% false positive in mimic group and no false positive subject in healthy control group while 5.9% patients had false negative D-dimer values.[4]

Because there is a correlation between limited sinus involvement and a negative D-dimer assay, it is tempting to speculate that the most important factor is the extension of thrombosis. In DVT, D-dimer levels are significantly higher in patients with proximal thrombosis than in those with thrombosis below the knee,[20] and they are correlated with clot volume and surface as shown using thrombus MRI.[21] In our study we found a positive correlation between the number of sinus involved and D-dimer values. The positivity of D-dimer rise as 2 or more venous sinuses are involved. In their study, Crassard I et al[5] found that positivity of D-dimer was more if more than 1 sinus were involved. On contrast, Usha K. et al[16] found no stastical correlation between number of sinus involved and D-dimer values. We also studied the correlation of MRI findings in the form of hemorrhagic vs non hemorrhagic infarct, side and occurrence of SAH with D-dimer values. Unfortunately we did not find any statistic correlation between MRI findings and D-dimer values.

Conclusion

Estimation of D-dimer in suspected CVT patients might be not only suitable in the context of diagnosing CVT but also may be helpful in estimating severity of disease. Thus in a developing country with less resources patients with negative D-dimer tests might be evaluated on an outpatient basis, possibly with less expensive neuroimaging protocols. Patients with positive tests should receive expedited MR imaging which might speed time to initiation of appropriate therapy.

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