

Clinical Profile, Risk Factors and Outcomes in Patients with Cerebral Venous Sinus Thrombosis: A Study from Western India

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Abstract

Aim: Study of cause and clinical profile of venous sinus thrombosis in Western India

Settings and Design: A retrospective study was conducted to ascertain the clinical profile, etiology, and follow up of patients with venous sinus thrombosis.

Methods and Material: Hospital database of patients suffering from venous sinus thrombosis from two tertiary care hospitals in West India were studied. A telephonic follow up was taken for assessment of outcome.

Inclusion criteria were a) Age more than 15 years of age b) clinically symptomatic patients c) Diagnosis confirmed by Magnetic resonance Venography (MRV) or CT Venography (CT Venography)

Exclusion criteria: Patients with infarct in arterial territory, hypertensive hemorrhage, metabolic encephalopathy and eclampsia were excluded from the study.

Statistical analysis used: Descriptive statistic was performed as frequency, mean and standard deviation or percentages. Difference in continuous variables was evaluated by using independent t-test while chi-square test was performed in categorical variables. Statistical $P < 0.05$ was considered statistically significant.

Results: We conducted a retrospective study of patients with venous sinus thrombosis in Rajasthan in western India. Out of 71 patients in our study group the mean age of presentation was 36.64 years. 42 patients were male (59.2%) and 29 were female (40.8%). Only 9 patients (12.6%) had pregnancy or puerperium related venous sinus thrombosis. The most common presenting feature was headache 47/71 (66.2), followed by seizures 33 (46.5%), paresis 20/71 (28.16%) and coma 15/71 (21.1%). MRI Brain recorded infarcts in 32/71 patients and predominant hemorrhage was recorded in 34/71. 4 cases were associated with malignancy (one CNS, one outside CNS and 2 hematological). Raised homocysteine level was found in 26/35 (74.3%) patients in whom they were measured. 9 patients had moderately elevated homocysteine levels (15-30), another 9 had intermediate values (31-64) and 5 patients had elevated homocysteine level > 65 . Hyperhomocysteinemia was the commonest causative factor and was far more common in men (21/25) than in women (5/10). (p value 0.019). 24 out of 71 patients were found to be anemic (33.8%). Anemia was far more common in women than in men. (p value .002). Protein C level was found abnormal in 5/27 patients, Protein S in 6/27 patients and Anti thrombin III in 1/23 patient studied respectively. History of oral contraceptive intake was recorded in only a minority of women with venous sinus thrombosis 7 (24.1%) compared to the western data where most of the venous sinus thrombosis are related to the contraceptive pills.

Conclusions: The clinical presentation of venous sinus thrombosis in tertiary care centers is changing outside the traditional puerperium / pregnancy related venous sinus thrombosis. Common risk factors include hyperhomocysteinemia, anemia, coagulopathy, pregnancy related, vasculitis, malignancy and oral contraceptive usage. Male involvement was far more common than females and was usually associated with a higher level of homocysteine.

Introduction

Cerebral vein and dural sinus thrombosis are an uncommon cause of stroke and is often more difficult to diagnose than usual causes of stroke. In the era of magnetic resonance imaging (MRI) and increased awareness of disease, more individual are being diagnosed with this condition. This study was carried out in Rajasthan, India which has a fairly hot and dry climate. There is a change in profile and presentation of this disease moving away from classical postpartum disease in women to a disease commonly observed in men.

Material and Methods

A retrospective study was conducted from hospital database of patients suffering from venous sinus thrombosis. Two sites were included both of which were tertiary care hospitals in West India. A computerized data base was accessed for discharge summaries and original files were then retrieved from Medical Research Department.

Inclusion criteria

Clinical symptoms consistent with diagnosis of venous sinus thrombosis, age > 15 years and cerebral venous thrombosis proven, either with CT venography or MRI venography.

Exclusion criteria

Patients with infarct in arterial territory, hypertensive hemorrhage, metabolic encephalopathy and

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eclampsia were excluded from the study.

A telephonic follow up was taken for assessment of outcome where long term outcome was not available. 58 patients were selected out of 3295 neurology admissions from the first center between January 2012 to Jan 2017 and 13 patients were selected from the second center for same duration. All patients were admitted in department of neurology with one or more features of venous sinus thrombosis like seizures, headache, papilledema, focal neurological deficit, altered sensorium and evidence of venous sinus thrombosis on magnetic

resonance venography (MRV) or computerized tomography venous study (CTV). Presenting features, detailed demographic profile, evaluation of risk factors including genetic and acquired procoagulant states and infections, malignancy (central nervous system, outside CNS and hematological), vasculitis, anemia, hyperhomocysteinemia, vitamin B 12 levels, drug usage including hormone replacement therapy, oral contraception, steroid usage, thyroid disorder, smoking, alcoholism, surgery, pregnancy and puerperium were recorded. Physical parameters at time of presentation including systolic and diastolic blood pressures heart rate

were recorded on admission with level of consciousness, papilledema and focal neurological deficits. On radiology presence or absence of infarct and/or hemorrhage and the site of venous sinus occlusion was recorded. Treatment during hospital stay was recorded in form of use of unfractionated heparin, low molecular weight heparin, mannitol, antiepileptic medications, oral anticoagulants and decompressive craniotomy. Outcomes were recorded in form of complete recovery, dependency and death/brainstem death. Descriptive statistic was performed as mean and standard deviation or percentages. Difference in continuous variables was evaluated by using independent t-test while chi-

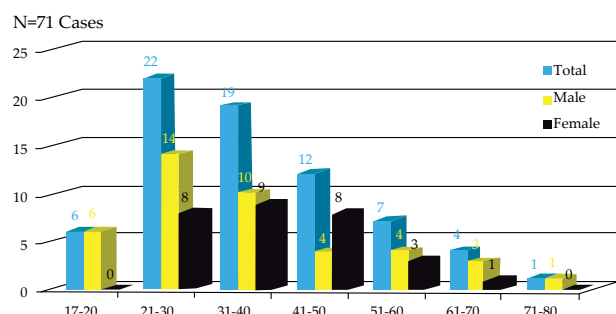


Fig. 1: The age band with gender distribution

Table 1: Common presenting symptom with CVST

Symptoms	Total	Male	Female	P
Vertigo	8(11.3%)	2(4.8%)	6(20.7%)	0.037
Numbness	11(15.5%)	9(21.4%)	2(6.9%)	0.096
Headache	47(66.2%)	29(69.0%)	18(62.1%)	0.541
Fever	11(15.5%)	6(14.3%)	5(17.2%)	0.735
Visual loss	4(5.6%)	1(2.4%)	3(10.3%)	0.153
Diplopia	13(18.3%)	6(14.3%)	7(24.1%)	0.291
Papilledema	9(12.7%)	4(6.5%)	5(17.2%)	0.337
Blurred vision	10(14.1%)	6(14.3%)	4(13.8%)	0.953
Coma	15(21.1%)	11(26.2%)	4(13.8%)	0.291
Seizure	33(46.5%)	23(54.8%)	10(34.5%)	0.092
Vomiting	26(36.6%)	15(35.7%)	11(37.9%)	0.849
Mental Disorder	6(8.5%)	1(2.4%)	5(17.2%)	0.027
Paresis	20(28.1%)	15(35.7%)	5(17.2%)	0.363

Table 3: Distribution of Thrombosis in MRV/CTV

Sinus	Total	Male	Female	P
Superior sagittal sinus	51(70.8%)	28(66.7%)	23(79.3%)	0.244
Transverse sinus left	28(34.4%)	15(35.7%)	13(44.8%)	0.440
Transverse sinus right	24(33.8%)	15(35.7%)	9(31.0%)	0.682
Sigmoid sinus left	28(39.4%)	16(38.1%)	12(41.4%)	0.268
Sigmoid sinus right	3(4.2%)	2(4.8%)	1(3.4%)	0.848
Both sigmoid sinus	1(1.4%)	1(2.4%)	-	0.403
Straight sinus	15(21.4%)	9(21.4%)	6(20.7%)	0.940
Internal cerebral vein of galen	9(12.7%)	5(11.9%)	4(13.8%)	0.544
Cortical veins	16(22.5%)	12(28.6%)	4(13.8%)	0.143
Jugular veins	13(18.3%)	7(16.7%)	6(20.7%)	0.667
Cerebellar veins	4(4.6%)	2(4.8%)	2(6.9%)	0.701
Cavernous sinus	1(1.4%)	1(2.8%)	-	0.403

Table 2: Risk factor for CVT in included patients

Factors	Total	Male	Female	P
Hematological				
Hyperhomocysteinemia	26(36.6%)	21(50%)	5(17.2%)	0.019
Vitamin B12 deficiency	26(36.6%)	19(45.2%)	7(24.1%)	0.189
Anemia	24(33.8%)	8(19%)	16(55.2%)	0.002
Lupus anticoagulant positive	5(7%)	5(11.9%)	0(0.0%)	0.132
Thrombophilia genetic	17(30.4%)	8(24.2%)	9(39.1%)	0.384
Thrombophilia acquired	8(14.3%)	6(18.2%)	2(8.7%)	
Malignancy				
Central nervous system	1(1.4%)	1(2.4%)	0(0.0%)	
Outside CNS	1(2.4%)	1(2.4%)	0(0.0%)	0.688
Hematological				
CNS disorder	2(2.8%)	1(2.4%)	1(3.4%)	
Dural fistulae	4(5.6%)	3(7.1%)	1(3.4%)	
Arteriovenous malformation	2(2.8%)	2(4.8%)	0(0.0%)	0.560
Vasculitis				
Behcet's disease	1(1.4%)	1(2.4%)	0(0.0%)	
Sarcoidosis	2(2.8%)	1(2.4%)	1(3.4%)	
Mixed connective tissue disorder	2(2.8%)	2(4.8%)	0(0.0%)	0.932
Family History				
Deep vein thrombosis	3(4.2%)	3(7.1%)	0(0.0%)	
Pulmonary embolism	2(2.8%)	1(2.4%)	1(3.4%)	0.146
Artery embolism	4(5.6%)	4(9.5%)	0(0.0%)	
Drugs used in last six months				
Oral contraceptives	7(9.9%)	0(0.0%)	7(24.1%)	0.001
Steroids	6(8.5%)	3(7.1%)	3(10.3%)	0.634
Hormone Replacement Therapy	5(7%)	0(0.0%)	5(17.2%)	0.005
Pregnancy	2(2.8%)		2(6.9%)	
Puerperium	7(23.3%)		7(24.1%)	
Infections				
CNS	10(14.1%)	6(14.3%)	4(13.8%)	
Ear Nose Throat /Neck	2(2.8%)	2(4.8%)	0(0.0%)	0.062
Other Infections	4(5.6%)	0(0.0%)	4(13.8%)	
Other Medical History				
Hypertension	14(19.7%)	9(21.4%)	5(17.2%)	0.452
Diabetes	6(8.5%)	6(14.3%)	0(0.0%)	0.037
Thyroid Disorder	5(7%)	1(2.4%)	4(13.8%)	0.086
Surgery	14(19.7%)	8(19%)	6(20.7%)	0.864
Dehydration	18(25.4%)	11(26.2%)	7(24.1%)	0.845
Others				
Alcoholism	10(14.1%)	9(21.4%)	1(3.4%)	0.031
Smoking	15(21.1%)	15(35.7%)	0(0.0%)	0.001

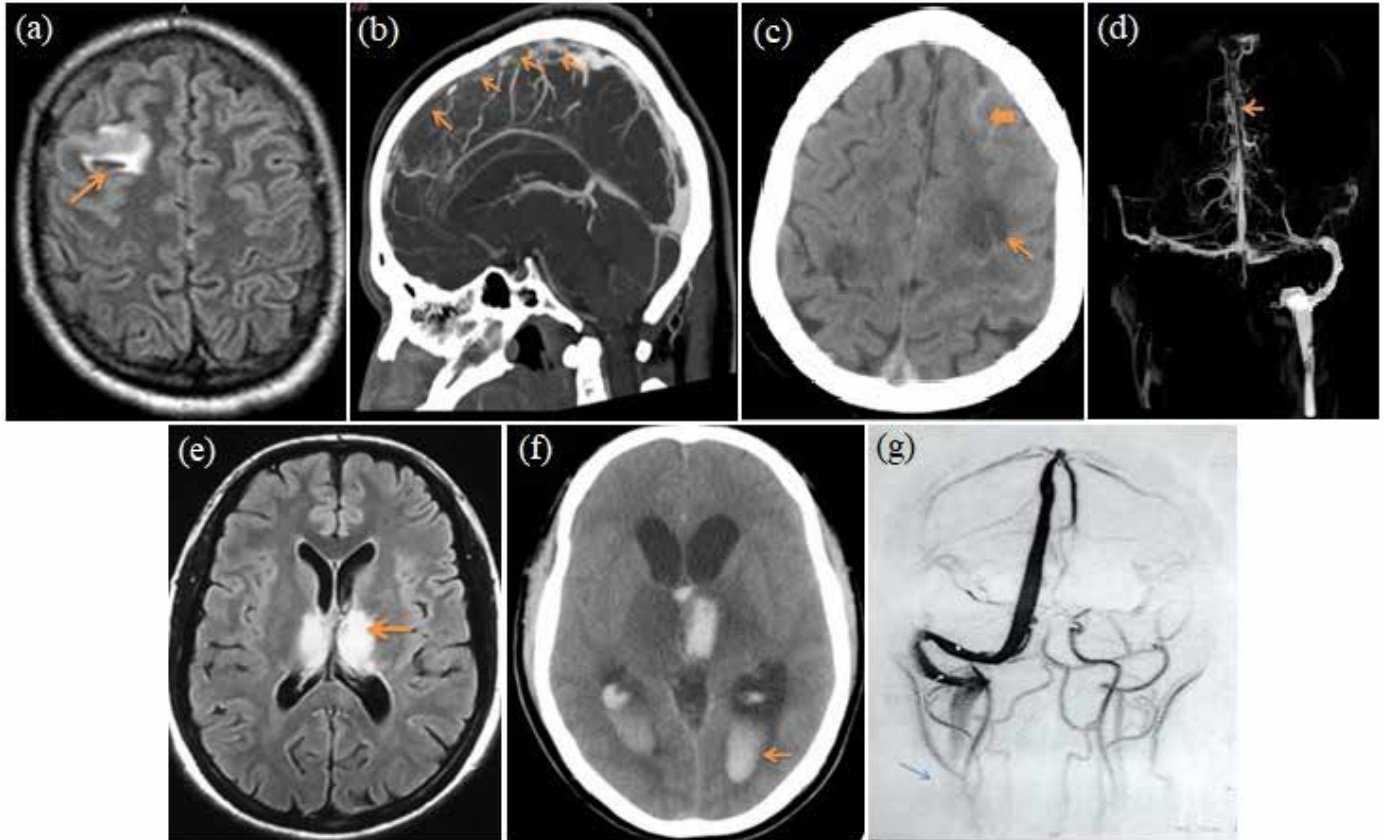


Fig. 2: 27 Year old male presented with complaints of headache, seizure and loss of consciousness had (a) FLAIR sequence of brain MRI showing hyperintensity (arrow) in right parietal region with hemorrhagic transformation and (b) CT venography showing superior sagittal sinus and left transverse sinus thrombosis (arrow). A 33 Year male patient presented with headache left upper limb weakness and seizure had (c) plain CT Head showing multifocal edematous hypodense area (thin arrow) in bilateral fronto-parietal lobes and left side subarachnoid hemorrhage (thick arrow) and (d) CT venography showing entire course of superior sagittal sinus (arrow), bilateral transverse sinus and sigmoid sinuses thrombosis. 39 year male, presented with fever, headache, confusion and alteration in sensorium had (e) MRI FLAIR sequence showing bilateral thalamic infarcts (arrow), (f) plain CT brain showing intraventricular hemorrhage (arrow) in bilateral lateral ventricles up to fourth ventricles and (g) MRI venography showing extensive venous sinus thrombosis including deep venous system

square test was performed in categorical variables. For the establishing the differences in clinical observations between male and female, data were analysed as male vs. female and p value < 0.05 was considered as statistically significant.

Results

Out of 71 patients in our study group the mean age of presentation was 36.64 years with minimum age of 17 years and maximum age of 79 years. 42 patients were male (59.2%) and 29 were female (40.8%). The age band of presentation with respect to number of cases is indicated in figure 1 with the gender distribution. Maximum numbers of patients were in 20 to 30 years age group and in almost all subgroups the number of men exceeded than women.

The most common presenting feature was headache 47/71(66.2%), followed by

seizures 33(46.5%), paresis 20/71 (28.16) and coma 15/71(21.1%). Vertigo was present in 8 patients (11.3) out of which 2 were men (4.8) and 6 were women (20.7) with a p value of 0.037. Fever at time of presentation was recorded in 11/71 patients. 6 patients, one male and 5 females presented with dullness, depression like picture preceded by headache and one had psychosis like presentation. This presentation was far more common in women than men. (P value 0.027). Diplopia was present in 13/71 patients and vomiting was present in 26(36.6%) patients (Table 1).

Among the women only 2 patients had venous sinus thrombosis during pregnancy and seven during puerperium. 20(28.18%) patient had limb paresis out of which 12 had left sided and 7 had right sided weakness and one patient had quadriparesis.

Family history of DVT and pulmonary embolism was recorded in 5 patients and arterial embolism was recorded in 4 patients. MRI Brain recorded infarcts in 32/71 patients and predominant hemorrhage was recorded in 34/71 (Figure -2f). 4 cases were associated with malignancy (one CNS, one outside CNS and 2 hematological). One case had Behcet's syndrome, two had sarcoidosis, 2 patients had mixed connective tissue disorder and 2 had nonspecific vasculitis, difference between sexes in these patients was not significant. Raised homocysteine level was found in 26/35 (74.3%) patients in whom they were measured. 9 patients had moderately elevated homocysteine levels (15 - 30 $\mu\text{mol/L}$), another 9 had intermediate values (31 - 64 $\mu\text{mol/L}$) and 5 patients had elevated homocysteine level >65 $\mu\text{mol/L}$. Hyperhomocysteinemia was the commonest risk factor and was far more

Table 4: Details of treatment received by patients with venous sinus thrombosis

Treatment	Total	Male	Female	P value
Oral Anticoagulant	59(83.1%)	36(85.7%)	23(79.3%)	0.479
LMWH	29(40.8%)	19(45.2%)	10(34.5%)	0.365
Heparin	10(14.1%)	5(11.5%)	5(17.2%)	
Antiplatelet	18(25.4%)	14(33.3%)	4(13.8%)	0.063
Antiepileptic	52(73.2%)	32(76.2%)	20(69%)	0.499
Mannitol	38(53.5%)	20(47.6%)	18(62.1)	0.230
Decompressive Craniotomy	3(4.2%)	2(4.8%)	1(3.4%)	0.787

common in men (21/25) than in women (5/10) (P value 0.019). B12 deficiency was found in 26/41 patients where it was checked, again more common in men than in women. This however did not reach statistical significance. 24 out of 71 patients were found to be anemic (33.8%). Anemia was far more common in women than in men. (P value .002). Protein C level was assessed in 27 patients and found to be low in 5 patients (18.5%). This derangement was far more common in men (4/5) than in women (1/5). Protein S level was also evaluated in 27 patients and found to be low in 6 patients (3 males and 3 females). Factor V Leiden mutation was not found in any of the patient studied (total no 16). Abnormal anti thrombin III levels were found in one patient (1/23). One patient had associated nephrotic syndrome with steroid intake. 16 patients had associated infections (Table 2). History of oral contraceptive intake was recorded in only a minority of women with venous sinus thrombosis 7(24.1%) compared to the western data where most of the venous sinus thrombosis are related to the contraceptive pills.

Maximal number of patients had sagittal sinus involvement, followed by transverse sinus and sigmoid sinus (Table 3). In majority of patients more than one venous sinus was affected. No gender difference was found in site of involvement between male and females. As far as treatment was concerned most of the patients received low molecular weight heparin / unfractionated heparin, number of patients receiving low molecular weight heparin were more than those receiving unfractionated heparin possibly due to the ease of administration. Only a small fraction received additional antiplatelet medication. 73.2 % patients were on antiepileptic medication. Three patients underwent decompressive hemicraniectomy. Most patients were treated with low molecular weight heparin followed by oral anticoagulants. Mannitol was used in 17/42 patients

(Table. 4). No difference was observed between groups receiving mannitol and otherwise in terms of recovery, dependency or death. A longer hospital stay was observed in the group receiving mannitol 9.5±6.3 days compared to the group not receiving same 5.2±4.3 (P 0.014). Average duration of hospital stay was 7.4 days. Most patients survived with good recovery 43.7%, complete recovery were observed in 18(25.4%) patients and death was an outcome in 4(5.6%) of total patients (Table 5). Dependency was present in 25.4 % patients.

Discussion

Venous sinus thrombosis has been traditionally considered a disease of women in the postpartum period in tropical countries. Most of the Indian studies done earlier have shown a female predisposition¹⁻³ with a few international studies⁽⁴⁾ also showing the same pattern. With time the clinical profile of disease is evolving and atypical presentation in men are now fairly common. A study from south India also revealed a male predominance in a large cohort of patients with predominant risk factors of anemia, hyperhomocysteinemia, and alcoholism.⁵ Similarly, in other studies from Chennai and Mumbai showed venous sinus thrombosis in younger patients and male female ratio of 1.5:1 and 1.6:1.^{6,7} Our study also revealed a male preponderance with 59.2% male patients and 40.8% female patients.

Anemia also was fairly common and was seen more frequently in women than in men. Most patients were seen in the younger age group for stroke between 21 to 40 years of age. In a study by Saroja et al⁸ in women with CVT anemia was found in 76.64% of women. History of alcoholism was far less in our study 10(14.1%) in comparison to study by Narayan et al,⁵ out of which 9 were men and one was of female gender.

In the ISCVT⁴ study hyperhomocysteinemia was found in

Table 5: Outcome in patients with venous sinus thrombosis

Outcomes	Total	Male	Female	P value
Recovery	31(43.7)	19(45.2)	12(41.4)	0.747
Dependency	18(25.4)	12(28.6)	06(20.7)	0.481
Death	04(5.6)	02(4.8)	02(6.9)	0.701

just 4.5 % of cases (28/624) compare to our study where hyperhomocysteinemia was found in 36.6% cases. The raised homocysteine level in men reached statistical significance in our study (0.019). Vitamin B 12 deficiency was also more common in men compared to females although it did not reach statistical significance. In the study from Narayan et al⁵ 18.2% of patients had raised homocysteine levels. In a study from south India⁶ hyperhomocysteinemia was found in 17/40 (42.5%). A study conducted in Karnataka, women of South India with CVT by Saroja et al⁸ found more patients with non-pregnancy related venous sinus thrombosis (81/150-54%) among which hyperhomocysteinemia was found in 11/48 (22.9%). Another study Martinelli I et al 2003⁹ conducted in Italy which specifically evaluated the role between raised homocysteine level and cerebral venous thrombosis found hyperhomocysteinemia in 27% patients with CVT compared to control where it was found in only 8% patients and concluded that it is associated with 4-fold increased risk of CVT. In a Japanese study by Takemaru M¹⁰ for patients of hyperhomocysteinemia and CVT found a strong association between elderly males. Their population was found to have a different demographic distribution compared to western literature. Very few studies have been done in our region where incidence of venous stroke appears fairly high. In a study by Pangariya et al¹¹ 1997 on CVT in pregnancy and puerperium, CVT was associated with half of young stroke and 40% of stroke in women. A comprehensive review by Dash et al¹² also eluted the unique Indian pattern of venous sinus thrombosis. Whether hot dry climate, with increased homocysteine level predisposes these individuals to venous sinus thrombosis is debatable. While most women with hyperhomocysteinemia had only mildly elevated levels, most men with same had moderate to severe elevation in these levels. Most of the Indian population in this part of India follows a vegetarian diet and low vitamin B12 levels are fairly common. Low Vitamin

B12 level is associated with a raised homocysteine level. Another patient in this study had stopped vitamin B12 and folate being used for treatment of increased homocysteine level and developed recurrence of thrombosis along with elevated homocysteine level without any trigger and in absence of any other hypercoagulable factors suggesting possible pathogenesis.

We had a few interesting presentations which were worth a mention. 16 patients had associated infections out of which 10 (14.1) were in central nervous system (CNS) infections and the rest were outside nervous system 02 (ENT / Neck) and four elsewhere. What was interesting about these infections was the fact that these patients often deteriorated after showing some improvement on treatment for these infections. One patient who was a diagnosed case of progressive supra nuclear palsy suffered with chikungunya. After a period of improvement secondary deterioration was observed due to CVT possibly as a result of immobility. Another patient had herpes encephalitis following which secondary

deterioration was observed. A third patient had concurrent tubercular granulomas brain /cold abscess (positive for Acid fast bacillus) with inferior vena cava and sagittal sinus thrombosis. There were a few cases of vasculitis / connective tissue disorder among these patients including Bechet's syndrome and mixed connective tissue disorder (MCTD).

Whether to use mannitol or not in patients with venous sinus thrombosis is debatable. In our study the mannitol group had a longer hospital stay compared to the group where it was not used. Most of the patients had a good outcome.

Conclusion

The clinical presentation of venous sinus thrombosis to tertiary care centers is changing outside the traditional puerperal / pregnancy related venous sinus thrombosis. Common risk factors include hyperhomocysteinemia, anemia, coagulopathy, pregnancy related, vasculitis, malignancy and oral contraceptive usage. Male involvement was far more common in our study than females and was usually associated with a higher level of homocysteine.

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