

Review of Patients with Cerebral Venous Sinus Thrombosis (CVST) in a Premier Neuroscience Institute in Nepal

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Abstract: Background and Purpose: The advent of sensitive diagnostic techniques along with widespread treatment of CVST with anticoagulation has transformed this once dreaded disease to a benign entity. Prompt diagnosis on hospital visit and effective therapeutic interventions are likely to improve the outcome of the CVST patients and we employed this good clinical practice in our study.

Materials and Methods: From 2007-2012, 45 adult patients with CVST confirmed by radiography and fully investigated for prothrombotic states were retrospectively studied. All patients were followed up for 6 months after inpatient hospitalization and the outcome at last follow-up visit was assessed by modified Rankin Scale (mRS). Primary outcome was mRS ≤ 2 at the end of follow-up signifying good outcome.

Results: Of the 45 patients, 26(57.8%) were men and the mean age was 37.8 years. The most common symptoms were headaches (84.4%), vomiting (37.8%) and seizures (21.9%). Papilledema (33.3%) and isolated intracranial hypertension (IIH) (33.3%) were the most common sign and clinical syndrome respectively. The most common risk factors were oral contraceptive pills (OCP) (28.1%) and dehydration (18.7%). Good outcome (mRS ≤ 2) and poor outcome (mRS 3-6) at the end of follow-up were observed in 39(86.7%) and 6(13.3%) patients respectively with mortality (mRS=6) of 3(9.4%) patients. Most patients were managed medically with use of anticoagulants 38(84.4%). Female gender (p value=0.033) and OCP use (p value = 0.001) were found to be statistically significant risk factors for CVST.

Conclusion: We had higher prevalence of CVST in men than previously reported. We had excellent prognosis with 86.7% of patients exhibiting good outcome (mRS ≤ 2) at the end of follow-up. We attribute this remarkable patient's outcome to increased awareness of this entity, prompt diagnosis and timely intervention with effective therapies. If feasible, use of OCP should be minimized.

Keywords: Cerebral venous sinus thrombosis, effective therapies, patient's outcome, risk factors.

1. INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare disease with highly variable symptoms and clinical course which was once considered an entity with high morbidity and mortality. During the past decade, increases awareness of this diagnosis, improved neuroimaging techniques, earlier diagnosis after the onset of symptoms and more effective treatments like anticoagulants have improved the prognosis. Several studies attest to the fact that over 80 percent of patients with CVST now have a good neurological outcome [1-3]. The largest international multicenter trial of CVST in 2004 included very few patients from Asia and Africa [1], hence leaving the need for more studies on CVST from Asia especially in the age of modern neuroimaging techniques and effective anticoagulant therapies. We aimed to study the natural course and response to treatment in patients afflicted with CVST in a specialized neuroscience facility in Nepal. We employ pro-active approaches to the prompt diagnosis of patients presenting to our hospital with suspicion of CVST and implement effective therapies without delay. We also aimed to ascertain the significance of this approach on the outcome of the patients with CVST.

2. MATERIALS AND METHODS

Demographics, Imaging, Clinical data and Risk Factors.

This retrospective observational study was conducted on the patients diagnosed with CVST between October 2007 and February 2012 in National Institute of Neurological and Allied Sciences, Kathmandu, Nepal. This tertiary care hospital is the major referral center for neurological diseases from all the strata of society in Nepal. Patients were either referred or came by themselves to this hospital which is known for providing state of the art care in neurological illness and catered by trained personnel (skilled neurosurgeon/neurologist and nurses). Doctors are trained to keep high index of suspicion for rare diseases like CVST which has highly variable symptoms and clinical course. When CVST is suspected in patients presenting to the Emergency Room (ER) or outpatient department (OPD), the patient is wheeled for imaging

to confirm the diagnosis within 2-4 hours of presentation. The clinical diagnosis was confirmed by brain MRI (1.5T) scan with MR Venography (MRV) or digital subtraction angiogram (DSA). The neuro-radiologist present in house interprets the scan results immediately upon its completion and confirmed CVST patients are admitted to neuro intensive care unit (NICU) within an hour of diagnosis.

All the admitted patients with confirmed CVST had following information: demographic data; time period between onsets of symptoms to presentation, timing from presentation to confirmation of diagnosis by imaging and initiation of appropriate therapies; symptoms and signs from onset to diagnosis; Glasgow Coma Scale (GCS) score on admission; imaging methods used; location of the thrombus; number, location, and size of any parenchymal lesions. Complete blood work up with thrombophilia screening (antithrombin III, anticardiolipin antibodies, antinuclear antibody and prothrombin time) along with Human Immunodeficiency Virus (HIV) testing was performed to detect the underlying etiology. D-dimer and fibrin degradation products (FDP) blood levels were estimated as a marker of thrombosis in many but not all the patients. These markers were evaluated at the entry of patients to the NICU, but prior to initiating anticoagulation therapy. A meticulous search for potential risk factors for CVST like oral contraceptive pills (OCP) use, dehydration and infection was extensively sought after.

Treatment:

The choice of treatment was left to the attending neurosurgeon, but all treatments were systemically recorded. The most common practice for CVST patients were prompt initiation of adjusted dose unfractionated Heparin with an approximate dose of 1000 units/h, with the target activated partial thromboplastin time (APTT) of 2-2.5 times the control. It was followed by the use of Warfarin with a target Internationalized Normalized Ratio (INR) of 2-2.5 for a period of 6 months for patients with transient risk factors and indefinite treatment for patients with established thrombophilia. Alternative medical treatments were subcutaneous low molecular weight heparin (LMWH) in approximate dose of 0.1 mg/kg for a period of 10 days or just the use of Heparin without concomitant Warfarin therapy or vice versa. Aggressive measures to lower the Intracranial Pressure (ICP) were performed in patients with isolated intracranial hypertension which included the use of Acetazolamide, Mannitol, Lasix, Dexamethasone; Lumboperitoneal (LP) shunts placement and evacuation of intracranial hemorrhagic lesions. The duration of hospital stay along with the response to treatment were noted for all patients.

Follow-up and outcome:

Outpatient follow-up visits were performed for all patients at 2 weeks, 1 month, 3 months and 6 months

after inpatient stay by direct interview. All these patients condition at their last follow-up visit was taken as the final follow-up results. The data recorded during follow-up visit were disability according to modified Rankin Scale (mRS), ¹ death, seizures, and persistent headaches, and visual impairments, other thrombotic events, repeat admissions, current antithrombotic and other treatments.

Outcome was classified according to the mRS on final follow-up visit as complete recovery (mRS 0 to 1); partial recovery, independent (mRS 2); dependent (mRS 3-5) and death (mRS 6). Primary outcome was good outcome at the final follow-up visit with mRS 0 to 2, while secondary outcome was poor outcome at the final follow-up visit with mRS 3 to 6.

Statistical analysis:

Inferential statistical analysis was conducted by using Chi Square and Fischer Exact for descriptive data and Multiple Logistical Regression analysis done to identify independent risk factors for CVST. Unpaired t-test employed for continuous data. Statistically analysis was performed using SPSS (Statistical Package for Social Science) version 24.0

3. RESULTS

A total of 45 adult patients (men 26, women 19, 1.3:1) with complete data sets were included in this study. The age range was 18-66 years (mean 37.8 years). Mean duration of symptoms before admission was 15 days and the median delay from onset of symptoms to confirmation of CVST was 5 days. Presentation was acute (<48 hour from onset of symptoms to presentation), subacute (48 hour to <30 days) and chronic (>30 days) in 10(22.2%), 30(66.7%) and 5(11.1%) patients, respectively. The mean GCS on presentation was 13 (median 15, range 3-15). Headache, vomiting and seizures were the most common symptoms found in 38(88.4%), 17(37.8%) and 9(29.9%) patients, respectively (**Table 1**). Papilledema was the most frequent neurological sign, seen in 15(33.3%) patients. In terms of most common clinical syndromes, isolated intracranial hypertension (IIH) was observed in 15(33.3%) and stroke like presentation was seen in 11(24.4%) patients. Normal neurological exam was found in 7(15.5%) patients.

The most common risk factors identified were OCP use in 13(28.8%) and dehydration in 8(17.8%) patients. No risk factor could be identified in 12(26.6%) patients (**Table 2**). The diagnosis of CVST was established by MRI/MR Venography in 39(86.7%) and by DSA in 6(13.3%) patients. Only 3(6.6%) patient had deep venous system involvement, while the rest (93.4%) had superficial venous system involvement. Most common sinuses involved were superior sagittal sinus in 26(57.7%) and transverse sinus in 20(44.4%) patients. Two or more sinuses were concomitantly involved in 16(35.5%) of patients (**Table1**).

TABLE 1. Demographic, Clinical, and Imaging Features of Included patients

Parameters	No. of cases (percentage)
Total number of patients with complete data entry	45
Mean Age irrespective of gender (years)	37.8
Age range (years)	18-66
Male population	26
Men (percentage of the total population)	57.8%
Acute presentation (<48 hr)	10(22.2%)
Subacute presentation(48 hr to <30 days)	30(66.7%)
Chronic presentation (>30 days)	5(11.1%)
Mean delay in diagnosis from onset of symptoms (days)	15
Median delay from onset of symptoms to diagnosis (days)	5
Mean duration in the hospital (days)	18
Symptoms and signs	
Headache	38(84.4%)
Nausea/Vomiting	17(37.8%)
Seizures	
Focal seizures	4(8.8%)
Generalized	5(11.1%)
Stroke like symptoms/any paresis	
Hemiparesis	4(8.8%)
Ocular findings	
Diplopia	5(11.1%)
Papilloedema	15(33.3%)
Blurring of vision	5(11.1%)
Altered sensorium	
Alert	28(62.2%)
Impaired consciousness	9(20.0%)
Coma on admission	3(6.6%)
Fever	3 (6.6%)
Normal neurological exam	7(15.5%)
MRI intraparenchymal findings	
MRI ischemic infarct	6(13.3%)
MRI hemorrhagic infarct	9(20.0%)
Any parenchymal lesion on MRI	20(45.5%)
Sites of CSVT as per MRV/DSA	
Superior Sagittal Sinus	26(57.7%)
Transverse Sinuses	20(44.4%)
Sigmoid sinuses	6(13.3%)
Straight sinus	3(6.6%)
Confluences of sinuses	1(2.2%)
2 or more sinus involvement	16(35.5%)
Cavernous sinuses	1(2.2%)
Deep Venous system	3(6.6%)

TABLE 2: Risk Factors Identified in Included Patients

Risk Factors	No. of patients (%)
Oral Contraceptive pills	13(28.8%)
Dehydration	8(17.8%)
Thrombophilia	3(6.6%)
Infection	6(13.3%)
Anemia and Chronic Renal failure	1(2.2%)
Autoimmune diseases/Vasculitis	2(4.4%)
Unknown	12(26.6%)

Out of the total 45 patients with CVST confirmed by radiography, only 25(55.5%) had D-dimer blood test performed. Of these tested patients, 22(48.8%) patients had abnormal D-dimer (above 500µg/l) and 3 had normal values.

Thirty eight (84.4%) patients received unfractionated Heparin for 7 days overlapping with oral anticoagulant (Warfarin) for 3 days, the latter was continued for 6 months in 43(93.3%) patients with transient reversible risk factors and indefinite Warfarin treatment for 3(6.6%) patient with confirmed thrombophilia. LMWH in combination with Warfarin was offered to 2(4.4%) patients. Unfractionated Heparin only and Warfarin only were used in 2(4.4%) patients each. No intra-arterial thrombolytic were given in our study. 7(21.8%) patients had surgical intervention for complications related to CVST. 5(10.8%) patients had LP shunts placed for isolated intracranial hypertension(IH) unresponsive to medical measures (mannitol, Acetazolamide, Dexamethasone and Lasix), out of which 3(6.6%) patients had shunt placed on subsequent hospital admissions for persistent IH. Two (4.4%) patients had decompressive craniectomy and evacuation of space-occupying hemorrhagic infarct.

Information on patient's outcome at discharge and subsequent outpatient follow-up visit was available for all patients. Mean hospital stay was 18 days. In-hospital mortality was noted in 3(6.6%) patients. Twenty one (46.7%) patients became normal (mRS 0-1), 12(26.7%) became functionally independent (mRS=2), and 9(20.0%) remained dependent (mRS 3-5) at hospital discharge (**Table 3**). Overall good outcome (mRS 0 to 2) at the time of discharge from hospital was noted in 33(73.3%).

TABLE 3. Patient's Clinical Outcome

Patient's outcome as assessed by mRS	Upon hospital discharge	At the last follow-up visit*
Complete recovery (mRS: 0-1)	21(46.7%)	34(75.6%)
Partial recovery but functionally independent (mRS=2)	12(26.7%)	5(11.1%)
Dependent (mRS= 3-5)	9(20.0%)	3(6.6%)
Death (mRS=6)	3(6.6%)	3(6.6%)
Good outcome (mRS 0 to 2)	33(73.3%)	39(86.7%)
Poor outcome (mRS 3 to 6)	12(26.7%)	6(13.3%)

*During 6 months follow up after hospital discharge.

All outpatients' visits (2 weeks, 1 month, 3 months and 6 months after discharge) were assessed by face-to-face interview in every patient. Persistent headache was the most common complications on follow-up visits seen in 5(11.1%) patients, followed by chronic intracranial hypertension and visual problems in 3(6.6%) patients each (**Table 4**). For the latter, LP shunts were placed in all 3 patients with chronic IH. We could not ascertain the incidence of recurrent sinus thrombosis radiographically as they were not performed. Symptomatically none of the patient deteriorated, in fact all of them improved or were stable on follow-up visits; hence repeat imaging was not obtained to save patient's expenses. Thirty four (75.6%) patients had complete recovery (mRS 0-1), 5(11.1%) had partial recovery but independent (mRS=2) and 3(6.6%) patient was dependent (mRS 3-5) at their final follow-up visit at 6 months (**Table 3**). No new mortality occurred in the outpatient follow-up period other than the known in-hospital mortality of 3(6.6%) patients. Hence good outcome (mRS 0 to 2) was observed in 39 (86.7%) patients.

TABLE 4. Events During Follow-Up

Events	No. of cases (%)
Persistent Headache	5(11.1%)
Chronic intracranial hypertension #	3(6.6%)
Visual problems	3(6.6%)
Seizures	0(0%)
Other Thrombotic events*	0(0%)

* Limb or pelvic venous thrombosis, pulmonary embolism, Stroke, TIA, Acute Limb ischemia

These 3 patients had LP shunt placed on 2nd or 3rd hospital admission for chronic IH

4. DISCUSSION

CVST is a rather rare disease which accounts for <1% of all strokes [4]. The largest prospective multicenter international study named ISCVT shed tremendous light on the natural course and long-term prognosis of patients with CVST [1]. The result of this study could not be generalized to Asia or Africa because very few patients from these continents were included in this study. The largest prospective single center series on this subject from the Indian subcontinent was reported by Narayan et al. in 2012 [5]. We report a single center retrospective case series on CVST patients in Nepal adding to the fund of knowledge of this entity from Asia. It is more prudent to have accumulation of scientific information across the globe on this uncommon disease especially in the era of modern imaging techniques and availability of effective therapies like anticoagulants to change the long held belief that CVST carries long-term morbidity and high mortality rate.

Unlike many studies reporting higher incidence of this entity in females (about 75%) [1, 3] but matching the study by Narayan et al. [5], we had higher incidence of CVST in male population (56.3%). It has been suggested that use of oral contraceptives (OCP) which has a pro-coagulant effect accounts for the disparity between the sexes in the studies reporting CVST patients to be predominantly women [3]. The high frequency of this disease in men in this study is probably due to its increased awareness and early detection by modern imaging, along with higher frequency of dehydration in elderly patients, hill/mountain climbers in Nepal and alcohol consumption.

The mean age in our study is 37.8 years and lacked pediatric population. The elderly (>60 years) constituted only 2(6.3%) patients in whom dehydration was the evident risk factor. Most common presenting symptoms were headache, vomiting, seizures and visual disturbances, as reported in the previous studies [1, 3-5]. Papilledema was the most frequent sign. The syndrome of isolated intracranial hypertension (IIH) with headache, vomiting and blurred vision due to papilledema is the most common clinical syndrome in this study accounting for 31.3% of the patients. We had no puerperal patients in our study. OCP use was the overall major risk factor irrespective of the gender and also the most common risk factor in women (28.1%), while dehydration was the most common risk factor in men (18.7%).

Most of the patients (84.4%) had CSVT confirmed by MRI in combination with the magnetic resonance venography (MRV). DSA was employed only in 15.6% of the patients. MRV has been suggested to be the most effective noninvasive technique to confirm this diagnosis [6-7]. MRI has the advantage of being better at detecting intracranial pathologies like infarcts secondary to sinus thrombosis. However cerebral angiography may demonstrate smaller clots like cortical vein thrombosis than CT or MRI, and obstructed veins may give "corkscrew appearance" [3]. If we suspect that the transverse sinus is hypoplastic/aplastic, rather than thrombosis, we look at the CT bone window to determine the size of the jugular foramen. If the size of this foramen is small compared to the contra lateral side, we presume the transverse sinus is hypoplastic and this type of patient is excluded from the study. Superior sagittal sinus (59.3%) and transverse sinuses (56.2%) were the most frequently involved sinuses. About 41% had involvement of two or more sinuses in combination. Only 1(3.1%) patient had deep venous system involved in our study. A significant proportion of patients (40.6%) had some sort of intra cerebral lesions secondary to sinus thrombosis including hemorrhagic and ischemic infarcts (**Figure 1a & 1b**).

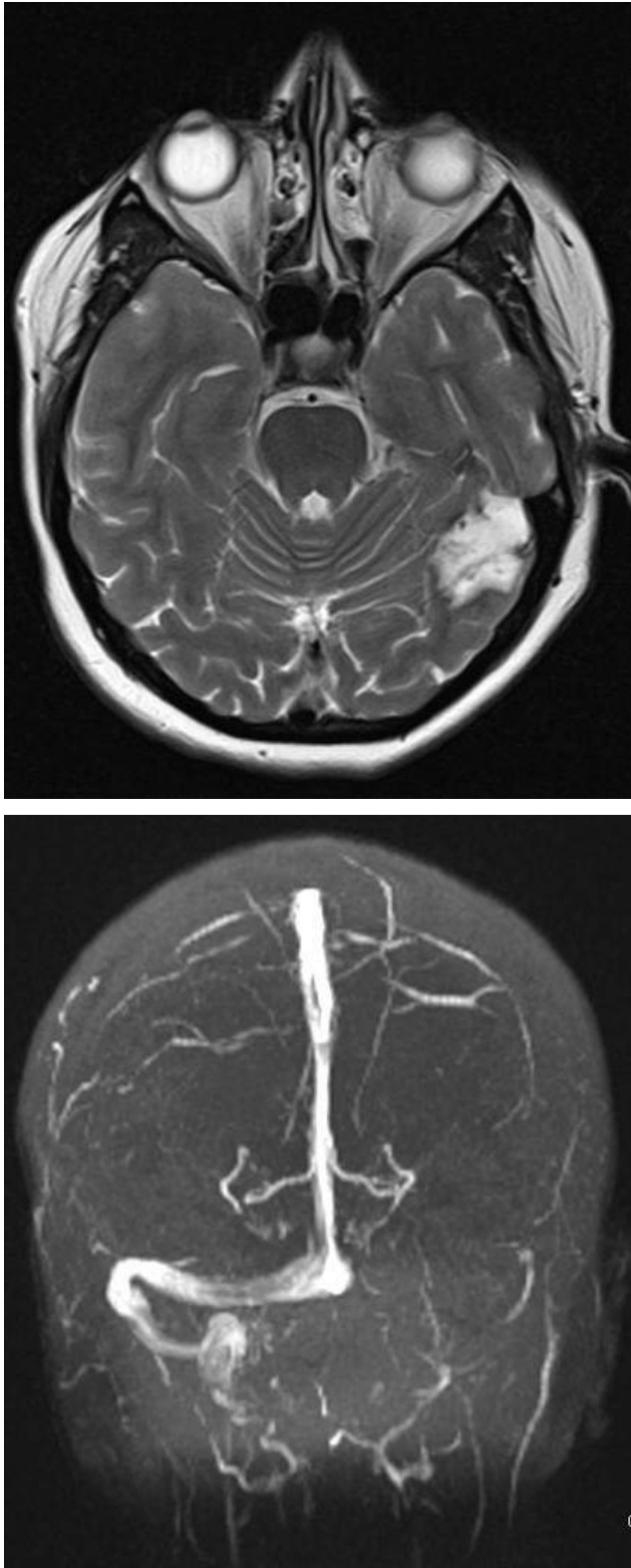


Figure 1(a&b). MRI brain of a patient showed left temporal hyper intense lesion on axial T2 Weighted image (Fig 1a) and absence of signal in the left transverse sinus compared to the right on MRV-TOF coronal image (Fig 1b). The jugular foramen was of normal size on the left side (not shown). A diagnosis of thrombosis of the left transverse sinus with left temporal hemorrhagic venous infarct was made.

We are a specialized neuroscience facility with skilled doctors who keep a close vigil for uncommon disease like CSVT. High index of suspicion for it following a patient's presentation to our hospital leads to prompt neuroimaging within 2-4 hours of visit. The in-house radiologist with significant expertise in neuroradiology interprets the imaging results immediately upon its completion. After the confirmed diagnosis of CSVT, patients are transferred to neuro ICU within an hour. Median delay from onset of symptoms to diagnosis is about 5 days in our study. It is even shorter compared to the ISCVT study which had a median diagnostic delay of 7 days which however included very few patients from Asia [8]. Still the loss of critical time due to diagnostic delay in our study may be attributed to lack of health awareness, monetary constraints and delay in transporting patients from remote areas in Nepal.

We started employing the practice of testing D-dimer blood level as a marker of thrombosis to augment the diagnosis of CVST by radiography only in the last 2-3 years. Hence many patients (15 out of 32), but not all had this test done. Out of the 15 patients tested for it, 3(20%) had normal value of D-dimer. There were no particular characteristics (in respect to clinical symptoms, acute versus chronic sinus thrombosis, extend of thrombosis etc.) which distinguished patients with normal versus patients with abnormal D-dimer values in our study. Even though previous reports have emphasized the clinical utility of D-dimer assay in the diagnosis of CVST [9], a subsequent study pointed out that a negative D-dimer assays does not rule out cerebral venous thrombosis [10].

We employ aggressive approach to initiate appropriate therapies for CSVT patients without further delay after hospital admission. Majority of the patients (81.2%) received Unfractionated Heparin as the initial treatment, followed by Warfarin for a period of 6 months if transient risk factors were present or indefinitely for patient(s) with confirmed thrombophilia. EFNS guidelines on the treatment of CVST recommend anticoagulation for it, provided that there is no contraindication to anticoagulation [4]. Concomitant intracranial hemorrhage related to CVST is not a contraindication for heparin therapy as per the EFNS guidelines. The Cochrane Stroke group concluded that despite limited evidence available, anticoagulant treatment for CVST appears to be safe and was associated with reduction in the risk of death or dependency [11]. No intra-arterial thrombolytic were employed in this study. Anti-edema treatment (including osmotic diuretics, corticosteroid et cetera) were used to control intracranial hypertension. Failure of medical treatment to control IIH resulted in surgical interventions. Five (11.1%) patients had LP shunt placed for refractory or chronic intracranial hypertension; among which 3 (6.6%) patients had it inserted on subsequent hospital admissions. Only

2(4.4%) patients had decompressive craniectomy and evacuation of hemorrhagic clot to lower the ICP.

At the time of hospital discharge, 33(73.3%) had good neurological outcome (mRS 0-2) and 12(26.7%) had poor outcome (mRS 3-6). Among the poor outcome group, there were 3(6.6%) in-house mortality (mRS=6). Out of these 3 deaths, 2 cases had raised ICP secondary to large hemorrhagic venous infarct and 1 case had septicemia along with bacterial meningitis.

All the surviving patients in this study had their final outpatient follow-up visit at 6 months after hospital discharge. During their follow-up visits, persistent headache was most common symptom and chronic intracranial hypertension was most common clinical syndrome (for which LP shunt was placed). Thirty nine (86.7%) patients had good outcome (mRS 0-2) at their final follow-up visit suggesting remarkable neurological outcome for treated CVST patients. This is a noticeable improvement compared to their neurological outcome at discharge from the hospital (see Table 3). We attribute this excellent neurological recovery for patients with CVST on increased awareness of this disease, prompt diagnosis after presentation to the hospital, specialized neurological care and institution of effective therapies including anticoagulation. The higher mean GCS on presentation (mean GCS 13), rare involvement of deep venous system and absence of cancer or puerperal patients all could have contributed to the remarkable patient's outcome in our study. Poor outcome (mRS 3-6) was noted in 6(13.3%) at the last follow-up visit including the known 3(6.6%) deaths (mRS=6) during first hospitalization. There were no new deaths in the outpatient follow-up period.

The only statistically significant risk factors associated with CVST found in our study were female gender (p value of 0.033) and use of OCP (p value of 0.001) (Table 5).

TABLE 5. Determining the significance of common risk factors found in our study

Risk Factors	P value
Female Sex	0.033
OCP use	0.001
Dehydration	0.080
Infection	0.286
Thrombophilia	0.334
Autoimmune disease/vasculitis	0.453
Anemia and Chronic renal failure	0.486

This study is limited in respect of small sample size, a retrospective rather than prospective case series and absence of certain demographics like children and patients with high risk for CSVT including malignancy, pregnancy and postpartum state.

5. CONCLUSION

CVST is an uncommon but important cause of stroke in adults affecting the male gender slightly more in our

study. Headache, vomiting, seizures and papilledema associated with intracranial hypertension were the most common presenting symptoms and signs. OCP use and dehydration were the most common risk factors in this study. We had an excellent neurological outcome for the patients with CVST suggesting that this disease is benign provided we keep an increased awareness of this entity, promptly diagnose it following presentation to the hospital and initiate effective therapeutic interventions likely to influence its outcome. Female sex and OCP use were found be significant risk factors associated with CVST. This study also provides the much needed resource on CVST from the Asia continent in the era of modern imaging and anticoagulant therapy.

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