Spectrum of Cerebral Venous Thrombosis in Uttarakhand

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Abstract

Background: CVT is an uncommon but important cause of stroke that is often misdiagnosed delaying its treatment. High suspicion is essential in early recognition and treatment.

Objective: To study the clinical features and etiology of patients with Cerebral Venous Thrombosis (CVT) and relation between septic and non septic CVT if any.

Patients and Methods: A prospective study was done in SMIH that enrolled 40 patients of CVT in 2 years duration (Jan 2014 to Dec 2015). The patients were diagnosed as CVT according to Magnetic Resonance Venogram (MRV) and clinical status.

Results: Forty (40) patients of CVT were enrolled during 2 years period, most were females (22/30) and aged between 18-50 years (mean age 30.2+4.9). Most common presentation was headache followed by seizures and focal deficit. Other symptoms encountered were cranial nerve palsies, meningeal signs, papilloedema. Most common headache type was tension type headache. Most common cranial nerve involvement was abducens nerve. Superior Sinus Thrombosis (SSS) involvement was most commonly thrombosed followed by its involvement with other sinuses. Isolated lateral sinus involvement also seen. On screening for cause, non septic CVT outnumbered septic CVT (22/8) and the most common cause of non septic CVT was unknown followed by coagulation defect. Among septic CVT group puerperal sepsis in females and mastoiditis in males were the dominant cause.

Conclusion: Septic CVT prognosis had better than non septic CVT. Hence, CVT presents with wide range of presentations and anticoagulation is the treatment. Septic CVT if intervened timely with proper antibiotics have better prognosis. Antibiotics are the mainstay of therapy for septic CVT.

Introduction

Cerebral venous thrombosis (CVT) is an uncommon cerebrovascular disease presenting with a remarkably wide spectrum of signs and modes of onset.1 It was first described by Ribes in 1825. The disease is characterized by headache, papilloedema, seizures and focal neurological deficit culminating to coma and death and pathophysiologically by hemorrhagic infarction.2 Advent of conventional angiography and more recently MRV allowed frequent recognition of CVT cases. We present a series of CVT patients with varied etiology.

CVT may occur as a complication of infectious or noninfectious processes. Although the majority of CVT is actually due to non infectious causes, however septic thrombosis is still a potential life threatening complication that needs to be recognized and treated on emergency basis. The incidence of CVT has dropped dramatically in recent years. In the past, before the introduction of antibiotics, infection was the main cause of CVT, early suspicion and recognition is very crucial to reduce mortality and morbidity rates of this potentially fatal disease. Unlike non septic CVT, intravenous wide spectrum antibiotics and early surgical drainage of primary site of infection whenever possible are essential in septic CVT.

In this series, we highlight the early use of antibiotics for CVT. The vast majority of cases of septic CVT have an acute presentation associated with prominent features of sepsis. The latent period between symptoms of the predisposing infection and the clinical features of septic CVT varies between one and twenty-one days, but averaged about five to six days in one series.3 In our series, patients presented within 3-5 days of the initial infection. Pyrexia occurs in over 90 per cent of cases, which is usually severe, and in the presence of clinical features of sepsis may be the presence of tachycardia, vomiting, hypotension, confusion, rigors and coma.3 Headache has been reported in about 52–90 percent and is typically unilateral, with a retro-orbital or fronto-temporal area distribution.4 The series highlights that signs of infection in form of high grade pyrexia, tachycardia and sick appearance and evidence of local infection in form of furuncle, ear discharge or vaginal discharge are core features of septic CVT which should be taken in account during history taking.

Material and Methods

We studied 40 patients of CVT from January 2014 to December 2015 of 2 years period in Department of Neurology, Shri Mahant Indiresh Hospital, Dehradun. The patients were enrolled both from Out Patient Department and In Patient Department. The diagnosis of CVT was made on basis of history of unremitting headache, focal deficit and confirmed by MR venography. Patients more than 15 yrs of age were included in the study. Patients whose radiological workup does not confirm CVT were excluded from the study. Institutional Ethical Committee clearance was obtained for conducting the study.

Initial Assessment included history taking of the patients who presented with clinical manifestations...
suggestive of CVT, such as headache, altered mental status, seizures, focal neurological deficits, especially in the absence of the usual vascular risk factors were considered for inclusion into study. Past medical history was obtained for each case. All medications that were used by patients including contraceptives use were noted.

All the participants were subjected to a detailed physical examination, including general physical examination, a detailed neurological examination, Glasgow coma scale and examination of other systems.

In all the patients, the following laboratory testing were carried: complete haemogram, coagulation profile [bleeding time, clotting time, prothrombin time with international normalized ratio (INR) and activated partial thromboplastin time]; workup for other prothrombogenic disorders (protein C and S, homocysteine levels); rheumatological work-up including rheumatoid factor (RF), antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA), anticardiolipin antibody (ACLa); and serological testing for human immunodeficiency virus (HIV) infection.

All patients were subjected to Magnetic Resonance Imaging (MRI) of the brain [T2 weighted (T2W) and diffusion weighted (DWI) images] and MR Venogram. Patients whose scans were suggestive of other pathologies such as arterial infarcts, tumors, arteriovenous malformations were excluded from the study. All the patients were managed according to standard guidelines. All the patients who have definite evidence of CVT were admitted in the neurology Intensive Care Unit. The treatment included management of predisposing/precipitating conditions, antithrombotics, lowering intracranial pressure and symptomatic treatment for seizures, headaches. Patients with CVT without contraindications for anticoagulation were treated with dose-adjusted intravenous heparin with an at least doubled activated partial thromboplastin time.

Analogous to patients with a first episode of CVT, oral anticoagulation was given for 3 months if CVT was secondary to a transient risk factor, for 6–12 months in patients with idiopathic CVT and in those with mild thrombophilia. Indefinite oral anticoagulation was given in patients with two or more episodes of CVT and in those with one episode of CVT and severe thrombophilia. Other symptomatic measures such as intravenous mannitol (100 ml, 6th hourly), were instituted. Antiepileptic drugs were started based on need. Large haemorrhages and infarcts associated with extensive cerebral oedema with progressive deterioration in sensorium were managed with decompressive craniectomy. Further course of illness, from hospital admission to the time of discharge, was assessed by progression of presenting complaints, neurological deficits and mental status assessment by Glasgow Coma Scale. We also assessed the treatment outcome in Septic versus non septic group. All the patients recruited in the study were assessed for functional status at the end of their hospital stay using Modified Rankin Scale (mRS) which were classified as complete recovery - 0 to 1, partial recovery independent - 2, partial recovery dependent - 3 to 5 and death - 6.

Statistical Analysis

Data were recorded on a predesigned proforma and Excel 2007 (Microsoft Corporation, Redmond, WA, USA) was used. All the entries were double-checked for any possible error. Descriptive statistics for the categorical variables was performed by computing the frequencies (percentage) in each category. For the quantitative variables, approximate normality of the distribution was assessed. Variables following normal distribution were summarized by mean and standard deviation.

Results

40 patients of CVT were enrolled, 10 were excluded not satisfying inclusion criteria. Thirty patients satisfying the inclusion criteria were included in the study.

Out of 30 patients, 8 were males, 22 were females, and their age ranged from 18 to 50 years. Their mean age was 27.67±9.1 years. Most of the patients were in the third decade of life; majority was women (70%). Headache was the predominant and first symptom to bring patients to medical services, in 90% of patients. Headache was moderate to severe in 70%, and in rest it was mild but nagging and not relieving by any measures like sleep, analgesics or rest. 10% of patients had seizures and focal deficit in 16% of patients as shown in Table 1.

Headache was tension type in 40%, migrainous in 30% patients, 10% had mixed type and 20% had Chronic Daily Headache. Visual blurring was seen in 12 cases (40%). Focal neurologic deficit was seen in form of hemiparesis was noted in 2 patients (6%), aphasia in 2 (6%) and 1 had hemisensory loss. Cranial nerve involvement was seen in 4 (13%) patients and 3 (10%) had unilateral VI palsy and on had associated VII nerve along with abducens palsy. Seizures seen in 3 (10%) patients and all had focal with secondary generalization. The mode of onset of symptoms was also highly variable-acute (<30 hrs) headache in 16 (53%) patients, subacute (>1 month) headache along with visual blurring and cranial nerve involvement in 8 (26%) patients and progressive in 6 (20%) patients over months and had exacerbation of headache intermittently. Neuro imaging in form of Magnetic Resonance Imaging of Brain with venogram was done in all patients. The results were as follows. Venous sinus thrombosis was present in all the patients. Hemorrhagic infarction was seen in 22/30 (73%) patients, non hemorrhagic infarct was present in 8/30 (26%) patients. Saggital Sinus Thrombosis (SSS) was the most common sinus involved (78%) with either partial or complete occlusion. Its involvement with other sinuses was seen in 14 patients and isolated lateral sinus thrombosis was seen in 5% and lateral and straight sinus thrombosis was seen in rest 3% patients as shown in Table 2.

<table>
<thead>
<tr>
<th>Table 1: Cardinal manifestations in 30 CVT patients</th>
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<tbody>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Headache</td>
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<tr>
<td>FND</td>
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<td>Seizures</td>
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<td>Cranial nerves</td>
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<td>Meningeal signs</td>
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<tr>
<td>Papilloedema</td>
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<td>Stupor</td>
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<th>Table 2: Sinuses involved in CVT patients</th>
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<tr>
<td>Sinuses involved</td>
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<tr>
<td>SSS</td>
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<tr>
<td>SSS with other sinuses</td>
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<tr>
<td>Isolated Lateral sinuses</td>
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<tr>
<td>Straight sinus</td>
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Table 3: Spectrum of etiology in CVT patients

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. of patients</th>
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<tr>
<td>Contraceptive pills</td>
<td>5/22 females</td>
</tr>
<tr>
<td>Post partum period</td>
<td>6/22 females</td>
</tr>
<tr>
<td>Puerperal sepsis</td>
<td>3/6 females</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>3</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Mastoiditis/otitis</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
</tr>
<tr>
<td>Furuncle over face</td>
<td>3</td>
</tr>
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### Etiology

Among twenty-two females patients, contraceptive pills were used by 5 females and rest 6 were in post partum state with duration varying from 2 weeks to 8 weeks. Evidence of puerperal sepsis was seen in three postpartum females, diagnosis made on basis of history of foul smelling discharge per vagum, lower abdomen pain and culture of vaginal swab. Culture from vaginal swab grew staphylococcus aureus and pseudomonas aeruginosa.

Among all 30 CVT patients, 8 had septic cause, 5 were females and 3 were males. One male had mastoiditis and rest two males had furuncle over face area. Three females had puerperal sepsis as mentioned above and 2 had furuncle over upper lip region. These septic CVT patients presented with high grade fever, facial erythema and swelling and headache. Among non CVT patients, no cause could be attributed in 14 patients and 4 were found to have coagulation disorder, most common being antithrombin III (3 patients) and protein S deficiency (1 patient). Collagen vascular profile was negative in all patients so as anti phospholipid antibody workup as shown in Table 3.

Septic CVT patients had more acute presentation, more severe, they responded to treatment early and dramatic than non septic CVT pts. Two patients among non-septic CVT died of raised Intracranial pressure (ICP) and cerebral herniation underwent decompressive craniotomy but developed ICU complication in form aspiration pneumonitis.

Septic CVT patients had sudden onset erythema of eyelids and limitation of ocular movements which alerted the possibility of CVT. All patients received heparin. Septic CVT patients received antibiotics in addition to anticoagulants and short duration steroids and improved.

### Discussion

Septic CVT can occur at any age but typically affect young adults, most commonly in the 3rd decade of life. The incidence is approximately 15% of all the cases of CVT that is 3 - 4 /1,000,000 with 3:1 female predominance. Although rare, septic vein thrombosis (SVT) remains a potentially lethal complication of infections that involve the sinuses, face, ears and oral cavity. The early recognition and differentiation from other diseases is keys to reducing mortality rates and long term sequelae. The dural sinuses and the cerebral and emissary veins have no valves, which allow blood to flow in either direction according to pressure gradients in the vascular system. This makes this venous system vulnerable to septic thrombosis resulting from spreading of infection from adjacent locations. Septic CVT involves mainly the cavernous sinus followed by lateral and then sagittal sinus. Infection may trigger the thrombosis directly by causing septic thrombosis or indirectly by precipitating thrombosis in people who suffer from a prothrombotic illness. Early diagnosis can be facilitated by prompt recognition of the clinical and radiological findings that are suggestive of venous occlusion of the cavernous sinus. Bacterial meningitis and paranasal sinusitis can be a Complication of superior sagittal thrombosis, resulting in an 80 % mortality rate.

Septic CVT patients are more toxic with features of facial infection. They would present with acute onset of headache, fever, and vomiting, facial redness and painful eyelid edema. Fever is a constant finding as was in our patients as well as orbital symptoms may start in one side then very shortly within 24-48 hours become bilateral. Patients usually have the triad of chemosis, proptosis (due to orbital vein congestion) and painful ophthalmoplegia (due to involvement of III, IV, VI) with occasional ophthalmic branch of trigeminal cranial nerve involvement. Papilloedema is seen in some patients and is usually mild and late. It was present in 8 patients in our series. Decreased visual acuity is reported in less than 50% cases, pupils can be dilated (parasympathetic involvement) or smaller and immobile (both parasympathetic and sympathetic dysfunction). Impaired vision is uncommon. Nevertheless, visual loss may be caused by corneal ulceration secondary to proptosis and loss of the corneal reflex, occlusion of the internal carotid, ischemic optic neuropathy, orbital congestion, toxic neuritis of the optic nerve, or embolic phenomena.

In our series, septic thrombosis patients were much sicker than those with non septic thrombosis. The illness is almost always acute in nature and patients were sick, toxic and febrile. Some had focal symptoms and signs suggestive of raised intracranial pressure varying on site of CVT, but responded early and better with lesser morbidity and mortality as compared to non septic group.

Clinically, the differential diagnosis includes meningoencephalitis, orbital cellulitis, orbital apex syndrome and non septic CVT. In Sebire et al series, 23/42 patients had infection precipitated venous thrombosis emphasizing that people with prothrombotic conditions may develop thrombosis after having any systematic infection and blood culture was positive in 70% of cases. Reviews of large single center series from the pre-antibiotic and early antibiotic era had documented that infections of the middle third of the face were responsible for most cases of Septic CVT. It was seen in 4 patients of Septic CVT in our series. Approximately 60 to 80% of these nasal furunculosis accounts for the most common cause. Organisms may reach the cavernous sinus from the face by an anterograde route along the ophthalmic veins, which is connected to the angular veins, or by a retrograde route along the emissary veins that are connected to the pterygoid venous plexus. In up to 25 percent of cases where a facial furuncle is responsible, it has either been previously manipulated by the patient or incised by the surgeon. *Staphylococcus* aureus is the most frequently cultured organism in these infections accounting for 70 %, followed by *Streptococcus* species at 20 %. In our cases, patients had different source of infections like furunculosis, puerperal sepsis, mastoiditis. The most sensitive investigation of intracavernous occlusive defects is venography. Previously, Cerebral angiography with late venous views was considered
to be gold standard in the diagnosis of CVT. but nowadays, it has been reserved for the definitive assessment of intracavernous aneurysms after they have been detected and monitored using CT or MRI. Diagnosis of cavernous sinus thrombosis is usually made with MRI scan with venogram; or contrast enhancement Computed Tomography. Fine -cut CT scan is less sensitive.  

Because it is often difficult to distinguish septic and non-septic causes of CST, the initial management is the same. Only when a septic etiology is ruled out definitively can antibiotics be withdrawn. Antibiotics are the mainstay of CST therapy. Anticoagulation, corticosteroids, and surgery are adjunctive treatment in appropriately selected patients. Undoubtedly, antibiotics have the greatest impact on the prognosis of SVT. The overall mortality and morbidity associated with cavernous sinus thrombosis (CST) continue to be high. Consequently, institution of intensive treatment at the earliest suspicion of disease should be emphasized. Postmortem studies have shown that there is less extensive thrombosis within the cavernous sinuses since the advent of antibiotics. Case reports and expert opinion recommends antibiotics have the greatest impact on the prognosis of septic CST. High-dose intravenous antibiotics should be instituted emergently at the earliest suspicion of this diagnosis. Appropriate selection of empiric antibiotic regimens should be directed at the probable organisms implicated as the primary source of infection. Complications such as brain or orbital abscesses, meningitis or subdural empyema should be kept in mind as these need surgical intervention at the earliest. Staphylococcus aureus is the most common pathogen identified in approximately 70% of cases and is seen in nearly all cases of facial infections and sphenoid sinuses. Our series also found this pathogen common in septic CVT group. Less common is Streptococci (including S pneumoniae, S milleri, and S viridans group). Infections of nasal sinus, dental, or tonsillar infections show anaerobes. Fungal infections from Aspergillus fumigatus or mucormycosis have been implicated rarely in CST. Therefore, empiric therapy should include vancomycin to cover potential methicillin-resistant Staphylococcus aureus (MRSA) until the actual culture results are available plus a third-generation cephalosporin, such as ceftriaxone. Quinolones should be used in patients allergic to penicillin. Intravenous metronidazole should be added if dental or sinus infection is suspected. Antifungal therapy has been advocated only in cases of biopsy-confirmed invasive fungal infection. Vancomycin is used routinely until culture results negate MRSA. It is also indicated for patients who have failed to respond to penicillins and cephalosporins. Empiric antibiotics can be switched to specific antibiotic therapy once culture sensitivities reports are available. Intravenous antibiotics are required because thrombus may limit penetration of antibiotics. Bacteria, sequestered within the thrombus, may not be killed until the dural sinuses have started to recanalize. Antibiotics also need to be administered over an extended period, for at least 2 weeks beyond the time of clinical resolution and in high doses. This insures complete sterilisation and prevents relapses. Supportive therapy is includes resuscitation, oxygen support, and local eye care. Considerable controversy exists concerning the efficacy of anticoagulation in the treatment of CST. As the condition is rare, prospective trials to establish any benefit from anticoagulation are unlikely to be performed. Anticoagulation carries the risk of hemorrhage, especially in patients with concomitant complications (e.g., cortical venous infarction, necrosis of intra-cavernous portions of the carotid artery, and cerebral or intra-orbital haemorrhages). Two retrospective reviews examining the use of anticoagulation for septic CST produced varying results (Level C evidence). However, some evidence says that the use of anticoagulation prevents propagation and contributes to re-canalisation of the thrombus. These are potentially beneficial effects, partly because the thrombus itself can harbour bacteria and sustain their growth. 

Two controlled trials comparing the use of placebo to anticoagulants in patients with cerebral sinus venous thrombosis. European Federation of Neurological Societies (EFNS) guidelines recommend either low molecular weight subcutaneous or intravenous heparin for aseptic dural venous thrombosis. European Paediatric Neurology Society (EPNS) in 2012 recommend the use of anticoagulants for dural venous thrombosis to lessen the risk of death and other sequelae. However, it should be noted that septic CST and aseptic dural venous thrombosis differ in many respects and that anticoagulation may be more hazardous in patients with septic CST. The differences include the presence of infective etiology, the site of the thrombosis, the acuteness of the process, and the presence of associated haemorrhagic complications. Anticoagulation should be cautiously used in patients with bilateral CST and/or concurrent intracranial haemorrhage. The types and protocols for anticoagulation have varied considerably in research protocols. Intravenous and intramuscular unfractionated heparin, subcutaneous low molecular-weight heparin (LMWH), and oral coagulation have all been used. Intravenous unfractionated heparin is rapidly reversible agent hence, advocated in the early stages of disease, followed by conversion to longer-acting agents, such as warfarin, when the patient’s condition has stabilized. New anticoagulants, including direct thrombin inhibitors and factor Xa inhibitors has a more predictable anticoagulant effect and an absence of induction of immune-mediated heparin-induced thrombocytopenia (HIT). But there is a paucity of reported cases of CST or other forms of dural sinus thrombosis that have been treated with these agents. The use of direct thrombin inhibitors, such as argatroban, can be considered as an alternate form of anticoagulation to heparin in patients with HIT (Heparin Induced Thrombocytopenia) or those at risk of HIT. Regarding duration of anticoagulation, some authors have suggested that anticoagulation should be continued until clinical or radiological evidence of complete resolution or until significant improvement of infection and thrombus. If a patient is considered suitable for anticoagulation but deteriorates despite this therapy, they may be considered for thrombolysis. This therapy is usually reserved for progressive, aseptic CST and carries with it the risks of intracranial haemorrhage, stroke, and the inability to re-canalise. Patients commenced on anticoagulants
are usually still in an unstable clinical condition and are therefore not candidates for surgical management. However, if the patient’s condition stabilises and surgical management is indicated, rapidly reversible anticoagulants can be discontinued to allow surgery. Corticosteroids have controversial role in many cases of CST because of their potentially harmful immunosuppressive effects. However, they are absolutely indicated in cases of pituitary insufficiency and Addisonian crisis secondary to ischaemia or necrosis of the pituitary that complicates CST. Steroids may be essential in the acute setting to prevent Addisonian crisis as well as in replacement doses in the long-term. Corticosteroids reduce intraorbital congestion in patients with orbital oedema and cranial nerve inflammation in patients with cranial nerve dysfunction. There are only a few anecdotal reports concerning the use of corticosteroids in CST in general and their efficacy has not been proved by these reports. Studies in which the use of corticosteroids has been reported, other treatments have been used concurrently. In one case, reported in 1962, cranial nerve dysfunction and orbital oedema failed to improve after 37 days of antibiotic and anticoagulant therapy but regressed dramatically 2 days after the addition of corticosteroid therapy, with eventual complete resolution in eye signs and symptoms. Prompt drainage of the primary site of infection (such as the para-nasal sinusitis, dental abscess) or other concurrent closed-space infection is advisable once patient condition permits. Different operations have been performed to decompress the sinuses, including transeptal sphenoectomy, endoscopic sphenoectomy and ethmoidectomy and external fronto-ethmoido-sphenoidectomy. In cases of otogenic CST, mastoidectomy has been performed, with decompression of sigmoid sinus thrombophlebitis.

Anticoagulation with heparin is the only modality with reasonable evidence to support its use in CVT, even in patients with cerebral hemorrhage. Endovascular thrombolysis is a promising option for patients with a severe form of CVT or following a failure of anticoagulation therapy. Mechanical thrombectomy is reserved for selected cases and decompression surgery for malignant CVT with impending herniation. With increasing awareness, not only is CVT being diagnosed more frequently, but less clinically severe cases of CVT are also being detected presently. However, despite substantial improvements, the diagnosis of CVT is often missed because of the remarkable variations in the clinical presentation and neuroimaging signs. Furthermore, existing studies on CVT patients are often limited by small numbers; their retrospective nature and short term follow-up periods. Thus, CVT remains a diagnostic and therapeutic challenge, and scanty information still exists on the natural history and long-term prognosis of this disease. Most patients with CVT have a benign prognosis. Only a minority of patients die during the acute phase or in the following months. Most patients surviving CVT recover completely, or have only mild functional or cognitive deficits.

Limitation of the study
The number of CVT patients was less and that of Septic CVT group further less which limits the definite conclusion on etiology causes and treatment guidelines.

But, in spite of lower number, the study strengthens the fact that septic CVT should be kept as high index of suspicion and timely management with antibiotics and steroids can decrease the mortality in these patients.

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References