Original Article

Clinical Profile and Outcome of Patients with Cerebral Venous Thrombosis Secondary to Bacterial Infections

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Abstract

Background: Cerebral venous thrombosis (CVT) secondary to infectious aetiology has become rare in the antibiotic era, but is still encountered in clinical practice occasionally. In this study, we describe the clinical profile, diagnosis, and management of patients with CVT secondary to an infectious aetiology. **Methods:** This retrospective study included all adult patients over 15 years (1 January 2002 to 1 January 2017). Adult patients with a diagnosis of infective CVT secondary to bacterial infections were included in the study. **Results:** Totally, 22 patients were identified with CVT complicating bacterial infections. The focus of infection in 12 (54.54%) patients was pyogenic meningitis, 9 (40.9%) patients had a parameningeal focus and one patient developed CVT secondary to bacterial sepsis from a remote focus. Fever was the most common symptom seen in 77.3% followed by headache and depressed sensorium in 72.7% and 63.6%, respectively. The most common organism in the meningitis group was Streptococcus species, and in the parameningeal group was *Staphylococcus aureus*. At presentation MRI identified CVT in all 7 patients as compared to CT brain with contrast in 2/3 (66.6%). Transverse sinus was the most commonly involved sinus in meningitis. All patients were treated with appropriate antibiotics and anticoagulation was used in 50% of the patients. The in hospital, mortality was 9%. **Conclusion:** Septic CVT, though rare can be a complication of bacterial meningitis and facial infections. Clinical symptoms that suggest a co-existing CVT should be identified and diagnosed at the earliest. The mainstay of treatment is antibiotics; the role of anticoagulation is controversial.

Keywords: Bacterial infection, cerebral venous thrombosis, meningitis, outcome

Introduction

Cerebral venous sinus thrombosis (CVT) is an uncommon cause of a cerebrovascular event which still poses a diagnostic challenge to the physicians. Patients present with a range of symptoms such as headache, seizures, and focal neurological deficits. Some of the risk factors for CVT include genetic thrombophilias, malignancies, autoimmune conditions, meningitis, and facial infections. The mainstay of treatment is anticoagulation; newer modalities such as endovascular therapy are being studied.[1,2]

Cerebral venous thrombosis secondary to infections has drastically reduced in the antibiotic era with mortality reducing from 100% to less than 20%.[3] However, this entity is still encountered in our clinical practice though. CVT in the background of infections is rare and needs early recognition, diagnosis, and treatment. This study attempts to look at the clinical features and outcome of patients with CVT secondary to bacterial infections.

Patients and Methods

Study design and data

This retrospective observational study was conducted among all adult patients who were admitted under the Department of General Medicine of a 2700 bed large tertiary care teaching hospital from south India. The study included all eligible patients over 15 years starting from 1 January 2002 to 1 January 2017. The diagnosis of cerebral venous thrombosis was confirmed by imaging studies (Computed Tomography or Magnetic Resonance Imaging) by independent radiologists. These imaging studies were performed as per the treating physician's discretion in symptomatic patients. A diagnosis of infective CVT was made in patients with cerebral venous thrombosis and a bacterial infectious etiology attributed to the same, as documented in the patient's medical records and discharge summary. Patients who developed CVT secondary to other aetiologies including non-bacterial infections were excluded from the study [Figure 1]. In patients with clinical suspicion of meningitis, CSF analysis was done for cell counts, proteins, and bacterial cultures and a diagnosis of

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pyogenic meningitis was established based on the cell counts and culture report. In patients with parameningeal focus of infection, additional imaging such as CT Orbit or Osteomeatal complex was done as per the clinical condition; the etiological diagnosis was aided by bacterial culture of the pus from the source of infection or the surgical specimen. Details on clinical symptoms, hematological parameters, imaging findings, and details of outcomes including morbidity were obtained from the hospital records. Data were obtained by trained clinicians.

Ethical approval and funding

This retrospective study protocol was approved by the Institutional Ethics Review Board (IRB NO: 11088), Christian Medical College, Vellore, India. In this study, data was collected from the hospital database and the information collected was anonymized. Patient identifiers were removed. Only the senior author had access to the complete data set.

Statistical analysis

Descriptive statistics were employed for all the variables in the study. All continuous data were expressed as mean with standard deviation (SD) unless the data was not normally distributed. A *P* value of < 0·05 was considered statistically significant. Statistical analysis was done using Statistical Package for Social Sciences for Windows (SPSS Inc. Released 2007, version 16.0. Chicago).

Results

Of the 238 patients who presented with cerebral venous thrombosis to the Department of Medicine, 22 (9.2%) patients were enrolled in the study as per the inclusion criteria. The focus of infection in 12 patients (54.54%) was pyogenic meningitis, 9 patients (40.9%) had a parameningeal focus and one patient developed CVT secondary to bacterial sepsis from a remote focus as shown in Table 1.

The causative organisms were different based on the focus of infection, shown in Table 2. In the group with pyogenic meningitis, the commonest organism as detected in the CSF culture was *Streptococcus pneumonia*, followed by *Klebsiella*.

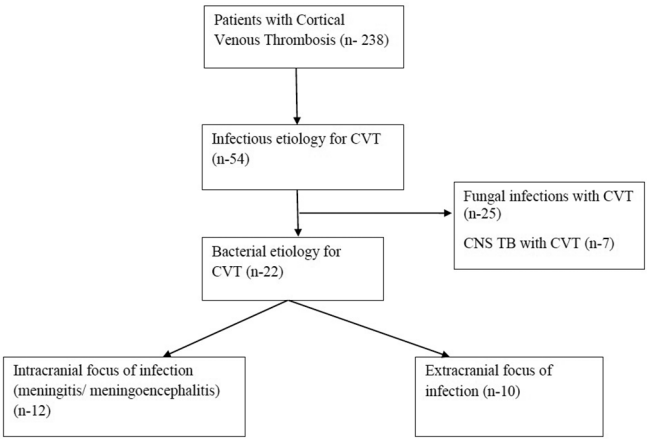

Figure 1: Strobe figure

In the parameningeal focus, *Staphylococcus aureus* was the commonest causative agent, as obtained from surgical specimens or pus swabs.

Of the 22 patients who presented, 19 patients had CNS imaging at the time of presentation; 3 were treated as pyogenic meningitis based on the clinical picture and CSF findings. 13 (59%) patients were diagnosed with CVT at admission. In 9 (41%) patients the onset of new symptoms such as headache, ear pain, focal deficits, proptosis and chemosis, and failure to improve within 48–72 hours with appropriate antimicrobial therapy prompted a re-imaging and diagnosis of CVT. At

Table 1: Baseline characteristics of patients with CVT secondary to bacterial infection (*n*-22)

Variable	Value, *n* (%)
Age (mean±SD), years	43.05±17.71
Sex (Male/Female)	17/5
Co morbidities	
Diabetes Mellitus	6 (27.3)
Hypertension	3 (13.6)
Presenting complaints	
Fever	17 (77.3)
Headache	16 (72.7)
Depressed sensorium	14 (63.6)
Vomiting	11 (50)
Focal deficits	9 (40.9)
Seizures	5 (22.7)
Focus of infection	
Pyogenic meningitis	12 (54.5)
Chronic suppurative otitis media	4 (18.2)
Malignant otitis externa	1 (4.5)
Orbital Cellulitis	4 (18.2)
Bacteremia	1 (4.5)
CSF analysis (*n*-15)	
CSF WBC counts, median (IQR), cells/cumm	115 (40-2300)
CSF Neutrophil count, median (IQR), cells/cumm	85 (23-96)
CSF Lymphocyte count, median (IQR), cells/cumm	11 (4-76)
CSF Protein, median (IQR), mg %	98 (66-430)
CSF Glucose, median (IQR) mg %	59 (10.0-71.0)
Duration of antibiotic, mean (SD) days	18.9 (10.2)
Duration of hospitalisation, mean (SD) days	13.1 (8.1)

CSF-cerebrospinal fluid, WBC- White blood cells, IQR- Interquartile range

Table 2: Aetiological agents of patients with CVT secondary to bacterial infection (*n*-22)

Pyogenic CVT with meningitis (CSF Culture)		Pyogenic CVT with parameningeal focus	
Streptococcus pneumoniae	2	MSSA	3
Klebsiella pneumoniae	1	MRSA	2
Streptococcus suis	1	Pseudomonas aerugniosa	1
Culture negative	7	Proteus mirabilis	1
		Culture negative	3

CVT-cerebral venous thrombosis, CSF- Cerebrospinal fluid, MSSA-Methicillin sensitive staphylococcus aureus, MRSA- Methicillin resistant staphylococcus aureus

presentation MRI identified CVT in all 7 patients as compared to CT brain with contrast in 2/3 (66.6%), repeat diagnostic imaging was positive in 4 out of 5 patients when CT was used as the imaging modality and in 100% when MRI was used [Figure 2].

Transverse sinus involvement was common in pyogenic meningitis and sigmoid sinus in middle ear infection as summarised in Table 3. All patients received appropriate antibiotics, 11 (50%) patients received anticoagulation along with antibiotics and 1 patient required a ventriculoperitoneal shunt for secondary hydrocephalus. Patients who had orbital cellulitis, otitis media, and otitis externa underwent appropriate source control with surgical debridement. Totally, 17 patients recovered and were well at follow up; 2 patients died and 3 were discharged against medical advice.

Discussion

Cerebral venous drainage occurs through two main systems, which is the superficial and deep venous system. The identified risk factors for cerebral venous thrombosis include inherited prothrombotic states, malignancies, head trauma, vasculitis, and CNS infections.[4] Cerebral venous thrombosis secondary to infectious etiology has drastically reduced in the antibiotic era with only a few case reports in the literature.[4] Septic cavernous sinus thrombosis is the most commonly encountered due to spread of infections from the face, sinuses, orbits, and oral cavity through the facial veins and pterygoid veins. Septic transverse sinus thrombosis which is mainly from the ear and mastoid infections has also reduced in frequency due to early antibiotic initiation for mastoiditis, otitis media, and externa. Sagittal sinus thrombosis is rare and secondary to meningitis and bacteremia.

In our study, 12 patients (54.4%) developed CVT secondary to pyogenic meningitis and the commonest sinus involved was transverse sinus followed by sigmoid sinus and the superior sagittal sinus. In our series about 9.2% had CVT complicating pneumococcal meningitis and the pathophysiology postulated is probable infectious

Table 3: Sinus involved in patient with CVT secondary to bacterial infections (*n*-22)

	Pyogenic Meningitis	CSOM/MOE	Orbital Cellulitis	Bacteremia
Transverse Sinus	11	3	0	0
Sigmoid Sinus	7	4	0	0
Cavernous Sinus	2	1	4	0
Superior Sagittal Sinus	5	0	0	1

CSOM- Chronic suppurative otitis media, MOE-Middle ear infection

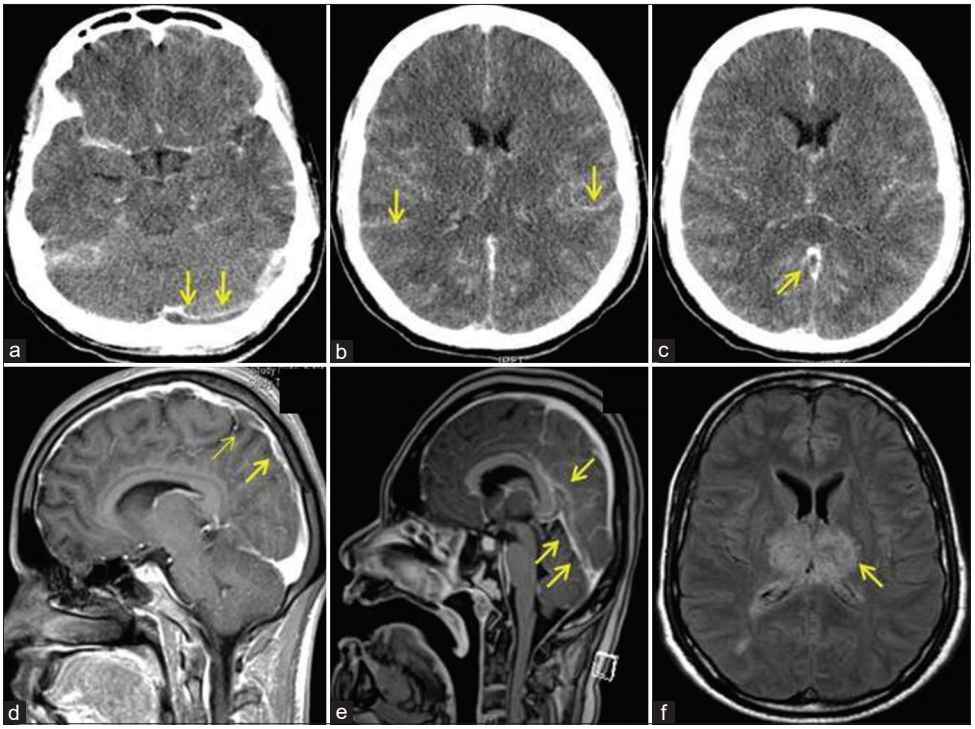

Figure 2: Contrast enhanced CT brain and MRI images, (a)- shows filling defect in the left transverse sinus, (b) - shows leptomeningeal enhancement and (c) - shows filling defect in the straight sinus, (d) - post contrast MRI showing filling defect in the posterior third of superior sagittal sinus, (e) - post contrast MRI imaging shows thrombosis of the deep venous system, (f) - T2 Flair image showing bilateral thalamic hyperintensity suggestive of deep venous CVT

vasculitis. Direct vascular invasion by the bacteria leading to intraparenchymal edema and intravascular coagulation due to the release of procoagulant and antifibrinolytic agents is also a possible mechanism.[5,6] Systemic infection can also trigger an underlying prothrombotic illness in susceptible individuals.[7] The other possible hypothesis includes severe cerebral vessel vasospasm owing to catecholamine excess, inflammation of the vessel wall. Lemierre's Syndrome (infectious thrombophlebitis of the internal jugular vein) has been reported with *Klebsiella pneumonia* secondary to an oro-pharyngeal infection, orbital cellulitis and brain abscess; however, meningitis is rare and there have been no case reports of CVT complicating the same in the literature.[8-10] For the parameningeal focus, *Staphylococcus aureus* was the commonest etiological agent in our study. The common sinus involved was as per the drainage pattern of the area, cavernous sinus was predominantly affected in orbital cellulitis, transverse sinus was involved with the ear focus (spread from the mastoid air cells via the emissary veins or directly to the epidural space overlying the transverse sinus) and superior sagittal sinus and sigmoid sinus in bacteremia.[11]

The imaging modality of choice for diagnosis of CVT is MRI or MR venography with the demonstration of the thrombus in the venous system.[12] The sensitivity of CT Brain plain is only 40% and hence is not the preferred mode of imaging for the diagnosis of CVT. The diagnosis of CVT was missed in 9 out of 22 patients on the day of presentation, due to lack of clinical suspicion of CVT along with the infection. The mean delay in the diagnosis of CVT was 3.14 days in our study. In our cohort, MRI appeared to be better, as it was diagnostic in 100% of the cases, as compared to CT scan. MRI is superior to CT in the diagnosis of CVT[13]; it detects the thrombus and also additional complications such as venous infarcts and intracranial hypertension.[14,15] The clinical features that should raise the suspicion of a co-existing CVT and warrant MR imaging include signs of raised intracranial pressure, focal neurological deficits, new onset seizures, new onset or persistent clinical symptoms while on appropriate antibiotics for meningitis and other facial/ear infections.

The mainstay of treatment in septic CVT is appropriate antibiotics as per culture or the focus of infection. The role of anticoagulation is controversial and was given only in 50% of the patients included in our study. Review of literature by Levine SR *et al*. for the use of anticoagulation in septic cavernous sinus thrombosis showed reduced morbidity among the survivors, whereas other studies show that adjunctive anticoagulation may be beneficial and reduces mortality.[16,17] However, RCTs are lacking due to the rarity of the condition and the decision for the same has to be made by the treating physician on an individual basis. Appropriate surgical drainage has to be done as indicated for patients with facial and ear infections. Features of raised intracranial pressure, intracranial hemorrhage, hydrocephalus, or herniation warrant surgical interventions such as decompressive surgeries or VP shunt. In hospital mortality in our study 2 (9%) was similar to the other CVT studies.[18,19] Our study also had its limitations. Given the retrospective nature of the study, we did not have follow-up imaging, details of prothrombotic, vasculitis, and autoimmune workup. We also did not have the details of interactions of medications, and long-term follow-up data of these patients. However, the strength of this study was a large series of patients with CVT secondary to bacterial infections and radiologically confirmed diagnosis along with multidisciplinary care for patients.

Conclusion

Septic CVT, though rare is still a prevalent complication of meningitis and facial infections. Early clinical suspicion and diagnosis with MRI, followed by appropriate antibiotic therapy is the key to optimal management.

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Conflicts of interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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