

## **Infection related cerebral venous thrombosis**

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### **Abstract**

The incidence of cerebral venous thrombosis (CVT) has dropped dramatically in recent years. In the past, before the introduction of antibiotics, infection was the main cause of CVT. But this is no longer true. Recently, the occurrence of septic CVT is rare, which leads to an increased chance of misdiagnosis and treatment delay. Early suspicion and recognition is very crucial to improve mortality and morbidity rates of this potentially fatal disease. Intravenous, wide spectrum, antibiotics and early surgical drainage of the primary site of infection whenever possible are essential. Anticoagulation with intravenous heparin infusion and corticosteroids use are of uncertain benefit, although some reports have shown some favorable response.

### **Background**

Septic sinus thrombosis is a potentially fatal disorder if passed unrecognized. In the past, infection was the main cause of cerebral venous thrombosis (CVT), which was associated with a very high rate of morbidity and mortality. However, since the introduction and widespread use of antibiotics, the incidence of septic sinus thrombosis including those involving the cavernous sinuses has declined dramatically. Its true incidence is not known, however, it is quite rare. In one study it was estimated that 15% of all cases had cerebral venous thrombosis.<sup>1</sup> Sebire et al reported a total of 42 children with cerebral venous thrombosis. These 42 cases were collected from five European paediatric neurology stroke registries showing how rare this disorder is. When etiologies were analyzed, 23 of 42 patients had recent infection, but none of the reported cases had septic thrombosis.<sup>2</sup> In our series of CVT at King Abdulaziz Medical City, Riyadh, KSA, there were 25 patients diagnosed and treated between the year 1993 and 2003. In only 2 patients, infection was the cause of thrombosis.

Although the majority of cerebral venous thrombosis 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. Given that septic thrombosis, nowadays, is extremely rare, this disease is often misdiagnosed and treatment is delayed. High suspicion is essential in early recognition and treatment.

### **Pathophysiology**

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 these venous systems vulnerable to septic thrombosis resulting from spreading of infection from adjacent locations. Any part of the cerebral venous system can be affected by septic thrombophlebitis, but certain sinuses are more prone than others [the cavernous followed by lateral and then sagittal sinuses are most commonly affected].<sup>3</sup>

The infection usually spreads from adjacent structures such as sphenoid and ethmoid sinuses in cavernous sinus thrombophlebitis and the mastoid in lateral sinus thrombophlebitis. But infection in other sites, i.e., face, nose, tonsils, soft palate, teeth and ears may be complicated with thrombophlebitis in the cavernous and lateral sinuses as well as other sinuses. However, orbital infection is rarely complicated by cavernous sinus thrombosis.<sup>4</sup>

Infection may trigger the thrombosis directly by causing septic thrombosis or indirectly by precipitating thrombosis in people who suffer from a prothrombotic illness. Heller et al concluded from his study that CVT in children is a multifactorial disease, which, in the majority of cases, results from a combination of prothrombotic risk factors and/or underlying clinical condition that may be an infection.<sup>5</sup> And the fact that 23 of the 42 patients, in Sebire et al series, had infection precipitated CVT, emphasizes that people with prothrombotic conditions may develop thrombosis after having any systemic infection.<sup>2</sup>

Septic sinus thrombosis due to complicated meningitis has been reported. Although, non-specific, it has been reported more with pneumococcal meningitis.<sup>6</sup> Other causes of meningitis such as Coccidioidomycosis<sup>7</sup>, cytomegalovirus and herpes simplex as well as measles<sup>8</sup> infection have been reported to be complicated with CVT.

There have been some reports<sup>9-13</sup>, indicating increased risk of CVT in AIDS patients. However, it seems that HIV infection itself does not, directly, play a significant role. It also seems that a combined opportunistic infection and/or coagulopathy and HIV infection are required to develop this serious complication.

## Clinical presentations

Patients with septic thrombosis of the cerebral venous system are, generally, much sicker than those with non-septic thrombosis. The illness is almost always acute in nature and patients are very sick, toxic and febrile. They may have focal symptoms and signs as well as symptoms and signs of high intracranial pressure. The focal symptoms and signs may vary depending on which site of the cerebral venous system is involved.

High level of suspicion is essential for early recognition and management. The initial work up should include complete blood count, blood cultures, x-ray films of the paranasal sinuses and enhanced brain MRI and/or Head CT scanning. Cerebrospinal fluid (CSF) analysis as well as culture is very helpful to diagnose or to exclude the septic nature of the CVT. The CSF analysis in non-septic sinus thrombosis is usually normal, but occasionally, it may be bloody or xanthochromic as the result of cortical and meningeal haemorrhage; however, in septic thrombosis, it is often abnormal and has high granulocyte count and elevated protein. The CSF culture may be positive in some of the cases. In this era conventional angiography is rarely needed to confirm the diagnosis of sinus thrombosis.

Early management with intravenous antibiotics and early surgical drainage of the primary site of infection (usually the air sinuses or the mastoid regions) whenever possible are the treatments required to improve the mortality and morbidity in this otherwise fatal illness. Anticoagulation with intravenous heparin infusion and corticosteroids are of uncertain benefit, although some reports have shown favorable response.<sup>5,14</sup>

Although sinuses other than lateral sinuses can be affected, and for the purpose of practicality we will concentrate in our discussion on the lateral sinus thrombosis.

## Septic Cavernous-Sinus Thrombosis

Septic cavernous sinus thrombosis (CST) is the most common site of septic thrombosis in the CNS (3). It is a rare complication of infection in the face and/or paranasal sinuses particularly at sphenoid and ethmoid sinuses and the middle third of the face, mostly at the dangerous triangle (nose and upper lip), and less often of the orbit, middle ear, pharynx or teeth. The infection reaches the cavernous sinus through venous spreading. It is more likely to be bilateral but unilateral cases have been reported.<sup>15</sup>

The staphylococcus spp. [the most common pathogen, seen in 60-70% of the times<sup>16</sup>], streptococcus spp., haemophilus influenzae and anaerobic organisms are considered the most frequent etiological agents followed by gram-negative rods. However, fungal infections such as

aspergillus<sup>17</sup> and mucormycosis<sup>18</sup> are rarely found. Other pathogens such as Eikenella corrodens, Pseudomonas aeruginosa, and not uncommonly mixed flora have been encountered.<sup>14,15,19-21</sup>

Patients are usually septic, toxic and have features of facial infection. They would present with acute onset of headache, fever, vomiting, facial redness and pain and eyelid edema. Fever is a constant finding as well as the orbital symptoms but headache may not be prominent. The orbital symptoms may start in one side then very shortly, within 24-48 hours, become bilateral. The patients usually have the triad of chemosis, Proptosis (due to orbital venous congestion) and painful ophthalmoplegia (due to involvement of the III, IV and VI cranial nerves) with occasional ophthalmic branch of trigeminal cranial nerve involvement. Papilledema is seen in some patients and is usually mild and late in the course. Decreased visual acuity is reported in less than 50% of the times. The pupils can be dilated (parasympathetic involvement) or smaller and immobile (both parasympathetic and sympathetic dysfunction).

Clinically the differential diagnosis would include meningoencephalitis, orbital cellulites, preseptal cellulites, orbital apex syndrome and certainly a non-septic thrombosis. The diagnosis should be suspected on clinical ground and immediate management with intravenous administration of broad-spectrum antibiotics is essential.

The diagnosis is, usually, easily confirmed by the availability of Magnetic Resonance (MR) brain Imaging with MR-venogram or contrast enhanced computed tomography.<sup>22</sup> Recently the MRI has become the diagnostic procedure of choice but enhanced CT scanning is also helpful. The signs that are usually seen include:

1. Filling defect in the cavernous sinuses
2. Heterogeneous enhancement within the cavernous sinuses
3. Enlargement and/or bulging of the lateral walls of the cavernous sinus
4. Intensive enhancement of the lateral wall
5. Some times indirect orbital signs
  - a. Exophthalmus
  - b. Densification of the retro-orbital fat
  - c. Superior ophthalmic dilatation with partial or no enhancement in case of thrombosis extension

The blood culture is positive in about 70% of the cases and the cerebrospinal fluid is usually abnormal with pleocytosis and elevated total protein but culture is positive in less than 20% of the cases.<sup>16</sup>

The management should include early wide antimicrobial coverage. A reasonable, initial, coverage may include intravenous Vancomycin, ceftriaxone and metronidazole. The period of treatment is unclear but should last for at least 3-4 weeks. The role of anticoagulation in septic CST is uncertain and the literature lacks prospective studies. However, retrospective analysis of available data is suggestive of favorable response if the intracranial haemorrhage is excluded by appropriate neuroimages. Plus the available data shows no clear risk from anticoagulation in these circumstances.<sup>3,23</sup> The role of corticosteroids use is also uncertain, however, some reports have shown favourable response in relation to reduction of inflammation and oedema, which may improve the cranial nerve dysfunction and orbital oedema.<sup>24</sup>

The prognosis of septic CST has improved dramatically with the recent advances in antibiotic therapy as well as early recognition and management of this disease. The mortality rates improved from nearly 100% before the antibiotic era to about 20-30% with the current management strategies. The complications and morbidities have also improved with current managements from about 75% to 22%.<sup>25</sup> So the full recovery is actually achieved in less than 50%.

Potential complications may include meningitis, subdural empyema, pituitary necrosis, visual loss (due to corneal ulceration, anterior ischemic optic neuropathy, central retinal artery occlusion, etc.), stroke and AV fistula.

### Septic Lateral-Sinus Thrombosis

Septic lateral thrombosis is very rare these days due to the widespread use of antibiotics. Its frequency is next to septic CST.<sup>3</sup> It is rare in both adult and paediatric populations. Teichgraeber et al reported only 6 cases of septic lateral sinus thrombosis over a ten-year period at Emory.<sup>16</sup> Garcia et al reported the third case of lateral sinus thrombosis due to otitis media and mastoiditis in a 5-year period at the Massachusetts General Hospital, Boston, USA.<sup>26</sup> And Seven et al reported 11 cases of otogenic lateral sinus thrombosis seen between 1992 and 2002.<sup>27</sup>

It is usually a complication of chronic ear infection, and other intracranial complications are possible. Seven et al reported that 8 of his 11 patients with septic lateral thrombosis had at least one other Intracranial complication.<sup>27</sup> Patients usually present with symptoms related to the primary site of infection, high intracranial pressure (especially if the right lateral sinus is involved), and possibly symptoms of focal neurological lesion due to venous congestion and/or infarction.

The most common presenting symptoms are fever, headache and otalgia. Patients are usually sick, febrile and

complaining of headache and mastoid and neck pain. Almost all patients would have fever and mastoid and neck tenderness. Some patients may present with seizures. However, rarely, patients do present with progressive anaemia and evidence of septic emboli.

Blood cultures are often negative due to antibiotics used before the diagnosis is made. But positive cultures, most commonly, show mixed flora. Pathogens, usually identified, include beta haemolytic streptococcus, fusobacterium necrophorum, Proteus species, Escherichia coli, staphylococcus aureus, gram-negative bacilli and anaerobes.

The diagnosis of lateral sinus thrombosis is usually confirmed with MR-Venography or enhanced CT scan with, preferably, CT-venogram. There are, usually, changes in the mastoid region and/or middle ear indicating the presence of ear and/or mastoid infection. However, signal abnormalities in the ipsilateral mastoid (probably due to venous congestion) have been reported in non-septic lateral sinus thrombosis as well. Fink et al reported that 39% of their patients with lateral sinus thrombosis had signal abnormalities in their Ipsilateral mastoid without clinical symptoms or signs of mastoiditis.<sup>28</sup> This has been our experience as well.

The disease is associated with high rate if morbidity and mortality and early management with high doses, intravenous, broad spectrum, antibiotics and surgical intervention involving mastoidectomy, exposure of the sinus, incision and drainage. Internal jugular vein ligation should be preserved for those cases in which septicemia and embolization do not respond to initial surgery and intravenous antibiotics. Landsberg et al reported a case of lateral sinus thrombophlebitis who developed septic pulmonary embolism despite early intravenous antibiotic use and surgical intervention.<sup>29</sup> Anticoagulation has uncertain indication, but some short series showed favorable response.<sup>30</sup>

It is clear that septic lateral sinus thrombosis is associated with high mortality rate. Its mortality rate is reported to be between 5 to 30%.<sup>31,32</sup> Sequelae may include VI nerve palsy, ataxia and deafness.

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