

Cerebral Venous Sinus Thrombosis

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Cerebral venous sinus thrombosis is an uncommon condition, which over the past 10 years has been diagnosed more frequently due to greater awareness and the availability of better non-invasive diagnostic techniques. Because of the generally good prognosis and variable clinical signs, many cases remain clinically undetected but some patients suffer complications and die. CVST is slightly more common in women, particularly in the age group 20–35, due to pregnancy, puerperium and oral contraceptive use. The mean age in different studies was 37–38 years, although all ages can be affected [1-4]. The clinical spectrum, however, is wide and recognition remains a challenge for the clinician [1-8].

PATHOLOGICAL CONSIDERATIONS

The venous territories of the brain are less well defined than arterial territories due to the presence of extensive anastomoses between cortical veins. These allow the development of collateral circulation in the event of an occlusion. The main cerebral venous sinuses affected by CVST are the superior sagittal sinus (72%) and the lateral sinuses (70%). In about one-third of cases more than one sinus is affected [4]. In a further 30–40%, both sinuses and cerebral or cerebellar veins are involved [1,4]. CVST

has been described as a continuing process in which the balance of prothrombotic and thrombolytic processes is disturbed, leading to progression of the venous thrombus with time [2]. This slow growth of the thrombus and the good collateralization of the venous vessels probably explain the gradual onset of symptoms, often over weeks and months [1,2]. Sudden onset, however, has been described [5]. From the large number of patients with complete reversibility of their neurological deficit, it can be inferred that there must be

a large area of only transiently and reversibly disturbed cerebral tissue. Recovery appears to be unrelated to the duration of symptoms and signs [2,4]. Hemorrhagic infarction occurs in approximately 10–50% of cases, principally affecting the cortex and adjacent white matter [2,6-8].

ETIOLOGIC FACTORS

Predisposing underlying factors can be identified in up to 80% of patients [9,10]. Numerous conditions can predispose to CVST and frequently more than one cause will be found in an individual patient. Infective causes have declined and were responsible for only 8% of cases in recent series [1,2], typically affecting the cavernous sinus following staphylococcal infection of the face. Meningitis, mastoiditis, ear infections, tonsillitis and sinusitis may be complicated by CVST [10]. Among the non-infective causes, systemic conditions such as connective tissue diseases, anemias, granulomatous and inflammatory bowel diseases, as well as malignancies are most common [1,10]. In young women, CVST occurs more frequently during the puerperium than during pregnancy [1]. Oral contraceptives and various coagulation disorders have frequently been implicated. A Dutch study found age-adjusted odds ratio of 13 for oral contraceptive use and risk of CVST [11]. Hereditary prothrombotic conditions such as factor V Leiden, deficiency of proteins C and S and antithrombin III, as well as prothrombin gene mutations may account for one-third to two-thirds of children and for 10–15% of adults with CVST [10-13]. The risk of a carrier of any of these prothrombotic conditions developing CVST is increased by the coexistence of other

A high index of clinical suspicion is needed to diagnose this uncommon condition so that appropriate treatment can be initiated

predisposing factors. For example, the odds ratio for women using oral contraceptives and also carrying a prothrombotic defect was calculated as 30, compared to women who had neither risk factor [11]. It is therefore advisable to discourage women who have a history of venous thrombotic disease from using oral contraceptives, especially if they are carriers of a prothrombotic disorder. Whether young women who wish to take oral contraceptives should be screened for these disorders remains controversial [14]. In 20–30% of cases of CVST extensive search revealed no underlying cause [1,15] indicating the need for close follow-up.

CVST = cerebral venous sinus thrombosis

CLINICAL PRESENTATION

CVST presents with a wide spectrum of symptoms and signs, and sometimes the clinical manifestations are non-specific and subtle. Headache is the presenting symptom in 70–90% of cases [1,2,5]. Focal deficits such as hemiparesis and hemisensory disturbance, seizures, impairment of level of consciousness, and papilledema occur in one-third to three-quarters of cases [1,6]. Most patients present with symptoms that evolved over days or weeks. There are several typical clinical constellations [2-4]: 18–38% of cases present with a syndrome resembling benign intracranial hypertension with headache, papilledema and visual disturbances; up to 75% of cases are characterized by a focal neurological deficit and headache; a third group of between 30% and 50% may present with seizures. Rare but classical clinical pictures are that of superior sagittal sinus thrombosis with bilateral or alternating deficits and/or seizures and cavernous sinus thrombosis with chemosis, proptosis and painful ophthalmoplegia [1]. An even less frequent presentation is a rapidly progressive illness with consciousness deterioration, headache, nausea and pyramidal signs, due to extensive involvement of the deep cerebral veins [16]. Sudden-onset severe headache with neck stiffness mimicking subarachnoid hemorrhage has been described [5]. In the early stages there may be cortical vein thrombosis without sinus thrombosis, the latter developing only later due to progression of the thrombotic process. There is no well-defined clinical syndrome to suggest this, although the rapid onset of focal deficit and/or seizures is thought to be typical of this situation. There is strong overlap between all these outlined groups, and patients may progress from one to the other in the course of their illness.

DIAGNOSIS

Magnetic resonance venography and computed tomography venography are the imaging modalities of choice for the diagnosis of CVST. Magnetic resonance imaging combined with MRV have largely replaced invasive cerebral angiography and conventional computed tomography in the diagnosis of CVST [17,18]. MRI confirms the diagnosis and shows the consequences of thrombosis such as cerebral edema, infarction and hemorrhage, as well as the anatomy of the disturbed venous circulation. There are, however, pitfalls of this technique, which may, in doubtful cases, make cerebral angiography necessary [8,17]. CT often remains the first imaging modality to be used – simply because of availability, and also to exclude other conditions such as intracerebral hemorrhage

or abscess. The ‘empty delta sign’ on CT, reflecting the opacification of collateral veins in the wall of the superior sagittal sinus after contrast injection, is present in only 10–20% of cases. CT is entirely normal in 10–20% of proven CVST [1]. CTV has been shown in at least one series [19] to be superior to MRV in visualizing sinuses or smaller cerebral veins or cortical veins with low flow. Examination of the cerebrospinal fluid remains important in the appropriate clinical context to rule out meningitis or subarachnoid hemorrhage before the diagnosis of CVST has been established. Its other value is in patients who are thought to have benign intracranial hypertension where the presence of any abnormal findings in the CSF should point at CVST as the underlying cause of raised pressure. All other investigations are directed to demonstrating the underlying cause. Clinically obvious cases such as local infection or head injury may be self-evident, whereas extensive investigations are needed in the idiopathic cases. Suspicion of malignancies or connective tissue diseases should be confirmed with appropriate tests. Coagulation studies are important, particularly in patients with a family or medical history of thrombotic episodes in addition to the unexplained cases. The investigations should include a search for the factor V Leiden mutation if resistance to activated protein C is abnormal, and evaluation of the activities of proteins C and S and antithrombin III, plasminogen, fibrinogen and anticardiolipin antibodies [12]. All these investigations should be performed repeatedly.

Magnetic resonance imaging with venography is the diagnostic modality of choice

TREATMENT

Treatment of CVST includes supportive or symptomatic measures such as hydration, appropriate antimicrobials, control of seizures with anticonvulsants, and control of intracranial pressure. The antithrombotic treatment modalities include heparin, oral anticoagulants, thrombolysis and endovascular approaches. The safety of heparin treatment has been shown in large studies [1,6,20-22] as well as many smaller series and case reports. The benefits of heparin were demonstrated in a randomized and placebo-controlled trial of 20 patients [20]. There was a significant difference in favor of intravenous heparin with respect to neurological recovery and mortality. Eight patients in the heparin group but only one in the placebo group recovered fully. The authors also retrospectively analyzed 102 patients with CVST, and showed that intravenous heparin was even beneficial in those patients who had an intracranial hemorrhage prior to starting treatment. A randomized, placebo-controlled trial of subcutaneous low weight molecular heparin

MRV = magnetic resonance venography

CTV = computed tomography venography
CSF = cerebrospinal fluid

in adults showed a trend for better outcome in the treated group [21], but the mortality was lower in this series, and there were more patients with milder presentations in the placebo arm. On the basis of these limited data, a Cochrane review concluded that anticoagulation with heparin was safe and that there was some evidence of a clinically important benefit [22]. Intravenous heparin should be the first-line treatment, even in the presence of hemorrhagic infarction, provided there are no general contraindications to its use. If the patient deteriorates despite adequate heparinization, selective catheter-guided local thrombolysis may be an option in spite of the increased hemorrhagic risk. There have been several reports of thrombolysis via selective catheterization of the occluded sinus [23–30].

Horowitz et al. [23] reported a series of 12 patients of whom 4 had hemorrhagic infarcts, were pretreated with intravenous heparin and were then given urokinase boluses followed by continuous infusion via a transfemoral venous catheter into the occluded sinus. There was no major therapeutic morbidity, and 10 patients had good or excellent clinical outcome. Functional sinus patency was achieved in 11 of 12 patients. Treatment duration was between 12 and 84 hours with repeated angiograms performed at 24 hour intervals. Smith and colleagues [24] reported seven patients whose condition deteriorated despite heparin and were treated with selective transcatheter urokinase infusion. There were no major complications and all patients either

fully recovered or their situation improved. Sinus patency was achieved in all patients following thrombolysis for between 88 and 244 hours. In the study by Kim and Suh [25], nine patients were given recombinant tissue plasminogen activator with concomitant intravenous heparin via the transfemoral route. Complete flow restoration was achieved in all cases within, on average, 18 hours and all the patients completely recovered. Frey and co-workers [26] used the same agent and achieved complete flow restoration in 6 of 12 patients. Complete recovery occurred in 7 of 12 cases. A non-randomized study comparing urokinase thrombolysis with heparin in adults suggested a better functional outcome for the patients undergoing thrombolysis but a higher risk of hemorrhage [27]. The need for enormous organizational efforts and expertise limit this intervention to specialized centers. Most investigators suggest oral anticoagulants for 3–6 months following treatment of the acute phase, except when there is a known prothrombotic condition in which treatment may have to be life long [1,4,31]. The use of antibiotics, anticonvulsants, anti-emetics and analgesia will depend on specific circumstances. Special interventions to reduce significantly raised intracranial pressure – for example when vision is threatened – include acetazolamide, steroids, repeated lumbar punctures, mannitol, shunt procedures and barbiturate-induced coma. Favorable functional outcome in

selected patients with most severe courses of CVST can be achieved after decompressive craniectomy [32,33]. Precise indications and techniques for combined surgical decompression and thrombectomy warrant further evaluation. Discontinuing oral contraceptives may reduce the risk of recurrent CVST, and several low risk strategies can be recommended such as improving the quality of the diet.

PROGNOSIS, PREDICTION OF RECURRENT CVST AND FOLLOW-UP

Three of four patients have complete functional recovery [2,34–37]. Mortality ranges between 5.5% and 18% [1,2]. Several factors are associated with a poorer prognosis: infancy and advanced age, rapid onset with coma and focal deficits, and thrombosis affecting mainly the deep venous system [9]. The underlying condition, particularly sepsis and malignancies, adversely affect outcome. Twelve percent of patients suffer a recurrence of CVST and 14% a different form of venous thrombosis [34]. Kenet et al. [35] summarized 396 consecutive children with CVST; the predictors of recurrent thromboses included persistent occlusion on follow-up venous imaging, heterozygosity for the G20210A mutation in factor II, and the lack of anticoagulant therapy. Because of the risk of visual loss resulting from increased intracranial pressure in individuals with CVST, it is reasonable to promote neurological and ophthalmological follow-up, especially during the first year [36]. Cognitive and neurological sequelae have also been reported and may require rehabilitation and longer-term therapy [37]. Occasionally, patients with cryptogenic CVST later manifest symptoms of an underlying disease. The outcome of CVST is therefore generally favorable, and aggressive and potentially dangerous therapeutic interventions should be confined to those patients who deteriorate rapidly despite heparin or who demonstrate poor prognostic indicators.

Heparin is the first-line treatment for cerebral venous sinus thrombosis because of its efficacy and safety

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