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Prognostic indicators in cerebral venous sinus thrombosis

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Review Article

Prognostic indicators in Cerebral Venous Sinus Thrombosis

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Abstract

Cerebral venous sinus thrombosis (CVT) can affect all age groups, particularly women of childbearing age. Overall prognosis for survival and functional independence is better than it was believed. Mortality usually ranges from 6-15% and transtentorial herniation is the major cause of death. Approximately 80% of patients are functionally independent in the long term. Altered mental status and cerebral haemorrhage at presentation are the strongest predictors of death and disability. Patients with CVT related to pregnancy and puerperium generally do better than patients with other causes. Septic CVT carries a worse prognosis than aseptic CVT and of the latter, patients with syndrome of isolated intracranial hypertension have a better prognosis than those with focal deficits or encephalopathy. Anticoagulation is believed to improve outcome in CVT although robust data are lacking. Epilepsy, headaches, visual loss, pyramidal deficits and cognitive impairment are some of the long term sequelae. The risk of recurrence of CVT is low, particularly after the first 12 months of the first episode.

Introduction

CVT is a cerebrovascular disorder that can affect all age groups.[1] Although CVT causes stroke far less frequently than arterial pathologies[2,3], it has a predilection for younger individuals, particularly women of childbearing age.[4] Four main clinical patterns of CVT are generally recognizeed and these include presentation with focal neurological deficits and/or seizures, isolated intracranial hypertension, subacute diffuse encephalopathy and painful ophthalmoplegia and the distinction of patients into these clinical patterns carries prognostic implication.[5,6]

Earlier reports of CVT, in the first half of the 20th century, were usually based on autopsy findings and CVT was generally considered to be a fatal disease.[7] Diaz et al reviewed 203 cases of CVT reported between 1942 and 1990 and found an overall mortality of 49.3%.[8] An Austrian retrospective study of 42 cases showed a mortality as low as 2%[9] while a Mexican study reported a comparatively higher figure of about 23%.[10] In other series reported since 1980's, however, the mortality rates have been consistently found to be between 6 and 15% in reports emerging from different parts of the world.[11-13] The mortality rate was 8% in a French study, 6% in a German study and 8% in an Italian study.[14-16] In the largest reported prospective series of 624 patients by the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) the mortality was 8.3%. In this study, a significant majority (92%) of deaths attributable to CVT occurred within 30 days of symptom onset[17], a finding that is shared by other series as well.[18,19]

The main cause of death occurring within the first few days of presentation of CVT is transtentorial herniation due to a focal lesion, multiple lesions or diffuse oedema while causes of death over the next few weeks include transtentorial herniation, uncontrolled seizures, sepsis, pulmonary embolism, underlying infection or malignancy.[4,16,17]

The extent of functional recovery in survivors of CVT is better as compared to patients with arterial thrombosis in which the proportion of permanent dependent patients ranges between one third and two third of survivors[20] which is in contrast to CVT in which an independent survival of around 80% is commonly found. Of 59 patients in the study by Cerebral Venous Sinus Thrombosis Study group, conducted in Netherlands and United Kingdom, 83% of the patients had independent survival (Oxford handicap score =2) while 17% of patients had poor outcome, defined as death or dependency (Oxford handicap score =3) at 12 weeks.[5] Eighty two percent of 91 prospective cases of Portuguese cohort of VENOPORT study had complete recovery at 1 year.[18] Of 79 patients, collected both retrospectively and prospectively, over a period of about 16 years by a German group, 73% had excellent recovery with modified Rankin score (mRS) of 0-1, 4% had partial recovery with mRS of 2, 8% had significant disability with mRS of 3-5 while 15% died at 6 months.[15] After a median follow-up of 16 months in ISCVT, 79% made complete recovery (mRS 0-1), 8% made partial recovery though they were independent (mRS 2), 5% were dependent (mRS 3-5) while 8% had died (mRS 6).[3] In a French cohort of 55 patients, 82% of patients were independent (mRS 0-2) while 18% were dependent or dead (mRS 3-6) at 3 years.[14]

Altered mental status and cerebral haemorrhage at presentation have been found to be the most consistent and strongest predictors of death and disability.[3,5,13] Older age (>37 years in ISCVT), male sex, seizures at admission, rapid evolution of thrombosis, the presence of focal deficits and CNS infection and cancer as the underlying cause also predict poor outcome.[3,15,21] Although the site of thrombosis has not been found to correlate with the outcome in certain studies[5,16], ISCVT found involvement of cortical veins, deep cerebral veins and superior sagittal sinus, intracerebral haemorrhage on right side, posterior fossa lesions and parenchymal lesions especially ones >5 cm in their larger diameter to be poor prognostic factors.[17] Patients who deteriorate during hospital stay in terms of their encephalopathy or focal neurological deficits or those who either develop new focal deficits or new lesions on neuroimaging (infarction, haemorrhage or oedema) are more likely to die than those without these findings.[17] The VENOPORT study

identified anticoagulation, absence of aphasia, age <45 years, no encephalopathy at admission and no worsening after admission as predictors of good outcome.[13,18]

Intracranial circulation time (ICT) and the degree of recanalization have also been proposed as possible prognostic markers in CVT.[21,22] ICT is defined as the time from the first appearance of the contrast agent in the arterial system to the complete clearing from the venous system on cerebral angiography and has a normal value of <9 seconds. In a German series in which patients were treated with dose-adjusted intravenous heparin, a markedly delayed ICT (mean 21.2 s) was more frequently found in patients who died than in survivors (mean ICT 13.3 s).[21] Strupp et al showed after a long-term follow-up of 40 patients using MRI and MRA that although the prevalence of persisting neurological deficits did not differ between patients with complete or partial recanalization, patients with no recanalization had significantly more neurological sequelae.[22] Some investigators have identified presence of empty delta sign on CT scan as a predictor of poor outcome.[11]

The prognosis of CVT related to pregnancy and puerperium is considered to be better compared to CVT related to other causes. Cantu et al compared 67 patients of obstetric CVT with 46 patients of nonobstetric CVT and found that although the initial severity of illness was similar in both groups with comparable neurological and neuroradiological findings, the final outcome was good in 80% of the former group and 58% of the latter group with significant difference in mortality as well which was 9% in patients with pregnancy-related CVT and 33% in patients with other causes[23], others have also noted similar findings.[4,15]

The prognosis of septic CVT is worse than nonseptic CVT with a reported mortality of 30% and 78% in cavernous and superior saggital sinus thromboses respectively.[24] Although no convincing data exist, anticoagulation (AC) may improve prognosis by reducing morbidity and mortality in septic CVT and is generally considered a part of treatment in addition to antibiotics.[2,25]

Amongst patients with aseptic CVT, patients who present with syndrome of isolated intracranial hypertension (IIH) have a better prognosis compared with those who present with focal deficits or encephalopathy. In Preter et al's series of 77 patients, 11 patients were left with permanent neurologic sequelae and only 2 of them had initially presented with IIH.[26] In ISCVT, patients presenting with IIH had a better outcome (7% dead/dependent) than the remaining patients (13.6% dead/dependent) after a follow-up of median of 16 months.[3] Others have had similar results8 and IIH has been identified as a marker of good outcome.[5,14]

ISCVT investigators have reported that the prognosis of elderly patients with CVT is worse than that of younger patients. In ISCVT at the end of follow-up of median of 16 months, only 49% of elderly patients (= 65 years) made a complete recovery (versus 82% in younger patients), whereas 27% died and 22% were dependent (versus 7 and 2% respectively in younger patients).[27]

An Italian retrospective study of 48 patients reported that the outcome of CVT patients from non-selected first-referral centres was similar to that from specialized centres.[16] ISCVT which recruited patients from 5 continents found no significant difference in outcome between patients enrolled in different countries or world regions.[3]

Barinagarrementeria et al proposed a prognostic scale based on clinical, computed tomography (CT) and cerebrospinal fluid (CSF) analysis. The presence of coma or bilateral pyramidal signs was rated at 3, that of generalized seizures at 2 and that of meningeal signs, bilateral lesions on CT scan and haemorrhagic CSF all at 2. The prognosis was found to be 100% good when total score was $\leq$3, usually good (85%) with a score of 4-5, usually bad (90%) with a score of 6-8 and 100% bad with a score of $\geq$9.[10] The scale, however, has not been consistently validated in various series of CVT.

It is generally recognized that although several predictors of good and bad outcome have been identified in patients with CVT, the prognosis of a given individual patient remains variable and highly unpredictable.[28]

Whether AC improves outcome in CVT remains uncertain. Following initial reports of benefit of heparin in CVT, AC was used in many patients and encouraging results were reported in various series.[9] A trend towards benefit in patients treated with AC was noted in three prospective randomized trials comparing the efficacy of heparin vs. placebo in CVT.[19,29,30] In the German trial of dose-adjusted intravenous heparin vs. placebo in 22 patients, 8 patients recovered fully and none died in the heparin-arm while 1 patient recovered fully and 3 died in the placebo-arm.[29] In the British-Dutch trial of 60 patients with CVT, low molecular weight heparin was compared with placebo. A poor outcome was noted in 6 of 30 patients (20%) at 3 weeks and in 3 patients (10%) at 12 weeks in the heparin group as compared to 7 of 29 patients (24%) at 3 weeks and 6 patients (21%) at 12 weeks in the placebo group.[19] A meta-analysis of these two trials showed that the use of AC led to an absolute risk reduction in mortality of 14% and in death or dependency of 15% with relative risk reductions of 70% and 56% respectively.[19] The third trial compared intravenous unfractionated heparin with placebo in 57 patients with puerperal CVT and found a nonsignificant improvement in patients treated with AC.[36] The data, though not statistically significant, are generally considered to be clinically meaningful and AC is believed to improve prognosis in CVT.[2,31]

Few studies have looked at the long-term outcome in patients with CVT. One of the common sequelae in these patients is epileptic seizures. These almost always occur in those patients who had seizures during the acute stage of the disease and a rate of 5-16% has been reported in various studies.[14,32,33] Occurrence of >2 seizures despite antiepileptic treatment during initial hospitalization has been found to increase the risk of subsequent epilepsy while the presence of venous infarct possibly increases the risk.[15] Headaches of variable types and intensities are another long-term problem affecting the quality of life in these patients and have been reported to occur in 11-60% of these patients in various studies, the wide difference likely to be attributable to different ascertainment criteria.[3,18,32] Motor deficits (in about 10%), visual loss or visual field defects (in 0.6-10%) and development of leptomeningeal fistula (in about 3%) have also been reported.[15,18,32] Studies using various neuropsychological batteries aimed at assessing long-term cognitive outcome have reported cognitive impairment in approximately 35% of the patients in different cohorts usually in the form of non-fluent aphasia, working memory deficits and depression.[32,34] Anticoagulation has not been shown to alter the long-term cognitive outcome.[34] The available data also suggest that although functional disability is uncommon amongst survivors, many of them (40% in the series reported by cerebral venous thrombosis study group) are not able to resume all prior activities or enjoy a previous level of social and occupational functioning.[34]

The risk of recurrence of thrombosis, cerebral as well as extracerebral, appears to be low particularly after the first 12 months. Of Ameri's original series of 110 patients, Preter et al followed 77 patients for a median of 63 months and found recurrence of CVT in 9 patients (12%) in 8 of whom the recurrence occurred within 12 months of the first episode. Eleven patients (14.3%) had thrombotic events other than CVT.[26] In Einhaupl's series with a mean follow-up of 10 years, recurrence of CVT was noted in 5 patients (6%) out of whom 4 had a relapse in the first 19 months (mean latency of 10.3 months).[2] ISCVT investigators reported recurrence of CVT in 2.2% and of other thrombotic events in 4.3% after a median follow-up of 16 months.[3] In a German series in which 58 patients were followed up for a median of 31 months, 2 patients (3%) developed recurrent CVT and 5 patients (9%) had extracerebral venous thrombosis.[15] Recurrence of CVT occurred in only 1 of 34 patients in an Italian series (median follow-up of 3.5 years)[32] and in none of 55 patients in a French series (median follow-up of 3 years).[14] The VENOPORT study reported a recurrence of CVT in 2% of patients.[18]

The risk of recurrence of CVT during pregnancy and puerperium in women who previously suffered from CVT also seems to be low, again at least after the first 12 months. Mehraein et al, from their own series and those of others, found reports of 63 pregnancies with no recurrence of CVT including 21 women whose initial episode was related to pregnancy or puerperium41. In their own series of 22 pregnancies in 14 women, the mean interval from CVT to subsequent pregnancy was more than 2 years and this interval might have contributed to lack of recurrence as relapses of CVT are more likely to occur in the first 12 months.[35] In ISCVT, over a median follow-up of 16 months, 34 women became pregnant after CVT. Recurrence of CVT was noted in 1 patient while extracerebral venous thrombosis occurred in 2 patients.[3]

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