Review Article

Incidence and Epidemiology of Cerebral Venous Thrombosis

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Abstract

Cerebral venous sinus thrombosis is a disorder whose epidemiology has changed over the past few decades. It is no longer regarded as a uniformly fatal disease. CVST is not a rare disorder. It may have a differential geographic distribution with a higher incidence in the Asian world. It is a disease of neonates, younger women and men, often a hypercoagulable state, either acquired (eg cancer) or a genetic prothrombotic condition may be present. Outcome is not uniformly dismal and prognostic criteria that detect patients with a poor outcome have become available from prospective studies. There is a paucity of well designed large scale epidemiologic studies focused on venous thrombosis from regions where it is relatively frequent (South Asia, Middle East). The newer epidemiologic data derived from a Caucasian database; suggest a better overall prognosis, younger age at distribution than arterial stroke.

Introduction

In 1825, Ribes described a 45 year old man who died after a 6 month history of epilepsy, seizures and delirium. Autopsy revealed thrombosis of the superior sagittal sinus, the left lateral sinus and a cortical vein in the parietal region. This was probably the first detailed description of extensive cerebral venous sinus thrombosis in literature. Since then, the literature describing this disease has comprised of case reports, series and some newer prospective studies. The purpose of this review is to summarize the epidemiologic data on cerebral venous sinus thrombosis with emphasis on the incidence, world wide age and sex distribution and the typical clinical settings that should lead to the clinical suspicion of cerebral venous sinus thrombosis. Detailed discussions on etiology are available elsewhere in this review.

Methods

A Medline search of all articles detailing incidence of CVST was done, using keywords: cerebral venous thrombosis, incidence, and epidemiology. In addition, major texts were reviewed for additional references. Each article was scrutinized for quality. Due to the dearth of large series, partly due to the relative rarity of this disease, all retrospective controlled data and prospective trials were included.

Incidence

Cerebral venous sinus thrombosis was thought to be a rare disease as a result of earlier reviews on its incidence, that were mostly based on autopsy studies performed in Western countries.

Ehlers and Courville found only 16 SSS thrombosis in a series of 12, 500 autopsies.[1] Barnett and Hylland found only 39 non infective CVT in 20 years.[2] Kalbag and Woolf found that CVT was the principal cause of death in only 21.7 persons per year in England and Wales between 1952 and 1962.[3] The largest autopsy reported incidence of CVST is 9%. These studies precede the larger clinical studies and give the impression that CVST is a rare disease. This has been disproved by subsequent large prospective clinical series.

The largest clinical series is the International Study on CVT (ISCVT) ; this study recruited 630 patients over a 3 year period. In 1995, Daif reported a frequency in Saudi Arabia of 7 per 100,000 hospital patients.[4] Most Indian studies have a large number of cases thereby suggesting that the incidence there is not as rare as previously thought of. It has been reported to cause 10-20% of young strokes in India.[5]

If we estimate the incidence of CVT, it would be about one to two cases per million based on autopsy studies. In addition, the current MRI based studies give an incidence of 1.5 to 3 million in adults.

Age

A recently published study of 160 cases from the Canadian Pediatric Ischemic Stroke Registry calculated an annual incidence among children (up to 18 years) of 6.7 per million. Almost 50% of the sample were neonates (younger than 3 months), which indicates a higher incidence in that age group.[6] Thus it appears that CVST is more common in the pediatric and especially the neonatal age group.

CVST is a disease of young people. According to an Indian study, it is a major cause of stroke in young population with a mean age of 32.27 years and therefore should be considered in all cases of young stroke and neurological syndromes in appropriate setting.[5] In 1992, Ameri and Bousser reported a uniform age distribution in men with CVT, while 61% of women with CVT were aged 20-35 years.[7] This may be related to pregnancy or the use of oral contraceptives.

Data from a US study in 1993-4 estimated that Dural sinus thrombosis might complicate 11.6/100,000

deliveries.[8] So it is obvious that children are more likely to have this disease than their adult counterparts.

Sex Ratio

CVT is believed to be more common in women than men. In a series of 110 cases, Ameri and Bousser found a female-to-male ratio of 1.29:1.[7] Ferro et al.[9] made the same observations in a prospective study from 1995 to 1998. This slight preponderance in females is probably due to specific causes such as oral contraceptives, pregnancy and pueperium. This preponderance of females did not exist before the era of the oral contraceptive pills.

Race and Geographical Distribution

There is no reliable data on racial or geographical distribution but researches done in India on CVST claim that this disease is more common in underdeveloped countries of Asia than the western world.[5]

Anatomical Distribution

The Sagittal (70-85%) and lateral sinuses (70%) are involved more than the deep venous system (40% in cerebral veins and rarely the galenic system, petrosal sinus, isolated cortical and cerebellar veins are involved).In about 75% of cases, multiple veins or sinuses are affected. Isolated involvement of superior sagittal sinuses and lateral sinuses is rare with less than 30% evidence for superior Sagittal and less than 10% for lateral sinuses in different studies.[10]

Clinical settings that raise the suspicion for CVST

More than one hundred putative risk factors, causes and conditions associated with CVST have been described. There are certain clinical settings in which CVST should be suspected. The patient is often younger, female, or a neonate or may have a genetic or acquired prothrombotic state. Certain acquired clinical states lead to a condition of hypercoagulability that may predispose to CVST. In these are included nephrotic syndrome (loss of protein C, S and antithrombin III), puerperium, oral contraceptive pills, infections, otitis and mastoiditis, cancer, dehydration in the very extremes of life, haematologic disorders like leukaemia, polycythaemia, anaemia, non infectious inflammatory disease like Behcets, antiphospholipid antibody syndromes. The genetically acquired conditions that predispose to a generalized prothombotic state often manifest as leg vein thrombosis also predispose to cerebral venous thrombosis. These are hyper homocysteinaemia, deficiency of antithrombin III, protein C, S, Factor V Leiden mutation (common in Caucasians), and Prothrombin 20210 gene mutation. Mechanical causes of CVST include closed head injury, direct injury to the sinuses, neurosurgical interventions, or lumbar puncture. In at least 17 % to 27 % of adults, and 2% of children no causative risk factor can be identified and the cause of CVST remains elusive.

Clinical outcome and long term prognostic factors

Mortality in untreated cases of venous thrombosis has been reported to range from 13.8-48%; this high mortality rate may be a reflection of clinical severity at entrance into the study. Between 25% and 30% of patients have full recovery.

More recently, a Portuguese study group prospectively analyzed 91 consecutively admitted patients from 1995 to 1998 over a mean 1-year follow-up interval.[9] Of the patients analyzed, 7% died in the acute phase, 1% died during the one year follow-up, 82% recovered completely, and 1% were dependent; 59% developed thrombotic events during the follow-up, 10% had seizures, 11% complained of severe headaches, and 1 patient experienced severe visual loss.[9]

Even in those surviving 'intact' a Dutch study group, looking at the long term prognosis of a series of 59 cases found out that after one year 35% had cognitive impairments, 6% were dependent, 40% had symptoms that led to restriction in lifestyle, and 40% could not resume their previous level of economic activity.[8]

According to the results of the 'International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)'.[10] coma, cerebral haemorrhage, and malignancy are important prognostic factors for death or dependence. In addition, male sex, age >37 years, mental status disorder, thrombosis of the deep cerebral venous system, and CNS infection are variables that increase the risk of death or dependence. The Dutch study adds papilloedema and diagnostic delay >10 days to the list.[8] Good outcome was associated with an isolated intracranial hypertension presentation and a delta sign on CT. Seizures (10%) and new thrombotic events (4%) were the most frequent complications during follow-up. Recurrence of CVT and severe visual loss were exceptional but severe and potentially preventable occurrences. Another finding in ISCVT was that except for spontaneous abortions, other complications rarely occurred during or after new pregnancies, which strongly support the evidence that past CVT (including puerperal CVT) is not a contraindication to pregnancy.[10]

The prognosis for those who may have a fatal course still remains difficult to predict. There is one retrospective case series that studied the clinical course of patients with CVST who died despite AC therapy to look for clinical features that might explain the lethal course of these patients.Seventynine consecutive patients with CVST who

were treated with a standard regimen of dose-adjusted iv heparin were identified in this series. All patients were stuporous or comatose at the start of AC, and four patients showed markedly delayed intracranial circulation times, indicating extensive venous thrombosis Two patients improved, but deteriorated secondarily after reduction or discontinuation of AC. Sufficient activated partial thromboplastin time levels were reached only after a delay in three patients, and critical deterioration occurred in two of them during this time. Extensive thrombosis, the inadequacy of anticoagulation and poor presenting neurologic status were identified as contributing factors to mortality in this retrospective review.[11]

The long-term neurologic outcome of sinovenous thrombosis in children is unclear. The best available estimate is that after a mean of 2.1 years, 77 percent of neonates and 52 percent of nonneonates are neurologically normal.[6]

Delays in presentation

A consecutive study reported the interval (days) between the onset of symptoms and hospital admission in 91 consecutive patients admitted to 20 Portuguese hospitals between June 1995 and June 1998. They also studied the impact of admission delay on treatments (prescription of anticoagulants and the number of days elapsed between the onset of symptoms and start of anticoagulation and admission). Median admission delay was 4 days. Twenty-two (25%) patients were admitted within 24 hours. Two thirds of the patients were admitted within 7 days and 75% within 13 days. The interval between onset of symptoms and start of anticoagulation was shorter in patients admitted earlier ($p = 0.0001$, for either admission within 24 hours, 4 or 13 days). There is a considerable delay until the clinical picture associated with CVT is recognised as justifying hospital admission, especially when patients present with symptoms identical to isolated intracranial hypertension syndrome.[12]

Recanalization in CVST

Thirty-seven consecutive patients with CVST were prospectively examined. Neurological deficits were graded with the National Institutes of Health Stroke Scale (NIHSS) on hospital admission and discharge. Functional outcome was assessed with the modified Rankin Scale (mRS) on hospital discharge and after 12 months. All patients were treated with intravenous heparin in the acute stage of illness, followed by oral anticoagulation for 12 months. Imaging follow-up with MR angiography and, in a few cases, with CT or conventional angiography was performed on hospital discharge and after 6 and 12 months. Twelve-month functional outcome was excellent in 89% of patients with an mRS of 0 or 1. Data from this study show that CVST patients display a high spontaneous and intrinsic thrombolytic potential, with recanalization rates of 60% during the first 20 days. Thereafter, recanalization rates increase insignificantly. Neither heparin nor oral anticoagulants pharmacologically possess thrombolytic action, so the rationale for treatment is to prevent recurrent thrombosis and appositional thrombus growth.[13] This suggests that recanalization may not be the only effective marker of prognosis, the presence of venous collaterals may also be important.

Conclusion

CVST is not a rare disorder as previously supposed, it may have a differential geographic distribution with a higher incidence in the Asian world. It is a disease of neonates, younger women and men, often a hypercoagulable state, either acquired (e.g cancer) or a genetic prothrombotic condition may be present. Outcome is not uniformly dismal and prognostic criteria that detect patients with a poor outcome have become available from prospective studies.

References

1. Ehlers H, Courville CB: Thrombosis of internal cerebral veins in infancy and childhood: Review of literature and report of five cases. Brain 1953;76:36.
2. Barnett HJM, Hyland HH: Non infective intracranial venous thrombosis. Brain 1953; 76:36.
3. Kalbag RM, Woolf AL: Cerebral Venous Thrombosis, vol 1. Oxford, Oxford University Press, 1967; pp
4. Daif A, Awada A, al-Rajeh S, Abduljabbar M, al Tahan AR, Obeid T, et al: Cerebral venous thrombosis in adults. A study of 40 cases from Saudi Arabia. Stroke 1995; 26:1193-5.
5. Pillai LV, Ambike DP, Nirhale S, Husainy SMK, Pataskar S, et al. Cerebral venous thrombosis: An experience with anticoagulation with low molecular weight heparin. Indian J Crit Care Med 2005; 9:14-18.
6. DeVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, et al. Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. NEnglJMed. 2001; 345:417-23.
7. Ameri A, Bousser MG. Cerebral venous thrombosis. Neurol Clin 1992; 10: 87-111.
8. Kimber J. Cerebral venous sinus thrombosis.QJM.2002; 95:137-42.
9. Ferro JM, Lopes MG, Rosas MJ, Femo MA, Fontes J: Long-Term Prognosis of Cerebral Vein and Dural Sinus Thrombosis. Results of the venoport study. Cerebrovasc Dis 2002; 13:272-8.
10. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators.Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT).Stroke 2004;35:664-70.
11. Masuhr F, Mehraein S. Cerebral venous and sinus thrombosis: patients with a fatal outcome during intravenous dose-adjusted heparin treatment. Neurocrit Care. 2004; 1:355-61.
12. Ferro JM, Lopes MG, Rosas MJ, Fontes J. VENOPORT Investigators. Delay in hospital admission of patients with cerebral vein and dural sinus thrombosis. Cerebrovasc Dis. 2005; 19:152-6.
13. Stolz E, Trittmacher S, Rahimi A, Gerriets T, Röttger C, Siekmann R, et.al.Influence of Recanalization on Outcome in Dural Sinus Thrombosis. A Prospective Study. Stroke. 2004;35:544-47.