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Original Research Article

A Hospital Based Retrospective Assessment on the Distinctive Clinical Manifestations, Neuro-Imaging Features, Treatment Administered, and Outcomes of Children with Cerebral Venous Sinus Thrombosis (CVST)

Supriya Chauhan

Neurosurgery Resident, Department of Neurosurgery, JIPMER, Pondicherry, India

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Corresponding author: Dr. Supriya Chauhan
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Abstract

Background: CVST is a cerebrovascular condition characterized by thrombosis in the dural venous sinus or one or more cerebral veins. CVST can affect people of any age, although young females, particularly those in their peripartum and postpartum periods, are more likely to be impacted. The study's goal was to meticulously document the clinical manifestations, neuro-imaging features, treatment administered, and long-term outcomes of children with cerebral venous sinus thrombosis (CVST).

Methods: The study was carried out in the department of neurosurgery, JIPMER, Pondicherry, India. The study design was a retrospective review of case records, with patient data retrieved from our electronic database for 12 years. A total of 20 patients were identified as confirmed CVST in the pediatric age group (<18 years).

Results: The present study comprised 12 males and 8 females. The age range at presentation was between 2 days and 17 years with a median age of 5.5 years. Among these, seven were <1 year old (two neonates), four were 1–5 years, and nine were over 5 years old. The commonest predisposing factors were otitis media/mastoiditis which was seen in eight patients. Three patients had acute leukemia, while three critically ill neonates had central line-related thrombosis. Two patients with CVST were felt to be secondary to non-accidental head injuries (NAHIs).

Conclusion: Pediatric CVST is uncommon and has a different range from adults, with specific clinical triggers and thrombophilic states. Management differs significantly across practitioners, partly to the scarcity of trial evidence and also due to the variability of this illness in children.

Keywords: Cerebral venous sinus thrombosis, pediatric, thrombophilia

Introduction

Cerebral venous sinus thrombosis (CVST) was first described by Ribes in 1825. CVST is a cerebrovascular disorder where thrombosis occurs in the dural venous sinus or one or more cerebral veins. CVST can affect any age group, but the young females, especially in their peripartum and postpartum period, are more commonly affected. [1] CVST accounts for 0.5%-1% of all types of strokes. [2] It also accounts for 10%-20% of strokes in the young population. [3] The incidence is also

higher in the developing countries. In comparison to other stroke types, CVST has more variable presentation. It can take up to a few weeks until the symptoms fully appear. [4,5] The clinical presentation of CVST can be with focal neurological deficits and/or seizures and coma and may lead to death. Other cases can be with headache, papilledema, and intracranial hypertension. Headache is one of the common presenting symptoms in around 70%-90% of patients. Still others can present with diffuse encephalopathy, painful ophthalmoplegia, or status epilepticus. [6] Acute symptomatic seizures are reported in about 35%-50% and around 76% in peripartum period. [7-10] In 29% of the patients, seizure is the presenting sign, and 59% of them had a generalized seizure. [11]

The risk factors associated with CVST are not the usual arterial vascular risk factors. CVST risk factors can be grouped into two: (1) Transient risk factors, including oral contraceptives and other medications with prothrombotic effects; pregnancy and puerperium; infections of the central nervous system, paranasal sinuses, the ear, and the mastoid. (2) Permanent risk factors, including general prothrombotic medical conditions, genetic thrombophilic diseases, antiphospholipid syndrome, myeloproliferative disorders, and malignancies. No risk factors are identified in 13% of patients with CVST. Apart from clinical signs and symptoms, the diagnosis of CVST is confirmed by neuroimaging. In a large multi-center study, 17.1% of patients with CVST had concomitant cortical venous thrombosis (CVT) along with occlusion of the major sinuses. [12]

Venous sinuses are located between two rigid layers of dura mater. This prevents their compression when intracranial pressure rises. As the cerebral veins and sinuses lack both valves and tunica muscularis, blood flow is possible in different directions. In addition, the cortical veins are linked by numerous anastomoses, allowing the development of a collateral circulation, and this may explain the good prognosis of cerebral venous thrombosis. [13] In addition to draining most of the cerebral hemisphere, the superior sagittal sinus (SSS) also receives blood from diploic, meningeal, and emissary veins. This explains the frequent occurrence of CVST as a complication of infective pathologies in the catchment areas. The dural sinuses, especially the SSS, contain most of the arachnoid villi and granulations, in which absorption of cerebro spinal fluid (CSF) takes place. Dural sinus thrombosis blocks these villi and causes CSF back pressure, which leads to intracranial hypertension and papilloedema. [14] Early diagnosis and aggressive treatment are critical and lifesaving in any form of CVT. [15]

The objective of the study was to systematically bring out the clinical presentations, neuro-imaging features, treatment given, and long-term outcomes of children with cerebral venous sinus thrombosis (CVST).

Materials and Methods

The study was carried out in the department of neurosurgery, JIPMER, Pondicherry, India. The study design was a retrospective review of case records, with patient data retrieved from our electronic database for 12 years. A total of 20 patients were identified as confirmed CVST in the pediatric age group (<18 years).

Only patients with age below 18 years and with a firm diagnosis of CVST based on clinical profile of raised intracranial pressure, seizures, with or without focal neurological deficits, and further confirmed on magnetic resonance imaging (MRI) of the brain with magnetic resonance venography (MRV) were included in the study. Patients were excluded in cases of

(i) Inconclusive neuro-imaging,
(ii) Arterial strokes,

(iii) Space occupying lesions, and
(iv) Insufficient data

All the patients underwent MRI and MRV of the brain on a 1.5 Tesla MRI system (Symphony; Siemens, Erlangen, Germany). The scan protocol included an axial fluid attenuated inversion recovery (FLAIR), axial and coronal T2W, T1 3D sagittal, diffusion-weighted images with the generation of apparent diffusion coefficient map and axial gradient sequence. All details of clinical examination, laboratory investigations, pattern of venous sinus involved, and therapy given were captured in a detailed predesigned proforma for analysis. The study protocol was approved by the institutional ethics committee. All patients at our center with infection-triggered

CVT (para-infectious CVST) were managed usually with broad-spectrum or culture-sensitive antibiotics as per protocol, and anticoagulation was avoided in such cases. However, in other cases of CVST without any obvious infective focus, the use of anticoagulation with heparin or vitamin K antagonists was based on the discretion of the treating team. Antiepileptics, anti-edema, and other supportive therapy were used wherever required. Follow-up records were available in all cases for periods ranging from 6 months to 8 years. A pro-coagulant workup was done, usually 3–6 months after the ictus, to avoid false lowering of ant-coagulant factors in the acute phase of a thrombotic event.[16] The workup included a standard testing panel of protein C and S, anti-phospholipid antibody (APLA) panel, and anti-thrombin III. The genetic testing panel included Factor V Leiden (FVL) mutation and MTHFR mutation studies. The retrospective data thus collected were entered into Microsoft Excel worksheets. Analysis of the data was carried out using appropriate descriptive statistics.

Results

Table 1: Demographic details

Demographic	**N %**
Male	12 (60)
Female	8 (40)
Age in years	
<1 year old	7 (35)
1-5 years old	4 (20)
>5 years old	9 (45)

The present study comprised 12 males and 8 females. The age range at presentation was between 2 days and 17 years with a median age of 5.5 years. Among these, seven were <1 year old (two neonates), four were 1–5 years, and nine were over 5 years old.

Table 2: Predisposing factors

Predisposing factors	**N=20**
Ear infections/mastoiditis	8
Acute leukemia	3
Central line related	3
Pneumonia	2
NAHI	2
Cyanotic heart	1
Contraceptive pills	1

The commonest predisposing factors were otitis media/mastoiditis which was seen in eight patients. Three patients had acute leukemia, while three critically ill neonates had central line-related thrombosis. Two patients with CVST were felt to be secondary to non-accidental head injuries (NAHIs).

Table 3: Presenting features

Signs & Symptoms	N=20
Focal neuro deficits	10
Headache	8
Vomiting	6
Papilledema	5
Seizures	3

Headache was the commonest symptom in eight children who were old enough to communicate. This was followed by vomiting in six patients and visual disturbance in three patients. Focal neurological signs were seen in 10 patients and included limb weakness (seven), cranial nerve palsies (four), and focal seizures (three). Papilledema confirmed by a pediatric ophthalmologist was seen in five patients.

Table 4: Anatomical sites of the thrombus

Venous sinus involved	N=20
Transverse sinus	10
Superior sagittal	6
Sigmoid sinus	5
Straight sinus	3
Internal jugular vein	2

The commonest venous sinus involved were the transverse sinus in 10 cases followed by the SSS in six cases and the sigmoid sinus in five cases. Four children had features of mastoiditis on MRI of the brain, with thrombosis of adjacent transverse and/or sigmoid sinuses.

Investigations

Systemic infections were identified in seven of 20 children in the study, which included ear/mastoid infections in six children and pneumonia in one child. The children who had an obvious infection as the predisposing cause for CVST (seven children) were considered to have a para-infectious, pro-thrombotic state, and did not have a thrombophilia screen. Thus, only 13 children with other noninfectious provoking events underwent detailed screening for markers of thrombophilia, because thrombosis in these children is considered as a complex interplay between genetic and acquired causes. (It included protein C and S levels, anti-thrombin III, APLA, FVL mutation, and MTHFR mutation.) The screen was abnormal in four children, of which two were heterozygote for FVL mutation and one each had deficiency of protein C and anti-thrombin III. The contribution of such abnormalities to the etiology of childhood thrombosis remains unclear, and many other metabolic factors and genetic mutations could be at play, in the pediatric population.

Treatment and outcomes

Although, all children were managed in the same hospital and the management varied based on the discretion of the treating team and also on the clinical setting. Medications used varied between antibiotics for suspected or proven infections in seven of 20 cases, low molecular weight heparin (LMWH) in six

of 20, and warfarin in only three of 20 cases. Supportive therapy with anti-edema and anticonvulsants was used in the majority of cases (17 of 20).

Of the 20 patients in this series, 14 children had a complete recovery, four had a residual neurological sequel, and two kids died in the cohort. Death was attributed to NAHI in one patient and in the other patient was due to the underlying CHARGE association. Of the patients with abnormal thrombophilia screens, two children were heterozygote for FVL mutation. One of these had a residual weakness with spasticity of one arm, while the other one had recurrent internal jugular vein thrombosis with partial resolution on follow-up imaging. Notably, two patients each who had deficiency of protein C and anti-thrombin III recovered completely with no residual deficits.

Discussion

Cerebral venous sinus thrombosis (CVST) is an uncommon condition, with extremely diverse clinical features, predisposing factors, brain imaging findings, and outcome. [16,17] It is one of the common causes of young stroke in India, [18] about 20% in people aged 40 years or less. [19] Depending on the site, size, duration, and rapidity of development of thrombus, it can be present as seizure, space occupying lesion, benign intracranial hypertension, subarachnoid haemorrhage, unexplained loss of consciousness, or meningoencephalitis. [20] CVST most commonly involves superior sagittal sinus (72%) followed by lateral sinus (70%), in 30 to 40% of cases more than one sinus is involved. [21] Children with CVST commonly present with headaches or seizures. About half of the children presenting with an acute focal neurological deficit have a previously identified risk factor. The list of associated conditions ranges from head and neck infections to systemic conditions such as inflammatory bowel disease, nephrotic syndrome, and autoimmune disorders. [22] Head trauma, sickle cell disease, and congenital or acquired heart disease appear to be a trigger for arterial stroke [23,24] whereas dehydration, cyanotic heart disease, and chronic anemia predispose to venous strokes. [25]

We included neonates with CVST in our study. The commonest underlying illness in neonates was perinatal hypoxia, surgical intervention, and/or the presence of central lines. The most common risk factor for CVST in older children was infection (particularly middle ear or mastoid infection). Other studies have also reported higher frequencies of both systemic and local infections in children with CVST, as compared to adults.26 In our study, of the 13 children tested for thrombophilia, only four had abnormal results and none of these patients died. However, in the Bristol study, [26] of the three children with abnormal thrombophilia screens, two with a heterozygous FVL mutation died. In the same study, one child was found to have low antithrombin III and low protein S levels, similar to our study where one child each was deficient in protein C and anti-thrombin III activity.

In our study, there were seven children with an obvious infection (para-infectious CVST) as the provoking cause for venous thrombosis. They were treated with broad spectrum antibiotics, and resolution of infection usually coincided with neurologic recovery. Supportive therapy with anti-edema measures and anti-epileptic drugs were used as and when indicated. Only six of 20 children in this cohort received anticoagulation with LMWH and further only three of these 20 children were transitioned to oral anticoagulation with vitamin K antagonists. Unlike in adults, the rationale for treatment with anticoagulants in CVST is not yet well established due to the paucity of data in this age group and hesitancy among clinicians in starting anticoagulants when hemorrhagic lesions

are seen on brain imaging. A study which was conducted in 2007 on adults concluded that anticoagulation on its own appears to be an adequate treatment for patients with acute dural sinus thrombosis. [27] In a systematic review in 2009, the recommendation for all patients with CVST without contraindications for anticoagulation suggested that patients should be treated either with body weight-adjusted subcutaneous LMWH or dose-adjusted intravenous heparin. [28]

In our study, 14 of 20 children recovered completely while 4 had residual neurological deficits, and only two died. In the Bristol series, almost half of the 21 cases had an adverse outcome from CVST, although cognitive outcome was not assessed in this study. [29] Two of the 20 children in our study developed chronic intracranial hypertension, with recurrent headaches and papilledema, requiring lumbar punctures and cerebral decongestants with close ophthalmic monitoring. Children with confirmed CSVT require monitoring for neurological and ophthalmological symptoms and signs related to raised intracranial pressure and optic nerve compression. This is particularly the case in nonverbal patients as visual impairment may go undetected by parents. [30]

Conclusion

Pediatric CVST continues to remain a clinical challenge, with a wide spectrum of presentations and unique provoking events. It is important to maintain a high index of suspicion to diagnose this relatively uncommon condition in children, especially where the risk factors for venous thrombosis are not evident. The study concluded that Cerebral Venous Sinus Thrombosis (CVST) is mainly a disease of child-bearing women, although significant proportions of men were affected. Cerebral Venous Sinus Thrombosis (CVST) presents in a wide variety of signs and symptoms. Headache was the commonest presenting symptoms followed by blurred vision, seizures and vomiting. On examination most of the patients have papilledema followed by unilateral motor deficit. After imaging, The Sagittal Venous Sinus (SSS) and the transverse sinuses were the most affected sinuses. Concerning treatment, LMWH followed by warfarin were the major treatment options.

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