Research Article

Cerebral Venous Sinus Thrombosis: Clinical Profile, Risk Factors, Neuroimaging Results, and Treatment Outcomes in the Pediatric Population

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ABSTRACT

Objective: To determine the clinical profile, neuroimaging results, risk factors and treatment outcomes of children with cerebral venous sinus thrombosis (CVST).

Methods: A prospective observational study consisting of 80 patients was conducted at The Children's Hospital and Institute of Child Health in Pakistan between January 2018 to June 2020. Children aged between one month and 18 years with confirmed diagnosis of CVST and focal neurological deficits for more than 24 hours were included. Patients of neonatal age or those suffering from arterial ischemic stroke were excluded. Medical chart reviews, physical examination, neuroimaging along with laboratory testing were conducted to ascertain the cause of CVST, determine its clinical profile, and explore its structural effects on the pediatric brain.

Results: Fever was the most common clinical feature , followed by headache and lethargy occurring in (88.8%, n=71), (68.8%, n=55) and (67.5%, n=54) of patients respectively. Neuroimaging results showed thrombosis in the superior sagittal sinus in all the patients (100%, n=80), while transverse sinus was involved in (right 61.3%, n=49; left 8.8%, n=7; both 30%, n=24), straight sinus in (right 93.8%, n=75; both 6.3%, n=5) and sigmoid sinus in (right 67.5%, n=54; left 17.5%, n=14; both 15%, n=12) of patients. Infection and dehydration were precipitating factors for disease development. Neurological care and heparin were given to all patients while warfarin and aspirin were administered in 93.8% (n=75) and 81.3% (n=65) of patients respectively. At the two-week follow-up, 12.5% (n=10) of patients had complete recovery while 81.3% (n=65) had partial recovery. Mortality rate was found to be 6.3% (n=5).

Conclusion: Fever, lethargy and headache are clinical manifestations in CVST. Most patients are pale with focal neurological deficits and suffer from dehydration, infection, anemia and thrombocytosis in multiple sinuses. Mortality rate post-treatment with anti-coagulants is concerning.

Keywords: cerebral venous sinus thrombosis, sinus thrombocytosis, thrombosis, neuroimaging findings, clinical manifestations, risk factors, treatment, children

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) consists of acute thrombosis (blood clot formation) in the dural venous sinuses, that drain blood from the brain. Cerebral venous drainage involves the movement of blood through the superficial and deep systems into the jugular veins. An enlarged thrombus results in venous blockage and causes cerebral edema, raised intracranial pressure, venous infarction, and/or hemorrhagic stroke. If this condition prevails, it can lead to complete venous system obstruction and death can ensue.[1,2]

CVST is a rare but serious clinicopathological condition that occurs in 0.67 per 100,000 children per year, comprising 0.5% of all stroke cases.[3-5] In adults, the incidence of CVST has been estimated to be 3-4 cases per million people, while the incidence in children and neonates is about 7 cases per million.[1,5,6]

Although more than 100 causes of CVST have been discussed in the scientific literature, no cause is identified in as many as 20-25% of cases.[7,8] Infective causes target the central nervous system, middle ear or facial skin. Penetrating head trauma occurs infrequently with aggressive antibiotic treatment, accounting for less than 10%

of cases. Hypercoagulable states, dehydration, adjacent infectious processes and iron deficiency (anemia) are conditions that increase CVST risk in children.[9]

Clinical presentation in CVST patients is typically gradual, variable, and non-specific compared to acute ischemic stroke.[2] In a Dutch-European study, headache (95%), focal seizures with or without secondary generalization (47%), paresis (uni- or bilateral) (43%) and papilledema (41%) were frequently observed.[10] Fifteen percent of patients were comatose, 39% had some impairment of consciousness and 20% presented with isolated intracranial hypertension (headache, visual disturbance and papilledema). Less commonly noted symptoms included thunderclap headache mimicking subarachnoid hemorrhage.[10,11]

Given its diverse clinical profile, diagnosis of CVST requires high clinical suspicion and proper neuroimaging.[12] Non-invasive imaging by magnetic resonance venography offers superior parenchymal visualization and is preferred over cerebral angiography to demonstrate filling defects in the cerebral venous system. Specific labs can be done according to history and examination.[12]

Treatment comprises of general and specific measures. General treatment includes supportive care to regulate body temperature, hydration status, blood sugar levels, blood pressure, seizures, and intracranial pressure.[13] Specific treatment consists of anticoagulant therapy in the form of low molecular weight heparin in an acute setting, followed by oral warfarin and/or aspirin. Endovascular thrombolysis is generally reserved for severe cases.[14] Nevertheless, randomized controlled studies fail to determine the appropriate duration of antithrombotic therapy. In the past, CVST had been associated with a high mortality rate (30-50%), however, recent studies report a much lower rate (8-14%) due to advances in the field of the disease.[15,16]

Most of the population-based studies on CVST have focused on data from developed countries. Given the higher mortality rate and prevalence in developing countries, this study aims to fill the gaps in the medical literature by exploring CVST's underlying causes, clinical presentation, neuroimaging findings and outcomes in Pakistani children to provide insight on disease etiology, diagnosis and treatment from a developing world perspective.

METHODS

An observational prospective study was conducted for CVST patients at the Department of Pediatric Neurology in The Children's Hospital and Institute of Child Health, Lahore, Pakistan for period of 2.5 years (January 2018 to June 2020). The sample size of 80 patients was calculated with the World Health Organization's sample size calculator, using a confidence level of 90%, an absolute precision of 10% and the proportion of prothrombotic etiology in the study population.[17]

After approval from the Institutional Review Board, the study sample was devised based on the following selection criteria: patients of both genders between one month to 18 years of age who had focal neurological deficits for more than 24 hours were included, while patients of neonatal age and those who had previously suffered from arterial ischemic stroke were excluded. Informed consent was obtained from parents prior to recruitment. Disease status was determined by a consultant neurologist on the basis of medical history, physical examination and neuroimaging results. This information was analyzed alongside laboratory testing to investigate the clinical features of CVST and understand its structural implications on the pediatric brain. All data was collected on a carefully designed proforma and the results were analyzed using SPSS Version 20.

RESULTS

In total, 20 out of 80 patients (25%) were female while 75% (n=60) were male. Moreover, 75% (n=60) patients were under five years of age while the rest (n=20, 25%) were between 5 to 18 years (Table 1).

Table 1. Patient demographics

Demographic	Result	Numbers(n)	Percentage (%)
Gender			
	male	60	75.0
	female	20	25.0
Age			
	<5 years	60	75.0
	5-18 years	20	25.0

Table 2: Findings from patient history, lab, neuroimaging, and physical examination

Patient history			Physical examination		
	Result(n)	Percentage (%)		Result (n)	Percentage (%)
Fever			Well or sick		
yes		88.8	sick	70	87.5
no		11.3	well	10	12.5
Lethargy			Pale		
yes		67.5	yes	65	81.3
no		32.5	no	15	18.8
Decreased Appetite			Hydration status		
yes		56.3	mild	50	62.5
no		43.8	moderate	25	31.3
			severe	5	6.3
Irritability			Glasgow Coma Scale		
yes		37.5	unconscious	60	75
no		62.5	conscious	20	25
Headache			Bulging fontanel		
yes		68.8	yes	30	37.5
no		31.3	no	50	62.5
Seizure			Papilledema		
yes		37.5	yes	30	37.5
no		62.5	no	50	62.5
Focal deficit			Focal neurological deficit		
yes		32.5	hemiplegia	30	37.5
no		67.5	cranial nerve palsies	30	37.5
			none of the above	20	25
Altered state of consciousness			**Neuroimaging**		
conscious		25			
unconscious		75			
Family history			Superior sagittal sinus		
yes		0	yes	80	100
no		100	no	0	0
			Straight sinus		
Trauma			right	75	93.8
yes		0			
			left	0	0
no		100			
			both	5	6.3
Head and neck infection			Transverse sinus		
yes		17.5	right	49	61.3
no		82.5	left	7	8.8
Systemic illness			both	24	30
yes		75	Sigmoid sinus		
no		25	right	54	67.5
Diarrhea			left	14	17.5
yes		32.5	both	12	15
			Internal cerebral veins		
no		67.5	yes	20	25
			no	60	75

Laboratory Findings		
Hemoglobin	**Numbers (n)**	**Percentage (%)**
anemia		
normal	20	25
Platelet count	20	25
thrombocytosis		
normal	30	37.5
Sodium level	30	37.5
hypernatremia		
normal	74	92.5
Blood glucose	74	92.5
abnormal		
normal	80	100
Serum urea	80	100
abnormal		
normal	80	100
Cholesterol	80	100
hypercholesterolemia		
normal	74	92.5
CSF finding	74	92.5
abnormal		
normal	40	50
Protein C, protein S & anti-thrombin 3 levels	40	50
deficiency		
normal	54	67.5
Anti-phospholipid antibodies level	54	67.5
increased		
normal	74	92.5
normal	74	92.5

Fever was the most common clinical finding (88.8%, n=71) based on patient history, followed by headache (68.8%, n=55) and lethargy (67.5%, n=54). Also, 75% (n=60) of patients were unconsciousness and suffered from underlying systemic illness, while 37.5% (n=30) had seizures and/or irritability. Furthermore, 56.3% (n=45) had decreased appetite. None of the patients had a family history of CVST or traumatic injury. Head and neck infections were found in 17.5% (n=14) of patients while 32.5% (n=26) had focal deficits and/or diarrhea (Table 2).

Laboratory investigation indicated that 75% (n=60) of patients had anemia, 62.5% (n=50) had thrombocytosis, and 50% (n=40) had abnormal cerebrospinal fluid findings. Normal sodium, cholesterol and anti-phospholipid antibodies levels were observed in 92.5% (n=74) of cases. Protein C, protein S and anti-thrombin III levels were also normal in 67.5% (n=54) of patients (Table 2).

Magnetic resonance imaging illustrated that the right transverse sinus was affected in 61.3% (n=49) of patients, 8.8% (n=7) had left transverse sinus occlusion, while 30% (n=24) had both transverse sinuses affected. Furthermore, 67.5% (n=54) and 17.5% (n=14) of patients had thrombocytosis in their right sigmoid sinus and left sigmoid sinus respectively, while 15% had both sigmoid sinuses affected (n=12). The right straight sinus was affected in 93.8% (n=75) of patients while the remaining 6.3% (n=5) had both straight sinuses affected. All patients had superior sagittal sinus thrombosis (n=80, 100%) and internal cerebral veins were impacted in 25% (n=20) of cases (Table 2). The association between gender and straight sinus thrombocytosis was insignificant according to a chi-square test performed at 5% level of significance. More male patients had transverse sinus and sigmoid sinus thrombocytosis than females. These two associations were significant at 5% according to the chi-square test.

Physical examination indicated that 87.5% (n=70) of study participants were sick, 81.3% (n=65) were pale, 37.5% (n=30) had bulging fontanel and papilledema, and 75% (n=60) were unconscious and/or had focal neurological deficits. Mild dehydration was observed in 62.5% (n=50) of patients while 6.3% (n=5) were severely dehydrated (Table 2).

Neurological care and low molecular weight heparin were given to all patients while warfarin and aspirin were administered to 93.8% (n=75) and 81.3% (n=65) of patients respectively. Two weeks post-treatment,

consciousness level of 75% (n=60) of patients improved immediately while neurological deficits persisted in 87.5% (n=70). Complete recovery was observed in 12.5% (n=10) of patients, 81.3% (n=65) had partial recovery and 6.3% (n=5) died (Table 3).

Table 3: Clinical outcomes observed two weeks post-treatment

Immediate outcome after Rx	Result	Numbers (n)	Percentage (%)
Conscious level			
	not improved	20	25
	improved	60	75
Neurological deficit			
	persisted	70	87.5
	improved	10	12.5
Complete recovery			
	yes	10	12.5
	no	70	87.5
Partial recovery			
	yes	65	81.3
	no	15	18.8
Death			
	yes	5	6.3
	no	75	93.8

DISCUSSION

CVST is an uncommon but life-threatening neurological disorder whose clinical presentation, neuroradiological findings, risk factors, and treatment outcomes in Pakistani children are described in this study. We found that prominent clinical manifestations of the disease included fever, headache, lethargy, coma, seizures and papilledema. In addition, focal deficits such as hemiplegia and cranial nerve palsies, were observed in the majority of cases. This clinical profile is consistent with the current literature, which reports headache as one of the most common findings and notes fever, seizures, coma, focal deficits, weakness and papilledema as relevant presentations.[2,18-21] A notable discrepancy is the absence of vomiting in our patients, which has been identified as a key clinical feature of CVST in some studies.[18-21]

Given this diverse and non-specific clinical profile, neuroimaging serves an important role in diagnosis and disease monitoring.[19] Our MRI results found that CVST affects multiple sinuses, including the superior sagittal sinus, transverse sinus, straight sinus, and sigmoid sinus. In 25% of patients, the internal cerebral veins were also impacted. Allroggen and Abbott (2000) reports that the main cerebral venous sinuses affected by CVST are the superior sagittal sinus (72%) and the lateral sinuses (70%), while more than one sinus is affected in 33.3% of cases. In addition, both sinuses and cerebral or cerebellar veins are affected in 30-40% of patients.[22] Another study, Wang et al (2015), observed that multiple sinuses were involved in 78.9% of cases, and transverse and sigmoid sinus were the most commonly involved combination. In this study, the transverse sinus (84.2%), sigmoid sinus (73.7%), and superior sagittal sinus (52.6%) were greatly affected.[23] In addition, Teksam et al. (2008) states that key locations affected in CVST patients in neonates and older children are the transverse sinuses and the superior sagittal sinus, followed by the straight sinus in the neonates and infants and the sigmoid sinus in older children.[24] As can be seen, our findings on the structural effects of CVST on the pediatric brain are consistent with the current medical literature.

CVST in Pakistan is an outcome of a significantly prevalent systemic illnesses, contributed by high rates of malnutrition, infection and consanguinity; such is typical in many developing countries. Based on patient history and physical examination analyzed in this study, dehydration and infection can be speculated as causes of CVST. This observation aligns with results presented in Patil et al. (2014) and Wang et al (2019).[18,19] Infection might be noted by the presence of fever while diarrhea can be used to explain the varying degrees of dehydration observed in all patient cases. This analysis potentially explains the higher incidence of CVST in the developing world context, where said risk factors tend to be more prevalent.[18]

Studies suggest that prothrombic conditions and congenital thrombophilia are common risk factors for CVST in well-developed countries.[4,25,26] Although we did not examine congenital data, our results are congruent with these risk factors.

In addition, according to the International Study on Cerebral Venous and Dural Sinuses Thrombosis, uncommon causes of CVST include anemia and thrombocytosis, found in 75% and 62.5% of study cases respectively.[26] These associations are less understood because their correlation is described in research studies of low quality.[26] Iron deficiency has been reported as a risk factor across several case reports and case series in the literature, including Belman et al. (1990), Beri et al. (2012) and Benedict et al. (2014).[26-31] Likewise, thrombocytosis has been implicated in CVST by studies like Jensen et al. (2007).[26,32]

CVST is commonly treated with anticoagulant therapy.[2] Although both LMWH and unfractionated heparin (UFH) can be used, LMWH is deemed more appropriate due to the corresponding lower hospital mortality, better functional prognosis, and reduced likelihood to develop new intracranial hemorrhage.[2] Traditional therapy for venous thromboembolism also includes an overlap between LMWH and vitamin K antagonist warfarin. The treatment provided to our participants (heparin and warfarin) followed these clinical care guidelines.[33]

Consistent with Wang et al (2019), our study's mortality rate was 6.3% and both death cases had thrombocytosis affecting multiple sinuses (i.e., right transverse, straight sinus, as well as sigmoid sinus).[19] Ten male (12.5%) patients completely recovered while 65 patients (82.3%, 45 males and 20 females) partially recovered. Males had better outcomes than females, a result contrary to the findings of Continho et al. 2009.[14]

This study had a few limitations. It did not investigate central nervous system infections (e.g. meningitis) as a possible cause for CVST because CSF examination was inadequately reported (e.g. as "normal" or "abnormal"). The study was conducted at a single center and had a relatively small sample size. Most patients were also under 5 years old. All clinical testing was performed by a single consultant neurologist, which suggests the potential for bias. Furthermore, post-treatment follow-up was limited to two weeks. Higher quality studies (e.g. randomized-controlled trials) involving multiple centers, a longer follow-up duration, a larger sample size, and a more diverse age group are recommended for future analysis.

CONCLUSION

We concluded that mortality is relatively minimal in the treatment of CVST. Thrombosis commonly affects the straight, transverse, superior sagittal, and sigmoid sinuses. Fever is the most common clinical feature, followed by headache and lethargy. Dehydration and infection are the most common precipitating factors for disease development. Keeping in view the limited data worldwide, larger and longer studies are required for a better understanding of CVST.

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