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Original Article

Cerebral sinovenous thrombosis in children: clinical presentation, locations, and acquired and inherited prothrombotic risk factors

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ABSTRACT

Background. Cerebral sinovenous thrombosis (CSVT) in children is a rare and life-threatening cerebrovascular disease. Hence, we evaluated its clinical presentations, inherited and acquired prothrombotic risk factors along with the accompanying diseases, the thrombosis locations as well as the outcomes of anticoagulant therapy in children with CSVT.

Methods. The medical records of pediatric CSVT patients treated between January 2011 and September 2018 were analyzed retrospectively.

Results. The study included 29 children, 15 boys (51.7%) and 14 girls (48.3%), with the median age being 11 years (range:3 days-17 years). The most commonly presented complaint in neonates was seizures and in the non-neonatal age groups was a headache. Also, at least one acquired and/or inherited thrombophilic risk factor was identified in 89.7% of the patients. The most commonly acquired prothrombotic risk factors along with the accompanying diseases included infections, central venous catheter, and dehydration, while the most commonly inherited thrombophilic risk factors included heterozygous factor-V Leiden mutation and elevated lipoprotein (a). The most common thrombosis location was found to be the transverse sinus. Also, none of the patients died due to the thrombotic episode. Complications included epilepsy in five patients, hydrocephalus in one patient, and intracranial hypertension in another patient.

Conclusions. Clinicians need to be well aware of the inherited and acquired prothrombotic risk factors in CSVT. It should also be kept in mind that at-risk patients may also present with nonspecific signs and symptoms with no apparent neurological manifestation. The risk of acute complications and long-term sequelae can be substantially reduced if diagnosed early and initiated with appropriate treatment at the early stages.

Key words: cerebral sinovenous thrombosis, children, risk factors.

Cerebral sinovenous thrombosis (CSVT) in children is a rare and life-threatening cerebrovascular condition, and with increased clinical awareness and improved neuroradiological techniques, the disease can now be diagnosed more frequently and at earlier stages. Early diagnosis of CSVT is crucial since the risk of acute complications and long-term sequelae can be substantially reduced if appropriate treatment is initiated within the first few hours.[1] The incidence of childhood CSVT occurs between 0.4 and 0.7 children per 100,000 children per year.[2] The incidence is higher among neonates (30–50%) compared to other pediatric age groups. There is a male predominance with boys accounting for approximately two-thirds of all cases in children.[3]

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The etiology of childhood CSVT is multifactorial. Also, 33% to 99% of patients have inherited or acquired prothrombotic risk factors. The most well-known acquired prothrombotic risk factors along with the accompanying diseases include catheters, infection, dehydration, chronic inflammatory diseases, nephrotic syndrome, and malignancies.[4] Studies have reported inherited thrombophilic risk factors including antithrombin deficiency, protein C and protein S deficiency, Factor V Leiden and prothrombin G20210A mutations, hyperhomocysteinemia, elevated circulating levels of factors II, VIII, IX, XI, and fibrinogen[5], and high lipoprotein (a) level.[6,7] Recent studies have indicated that mutations in the heterozygous methylenetetrahydrofolate reductase (MTHFR) gene alone cannot increase the risk of thrombosis. Hyperhomocysteinemia occurs in cases with homozygous MTHFR mutation due to the remethylation of impaired homocysteine to methionine. Hyperhomocysteinemia is also considered a strong risk factor for thrombosis in children.[8,9]

The most commonly recommended treatment for CSVT without significant intracranial hemorrhage includes anticoagulation treatment initially with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for neonates and children. This initial therapy is followed by LMWH for 6 weeks to 3 months in neonates and LMWH or oral anticoagulant therapy for 3 to 6 months in children.[10] The present study evaluated the clinical presentations, inherited and acquired prothrombotic and accompanying diseases risk factors, thrombosis locations along with the results of anticoagulant therapy in CSVT patients treated in our hospital over the last 8 years.

Material and Methods

1. The medical records of pediatric patients with CSVT who underwent treatment and follow-up in the pediatric and neonatal intensive care units between January 2011 and September 2018 were analyzed retrospectively. The study was approved by the local ethics committee of Eskişehir Osmangazi University Clinical Researches (09.10.2018, no:17). The patients' age, sex, inherited and acquired prothrombotic risk factors and accompanying diseases, neurological symptoms and findings, thrombosis locations, treatment, and outcomes were reviewed from their medical records.

CSVT was diagnosed using brain magnetic resonance imaging and/or brain magnetic resonance venography. The results of etiological investigations were analyzed in all patients which included the complete blood count, cholesterol, triglycerides, lipoprotein (a), protein C, protein S, D-dimer, fibrinogen, antithrombin, homocysteine, C-reactive protein levels, activated protein C resistance, prothrombin time, activated partial thromboplastin time, antinuclear antibody (ANA) and extractable nuclear antigen antibody (ENA) profiles, and antiphospholipid and anticardiolipin IgG antibodies. The genetic mutation analysis in Factor V Leiden G1691A, prothrombin G20210A mutation, *MTHFR* C677T, and *MTHFR* A1298C were evaluated.

Statistical analysis

Data were analyzed with SPSS 17.0 statistical software package (SPSS Inc., Chicago, NY, USA) using descriptive statistics. The Shapiro–Wilk test was used to check whether numerical variables were normally distributed while the Chi-square (χ^2) test (exact method) was used to compare categorical variables.

Results

Patient Population

This study included a total of 29 children. Of which, five were neonates (0–28 days); with two (40%) females and three (60%) male neonates. The non-neonatal age groups (29 days-18 years) included 12 girls (50%) and 12 boys (50%) with a median age of 11 years (minimum 3 days, maximum 17 years) (Fig. 1).

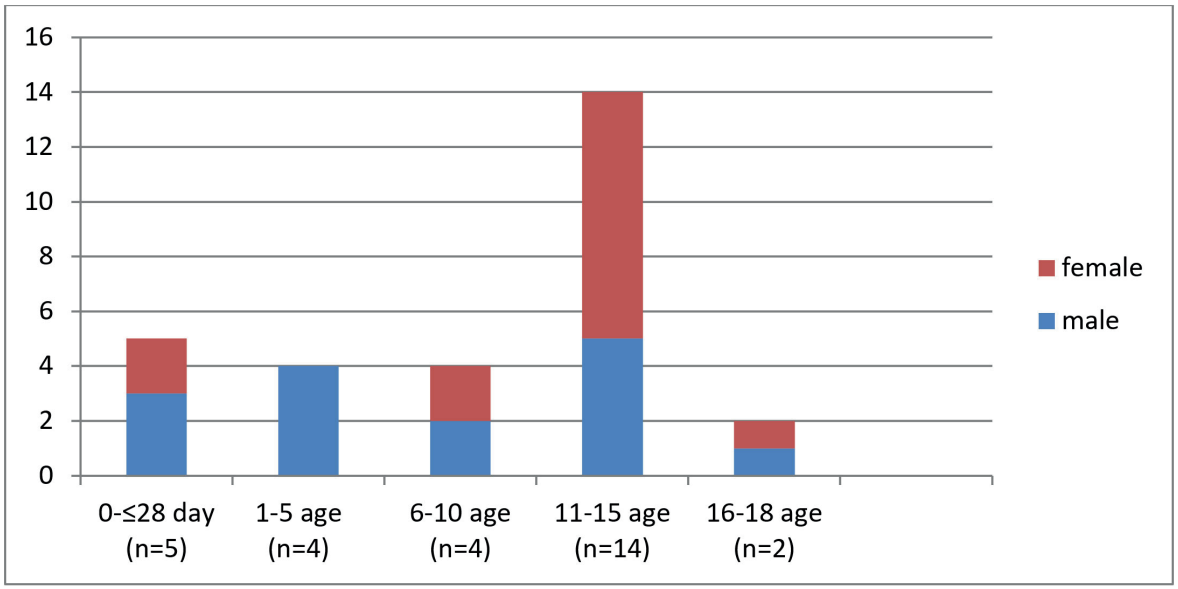

Fig. 1. Sex distribution of pediatric cerebral sinovenous thrombosis patients according to age group.

Clinical presentation (Neurological symptoms and findings)

All five neonates with CSVT presented with seizures (100%), accompanied by hemiparesis in two patients (40%), change in consciousness in two (40%) patients, and respiratory failure in one (20%) of the patients. Patients in the non-neonatal age groups presented with a headache (87.5%), vertigo (50%), diplopia (29.2%), papilledema (29.2%), hemiparesis (29.2%), change in consciousness (25%), seizures (20.8%), facial paralysis (12.5%), ptosis (8.3%), and numbness (8.3%) (Table I).

Table I. Distribution of the patients age, sex, and neurological symptoms and findings.

Neonates (0–28 days)	n	%
Seizures	5	100
Change in consciousness	2	40
Hemiparesis	2	40
Respiratory failure	1	20
Infants, children, and adolescents (29 days–18 years)		
Headache	21	87.5
Vertigo	12	50
Hemiparesis	7	29.2
Double vision	7	29.2
Papilledema	7	29.2
Change in consciousness	6	25.0
Seizures	5	20.8
Facial paralysis	3	12.5
Ptosis	2	8.3
Numbness	2	8.3

Acquired and inherited thrombophilic risk factors

At least one acquired and/or inherited thrombophilic risk factor was identified in 26 patients (89.7%), while the other three patients (10.3%) showed no known risk factors. Seven of the 21 patients with acquired risk factors also had inherited thrombophilic risk factors. The most commonly acquired risk factors included infections (24.1%), a central venous catheter (6.9%), and dehydration (6.9%), while the most commonly inherited thrombophilic risk factors included heterozygous factor V Leiden mutation (13.8%) and elevated lipoprotein (a) level (13.8%) (Table II). All five of the neonates had an acquired risk factor and accompanying diseases (dehydration in two, severe infection [sepsis] in two, and ventriculoperitoneal shunt

Table II. Acquired and inherited thrombophilic risk factors of the patients.

Risk Factors	n (%)
Acquired Prothrombotic Risk Factors	21 (72.4)
Infection (4)*	7 (24.1)
Jugular venous catheter	2 (6.9)
Dehydration (1) ≠	2 (6.9)
Obesity	2 (6.9)
Chronic kidney disease + oxalosis (1) μ	1 (3.5)
Juvenile idiopathic arthritis (1) ∞	1 (3.5)
Nephrotic syndrome	1 (3.5)
Mental retardation + epilepsy	1 (3.5)
Congenital heart disease	1 (3.5)
Acute leukemia	1 (3.5)
Hereditary spherocytosis	1 (3.5)
Hydrocephalus + ventriculoperitoneal shunt	1 (3.5)
Inherited Thrombophilic Risk Factors	13 (44.8)
Factor V Leiden mutation (heterozygous)	4 (13.8)
Lipoprotein(a) elevation (>30 mg/dL)	4 (13.8)
Prothrombin G20210AI mutation (heterozygous)	2 (6.9)
Hyperhomocysteinemia + homozygous/compound heterozygous *MTHFR*	3 (10.3)
No known risk factors	3 (10.3)

*Accompanied by heterozygous factor V Leiden mutation in 2 patients, lipoprotein(a) elevation in 1 patient, hyperhomocysteinemia + homozygous/compound heterozygous MTHFR in 1 patient.
≠Accompanied by lipoprotein(a) elevation in 1 patient.
μAccompanied by heterozygous factor V Leiden mutation and hyperhomocysteinemia + homozygous/compound heterozygous MTHFR in 1 patient.
∞Accompanied by heterozygous prothrombin G20210AI mutation in 1 patient.

and hydrocephalus in one neonate). One of the neonates with dehydration also had elevated lipoprotein (a) level as an associated inherited risk factor. However, no inherited risk factors were identified in the other neonates.

Of the two neonates with infection as an acquired risk factor, one developed transverse and sigmoid sinus thrombosis following sepsis, while the other developed cerebral and Galen vein thrombosis after sepsis. Cases associated with infection in the other age groups included three patients developing lateral sinus thrombosis after otitis and mastoiditis, one developing cavernous sinus thrombosis after periorbital cellulitis, and the other developing bilateral transverse sinus thrombosis after meningitis.

Thrombotic Locations

Of the CSVT patients in this study, 44.8% had thrombosis in a single anatomic venous system, while 55.2% showed involvement of multiple venous systems. The most common anatomic site of thrombosis was the transverse sinus (Table III). None of our patients had thrombosis with intracranial hemorrhage.

Treatment

Treatment was initiated with unfractionated heparin or LMWH in all patients. LMWH was preferred over UFH due to its ease of administration, particularly in newborns and infants, patients with high hemorrhage risk, and the one for whom continuous vascular access was not possible.[8]

Table III. Thrombosis locations of patients diagnosed with central sinovenous thrombosis.

Thrombosis Location	n (%)
Single anatomic venous system	13 (44.8)
Transverse sinus*	9 (31.0)
Sagittal sinus	1 (3.5)
Jugular vein thrombus	1 (3.5)
Cavernous sinus	1 (3.5)
Sphenoparietal sinus	1 (3.5)
Multiple anatomic venous systems	16 (55.2)
Transverse sinus + Sigmoid sinus≠	5 (17.2)
Bilateral transverse sinus	3 (10.3)
Bilateral sagittal sinus	1 (3.5)
Sinus rectus + Inferior sagittal sinus	1 (3.5)
Sinus rectus + sinus confluence	1 (3.5)
Transverse sinus + Galen veinα	1 (3.5)
Sagittal vein + Transverse sinus	1 (3.5)
Cerebral vein + Galen veinβ	1 (3.5)
Jugular vein + Transverse sinus	1 (3.5)
Transverse sinus + Sigmoid sinus + Jugular vein	1 (3.5)

*1 neonate, ≠2 neonates, α1 neonate , β1 neonate.

All neonates received anticoagulant therapy of LMWH for 3 months. In three non-neonatal patients, anticoagulation was initiated with UFH for the first 5 to 7 days, which was then continued with an oral anticoagulant (warfarin) administration. Twenty-one patients started treatment with LMWH, where 15 continued treatment with LMWH while six of them were switched to oral anticoagulant (warfarin) after 5 to 7 days. All patients were treated for at least 3 to 6 months. None of the patients had anticoagulant-related bleeding complications.

Outcomes

The mean follow-up time was 24 months. None of the patients died due to their thrombotic episodes. Five patients developed epilepsy, one patient developed hydrocephalus, and one patient developed intracranial hypertension. Two epilepsy patients and one hydrocephalus patient were neonates while the non-neonatal age group showed other complications. One patient's ptosis resolved after about one year.

Discussion

CSVT is a rare cerebrovascular disease that can occur in children of any age starting from the neonatal period, and carries a high risk of mortality and neurological sequelae. It is observed more commonly in males (56–75%).[6,8,11-16] In the present study, male predominance was observed in the neonatal group consistent with the literature, whereas males and females were equally represented in the other age groups. The incidence of CSVT is reported to be highest in the neonatal period.[6,11,14,17-20] Beside the neonatal period, it was more common in the 6–11 year age group (36.84%) and in the 15–18 age group patients (35.29%).[15,21]

CSVT patients can exhibit various signs and symptoms such as headaches, seizures, papilledema, cranial nerve palsies, motor weakness, and altered mental status. The most common neurological symptoms and findings in the literature include seizures in neonates[4], whereas the headache was reported in 90% of

adults and 60% of children.[22] All the neonates in this study presented with seizures. The most common neurological symptoms and findings in the non-neonatal age groups were headache (87.5%), dizziness (50%), hemiparesis (29.2%), and seizures (20.8%). Less frequent findings were diplopia, papilledema, numbness, ptosis, and facial paralysis. Although seizures were more common in neonates, they may also occur in any child with CSVT. In addition to seizures, two of our neonates showed changes in consciousness, two showed hemiparesis, while one developed respiratory failure. The incidence of seizures in all childhood CSVT was reported as 26.9% by Lolli et al.[20], 34.8% by Ozcan et al.[5], 37.5% by Javed et al.[16], 37.9% by Heller et al.[11] and 40% by Sèbire et al.[14]. Hemiparesis was reported at a rate of 13–37.5% in the literature, which was consistent with our findings. Alterations in mental status may have manifested as irritability, stupor, or coma.[6,23,24] Clinically, seizures and coma were reported as poor prognostic factors[23], while isolated headache was considered a favorable prognostic factor.[24] Isolated headache was the most commonly presented complaint in most of our patients. Also, none of our patients went into a coma or died due to CSVT.

Acquired prothrombotic risk factors along with the accompanying diseases reported in the etiology of CSVT include infections, dehydration, surgery, jugular or subclavian central venous catheters, solid tumors, leukemia and lymphomas, anemia, autoimmune diseases, renal diseases, obesity, metabolic disorders, birth asphyxia, and cardiac malformations.[13] In this study, 10.3% of the patients showed no known acquired prothrombotic risk factors and accompanying diseases or inherited risk factors, while the other 89.7% showed at least one acquired and/or inherited risk factor. Similar to our study, Wasay et al.[19] and Lolli et al.[20] reported that 90% and 84.3% of all childhood CSVT cases, respectively, indicated the presence of one or more acquired prothrombotic risk factors and/or inherited thrombophilic risk factors. Acquired prothrombotic risk factors were identified in 70.5% of patients in the study by Heller et al.[11], 77.4% by Carvalho et al.[18], 81.5% by Kenet et al.[25], 86.8% by Viera et al.[12], 88.8% by Suppiej et al.[26], and 100% by Sèbire et al.[14]. The prevalence of acquired prothrombotic risk factors along with the accompanying diseases in the present study was 72.4%, which is consistent with the literature. Infection was the most commonly acquired prothrombotic risk factor in our study. Most infection-associated cases occurred in patients with head and neck infections.[6,20,22,27] Also, head and neck infections were most common in our patient series, with three out of seven cases associated with infection occurring after otitis and mastoiditis, while one case occurred after periorbital cellulitis, and one after meningitis.

In 44.8% of our patients, at least one inherited thrombophilic risk factor was identified In previous large-scale studies conducted in Turkey, inherited thrombophilic risk factors were reported in 30–54% of patients.[28-30] According to the literature, factor V Leiden mutation is the most commonly detected inherited thrombophilic risk factor in venous thromboembolism.[5,21,28,29] In the present study, the most commonly inherited thrombophilic risk factors were factor V Leiden mutation (13.8%) and elevated lipoprotein (a) level (13.8%). According to a study by Heller et al.[11], these were also the most commonly identified inherited thrombophilic risk factors. Population-based studies have shown that homocysteine metabolism-related gene polymorphisms such as *MTHFR* C677T and *MTHFR* A1298C do not alone cause thrombosis but increase the risk of thrombosis and cardiovascular disease when accompanied by elevated plasma homocysteine levels. Particularly, two known polymorphisms of the *MTFHR* gene (C677T and A1298C) have been associated with high homocysteine levels.[5] Homocysteine is an amino acid that is formed as an intermediate product while converting methionine to cysteine and requires Vitamin B for conversion to either methionine or cysteine in reactions. Both B vitamin deficiencies (B_6, folic acid, B_{12}) and mutations in the MTHFR

gene plays a role in the conversion of folate to its active form and are risk factors for hyperhomocysteinemia.[22,31] In our study, hyperhomocysteinemia with homozygous/compound heterozygous *MTHFR* mutation was the third most commonly inherited thrombophilic risk factor, which was detected in 10.3% of the patients.

The involvement in more than one anatomical region (multiple venous sinuses) was reported as more common in pediatric CSVT cases, with the transverse sinus being the most frequently involved region.[5,19,32] Multiple venous sinus thrombosis (55.2%) and transverse sinus thrombosis were also more common in the present study. Wasay et al.[19] observed multiple venous sinus involvement in 74% of their patients, with transverse sinus involvement being the most common (73%). Ozcan et al.[5] also reported that multiple sinus involvement was more frequent and reported the transverse sinus as the most commonly involved region (69.6%). Viera et al.[12] reported the transverse sinus to be most commonly involved as well (67.9%). In contrast, Lolli et al.[20] reported that 40.7% of patients had multiple sinus involvement while thrombosis was most frequently located in the transverse sinus in neonates (27.3%) and the cortical veins in older children (31.3%). Superior sagittal sinus thrombosis was common in some studies, which was detected at frequencies of 100% by Javed et al.[16], 62.4% by Heller et al.[11], and 47.4% by Bonduel et al.[15]. Of the five neonates in our study, thrombosis was located in the transverse and sigmoid sinuses in two neonates; in one neonate, it was located in the transverse sinus thrombosis; in another neonate, the location was in transverse sinus and Galen vein, and cerebral vein and Galen vein in another neonate.

According to the scientific statement from the American Heart Association/American Stroke Association, anticoagulation is the main treatment except in the case of otogenic lateral sinus thrombosis. The type, dose, and route of the anticoagulant agent were selected based on the individual patient's circumstances. For patients with CSVT and hemorrhagic infarction, otitis media/mastoiditis, head trauma, or neurosurgery, a multidisciplinary approach for anticoagulation should be undertaken.

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommends anticoagulation treatment initially with either UFH or LMWH and subsequently with LMWH or vitamin K antagonists (VKA) for a minimum of 3 months for children with CSVT without significant ICH. If CSVT occlusion or ongoing symptoms persist after the initial 3 months of therapy, further administration of anticoagulation was suggested for 3 more months.[7] For CSVT patients with significant hemorrhage, the radiologic monitoring of the thrombosis was suggested for 5 to 7 days, and anticoagulation was suggested if thrombus extension was noted at that time or initial anticoagulation was suggested for children without hemorrhage in close follow-up.[7,10] However, to choose one of these two options, the multidisciplinary decision has to be considered. In children with CSVT and recurrent risk factors (e.g., nephrotic syndrome, L-asparaginase therapy), prophylactic anticoagulation was suggested at times of risk factor recurrence. Thrombolysis, thrombectomy, or surgical decompression may be required only in children with severe CSVT, where no improvement was observed after initial anticoagulant therapy. Also, supportive care and neuroprotective measures such as replacement of intravenous fluids, oxygenation, the elevation of the head of the bed to 30°, and treatment of seizures are important too. Children with CSVT should be followed up for increased intracranial pressure and papilledema. Repeated MRV venography is required during the follow-up therapy to decide the duration of anticoagulation.[7]

None of our patients had thrombosis with intracranial hemorrhage. Therefore, anticoagulation was initiated in all our patients immediately upon diagnosis. Also, studies in children have reported that LMWH and UFH are safe in children, where anticoagulant therapy reduces mortality, preserves cognitive

functions, and lowers the rate of recurrent thrombosis.[7,24]

The limitations of our study were as follows: a small number of patients, a single-center center experience-based study, and the retrospective nature of the study.

In conclusion, CSVT in children is a rare and life-threatening condition. Early diagnosis is critical since the risk of acute complications and long-term sequelae can be significantly reduced with an appropriate treatment approach implemented in the early stage. Therefore, clinicians need to be well aware of the clinical picture of CSVT and it is important to keep in mind that these patients may not have neurological symptoms such as seizures, diplopia, papilledema, numbness, ptosis, or facial paralysis, and may only be presented with nonspecific symptoms and findings, such as headache, dizziness, fatigue, and respiratory failure. Also, thorough knowledge of the acquired prothrombotic risk factors along with the accompanying diseases and inherited prothrombotic risk factors facilitates the early diagnosis of patients at risk.

Ethical approval

The study was approved by the local ethics committee (09.10.2018, no:17).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: YDK, ZCÖ, ÖB; data collection: YDK, KBÇ, CY, NT; analysis and interpretation of results: YDK, ZCÖ; draft manuscript preparation: YDK, ZCÖ, ÖB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

No conflict of interest.

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