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Cerebral sinovenous thrombosis in children: A single-center experience

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What is already known on this topic?

- *Cerebral sinovenous thrombosis is an important cause of cerebral ischemic stroke in childhood. The diagnosis can often be missed because the disease occurs with subtle symptoms such as headache and vomiting.*
- *When cerebral thrombosis is detected, initiating anticoagulant treatment as soon as possible, reduces the risk of neurological sequelae.*

What this study adds on this topic?

- *Headache and focal neurological findings should be evaluated with fundus examination.*
- *Identification of "intraventricular and thalamic hemorrhage" is warning signs for investigating sinovenous thrombosis in neonates.*
- *Risk factors should be investigated in patients of all age groups, and those with identified risk factors should be followed up for a long time.*

ABSTRACT

Objective: The study aimed to evaluate the patients with a diagnosis of cerebral sinovenous thrombosis in terms of clinical findings, etiology and underlying risk factors, imaging findings, treatment, and prognosis in the long term.

Materials and Methods: Medical records of 19 patients whose ages ranged between 0 days and 17 years with clinical and radiological cerebral sinovenous thrombosis in Ege University Department of Child Neurology were retrospectively evaluated.

Results: Nine of nineteen cases were female (47.3%). The median age was 84 months (0-201 months). The most common complaint at the presentation was headache (n=12) and the most common physical examination finding was papilledema (n=11). In etiology, otitis/mastoiditis in three cases, iron deficiency anemia in three cases, sinusitis in two cases, catheter use in four cases, Behçet's disease in three cases were determined. The most common observed genetic factors causing thrombosis was methylenetetrahydrofolate reductase mutation. The transverse sinus (68.4%) is the sinus where thrombosis is most frequently observed. As a result of an average follow-up of 12 months (2-72 months), hemiparesis (n=3/19, 15.7%) and epilepsy (n=5/19, 26.3%) were recorded as sequelae findings, and no mortality was observed.

Conclusion: In cases presenting with headache, evaluation of papilledema on funduscopic examination should not be skipped. Neurological imaging should be performed in the change of consciousness of poor feeding infants and children with infections in the head and neck area or underlying chronic diseases. When cerebral sinovenous thrombosis is detected, anticoagulant therapy should be started immediately.

Keywords: Cerebral sinovenous thrombosis, pediatric stroke, treatment, neuroimaging

Introduction

Cerebral Sinovenous Thrombosis (CSVT) is an important cause of cerebral venous ischemic stroke in childhood. Its incidence in the pediatric age group has been reported as 0.4-0.7/100 000 per year (1). Symptoms, risk factors, and underlying causes of patients at the time of presentation vary depending on age (2, 3). While low levels of anticoagulant proteins (Protein C, Protein S, and antithrombin III) at birth and development of birth-related complications increase the tendency to thrombosis in newborns; also infections of the head and neck region, chronic inflammatory diseases, malignancies, dehydration, use of central venous catheters and intracranial surgical interventions in childhood cause CSVT (4-10). Hereditary thrombophilia is more common in children compared to adults (4, 6, 10-13). In studies conducted with pediatric patients, it is important to get an early diagnosis of this

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patient group presenting with a clinic that varies depending on the age, since morbidity and mortality (4-25%) are higher in children compared to adults, and there is a 20% risk of recurrence of cerebral or systemic thrombosis (4, 14, 15).

In this study, patients with CSVT who were followed up in different age groups for an average of 12 months (2-72 months) in our clinic were evaluated retrospectively in terms of etiological cause, underlying risk factors, clinical and radiological findings, anticoagulant therapy and long-term prognosis.

Materials and Methods

The data, patient files, and electronic record systems of 19 patients who were followed up with the diagnosis of CSVT between November 2007 and December 2018 in the Ege University Pediatric Neurology Department were analyzed retrospectively.

Diagnosis of cerebral sinus vein thrombosis was made by brain magnetic resonance imaging (MRI) and brain magnetic resonance venography (MRV) in all patients. In newborns, the diagnosis was confirmed by transfontanelle ultrasound and brain magnetic resonance imaging, and brain magnetic resonance venography in cases of suspected thrombosis. C-reactive protein, erythrocyte sedimentation rate (ESR), complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), protein C, protein S, antithrombin 3, D-dimer, fibrinogen, Homocysteine, antiphospholipid antibody, lupus anticoagulant, factor IX and factor VIII levels, activated protein C resistance, Factor XIII mutation, factor V Leiden mutation, prothrombin 20210 gene mutation, methylenetetrahydrofolate (MTHFR) gene mutation were investigated in patients for etiology. Pathergy test was performed in cases with suspected Behçet's disease and these patients were evaluated by pediatric rheumatology, dermatology, and ophthalmologist.

Patients' demographic information, symptoms at presentation, age of diagnosis, physical examination, laboratory examinations (immunological, biochemical, genetic), underlying diseases, findings at diagnostic and control brain magnetic resonance and magnetic resonance venography, use and duration of anticoagulant therapy, follow-up period and if any, sequelae findings were recorded.

The research protocol was approved by the Ege University Ethics Committee (dated 22.01.2020, decision number: E.24085). This research was conducted following the Declaration of Helsinki.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Numerical variables were expressed as mean and standard deviation, categorical variables were expressed as percentage and frequency values. T-tests were used for binary comparisons of numerical variables if normal distribution conditions were met, and Mann-Whitney U tests were used if normal distribution conditions were not met. Chi-square tests were used for paired comparisons of categorical variables. Statistical significance level was defined as $p<0.05$.

Results

The median age of 19 patients participating in the study was 84 months (range 0 months-201 months, mean 101.68±66.25 months). Three patients were diagnosed in the neonatal period and 16 patients outside the neonatal period. Ten of the patients were male and nine were female. The demographic data of our patients are shown in Table 1.

While the most common complaint at presentation was headache (n=13, 68.4%) outside the neonatal period, other complaints were determined as diplopia (n=10), change of consciousness (n=4), and fever (n=3). The change of consciousness was the main complaint in two patients who were admitted in the neonatal period, one patient presented with inability to feed/dehydration. In the neurological examination of the patients, papillary edema in twelve patients and sixth cranial nerve palsy, hemiparesis in three patients, seizures in 2 patients, and dysarthria in one patient were detected. Two of the newborn patients had lethargy and one had seizures.

When the etiology was evaluated, intracranial hemorrhage detected during the antenatal period in one of the patients diagnosed in the neonatal period, hypernatremic dehydration in one patient, and early-onset neonatal sepsis in the other patient were found. When the risk factors of childhood CSVT patients were evaluated, three patients had acute otitis media, three had anemia, three had Behçet's disease, three had acute lymphoblastic leukemia, and two had sinusitis and one patient had secondary hemophagocytic lymphohistiocytosis that developed based on immune deficiency and the use of a central catheter. In one of the patients who developed cerebral thrombosis based on sinusitis, some factors such as obesity and smoking increase thrombosis tendency. One patient was diagnosed with CSVT after the evacuation of a parapharyngeal abscess that developed after acute tonsillitis.

In our study, the inherited disease panel that causes thrombosis tendency in the acute period was studied in 13 of the childhood patients; Methylenetetrahydrofolate reductase (MTHFR) heterozygous mutation was found in ten patients, a homozygous mutation in three patients, Factor V Leiden mutation was found as homozygous in one patient and heterozygous in one patient (Table 2). While factor XIII mutation was detected as heterozygous in one patient, prothrombin G20210A mutation was not observed in our patients. Hemophagocytic lymphohistiocytosis developed in our patient with the diagnosis of immunodeficiency and Fas ligand mutation was found in the patient. The inherited disease panel was studied in all three neonatal CSVT patients, and MTHFR heterozygous mutation was detected in all patients, while an accompanying homozygous Factor XIII mutation was detected in one patient.

Factor VIII elevation in three of 16 patients diagnosed with childhood CSVT whose causes of thrombophilia were studied in the acute period, activated protein C resistance in three patients, lupus anticoagulant in three patients, protein S deficiency in two patients, factor IX elevation in two patients, protein C deficiency in one patient, antithrombin 3 deficiency in one patient, lipoprotein (a) deficiency in one patient were detected. Concomitant hyperhomocysteinemia was observed in a patient with MTHFR homozygous mutation. Causes of acquired thrombophilia in the neonatal period were not evaluated.

Table 1. Demographic characteristics of the cases

No	Age	Gender	Complaint	Neurological Examination	Etiology	Prothrombic risk factor	Follow Up (month)	Involvement	Prognosis
1	0	M	Change of consciousness	Lethargy	Early-onset neonatal sepsis	MTHFR C677T het	3	Transverse sinus Confluences of sinuses	Cure
2	0	F	Change of consciousness	Lethargy	Antenatal Intraventricular Hemorrhage	MTHFR C677T het	6	Sinus rectus Transverse sinus	Hemiparesis Epilepsy
3	0	M	Dehydration	Seizure	Hypernatremic dehydration	Factor XIII V34L hom MTHFR C677T het	4	Superior sagittal sinus Inferior sagittal sinus Sinus rectus Transverse sinus Confluence of sinuses	Epilepsy
4	17	F	HA Double vision Fever	PE Sixth cranial nerve palsy	Sinusitis Obesity Smoking	MTHFR C677T het MTHFR A1298C het Lp (a) deficiency Protein C deficiency	2	Transverse sinus Sigmoid sinus	Sixth cranial nerve palsy
5	6	M	Double vision	PE	AOM Sinusitis	MTHFR C677T het MTHFR A1298C het	12	Transverse sinus Sigmoid sinus	Cure
6	5	F	HA Double vision	PE	AOM	MTHFR 677T het	2	Transverse sinus Sigmoid sinus	Cure
7	12	M	Change of consciousness	PE Sixth cranial nerve palsy	-	MTHFR C677T het MTHFR A1298C het LA elevation FactorVIII elevation	12	Superior sagittal sinus Transverse sinus Sigmoid sinus	Cure
8	2	M	Change of consciousness	Hemiparesis	Anemia	Factor XIII V34L hom MTHFR A1298C het FactorIX elevation	6	Superior sagittal sinus	Cure
9	15	F	HA Double vision	Sixth cranial nerve palsy	Anemia	APC resistance LA elevation	7	Transverse sinus Sigmoid sinus	Cure
10	5	F	HA Change of consciousness Fever	Dysarthria Hemiparesis Seizure	ALL Central vein catheterization	MTHFR C677T hom Protein S deficiency APC resistance Antithrombin3 deficiency	12	Superior sagittal sinus	Hemiparesis Epilepsy
11	7	F	HA Double vision	PE Seizure	Hemophagocytic Lymphohistiocytosis	Fas Ligand mutation	10	Superior sagittal sinus	Hemiparesis Epilepsy
12	14	F	HA Double vision	PE Sixth cranial nerve palsy	ALL Central vein catheterization	FVIII, FIX elevation Pro S deficiency	4	Superior sagittal sinus	Epilepsy
13	12	M	Change of consciousness HA Double vision	PE Hemiparesis	ALL Central vein catheterization	-	8	Superior sagittal sinus Transverse sinus	Cure
14	12	F	HA Double vision	PE	Behçet's disease	FV G1691A(Leiden) het	48	Transverse sinus	Recurrence
15	14	F	HA Double vision	PE	Behçet's disease	MTHFR C677T het APC resistance	4	Transverse sinus	Recurrence

Table 1. Demographic characteristics of the cases (continued)

No	Age	Gender	Complaint	Neurological Examination	Etiology	Prothrombic risk factor	Follow Up (month)	Involvement	Prognosis
16	16	M	HA Double vision Fever	PE	Behçet's disease	MTHFR C677T hom Hyperhomocysteinemia FactorVIII elevation	18	Inferior sagittal sinus Sinus rectus Transverse sinus Sigmoid sinus	Cure
17	6	M	HA	PE Sixth cranial nerve palsy	AOM	MTHFR C677T het LA elevation	3	Transverse sinus Sigmoid sinus	Cure
18	12	M	HA		Anemia	FV G1691A(Leiden) hom	72	Transverse sinus Sigmoid sinus	Cure
19	6	M	HA	PE	Parapharyn-geal abscess surgery	MTHFR A1298C hom	12	Transverse sinus Sigmoid sinus	Cure

ALL, acute lymphoblastic leukemia; AOM, Acute otitis media; Het, heterozygote; Hom, homozygote; HA, Headache; Lp(a), Lipoprotein (a); APC, activated protein C; LA, lupus anticoagulant; PE, papilledema

Table 2. Prothrombotic risk factors of patients with cerebral sinovenous thrombosis

	Detected/Studied	
MTHFR C677T	Het: 9/16	Hom:2/16
MTHFR A1298C	Het: 4/16	Hom:1/16
FV Leiden G1691A	Het: 1/16	Hom:1/16
Factor 13 V34L	Het: 1/16	Hom:1/16
Prothrombin G20210A	Het: 0/16	Hom:0/16
Lupus anticoagulant		3/16
Protein S deficiency		2/16
Protein C deficiency		1/16
Antithrombin 3 deficiency		1/16
Lipoprotein(a) deficiency		1/16
Activated protein C resistance		3/16
Factor VIII elevation		3/16
Factor IX elevation		2/16
Hyperhomocysteinemia		1/16

Het, heterozygote; Hom, homozygote

Table 3. Radiological location of cerebral sinovenous thrombosis

Involved sinus	N	%
Transverse sinus	15	78.9
Sigmoid sinus	9	47.3
Superior sagittal sinus	7	36.8
Sinus rectus	3	15.7
Confluences of sinuses	2	10.5
Inferior sagittal sinus	2	10.5

N: Number of patients

Multiple venous involvement was detected in three of the neonatal CSVT patients, while multiple venous sinus involvement was observed in 62.5% (n=10/16) of childhood cases. Transverse sinus was the most commonly involved (n=15/19, 78.9%). Also, sigmoid sinus (n=9), superior sagittal sinus (n=7), sinus rectus (n= 3), confluent sinus (n=2) and inferior sagittal sinus (n=2) involvement was also detected (Table 3).

In one of the patients with acute leukemia, cerebral ischemic infarction, and bleeding in the brain parenchyma were detected in addition to cerebral thrombosis (Figure 1). In two of the newborns, intraventricular bleeding and intraparenchymal bleeding were observed together with CSVT. One of the newborns was the case who developed hydrocephalus due to intracranial hemorrhage detected antenatally and had transverse sinus and sinus rectus thrombosis, as well as a germinal matrix, bleeding, and bleeding within the lateral ventricles after ventriculoperitoneal shunt operation on the first postnatal day (Figure 2). In the other case, signal changes compatible with hemorrhage were observed in both lateral ventricles and the periventricular area adjacent to the 4th ventricle due to the involvement of deep and superficial veins.

Low molecular weight heparin (LMWH) was initiated as anticoagulant therapy in three of the neonatal patients and all patients except one of the childhood CSVT patients. Control cranial MR venography was performed at the end of the 3rd month in all patients who received LMWH treatment, and anticoagulant treatment was discontinued in patients with recanalization. No side effects of anticoagulant treatment were observed in the patients during the treatment. LMWH was discontinued by the detection of partial recanalization in the control MR venography performed in the first month of the patients with intraventricular and intraparenchymal hemorrhage accompanying CSVT in the neonatal period.

Acetazolamide treatment was initiated in the acute period in all 12 patients with papilledema. After serial ophthalmologic examinations (dilated fundus examination, visual acuity, color vision, contrast sensitivity, visual field, and optical coherence tomography) in the first 2 weeks of treatment, the treatment of patients whose papilledema regressed in the third month on average from the first month on monthly controls was discontinued. In the first week of the treatment, it was planned to reduce CSF pressure to normal values by adding topiramate and methylprednisolone (1 mg/kg) to the treatment in one case (case 4) with persistent papilledema in the fundus of the eye,

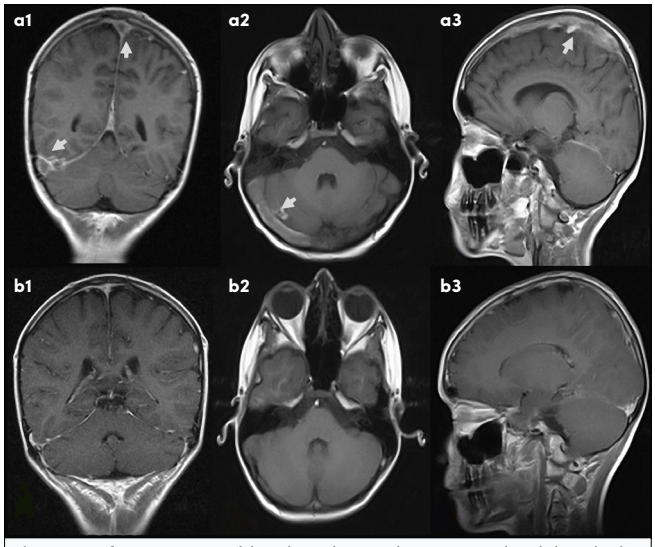

Figure 1. a, b. A 12-years-old male with ALL who presented with headache and drowsiness after L-asparaginase treatment (Case 13) (a) A1- coronal, A2-axial, A3- sagittal T1-weighted Cranial MR and MR venography with filling defects compatible with thrombosis of the superior sagittal sinus, right transverse sinus and sigmoid sinus in acute phase and sinus enlargement (arrow) (b) B1-coronal, B2-axial, B3-sagittal at the 1st month control MR venography showed thinning of the thrombus and recanalization in superior sagittal sinus, right transverse sinus, right sigmoidal sinus

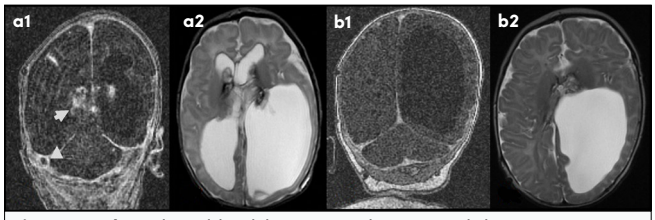

Figure 2. a, b. 0-day-old girl, has ventriculoperitoneal shunt operation due to hydrocephalus secondary to antenatal intracranial hemorrhage (Case 2) (a) A1 coronal, A2 axial The enlargement and thrombosis in bilateral transverse sinus, sigmoid sinus and sinus rectus (arrowhead) also; periventricular germinal matrix hemorrhage and hemorrhage of the lateral ventricles at the level of the basal ganglia in T2-weighted sequences MR venography (arrow) (b) B1 coronal, B2 axial at the 3rd month control MR venography, partially recanalized thrombi defined in bilateral transverse sinus and sigmoid sinus, asymmetric dilatation of lateral ventricules; thinning of right lateral ventricle and enlargement of the left lateral ventricle

and by lumbar puncture in three cases. In a patient diagnosed with Behçet's disease (case 15), optic disc fenestration was performed in the second week of follow-up, due to the persistence of papilledema during follow-up.

Cerebral sinovenous thrombosis recurrence was not observed in our cases except for two patients diagnosed with Behçet's disease. The duration of anticoagulant therapy was extended to 12 months in these patients due to recurrent cerebral thrombosis. Patients diagnosed with acute otitis media and sinusitis were treated with intravenous cephalosporin antibiotics. Papilledema was detected in both recurrent CSVT cases and acetazolamide was started and discontinued in the 3rd month of the treatment.

The patients were followed for 2-72 months and no mortality was observed in any of the patients. While full recovery was observed in one of our patients in the neonatal period in the long-term follow-up of the patients, hemiparesis and epilepsy were observed in one of the patients with intraventricular and intraparenchymal hemorrhage accompanying CSVT, and epilepsy was observed as sequelae in the other. A complete recovery was observed in 10 cases in non-neonatal patients, epilepsy (3 cases), hemiparesis (2 cases), and permanent sixth cranial nerve involvement (1 case) was observed as a long-term neurological sequela.

Discussion

Community-based studies of cerebral sinovenous thrombosis in children and newborns are rarely observed in the literature. Neonatal (<1 month) (69 cases, 43.2%) and non-neonatal (1 month-18 year) (91 cases, 56.8%) cases are reported in the article in which DeVeber et al. (4) evaluated the ischemic stroke records (160 cases) of 16 pediatric tertiary care centers in Canada and the epidemiology of sinovenous thrombosis in childhood. It is thought in the light of these data that approximately half of all pediatric CSVT cases occur in the neonatal period. Also, it is appropriate to evaluate cerebral sinovenous thrombosis patients in two sections as the neonatal period and childhood due to different etiology, clinical, and treatment plans. The distribution of patients was identified as neonatal (n=6, 50%), and non-neonatal (n=6, 50%) in a series of 12 cases in Turkey by Bektaş et al. (16). In the study where Heller et al. (6) evaluated the prothrombic risk factors of 149 cases, the distribution of the cases was observed as neonatal (40 cases, 26.8%) and non-neonatal (109 cases, 73.2%). In our study group, it was observed that newborn cases were less frequent (n=3, 15.7%) compared to the literature. It was thought that the absence of specific clinical findings of cerebral thrombosis in the neonatal period might lead to a deficiency in diagnosis.

The gender distribution in cerebral venous thrombosis is higher in boys in children (M/F: 3/1) (17). In our study, a similar distribution was observed between the genders forming our cohort (male/female: 9/10).

Since clinical findings are often not specific to the situation, delay in diagnosis and misdiagnosis are common problems in CSVT in children. In different studies, the most common signs and symptoms were defined as headache, seizure, paresis, papillary edema, and lethargy (4, 17-19). While neonatal patients present with clinical findings such as encephalopathy and seizures; Findings such as headache, vomiting, diplopia, encephalopathy, papilledema due to increased intracranial pressure, focal neurological findings (seizures, muscle weakness) in addition to sixth cranial nerve palsy may be observed in children (2). Similarly, headache (81.3%) was the most common complaint in our childhood patients in our series, and the other complaints were diplopia (69%), change of consciousness (19%), and fever (19%), while the change of consciousness (% 67) and dehydration (33%) were other findings in the neonatal period patients. Different researchers reported the incidence of papilledema in CSVT at a rate of 12-20%, and it was seen in 63.1% of our cases (4, 20, 21). Performing funduscopic examination of every patient presenting with headache, change in consciousness, focal neurological findings guide the clinician in the diagnosis of CSVT. Especially the detection of papilledema in fundus examination is a warning sign for planning emergency neuroimaging with cranial MR and MR venography considering cerebral sinovenous thrombosis in the differential diagnosis.

To determine the underlying cause in children diagnosed with cerebral venous sinus thrombosis is important to anticipate thrombosis recurrence to determine the treatment protocol and duration of treatment. It has been stated in the literature that factor V Leiden and prothrombin mutation are the most common inherited prothrombotic causes (22). Publications report the role of prothrombic diseases in pediatric CSVT patients at a frequency of 20% to 80%, which is higher than adult patients (4, 23-25). In newborns, it is difficult to screen for thrombophilic markers because the reference range of coagulation proteins varies with age and the amount of sample required for testing is high (26). Although no underlying hereditary problem was found in three newborn cases with CSVT in the review of Sirachainan et al. (27), antithrombin III deficiency was observed in one case, and protein C deficiency in one case. Fitzgerald et al. (7) detected 13% (3/24) Factor V Leiden mutation, 40% (4/10) MTHFR C677T mutation, 44% (4/9) MTHFRA1298C mutation in their study with 42 newborns, while did not detect the deficiency of Protein C, S, or antithrombin 3 in any of the cases. In the study of Bektaş et al. (16), 33% (2/6) in newborns, 33% (2/6) in non-neonatal patients, hereditary thrombophilic risk factors, factor V Leiden mutation (16.6%), MTHFR homozygous mutation (16.6%), PT G20210A mutation (8.3%), MTHFR heterozygous mutation (8.3%) were detected. Methylenetetrahydrofolate reductase (MTHFR) plays an important role in the conversion of homocysteine to methionine. Polymorphisms and common variants of the MTHFR gene (C677T and A1298C) have been associated with elevated plasma homocysteine levels. Although MTHFR deficiency was previously thought to increase the risk of venous thrombosis and coronary heart disease, no such risk has been identified in recent studies, and evaluation of MTHFR genotyping in thrombosis tendency is not recommended (28-30). In our study, although the most common hetero/homozygous MTHFR mutation was detected in the screening of genetic abnormalities that cause hereditary thrombosis, hyperhomocysteinemia was detected in only one of these cases. The heterozygous MTHFR mutation was detected in all of our newborn cases, an accompanying homozygous Factor XIII mutation was observed in one case. Although factor V Leiden mutation was detected in two patients with childhood CSVT, the Prothrombin G20210A mutation, which Dentali et al. (31) identified as the most common thrombosis predisposition mutation, was not detected in our patients. The heterozygous mutation causing increased Factor XIII levels was also detected in one patient with childhood CSVT. The low number of our patients does not constitute a sample for society. Multicenter studies are required to determine the prothrombotic causes of cerebral sinovenous thrombosis etiology.

When CSVT patients without prothrombic risk factors (31/149, 20.8%) were compared with CSVT patients with prothrombic risk factors (84/149, 56.4%) in the multicenter prospective study of Heller et al. (6), genetic prothrombic risk factors are observed to play an important role in the development of pediatric CSVT. In the prospective studies of Sebire et al. (10), 62% risk factor was found in 29 patients in the evaluation of thrombophilia in childhood CSVT, excluding newborns. In our study, 56.3% of acquired thrombophilia risk factors were found in our childhood cases. These are factor VIII elevation (3 cases), activated protein C resistance (3 cases), lupus anticoagulant (3 cases), protein S deficiency (2 cases), high factor IX level (2 cases), and protein C deficiency (1 case), antithrombin III deficiency (1 case), and lipoprotein (a) deficiency (1 case). Control tests were observed as returning to normal limits in the control values of the patients at the 3rd month, in two of the patients with elevated factor VIII levels, and in all patients with antithrombin III, protein C, protein S deficiency, and factor IX elevation. Since these markers are also acute phase reactants, they were thought to be high in the acute period. Factor VIII deficiency was one of the causes of thrombophilia with the highest rate with 54%. In the study of Sebire et al. (10), while factor VIII deficiency was observed in control tests in only one of our patients in our study. Long-term outpatient follow-up was continued in terms of thrombosis recurrence in cases in which activated protein C resistance, lupus anticoagulant, and lipoprotein (a) deficiency were detected during outpatient follow-up.

Sinusitis, acute otitis media, and mastoiditis are common etiological causes in children and adolescents, and in our patients, sinusitis (12.5%) and acute otitis media/mastoiditis (18.7%) were detected in non-neonatal patients (4, 19, 32). More than half of the cases of sinovenous thrombosis have underlying chronic diseases such as nephrotic syndrome, liver diseases, cancers, head trauma, anemia (iron deficiency anemia, hemolytic anemia, β-thalassemia, sickle cell anemia) (10, 33). Shi et al. (34) case-control study declared the incidence of CSVT in Behçet' s Disease as 2.5% Asian patients. In the case series presented from our country, Behçet's disease in the etiology was determined higher than this value by Bektaş et al. (16) (2/6), by Unver et al. (21) (3/11). Similarly, it was thought that the high rate of detection of Behçet's disease in 18.7% (n=3/16) in our patient group may be due to similar ethnic characteristics.

In Sweden, Grunt et al. (17) evaluated the prognosis of CSVT in children (44/65) and newborns (21/65) and reported as a result of the prospective follow-up of 65 patients for 18 months or more that being in the neonatal age group and having intraparenchymal hemorrhage are risk factors for poor prognosis. Wu et al. (35) recommend investigating CSVT in the presence of intraventricular hemorrhage and thalamic hemorrhage in newborns. Also, in another publication, the presence of thalamic bleeding accompanying CSVT in newborns has been associated with the development of cerebral palsy (36). In our cases, two newborn cases with intraventricular and parenchymal bleeding accompanied by CSVT showed improvement with sequelae (epilepsy, hemiparesis). In the study of Vieira et al. (37) including 53 cases (6 newborns) in which they evaluated CSVT of Portuguese children, 52.6% multiple sinus involvement was observed, and the most commonly involved sinuses were determined as transverse and sigmoid sinuses. Consistent with this, in our study, 62.5% of multiple sinus involvement was observed, and the most commonly involved sinuses were transverse sinus (78.9%) and sigmoid sinus (47.4%), respectively. Consistent with the literature, it was also observed in our study that multiple sinus involvement did not contribute to the determination of prognosis in any age group (17,36). In our patients, nine (56%) of thirteen patients with multiple sinus involvement showed complete recovery, and two (33%) of six patients with single sinus involvement showed complete recovery.

In children, heparin use, hydration, and antibiotic use in the treatment of CSVT are recommended and endovascular treatment methods are recommended in patients with rapid deterioration in neurological functions despite appropriate anticoagulant therapy. Although warfarin and LMWH are used safely in children, anticoagulant treatment is less preferred due to the risk of bleeding in newborns (38). While the Royal College of Physicians guide does not recommend treatment for newborns, the American College of Chest Physicians guide recommends anticoagulant therapy to be initiated in newborns without extensive ischemic or hemorrhagic infarction or cerebral bleeding if thrombosis is enlarged, and The American Heart Association recommends anticoagulant therapy to be initiated in selected newborns who have had radiologically and clinically proven CSVT despite only supportive treatments (hydration, infection, seizure, and increased intracranial pressure). In the non-neonatal period, each of the guidelines recommends anticoagulation until complete recanalization is achieved (39-41).

Low molecular weight heparin was initiated in all of our patients, except for one patient who had bleeding within the brain parenchyma (Case: 10), Treatment was discontinued in cases with recanalization in control cranial MRV. Three cases (Cases 4, 5, 15) who were outside the neonatal period and had a high risk of recurrence were evaluated and received secondary anticoagulant prophylaxis. Coumadin treatment was initiated in one of the patients with MTHFR mutation and in the adolescent patient with concomitant protein C deficiency, high lipoprotein (a) elevation, factor VIII elevation, and one of the patients with recurrent Behçet's disease (Case 15). The duration of anticoagulant treatment was extended to 12 months due to recurrence in the follow-up in two of the patients followed up with the diagnosis of Behçet's disease. Current treatment guidelines recommend follow-up for progressive vision loss in the diagnosis of CSVT, and urgent treatment of increased intracranial pressure when vision loss is detected (Class I; Level of Evidence C) (42). However, there is no explanation about the frequency or the method of follow-up in the guidelines. In our clinic, all patients diagnosed with papilledema by CSVT were initiated with acetazolamide in the acute period and evaluated with a serial ophthalmologic examination (dilated fundus examination, visual acuity, color vision, contrast sensitivity, visual field, and optical coherence tomography). Topiramate and methylprednisolone were used in one of our patients who had a refractory course in the first week of treatment, and lumbar puncture was performed in three patients to normalize the intracranial pressure. Papilledema resolved in an average of 6 months and permanent vision loss was observed in 40% of patients in the ophthalmologic evaluation of pediatric and adult CSVT patients in seven different tertiary health centers by Liu et al. (43). In our cases, papilledema resolved at 3 months, and permanent vision loss was not detected. We associated this result with the early diagnosis of papilledema, aggressive treatment protocol, and close clinical follow-up, as well as the low mean age of our patient population.

While mortality due to CSVT has been reported as 4-12% in children, this rate has been defined as high as 14-25% in newborns (3, 10, 27, 44). Mortality was not observed in any of the neonatal and non-neonatal patients in our patient group. In publications, morbidity in children with CSVT varies between 20 and 70% (19, 45). In our study, in patients followed up for 12 months (2-72 months), childhood CSVT patients had epilepsy (18.8%) as neurological sequelae, hemiparesis in two cases, and permanent sixth cranial nerve paralysis were observed in one case. Complete recovery was observed in one of the neonatal CSVT patients, hemiparesis and epilepsy in the other, and epilepsy sequelae in the other patient.

The recurrence rate in CSVT has been reported between 0% and 20% in different publications depending on the underlying reasons (3, 10, 14, 45). Recurrence is less expected in children under the age of two (10). In our study, CSVT recurrence was observed in two patients over the age of 2 who were diagnosed with 'Behçet's Disease', and the anticoagulant treatment period was extended to 12 months.

The most important limitation of our study was the retrospective performance of the study. The cases whose data could not be reached due to missing data in the file records were excluded from the study. This situation led to the limited number of patients included in the study. Despite this, when our study is evaluated with similar studies in the literature since it is a single- center, it is seen that the number of cases is sufficient. The low number of neonatal patients included in our study constitutes the weakness of our study since it does not meet the 50% distribution of neonatal cases among all CSVT in the literature.

Contribution of the study to the literature: While cerebral thrombosis should be kept in mind in the differential diagnosis of patients presenting with papilledema and headache in childhood, CSVT should not be missed in the neonatal period in unexplained encephalopathy. It is recommended to evaluate these patients with cranial MRI and MR venography, which are neuroimaging methods. Detailed consideration of the underlying hereditary factors in childhood is necessary to predict the possibility of recurrence and to determine the duration of treatment. Anticoagulant therapy can be safely applied at all ages in cases where intracranial bleeding accompanying sinus vein thrombosis is ruled out.

In conclusion, the diagnosis of cerebral sinovenous thrombosis in childhood can be overlooked due to its rare occurrence and subtle neurological symptoms. The diagnosis of cerebral sinovenous thrombosis should be suspected in the presence of headache and focal neurological findings in patients with inherited and acquired risk factors. In these patients, the fundus examination should be evaluated for papillary edema, and a diagnosis should be made with brain MRI and/or MR Venography. Initiating anticoagulant treatment as soon as possible under appropriate conditions reduces the risk of neurological sequela in the presence of thrombosis. After the underlying risk factor is identified in the patient, long-term clinical follow-up with control Cranial MRV is required by determining the treatment plan for the cause to prevent recurrent thrombosis.

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