

Theme Issue Article

Paediatric cerebral sinus vein thrombosis

A multi-center, case-controlled study

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Summary

The etiology and pathophysiology of cerebral sinus venous thrombosis (CSVT) in the paediatric population is still poorly understood, and the role of thrombophilic risk factors remains to be elucidated. In our multi-center case-controlled study we studied 46 patients with CSVT diagnosed from April 1996 to December 2003, consecutively referred for thrombophilia work-up. The results of thrombophilia screen were compared to 112 healthy paediatric controls. Anticoagulant therapy was applied according to treating physicians' decisions, and all cases were prospectively followed for a median of 4.1 years. Of 46 children, 8 had CSVT diagnosed in the neonatal period and therefore were analyzed separately. The prevalence of single thrombophilia markers and combinations of thrombophilic risk factors were similar among cases and controls. Among children

with CSVT co-morbid systemic illness was present in most patients at diagnosis. Seven out of 8 children with idiopathic CSVT had thrombophilic risk factors as compared to 31/38 patients with co-morbid conditions. Anticoagulation was initiated in most patients, 11/46 patients continued therapy for a total of one year or more post event. Neither clinical presentation nor initial treatment decisions were affected by presence of thrombophilic risk factors in our study group. Thrombophilia prevalence was not increased in children with CSVT as compared to controls, however thrombophilia was more frequent among children with idiopathic CSVT. Thus, those selected patients would benefit most from thrombophilia work-up, required for long-term therapy considerations.

Keywords

Cerebral sinus vein thrombosis, thrombophilia, paediatric

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Introduction

Cerebral sinus vein thrombosis (CSVT) is a serious and rare disorder with a reported annual incidence of 0.67 per 100000 children (1). The etiology and pathophysiology of CSVT in the paediatric population is still poorly understood, and the role of thrombophilic risk factors remains to be elucidated (1-6). Most

information currently available about childhood CSVT derives from two large studies: the Canadian paediatric stroke registry reported 160 consecutive paediatric and neonatal CSVT patients, recruited by 16 tertiary referral centers since 1992 (1). The German childhood stroke study-group published 149 paediatric patients (median age: 6 years) with CSVT, whose data were collected during 1995-2002 (6). Children presented with

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either focal or diffuse neurological manifestations, and neurological deficits later persisted in 38% of Canadian patients. Co morbid risk factors such as head and neck disorders, acute and chronic illnesses were demonstrated in 29-54% of Canadian cases whereas 70% of German patients presented with underlying clinical conditions. The prevalence of prothrombotic risk factors varied between 41% and 56.4% of patients in the Canadian and German studies, respectively. Most patients (about half the patients in the Canadian study and 87% of the German patients) were treated by anticoagulants, however the impact of this treatment upon long-term prognosis has not been determined (1). Given the increasing consideration about sinus venous thrombosis in children, we decided to perform a case-controlled multicenter study in Israel. Our aim was to unravel the role of prothrombotic risk factors in the etiology of paediatric sinus vein thrombosis and evaluate their potential impact upon its outcome in the paediatric Israeli patients' population.

Patients and methods

Study group

Forty-six paediatric patients admitted to 8 medical centers, including all tertiary Israeli referral centers, from April 1996 to December 2003 were considered eligible for the study. Children from newborn period (excluding preterm infants) to 18 years were enrolled to the study if cerebral sinus venous thrombosis was documented objectively and parental consent obtained. Children with symptoms who lacked radiographic confirmation of sinovenous thrombosis were excluded. Follow up and outcome data were obtained from medical records or assessment during visits at ambulatory clinics. Children were consecutively referred for laboratory evaluation of thrombophilic risk factors.

Control group

A total of 112 children referred between December 1996 to April 2004 for elective surgical procedures or routine ambulatory Paediatric clinic follow-up served as controls for thrombophilic markers. Patients with active cancer, acute infectious diseases or any known coagulopathies were excluded. Informed consent for blood sampling was obtained from all children's guardians. The study has been approved by the hospital's ethical committee in accordance with the ethical standards established in the updated version of the 1964 declaration of Helsinki.

Coagulation tests for analysis of thrombophilia

Citrated blood samples were obtained and prothrombin, partial thromboplastin, and thrombin times as well as fibrinogen assays were performed using standard techniques. Plasma factor VIII activity was assayed using one-stage clotting assay (Dade-Behring, Marburg, Germany). Protein C and antithrombin (AT)

activities were measured by chromogenic assays (Baxter Dade, Bonnstrasse, Switzerland). Free protein S antigen was measured by ELISA (Gradipore Elisa test kit, Riverside Corporate Park, Australia). Circulating anticoagulant was determined using two coagulation-based tests: PTT-LA test (Diagnostica, Stago, Ansiers, France) and the ratio of dilute Russell's viper venom test (DRVVT) time (LA screen, Gradipore, as compared to LA Confirm, Gradipore, Riverside Corporate Park, Australia). FVIII activity was measured using one-stage standard assays. Genomic DNA was extracted from EDTA-anticoagulated blood samples using standard methods. Factor V Leiden (FVL) and the C677T polymorphism in the Methylene-tetrahydrofolate reductase (MTHFR) gene were detected by PCR amplification, as previously described (7, 8). For identification of the G20210A substitution in the factor II gene (FIIIG20210A), a modification of the method used by Poort et al (9) was performed, as previously described (10).

Statistical analysis

Statistical analysis of data was performed using Statistical Program for Social Sciences (SPSS) version 8.0 software. The data were analyzed and compared with our control group using chi-square test. A p-value of ≤ 0.05 was considered to be significant.

Results

A total of 46 patients with documented CSVT met the inclusion criteria. All patients underwent complete thrombophilia work-up following the diagnosis. Abnormal results of coagulation tests were repeated at least twice within 6 months of the acute thrombosis, for further confirmation. Among our 46 patients, 38 were cases of non-neonatal CSVT, whereas 8 patients were diagnosed with CSVT during the neonatal period. The analysis for neonatal CSVT was conducted separately.

Demographic data

Paediatric patients consisted of 23 males and 15 females whose average age was 5.6 ± 4.5 years. The demographic data and ethnic origin of patients and controls are shown in table 1. Patients matched with controls regarding age, gender distribution and ethnic origin.

Underlying co-morbid conditions

Underlying co morbid illnesses were present at diagnosis in 31 out of the 38 children. Among neonates only 2/8 had co morbid conditions at diagnosis (Table 4), whereas others presented with seizures. Co morbid conditions among paediatric patients included the following:

1. Head and neck disorders (4/38) consisting of either cranial arterio-venous malformations (AVM) or status post head trauma (Table 3).

Table 1: Demographic data of paediatric patients and controls.

	Patients	Controls	P value
Age	5.6±4.5	6.3±5.8	0.49
Gender: males/ females	23/15	60/52	0.64
Origin: Arabs	7/38	20/112	0.94
Origin: Jews-Europe/US	10/38	31/112	0.87
Asia-Africa	16/38	44/112	0.76
Mixed Jews	2/38	18/112	0.09
Origin unknown/other	2/38	4/112	0.65

- Systemic illness was present in 8/38 patients at the time of diagnosis. This heterogeneous subgroup included a child with nephrotic syndrome, 4 children with cardiac anomalies, homocysteinuria and systemic lupus erythematosus (SLE-2 children).
- In 18/38 cases infectious etiology (sepsis, Varicella and acute encephalitis) preceded the diagnosis. Mastoiditis and sinusitis (16/18 cases) prevailed in this subgroup.
- One 18-year-old female developed CSVT while on oral contraceptive therapy.
- A group of 7/38 children presented with isolated neurological manifestations. Those consisted of pseudo tumor cerebri or convulsive disorder. These presenting signs may be a consequence of “idiopathic” CSVT, and not co morbid factors.

Prothrombotic risk factors

In 16 (42.1%) of the 38 patients (Table 2) and 5 out of the eight neonates (Table 4) at least one established prothrombotic risk factor was found as compared with 41 (36.6%) of the 112 children within the control group (p = 0.55). The distribution of single and combined prothrombotic risk factors in patients and controls is shown in Table 2.

Table 2: Thrombophilia among paediatric patients and controls.

Thrombophilia	Patients	Controls	P value
AT deficiency	0/38	0/112	0.57
PS deficiency	1/38	0/112	0.25
PC deficiency	2/38	2/112	0.25
APLA	4/38	6/112	0.27
FVL	3/38	7/112	0.72
MTHFR 677T*	5/38	17/112	0.76
FIIG20210A	1/38	4/112	0.78
Combinations	2/38 #	5/112 ##	0.84
Total	16/38	41/112	0.55

* MTHFR 677T homozygous cases only
 # Combined thrombophilic markers within patients' group:
 APLA+ MTHFR 677T homozygous+ FVL heterozygous (1 case) and
 APLA+ MTHFR 677T homozygous + PC deficiency (1 case)
 ## Combined thrombophilic markers within control group:
 FVL homozygous patients (n=2), FVL+ FIIG20210 heterozygous (n=2),
 FIIG20210A+677T-MTHFR homozygous (n=1)

No significant differences between the patients and the control group were noted with regard to prevalence of any of the single thrombophilia markers (Table 2), or combinations of thrombophilic risk factors (p = 0.84).

The association of prothrombotic risk factors with co morbid conditions and CSVT is shown in table 3. About one third (10/31) of CSVT patients with co-morbid conditions were diagnosed with thrombophilia. Among the patient sub-groups thrombophilia was not found among children diagnosed with CSVT and with head and neck disorders (4/31) or while treated with oral contraceptives (1/31) a significant proportion of patients with underlying systemic or infectious diseases had thrombophilic risk factors (Table 3). Interestingly, the prevalence of thrombophilia was significantly higher among children without co-morbid conditions: 6 out of 7 children with idiopathic CSVT had thrombophilic risk factors (p = 0.009).

Table 3: Co-morbidity and thrombophilia among paediatric CSVT patients.

Co-morbid conditions	Patients (%)	Thrombophilia (%) / combinations (%)
Total	31/38 (81.5%)	10/31 (32.2%) / 1/31 (3.2%)
Head and neck vascular disorders and or trauma	4/38 (10.5%)	0/4 (0%)
Systemic illness	8/38 (21.1%)	4/8 (50%)
Infection	18/38 (47.3%)	6/18 (33.3%) / 1/18(0.05%)*
Oral contraceptives	1/38 (2.6%)	0/1 (0%)
None	7/38 (18.4%)	6/7 (85.7%) / 1/7 (14.3%)**

* Combined thrombophilic markers: APLA+ MTHFR 677T homozygous+ FVL heterozygous
 ** Combined thrombophilic markers: APLA+ MTHFR 677T homozygous+ PC deficiency

Anti coagulant therapy

Most (88%) of the patients received anticoagulant therapy, which included either unfractionated Heparin(UFH) or Low molecular weight heparin (LMWH) in the acute phase, followed by coumadin for a median treatment duration of six months, aiming at target INR 2-3. Bleeding complications were never documented in patients treated at the non-acute phase. The decision to stop anticoagulants was made once clinical resolution of symptoms and radiological improvement, manifested by thrombus recanalization or presence of collateral vessels, were evident.

Decision for prolonged anticoagulant therapy (11/38) was influenced by presence of combination of thrombophilic risk factors and neurological sequels. Five patients with CSVT were treated for one year following the acute event. These were children diagnosed with AVM and nephrotic syndrome without thrombophilia as well as the young female patient suffering CSVT following oral-contraceptives. In cases of idiopathic CSVT and thrombophilia (2 patients with FVL) therapy was also continued for a total of one year after the acute event, whereas 6 children with either recurrent thrombosis (CSVT preceding DVT in one case), thrombophilia (FVL) and persistent neurological sequels (1 case) or increased risk for recurrence (PC deficiency, APLA with and without SLE, homocysteinuria, combination of PC deficiency+ APLA+ FIIG20210A) were treated indefinitely with coumadin.

Patient follow-up and outcome

Patients were followed for a median of 4.1 years. Eight out of 36 surviving patients (out of those: 7 presented with idiopathic CSVT), currently suffer neurological sequels including hypotonia, hemiplegia, hemi paresis, isolated sixth cranial nerve palsy, visual impairment, convulsive disorder and pseudo tumor cerebri. Three patients with sequels had either APLA alone or in combination with FVL heterozygosis and are treated with

coumadin indefinitely. None of the children had recurrent CSVT.

Two patients died within the acute phase of CSVT. The causes of death were brain herniation as a complication of delayed diagnosis in a 6-month-old baby girl and severe sepsis with multi-organ failure in a 15-year-old boy.

Neonates with CSVT

Our study group included 8 neonates whose data are shown in table 4. The prevailing presenting symptom of this small subgroup was seizures (7/8) and one case was diagnosed when magnetic resonance imaging (MRI) studies were performed for evaluation of a congenital neurological disorder, associated with hypotonia and arthrogryposis.

Co-morbidity (dehydration) existed only in 1/8 babies at time of diagnosis. One full-term infant suffered intra-ventricular hemorrhage (IVH) that may be a complication of CSVT, at diagnosis. Thrombophilia was detected among 5/8 neonatal CSVT cases, including two cases of combinations (Table 4). One neonate died of acute CSVT and brain hemorrhage, while treated with LMWH. This patient was heterozygous for both FVL and FIIG20210A mutations. Four out of 7 surviving patients did not receive anticoagulant treatment, one case with FVL and one other with high persistent plasma factor VIII levels received LMWH for 3 and 6 months, respectively whereas only one child suffering PC deficiency and heterozygous for FVL was anticoagulated for life. Interestingly, in the group of neonates only two children suffered mild neurological sequels, including the child diagnosed due to undefined disease with neurological symptoms.

Discussion

The incidence of thromboembolism among children is much lower as compared to adults (11-13). Among children, neonates

Origin	Sex	Thrombophilia	Co-morbidity	Treatment/length	Outcome
Jew-Asian	M	677T MTHFR-hom	none	none	AW
Arab	M	PC (3%) + FVL het	none	LMWH followed by coumadin	hypotonia
Arab	M	FVL+FIIG20210A het	dehydration	LMWH	died-brain hemorrhage
Jew-Europe	M	none	IVH	none	AW
Jew-mixed	M	none	none	none	AW
Jew-Europe	M	none	arthrogryposis	none	hypotonia
Jew-Asian	F	FVL	none	LMWH/3 months	AW
Bedouin	F	FVIII >200%	none	LMWH/6 months	AW

AW- Alive and well
 LMWH- Low molecular weight heparin
 IVH-Intra ventricular hemorrhage

Table 4: Characteristics of neonates diagnosed with CSVT.

exhibit the highest risk with a reported incidence of 0.24-0.51 per 10000 births for venous thrombosis (13-15). The number of paediatric and neonatal CSVT patients collected in Israel, though small to allow conclusions from our own study, enables, along with previously reported studies (1, 6), better analysis of variables affecting the pathogenesis, treatment and outcome of this rare disorder.

Genetic prothrombotic risk factors play an important role in the pathogenesis of infantile thrombosis (10-16). Nevertheless, the occurrence of thrombosis is often triggered by additional predisposing factors such as sepsis, cancer or the presence of central lines (17-18). Previous case reports and case-controlled studies indicated increased prevalence of thrombophilic risk factors among adult and paediatric patients with sinus vein thrombosis (1, 6, 19-23). In contrast to these manuscripts, the prevalence of single or combined thrombophilic risk factors in our patients was not increased as compared to controls (Table 2). This finding may stem from the small size of our study group.

Assuming that patient and population characteristics are about the same in Canada, Germany and Israel, a crude analysis of 318 paediatric CSVT patients screened for thrombophilia is now available and may be compared to 261 controls obtained by the German and Israeli groups. Out of the patients thrombophilia was diagnosed in 145 cases, as compared to 72 cases among controls. Since the Canadian study had no controls recruited, whereas the German and Israeli studies were designed in the same manner, we may calculate a very crude odds ratio finding thrombophilia among patients with CSVT significantly increased (OR = 3.13, 95% CI: 1.55-3.12) as compared to healthy paediatric population. We should mention that statistical analysis including Mantel Haenszel test demonstrated heterogeneity among the patient population in the German and Israeli studies, despite the similarity regarding patients' characteristics, probably due to the different size of study populations.

The overall prevalence of thrombophilia markers among patients and controls in our study was in concordance with previously published studies of adult (10) and paediatric (24) population in Israel.

The association of CSVT and co-morbid conditions that might induce hypercoagulability (such as: pregnancy, cancer, contraceptive therapy or systemic lupus erythematosus) in adults, has already been discussed (20, 25-27). In concordance with the Canadian and German data, reporting co-morbid conditions in 50-87% of children studied (1, 6), most of our patients had underlying diseases contributing to the occurrence of the acute event (Table 3). Since most cases of CSVT in children hospitalized during the study-period were diagnosed in close relation with co morbid infections, systemic diseases or vascular anomalies and surgeries of head area, we suggest that high index of suspicion should lead to early imaging studies in such patients, for the benefit of early diagnosis and initiation of proper treatment.

Among neonates with CSVT – co morbid conditions were rare and in contrast to the paediatric patients none suffered infectious diseases of the head and neck. Interestingly, thrombophilia was relatively frequent among neonates. Due to the small number of patients we are unable to comment whether the high prevalence of thrombophilia did confer a risk for CSVT in this group. Anticoagulant therapy was less common among neonates as compared to paediatric patients in our study group. The impact of therapy policy upon final outcome can not be determined due to the small cohort of patients. There is, however, an increased risk for bleeding among younger infants treated with anti-coagulants as shown in the case who died of brain hemorrhage, which may be either attributed to CSVT complications or present an undesired consequence of anticoagulant treatment.

Anticoagulant therapy is currently considered safe in adult and paediatric patients with CSVT and may reduce the risks of death or dependency (28-31). In our study group no bleeding complications were documented in paediatric patients treated at the non-acute phase. Interestingly, neither thrombophilia nor the presence of co-morbid conditions affected the initial decision to start anticoagulant therapy. Therapy was continued for a total of one year or more following the acute event only in patients with persistent risk factors, patients with severe neurological sequels and in presence of combined thrombophilic risk factors. The complete resolution of neurological symptoms in 30/36 surviving paediatric patients and the lack of recurrence support the efficacy of treatment, and the decision made to treat "high-risk" patients for longer periods.

Analysis of outcome data shows that within our cohort of non-neonate patients, prognosis, as previously reported (1, 31) was worse among those who presented with isolated neurological manifestations. As mentioned already, a significantly high percentage of our "idiopathic" subgroup had thrombophilia as well, thus for long-term treatment considerations thrombophilia screen of such paediatric CSVT patients is certainly valuable.

In conclusion, the risk for thrombophilia among children with CSVT may be increased yet only selected patients benefit from thrombophilia work-up, including children with either idiopathic CSVT or familial thrombophilia and combination of risk factors that may require prolonged or indefinite anticoagulant therapy. On the other hand, routine thrombophilia screening in young children with non-idiopathic sinus vein thrombosis does not always seem justified, since it usually does not determine initial therapy considerations. Our study though too small to be of statistical power adds to the knowledge about neonatal and paediatric CSVT case-studies already reported, paying special consideration to the issue of treatment. Due to rarity of CSVT further prospective international multicenter studies are warranted to define the impact of thrombophilia and anticoagulant treatment upon prognosis and outcome measures of children with CSVT.

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