

# Laboratory Findings, Medical Imaging, and Clinical Outcome in Children with Cerebral Sinus Venous Thrombosis

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Hamostaseologie 2023;43:188–195.

## Abstract

**Introduction** Cerebral sinus venous thrombosis (CSVT) is a rare disease, especially in children. Therefore, thrombophilia markers, risk factors, treatment strategy, and MRI, as well as clinical outcome need further investigation to support future diagnostic and therapeutic guidelines for children.

**Methods** We retrospectively identified all children with CSVT treated in our center between January 1, 2000, and December 31, 2015. Risk factors and laboratory findings were investigated. Furthermore, outcome and treatment satisfaction were evaluated using magnetic resonance imaging (MRI) analyses and a modified questionnaire.

**Results** All 43 patients, who agreed to participate, were treated with therapeutic levels of heparin; 86% of children had an increased risk for thromboembolic events upon onset of CSVT (acute disease: 58.1%, perinatal risk factors: 9.3%, medical intervention/immobility: 14%, chronic disease: 16.3%). Thrombophilia markers showed positive results (e.g., reduced values for protein C/S, factor-V–Leiden mutation) in 58% of children at the time of CSVT diagnosis but dropping to 20.9% over the course of the disease. Forty-two of 43 patients received MRI follow-ups and the outcome showed complete recanalization in 69% of the patients and partial recanalization in 31%. At the onset of CSVT, 88% of patients reported restrictions in everyday life due to CSVT; at follow-up this percentage declined to 18%. Satisfaction with the outcome among parents/patients according to the questionnaire was high with 1.7 (German school grades from 1 to 6).

**Conclusions** All 42 children with MRI follow-up demonstrated complete or partial recanalization under anticoagulation. This positive result underlines the need for future studies on anticoagulation to optimize therapy regimens of pediatric CSVT.

## Keywords

- ▶ cerebral sinus venous thrombosis
- ▶ anticoagulation
- ▶ prothrombotic risk marker
- ▶ outcome

\* Shared authorship.

received  
November 27, 2021  
accepted after revision  
August 22, 2022

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Georg Thieme Verlag KG,  
Rüdigerstraße 14,  
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1848-3649>.  
ISSN 0720-9355.

## Introduction

Cerebral sinus venous thrombosis (CSVT) is a rare condition in pediatric and neonatal cohorts with an incidence of 0.56 per 100,000 per year.<sup>1</sup> Data on clinical outcome and magnetic resonance imaging (MRI), as well as concurrent thrombophilia markers and other conditions leading to CSVT, are scarce. Neonatal CSVT seems to have a worse outcome.<sup>1</sup> CSVT is classically divided into neonatal and pediatric CSVT, as underlying risk factors differ substantially. Several hereditary thrombophilia markers (e.g., mutations in the protein C, protein S, or antithrombin gene; factor-V–Leiden mutation; prothrombin polymorphism G20210A) have been observed in relation to CSVT. Acquired risk factors have also been described such as asphyxia and medical interventions like central venous catheters mostly in neonates or chronic diseases (e.g., cancer, cardiac disorders), infection, other acute diseases (e.g. dehydration), and smoking in the pediatric age cohort.<sup>2–10</sup> Positive family history of thromboembolic events has been described as a risk factor as well.<sup>11</sup> MRI of CSVT is considered the gold standard in children<sup>12–15</sup> and low-molecular-weight heparin (LMWH) or vitamin K antagonists have been used for anticoagulation therapy.<sup>12,13,16–18</sup>

The aim of this study was to evaluate clinical outcomes of pediatric patients with CSVT treated with heparin in relation to MRI to inform future diagnostic guidelines and treatment strategies. In addition, we evaluated patients' characteristics regarding thrombophilia markers and other risk factors to investigate on changes between the acute and the chronic setting.

## Methods

### Study Design

We retrospectively identified all children with CSVT treated in the Department of Paediatrics and Adolescent Medicine, Medical Centre Freiburg, between January 1, 2000, and December 31, 2015. Identification of patients was performed by screening for the diagnosis of thrombosis and CSVT within the hospital digital medical records plus manual search of outpatients' folders. All patients ( $n = 56$ ) received a letter containing information about the study plan and they were given the option to return a letter of refusal. The Ethical Committee of the University Medical Center Freiburg approved the study (EK 233/16).

### Laboratory Parameters/Thrombophilia Markers

Based on medical records, we investigated the following laboratory parameters: protein C, protein S, antithrombin, lupus anticoagulants, fibrinogen, APC ratio, as well as factor-V–Leiden mutation, and prothrombin gene G20210A mutation. Immunological parameters such as antiphospholipid (aPL) antibodies and antinuclear antibodies (ANA) were also collected.

Methods of laboratory testing:

- APC ratio: aPTT-based APC resistance assay after dilution with factor V–deficient plasma. Positive results (reduced ratio) triggered genetic testing of FV gene.

- Free protein S: immunoassay. Reduced activity was considered as positive result and in case of persistent reduction after the acute setting we performed genetic testing of the protein S gene.
- Protein C and antithrombin III: chromogenic activity assays. In case of reduced activity, we performed genetic analysis after the acute phase.
- Lupus anticoagulants: dilute Russell's viper venom time.
- Fibrinogen: Clauss method.
- Factor-V–Leiden mutation: The point mutation G1691A leading to factor-V–Leiden mutation was detected by real-time polymerase chain reaction (PCR) and melting curve analysis.
- Factor II mutation: Prothrombin polymorphism G20210 was detected by real-time PCR and melting curve analysis.

All parameters were first investigated at the time of diagnosis of CSVT (within 24 hours). Those parameters are incorporated in the variable "thrombophilia marker at onset." To see which parameters are abnormal in acute setting and normalize over time, we also investigated most of the parameters when patients visited for follow-ups. These parameters are incorporated in the variable "thrombophilia marker at follow-up."

### Magnetic Resonance Imaging

Disease severity was defined by the number of affected sinuses: grade 1 (nonsevere CSVT) in case one sinus was occluded, grade 2 (severe CSVT) if there were several sinuses occluded. A recanalized sinus on follow-up MRI was defined as "complete therapeutic success." Partial recanalization with small residual thrombus was classified as "improvement." Parenchymal lesions caused by ischemia or stasis edema were documented. MRI follow-up was performed at the time of diagnosis, approximately after 6 months, and in case of residual thrombus an additional MRI was performed after 12 months. Two nonblinded radiologists performed the diagnosis of the MRI.

### Therapy

As soon as the diagnosis of CSVT was established, treatment with unfractionated heparin (UFH) was started for 24 hours and then switched to LMWH. Regular anti-Xa levels were aimed to be within the range of 0.6 to 0.8 IU/mL, which should be reached within 24 hours of LMWH treatment. Duration of treatment depended on radiological imaging and risk factors and ranged from a minimum of 3 months up to 2 years in case of persistent risk factors and persistent radiologic residual thrombus. In case of indication for continuous antithrombotic treatment, patients were switched to vitamin K antagonists. Anti-Xa levels were rechecked at every follow-up and LMWH dosing adapted to increased body weight.

### Questionnaire/Clinical outcome

In order to evaluate clinical outcome of patients and their satisfaction with the treatment outcome, we performed retrospective interviews (by telephone) using the five

main questions (questions 1–5 and 9–13) of the validated CSHCN (“Children with Special Health Care Need”) Screener of Bethell et al.<sup>19</sup> The original CSHCN Screener is a validated and standardized questionnaire, aiming to identify children with chronic physical, mental, behavioral, or other conditions who require health-related services beyond a normal quantity. Five questions were (1) prescription of medication; (2) higher than normal use of medical, mental health, or educational services compared to other children of the same age; (3) limitation of activities in day-to-day life; (4) specialized therapies; and (5) treatment or counseling for an emotional, behavioral, or developmental condition. The CSHCN Screener is used as part of the National Health Interview and Examination Survey for Children and Adolescents (KiGGS) in Germany.<sup>20</sup> We added question 6 (symptoms at onset), question 7 (anamnestic risk factors), question 8 (positive family history), question 14 (neurologic restrictions like cognition, seizures, language disabilities, motor impairment), and question 15 (satisfaction with treatment outcome (in German school grades ranging from 1 [excellent] to 6 [poor])). Because of our retrospective setting, we did not use the CSHCN subquestions regarding duration. These adaptations to the questionnaire were not validated. The study participants were interviewed using the questionnaire regarding two time points: The first part of the questionnaire (questions 1–8) addressed the time when the initial CSVT diagnosis had been made (past); the second part (questions 9–15) of the questionnaire addressed the patient’s present status (at the time of the study; [Supplement 1](#) [online only]). If the patient was below 18 years of age, the parents answered the questions in cooperation with the patient; for adult patients, there was a questionnaire for patients above 18 years. Additionally, patients were neurologically examined by an experienced pediatrician at every follow-up visit.

### Statistical Analysis

IBM’s “SPSS” version 24 for Windows program was used for descriptive and explorative data analyses. Median values and ranges were reported.

All *p*-values were two-sided and values less than 0.05 were considered statistically significant.

Association of “time to anticoagulation” and MRI outcome was calculated using the Kruskal–Wallis test.

Chi-square test was used to test for associations of nominal and ordinal variables (e.g., MRI outcome and gender). T-test was used to test the null hypothesis in two groups.

## Results

### Patient Characteristics

We retrospectively identified 56 patients with CSVT who had been treated in the Department of Paediatrics and Adolescent Medicine, Medical Centre Freiburg, between January 1, 2000, and December 31, 2015. Ultimately, 43 children (22 females/21 males) diagnosed with CSVT and/or their parents gave their informed consent and were included in the study.

Thirteen patients and/or parents did not consent to participate (missing contact data: *n* = 9, declining to participate: *n* = 2, not treated in our clinic: *n* = 2). As far as our medical record shows, none of these 13 patients died. Median age of the included patients was 5 years (0–17 years). Because of relevant differences in coagulation between neonates, non-adolescent children, and adolescent children, we divided the patients into three age groups: neonates (days 0–28, *n* = 8), pediatric patients (days 28–11 years, *n* = 24), and adolescents (12–18 years, *n* = 11).

Thirty-three children were diagnosed with “isolated CSVT,” 9 children suffered from “CSVT and hemorrhage due to increased intracranial pressure,” and 1 child presented with combined “CSVT and ischaemic stroke.” All patients were symptomatic. No progression, recurrence, CSVT-related death, or death occurred in this cohort.

### Risk Factors and Underlying Conditions

In total, 37 of 43 (86%) children presented risk factors for thromboembolic events. In 25 children (58.1%), the primary risk factor was “acute disease” (e.g., respiratory infection, sepsis, gastroenteritis, mastoiditis, sinusitis, neonatal infection, meningitis, dehydration, or trauma). Four children (9.3%) had “perinatal” risk factors (e.g., asphyxia). In six children (14%), the risk factor was “medical intervention and immobilization” (e.g., hemispherectomy, tumor resection, central venous line, and surgery for cholesteatoma). Nine children (20.9%) had other additional risk factors: birth control pill (two children), birth control pill in combination with nicotine abuse (three children), and cortisone or/and diuretics (four children). The underlying condition “chronic disease” was identified in seven children (16.3%; e.g., nephrotic syndrome, tumor, antiphospholipid antibody syndrome, bronchial illnesses, ulcerative colitis, hemolytic uremic syndrome with chronic kidney insufficiency, and transposition of the great arteries).

Sixteen (37%) children needed surgical interventions to eradicate the source of infections like mastoiditis. Eight children (18.6%) had a positive family history for thromboembolic events.

### Laboratory Results of Thrombophilia Markers

Our analyses of the variable “thrombophilia marker at onset” revealed that 25 of 43 (58%) children presented at least one marker for thrombophilia and 8 of 43 children (18.6%) had more than one such marker for thrombophilia. Some of these values physiologically normalized over the course of the disease; therefore, the “thrombophilia marker at follow-up” variable shows that the number of patients with one positive thrombophilia marker dropped to 9 (20.9%). The number of patients with more than one “thrombophilia marker at onset” dropped to 1 of 43 children (2.3%) over time, because patient 27 presented both a heterozygous factor-V–Leiden mutation and a protein S gene defect concurrently. Especially fibrinogen, antithrombin III, and aPL antibodies were often abnormal in the acute setting and normalized over time (antithrombin III 6/2, fibrinogen 11/0, aPL antibody 9/1).

**Table 1** Inherited risk markers for thrombophilia

	Number of children
Heterozygous factor V Leiden mutation	4
Homozygous mutation of prothrombin gene G20210A	1
Heterozygous mutation of prothrombin gene G20210A	2
Heterozygous missense mutation in the protein C gene	1
Heterozygous mutation in the protein S gene	1
Heterozygous polymorphism in the protein S gene	1
No mutations associated with thrombophilia found	34

In summary, 9 of 43 children had hereditary thrombophilia (–Table 1) and one patient had two mutations as described earlier.

We want to highlight three patients here: two patients (patients 25 and 27; –Table 2) presented consistently low protein C values. We detected a heterozygous missense mutation in the protein C gene in patient 25 (exon 7), which explains the reduced protein C activity of 66%. In patient 27, who additionally had temporarily low protein S values (lowest value: 56%), we did not identify a mutation in the protein C gene; however, a heterozygous polymorphism in protein S gene (c.2001 A > G, p.Pro667Pro) was detected and might explain the reduced protein S activity.<sup>21</sup> Patient 4, presenting consistently reduced protein S activity (30%), revealed a compound heterozygous protein S mutation (missense mutation in exon 13 and a deletion in exon 14). The disease-causing mutation in exon 13 (Ser 460 Pro) had already been reported<sup>22</sup>; the small deletion (Ser 512 fs X2) in exon 14 had not been described so far.

Testing for immunological risk factors was positive in 11 of 34 tested children initially: 8 children demonstrated temporarily increased aPL antibodies which normalized over time. One child had consistently increased aPL antibodies and was later diagnosed with aPL antibody syndrome. Two children showed elevated ANA titer.

### Therapy

All 43 children received anticoagulation as soon as CSVT was diagnosed. Initial treatment of choice for all 43 children was UFH or LMWH. One of these 43 children was given a combination of LMWH and acetylsalicylic acid because of three stents which had been placed in the superior caval vein. In another child, heparin-induced thrombocytopenia (HIT) type II was suspected during UFH therapy; therefore, UFH was changed to hirudin. The diagnosis was eventually not confirmed.

Thirty-seven of 43 patients received LMWH as long-term therapy. Median treatment duration in these 37 children was 11 months (range: 3–36 months). One child received LMWH

in combination with acetylsalicylic acid for 45 months (afterward, only acetylsalicylic acid). One child (patient 32) received phenprocoumon for many years because of the underlying congenital disorders of glycosylation syndrome. Four children received phenprocoumon as long-term therapy (median treatment duration was 21 months, range: 7–25).

Median time from symptom onset to start of anticoagulation was 3.5 days (0–42); patients 1, 2, and 24 were outliers in terms of time to treatment.

There was no significant association of “time from symptom to start of anticoagulation” to MRI outcome in terms of degree of recanalization (Kruskal–Wallis test,  $p = 0.79$ ; Supplement 2 [online only]). However, analysis is hampered by small sample sizes of the group “recanalization with parenchymal lesion” ( $n = 6$ ) and “recanalization with residual thrombus and parenchymal lesion” ( $n = 4$ ), and one patient who received anticoagulation at 42 days still experienced full recanalization. This patient had been referred to our center with delay.

### MRI Analyses

Initial MRI analysis showed that 17 (40%) patients suffered from nonsevere CSVT (13 males/4 females) and 26 (60%) patients from severe CSVT. Ten (23%) patients suffered parenchymal lesions caused by hemorrhage or stroke due to increased intracranial pressure. Five of these 10 children (11.6%) were neonates at CSVT onset.

Forty-two children received MRI follow-up (one family refused MRI follow-up due to full recovery without clinical signs of CSVT). Twenty-nine (69%) children showed complete recanalization; of those, 6 still showed parenchymal lesions. Thirteen (31%) children presented with partial recanalization with a minor residual thrombus; of those, 4 showed additional parenchymal lesions.

### Questionnaire—Satisfaction Rating of Clinical Outcome

The mean value of satisfaction rating regarding the clinical outcome (question 15 of the questionnaire) was 1.7 ( $n = 43$ , range: 1–6). Satisfaction levels were independent of the degree of severity at the onset of CSVT and at follow-up (–Fig. 1).

Three children’s ratings were below satisfaction: two of these were due to other complications (preexisting malignancy [patient 12], mental illness [patient 41]). The third patient (patient 37) who suffered from hemorrhage due to intracranial pressure was very disabled (care level 3). At the onset of the disease, his symptoms had already severely progressed before anticoagulation therapy could be started.

### Questionnaire—Clinical Outcome

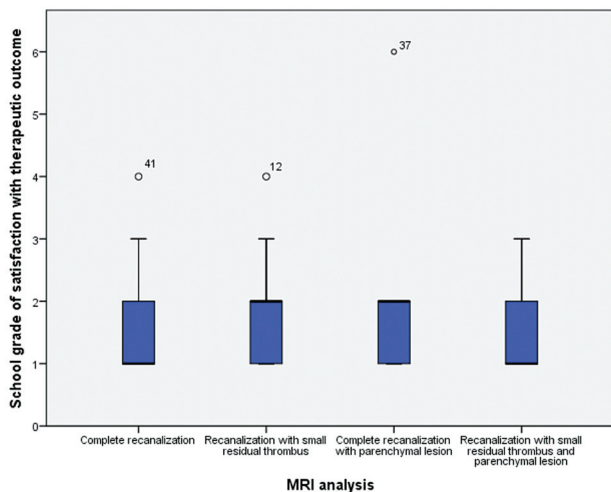
The CSHCN Questionnaire was answered after a median of 6 years post-CSVТ (range: 1–16 years); the patients’ median age was 12 years at the time of the study (range: 1–30 years).

At CSVТ onset, 38 of 43 children (88.4%) suffered from restrictions in their everyday life; most of the children (34/38) traced back these circumstances to CSVТ. At the onset of CSVТ, restrictions were due to headache, physical

**Table 2** Patient Cohort

Patient	Gender	Age at onset of CSVT (y)	Diagnosis	Grading of satisfaction regarding outcome
Patient 1	Female	17	CSVT	2
Patient 2	Male	4	CSVT	1
Patient 3	Female	6	CSVT	1
Patient 4	Female	7	CSVT with hemorrhage	1
Patient 5	Male	3	CSVT	1
Patient 6	Male	5	CSVT	1
Patient 7	Male	6	CSVT	2
Patient 8	Male	5	CSVT	2
Patient 9	Female	16	CSVT with hemorrhage	3
Patient 10	Male	1	CSVT	1
Patient 11	Female	16	CSVT	2
Patient 12	Male	3	CSVT and cancer	4
Patient 13	Male	6	CSVT	2
Patient 14	Male	Neonatal	CSVT	2
Patient 15	Female	8	CSVT	3
Patient 16	Male	14	CSVT	1
Patient 17	Female	3	CSVT	1
Patient 18	Female	16	CSVT	1
Patient 19	Male	2	CSVT	1
Patient 20	Female	2	CSVT	2
Patient 21	Female	17	CSVT	2
Patient 22	Female	12	CSVT	1
Patient 23	Male	Neonatal	CSVT with hemorrhage	2
Patient 24	Male	14	CSVT	1
Patient 25	Female	6	CSVT	1
Patient 26	Female	Neonatal	CSVT with hemorrhage	2
Patient 27	Female	8	CSVT	2
Patient 28	Female	9	CSVT	3
Patient 29	Male	Neonatal	CSVT with hemorrhage	1
Patient 30	Female	13	CSVT with infarct	1
Patient 31	Female	Neonatal	CSVT	1
Patient 32	Female	14	CSVT with hemorrhage	1
Patient 33	Male	Neonatal	CSVT with hemorrhage	1
Patient 34	Female	13	CSVT	1
Patient 35	Male	4	CSVT	1
Patient 36	Male	1	CSVT	3
Patient 37	Male	Neonatal	CSVT with hemorrhage	6
Patient 38	Female	Neonatal	CSVT	2
Patient 39	Male	11	CSVT	1
Patient 40	Female	0.8	CSVT	1
Patient 41	Male	3	CSVT	4
Patient 42	Female	1	CSVT with hemorrhage	2
Patient 43	Male	3	CSVT	1





**Fig. 1** Boxplot of question 15 (satisfaction with therapeutic outcome) and MRI analysis.

disabilities (e.g., balance problems, hemiparesis), and visual problems (N. abducens paresis). The other four children reported restrictions due to other diseases (e.g., cancer).

At the time of the study, 18 of 43 children (41.9%) were still reporting mild restrictions in their everyday life. However, 10 (55.6%) of these 18 children traced the restrictions not to CSVT but to other diseases like cancer, aPL antibody syndrome, or psychological disorders. Eight children attributed the restrictions to CSVT. Five of the eight children suffering restrictions due to CSVT had a parenchymal lesion. Remaining restrictions were headache, balance problems, or physical disabilities especially (e.g., walking over long distances).

The outcome of the five neonates in our study with seizures at their CSVT onset was not worse than that of the three neonates without seizures at CSVT onset. Only one of these five children was still suffering from seizures during follow-up. When contacted during our survey, the median age of those five children with seizures at CSVT onset was 5 years.

### Subanalysis of Children with Severe CSVT

Twenty-six children (18 females/8 males) had more than one occluded sinus. Five of the 18 female patients were taking birth control pills; additionally, three of them were smokers. Seventeen children (4 females/13 males) had only one occluded sinus. There was a correlation between the severity grade (in MRI) and gender, that is, significantly more female patients suffered from severe CSVT. Chi-squared test was significant ( $p < 0.01$ ). Interestingly, 7 of the 18 girls suffering severe CSVT presented elevated immunological parameters: 3 girls had increased aPL antibodies (1 of these 3 girls was later diagnosed with APS), 2 girls had increased ANA titers, and 2 girls revealed temporary positive values for lupus anticoagulants.

We also observed a significant difference in age of the female and male patients at CSVT onset ( $t$ -test,  $p < 0.05$ ): girls were significantly older (8 vs. 2 years).

### CSVT with Hemorrhage or Infarct

Ten children (six females/four males) suffered from additional hemorrhage or infarct due to increased intracranial pressure: more than one sinus was occluded in eight of these children. Five of these 10 children who suffered severe CSVT were neonates. The chi-squared test was significant for age ( $p < 0.01$ ).

### Hemorrhage and Infarct as Predictors of Unfavorable Outcome

CSVT with hemorrhage or infarct was a predictor for worse outcome. Directly after the onset of CSVT, 8 of the 10 children (80%) with hemorrhage/infarct were restricted in their everyday life (e.g., mental disability, seizures). At the time of the study, the everyday life restrictions for 50% of this group (5/10) remained unchanged (the time lag between onset of CSVT and our study for these 10 children was on average 7 years; range of 1–16 years).

The group with CSVT without hemorrhage or infarct also showed high levels of restriction at the time of diagnosis: 26 of 33 children (78.8%).

However, at the time of evaluation, only three children (9.1%) reported remaining restrictions due to CSVT.

### Discussion

The children's outcomes of CSVT in our study are remarkable. In our study, all 43 children received anticoagulation and all (100%) of the MRI follow-up exams ( $n = 42$ ) revealed recanalization (69% complete recanalization and 31% partial recanalization). Congruently, the satisfaction level of patients and parents regarding the outcome was very high.

Median time between onset of symptoms and start of heparin was 3.5 days, including one outlier who started treatment as late as 42 days after onset of CSVT. Therefore, one might speculate that most patients profited from early anticoagulation to explain the positive MRI outcome in this cohort. Additionally, the anti-Xa levels were monitored regularly and the dosing was adjusted according to increasing body weight. This may have improved the outcome as well.

Grunt et al described 21 neonates and 44 children with CSVT.<sup>1</sup> There was a significant correlation between bad outcome and the lack of anticoagulation ( $p = 0.03$ ). Neonates had especially worse outcomes in their study: only 7 of 21 neonates had received anticoagulation (heparin). Of the other 44 children, 36 were treated with anticoagulation (heparin) and 41 of 44 children had a follow-up with MRI. They reported 18 children (43.9%) with recanalization, 19 children (46.3%) with partial recanalization, and 4 children (9.8%) with a thrombotically occluded sinus.

Our study also revealed a high percentage of risk factors associated with CSVT in this pediatric cohort of 43 children. In total, 86% of children had a risk factor like acute disease (mainly infection), surgery, or perinatal comorbidities (e.g., asphyxia) appearing before the manifestation of CSVT. Therefore, unprovoked CSVT was rare in these children. During the acute phase, 58% of patients presented with

**Table 3** Thrombophilia markers in comparable studies

Study	Nation	Age	Participants (n)	At least one abnormal lab parameter
Vielhaber et al <sup>23</sup>	Germany	0–18 y	32	62.5%
DeVeber et al <sup>26</sup> (modified)	Canada	0–18 y	123	31.7%
Kenet et al <sup>25</sup>	Israel	1–18 y	38	42.1%
Sébire et al <sup>24</sup>	European Centres	3 wk–13 y	42	62.1% (n = 29)
Grunt et al <sup>1</sup> (modified)	Swiss	0–16 y	54	42.6%
<b>Current study (acute)</b>	Germany	0–18 y	43	58%
<b>Current study (latest follow-up)</b>	Germany	0–18 y	43	20.9%

abnormal laboratory results regarding thrombophilia markers. During the follow-up of these patients in the course of the disease, the percentage dropped to 20% after normalization of coagulation. Immunologic parameters were abnormal in 25% during the acute phase and mostly normalized over time as well. Vielhaber et al and Sébire et al reported “at least one conspicuous laboratory value” over time in 62.5 and 62.1% of patients, respectively; however, their patient cohorts were smaller.<sup>23,24</sup> Kenet et al described at least one abnormal laboratory parameter in 42.1% of the children<sup>25</sup> and Grunt et al in 42.6%.<sup>1</sup> The study of deVeber et al identified CSVT thrombophilia markers in 31.7% of the patients<sup>26</sup> (→Table 3). The set of thrombophilia markers differs between different studies. If, for example, we would incorporate the three patients with positive immunological antibodies, the percentage with patients with positive thrombophilia markers in our study would increase to 28% at follow-up.

This study shows that female teenagers may carry a higher risk to experience a more severe CSVT course. Medications (birth control pills or cortisone) and certain conditions (infections or immunological diseases) may raise the risk of developing CSVT. Therefore, immunological parameters (ANA titer, aPL antibodies) should be investigated, especially in female teenagers with CSVT.

Gunes et al described 75 participants (59 females/16 males) who suffered from CSVT.<sup>27</sup> Median age was 35 years (range: 16–76 years). The reasons for the CSVT were attributed to gender-specific risk factors (contraceptives, pregnancy). Fifty of the 75 participants (66.7%) suffered more severe CSVT with more than one thrombotically occluded sinus. Forty of these 50 patients (80%) were female.

In contrast, Golomb et al investigated a cohort of 170 children with CSVT<sup>28</sup>; 65% of the children were male. This may be due to the fact that a significantly larger cohort of male patients developed CSVT as neonates ( $p = 0.002$ ): 68 of 92 neonates were boys. In our study, within the neonate group five of the eight neonates with CSVT were male (62.5%) and 3 were female (37.5%).

Hemorrhage and infarction were more common among neonates and were also a predictor of worse clinical outcome according to the questionnaire. In our study, 5 of 10 children with CSVT and hemorrhage/infarct were neonates. DeVeber

et al claimed that seizures predict worse neurological outcomes.<sup>26</sup> The outcome of the five neonates in our study with seizures at their CSVT onset was not worse than that of the three neonates without seizures at CSVT onset. Only one of these five children was still suffering from seizures during the study.

Interestingly, our questionnaire showed that patients who were still suffering from disabilities after years which they attributed to CSVT did suffer from parenchymal lesions in most cases. Therefore, these patients may profit from additional health care provided.

### Limitations

The main limitation is the small number of patients and the lack of a control group regarding anticoagulation. Therefore, we cannot definitely account therapeutic success to heparin treatment. Nevertheless, our findings are well in line with those from other working groups investigating similar patient cohorts.

In summary, the results of the present investigation reveal that anticoagulation may improve the outcome of children with CSVT. All patients received anticoagulation as soon as CSVT was diagnosed and MRI follow-up showed complete or partial recanalization in all patients. Parents and patients were highly satisfied with the outcome. Although anticoagulation, especially subcutaneous application of LMWH, may be a challenge in a pediatric cohort, retrospectively parents and patients did not mind, as long as the outcome was as beneficial as this study showed. Yet, further evidence on the exact benefit of anticoagulation in CSVT in children is still needed.

### Author Contributions

N.G. and B.Z. initiated and developed the design of the study. N.G., B.Z., and all other authors were involved in writing and reading the manuscript. M.B. performed the laboratory testing and contributed to writing the manuscript. H.G. performed the final revision.

All authors finally approved the final manuscript.

### Ethics Approval

Ethical approval was received from the local Ethics Committee of Freiburg.

### Consent to Participate

Informed consent was obtained from all participants or legal guardians included in the study.

### Consent for Publication

All participants or legal guardians were informed in written form about publication of anonymized data.

### Funding

No funding was received for conducting this study.

### Conflict of Interest

M.U. have no conflicts of interest to declare. B.Z. Research support from CSL Behring, Biotest, Takeda. Payment for lectures were paid by CSL Behring and Grifols. The payment received the Medical Center of the University of Freiburg., Second leader of the Pediatric Commission of the GTH.

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