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Neonatal Cerebral Sinovenous Thrombosis From Symptom to Outcome

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Background and Purpose—Cerebral sinovenous thrombosis is a rare disease with severe neurological sequelae. The aim of this retrospective multicenter study was to investigate the clinical course, possible risk factors, and outcome of a cohort of neonatal patients with sinovenous thrombosis and, second, to estimate the incidence in The Netherlands.

Methods—From January 1999 to March 2009, a review of all neonatal patients with sinovenous thrombosis from 6 tertiary neonatal intensive care units was performed. Population characteristics, clinical presentation, (prothrombotic) risk factors, neuroimaging, interventions, and neurodevelopment were evaluated. An estimated incidence was calculated based on the Netherlands Perinatal Registry.

Results—Fifty-two neonates were included (39 boys) with a median gestational age of 39 weeks (range, 30 to 42 weeks; 5 preterm). An assisted or complicated delivery occurred in 32 of 52. Presenting symptoms developed at a median postnatal age of 1.5 days (range, 0 to 28 days) and consisted mainly of seizures (29 of 52). All sinovenous thrombosis cases were confirmed with MRI/MR venography. Multisinus thrombosis was most common followed by superior sagittal sinus thrombosis. FII G20210A mutation was present in 2 of 18 tested neonates (11%). Anticoagulation therapy (in 22 of 52) did not result in hemorrhagic complications. At follow-up (median age, 19 months; range, 3 to 72 months), moderate to severe neurological sequelae were present in 38%. The mortality was 10 of 52 (19%). A variable, although high yearly incidence of 1.4 to 12 per 100 000 term newborns was found.

Conclusions—Neonatal sinovenous thrombosis is a multifactorial disease. The estimated incidence in The Netherlands seems higher than reported elsewhere. (*Stroke*. 2010;41:1382-1388.)

Key Words: neonatal stroke ■ risk factors ■ sinovenous thrombosis ■ treatment

Neonatal cerebral sinovenous thrombosis (SVT) is increasingly diagnosed due to greater clinical awareness and improved neuroimaging techniques. Described incidences of pediatric sinovenous thrombosis range from 0.35 to 0.67 per 100 000 children per year with a higher incidence in neonates (2.6 to 2.69 per 100 000 newborns a year). An important data source is the Canadian Pediatric Stroke Registry.¹⁻³ The reported incidence of neonatal SVT is probably an underestimation; many patients may remain unidentified due to nonspecific clinical presentation, high dependence on clinician awareness, and use of appropriate neuroimaging techniques.⁴ Morbidity and mortality can, however, be

significant and depend on extent and localization of thrombosis and associated cerebral parenchymal lesions.^{1,4-6} Adverse neurological sequelae consist of general developmental delay, sensorimotor deficits, visual impairments, and epilepsy.^{2,5-8}

Most studies on pediatric SVT include children of all ages^{1,3,5,8-12} and only few, usually small case-series, focus on neonates.¹³⁻¹⁶ Therefore, the aim of our study was to gain more knowledge regarding clinical presentation, recognition of high-risk profiles, use of optimal neuroimaging techniques, interventions, and outcome in a large group of exclusively neonatal patients with SVT.

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Table 1. Population Characteristics of 52 Neonates With SVT

Parameter	No. (%) or Median (Range)
Gestational age, weeks	39.0 (30–42)
Birth weight, g	3030 (1403–4415)
Apgar score 5 minutes	8.0 (3–10)
Apgar score 10 minutes	9.0 (3–10)
Male	39 (75%)
Female	13 (25%)
Caucasian	49 (94%)
African	3 (6%)
Umbilical cord pH (n=13)	7.13 (6.76–7.27; n=4, pH <7.0)
Interval birth to symptoms, days	1.5 (0–28)
Interval symptoms to diagnosis, days	4.0 (0–26)
	No. (%)
Clinical symptoms	
Generalized seizure	18 (34.6%)
Focal seizure	11 (21.2%)
Apnea	9 (17.3%)
Asymptomatic (chance finding)	7 (13.4%)
Agitated	3 (5.8%)
Sepsis-like	2 (3.8%)
Depressed consciousness	1 (2%)
No data	1 (2%)
Outcome	
Died	10 (19%)
Survived	42 (81%)
Normal	19/42 (45%)
Moderately abnormal	12/42 (29%)
Severely abnormal	8/42 (19%)
No follow-up data	3/42 (7%)
Follow-up <9 months	13/42 (36.1%)

Methods

A retrospective, multicenter review was performed in neonates admitted to 6 of the 10 Level III neonatal intensive care units covering the most densely populated areas of The Netherlands between January 1999 and March 2009. Pediatric hematology, radiology, and neonatology databases of all participating centers were searched for patients with neonatal SVT. Only MRI and MR venography (MRV)-proven SVT was included. Because this was a

Table 2. Clinical and Prothrombotic Risk Factors in 52 Neonates With SVT

Risk Factors	No. (%)
Maternal	
Pre-eclampsia/HELLP syndrome	7 (13.4%)
Pregnancy induced- or pre-existing diabetes	3 (5.8%)
Maternal shock	1 (1.9%)
Maternal surgery	1 (1.9%)
History of clotting disease*	1 (1.9%)
Perinatal	
Complicated delivery†	31 (60%)
Perinatal asphyxia	3 (5.8%)
Fetomaternal transfusion	1 (1.9%)
Neonatal	
Sepsis or meningitis	8 (15.4%)
Dehydration	1 (1.9%)
Congenital heart defect	1 (1.9%)
ECMO	1 (1.9%)
	Patients Tested, Result, Median Value, Range
Prothrombotic Risk Factors	
Antithrombin level	29/52, normal, median: 69%, range 39–145%
Protein C level	32/52, normal, median: 37%, range 10–86%
Protein S level	32/52, normal, median: 56%, range 10–100%
FV G1691A mutation	41/52, present in 2/41 (4.9%)
FII G20210A mutation	18/52, present in 2/18 (11%)
MTHFR C677T- and A1298C homo- or heterozygous mutations	23/52, present in 13/23 (56.5%)
Homocysteine level	23/52, normal, median: 6.0 mg/L; range 4–16.3 mg/L
Lipoprotein a	16/52, normal, median: 21.5 mg/L; range 0–322 mg/L

*Deep venous thrombosis and pulmonary emboli.

†Ventouse, forceps delivery, or emergency cesarean section.

HELLP indicates hemolytic anemia, elevated liver enzymes, low platelet count; ECMO, extracorporeal membrane oxygenation procedure; MTHFR, methylene tetrahydrofolate reductase.

retrospective study, data on suspected SVT cases were unreliable or incomplete. To estimate yearly incidence of neonatal SVT, the number of term deliveries (home- and hospital-based) in the regions of the neonatal intensive care units concerned was requested from the Neth-

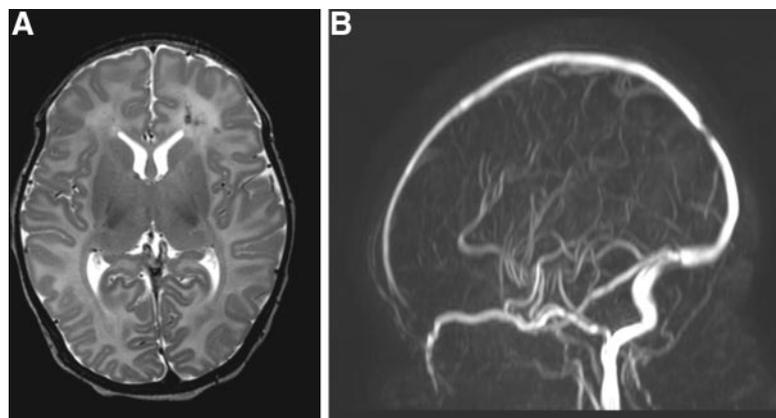


Figure 1. A, Axial T2-weighted spin echo (T2SE) image showing predominantly left-sided punctate white matter lesions. B, Time-of-flight MRV image showing absent flow in the straight sinus.

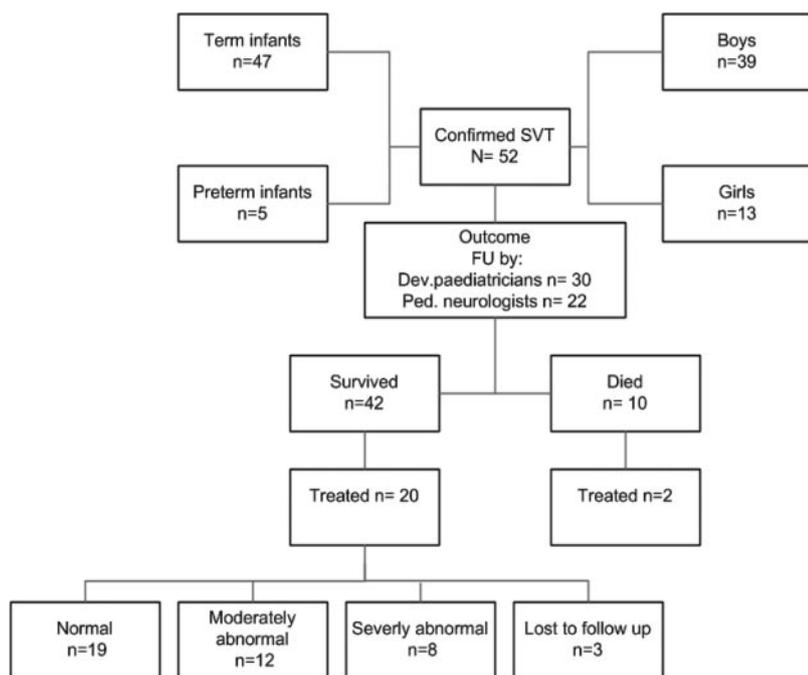


Figure 2. Population flow sheet. FU indicates long-term follow-up; Dev. pediatricians, developmental pediatricians; Ped. neurologists, pediatric neurologists.

erlands Perinatal Registry. In this register, birth data from the Dutch Midwives Registry (LVR1, 94% complete) and data from the Dutch Gynecological Society (LVR2, 99% complete) are recorded, culminating in a total coverage of >94% of deliveries in The Netherlands. Due to logistical reasons, only 2000 to 2007 data could be used for incidence calculation. To validate the number of patients with SVT identified in our cohort, we searched the National Newborn Classification of Diseases Code Registry (LNR). However, no code for cerebral venous thrombosis existed at the time. Therefore, we depended on databases of participating centers (nominator) and the birth registry (numerator).

Clinical Data Collection

Extensive chart reviews were performed to collect clinical data (Table 1).

Known or suspected maternal, perinatal, neonatal, and prothrombotic risk factors for SVT were evaluated. Each neonatal intensive care unit used a local protocol for investigating prothrombotic disorders. Although variability existed between local protocols, prothrombotic screening investigations were based on known guidelines for prothrombotic screening in pediatric patients^{17,18}. All neonates underwent routine hematologic and biochemical evaluation.

Neuroimaging and Neurophysiology

Cranial ultrasound using a broadband 5- to 8.5-MHz transducer (depending on the participating center) was part of every diagnostic workup. Color Doppler examination was performed in case of clinical or ultrasound suspicion of SVT. MRI (1.5- or 3.0-Tesla systems) was performed for clinical reasons and MRV (time-of-flight imaging) was added when indicated. SVT was confirmed with MRV in all cases. Neonatal MRI included T1-weighted sagittal, T2-weighted axial, T1-weighted or inversion recovery axial images, apparent diffusion coefficient, and diffusion-weighted images. Clearly visible complete or partial absence of flow in ≥ 1 cerebral venous sinus on MRV or color Doppler ultrasound was defined as a sign of venous thrombosis. Patients with suspected SVT were excluded. All imaging results were reviewed by the authors most experienced in evaluating neonatal sinus thrombosis (F.G., L.S.d.V., P.G.).

Neurophysiology studies included amplitude integrated electroencephalography (aEEG) and conventional EEG registrations (aEEG,

Olympic6000 and BRM2; Natus Medical Systems). These were reviewed for each patient for presence of seizures and background pattern. Tracings were scored as follows: seizure activity: none, single seizure, recurrent seizures, or status epilepticus; background activity: normal, abnormal, or severely abnormal according to age.

Neurodevelopmental Outcome

All patients received neurodevelopmental follow-up examinations by a developmental pediatrician skilled and trained in long-term neonatal follow-up or a pediatric neurologist. Outcome was determined by presence or absence of cognitive and/or motor deficits or seizures at the latest visit. Outcome was defined as normal in survivors with a normal clinical neurological examination, absence of hearing or visual impairment and normal age-corrected Bayley States of Infant Development (BSID-II),¹⁷ or Griffiths developmental assessment scales¹⁸ results. Outcome was recorded as moderately abnormal in infants with moderate cerebral palsy, delayed motor development, delay in speech development, and/or BSID-II-NL/Griffiths score <1 SD of the mean. Outcome was defined as severely abnormal in the presence of severe cerebral palsy, inability to sit at 2 years of age, nonambulatory status, sensorineural hearing loss requiring aids, bilateral blindness, and/or a BSID-II-NL/Griffiths score <2 SD of the mean.

Statistical Analysis

Statistical analysis was performed with SPSS Version 16.0 software package (SPSS, Chicago, Ill). Data are presented as median and range. Descriptive statistics were used to analyze patient demographic data. Comparison of platelet counts at presentation and time of diagnosis was performed using the Wilcoxon rank test for nonparametric data, because results were not distributed normally. The 95% CIs for incidence data were calculated with the Confidence Interval Analysis software, Version 2.2.0 (University of Southampton School of Medicine).

Results

Patient Characteristics and Risk Factors

Fifty-two neonates were included in the study (Figure 2). Table 1 describes patient characteristics. Forty-seven patients

were born in Level II hospitals, subsequently discharged, readmitted with severe symptoms after a disease-free interval, and transferred to 1 of the Level III centers. Five were born in a tertiary center because of perinatal asphyxia ($n=3$, according to American Congress of Obstetricians and Gynecologists criteria)¹⁷ known cardiac malformation (1), or antenatally diagnosed hydrocephalus. (1) The vast majority (75%) of our patients were male. Prevalence of known or suspected maternal, perinatal, neonatal, and prothrombotic risk factors for neonatal SVT in our cohort is shown in Table 2. Only term neonates were included in incidence calculation. We identified preterm newborns with neonatal SVT; however, their number was small and we assumed preterm and term SVT were not fully comparable due to gestational age-related differences in brain and clotting system development. Therefore, the incidence in this group is unknown. The yearly incidence rate in term newborns varied from 1.4 (95% CI, 0.04 to 8.01) per 100 000 in 2000 to 12 (95% CI, 5.20 to 23.73) per 100 000 in 2007 (supplemental Table I, available online at <http://stroke.ahajournals.org>).

Presenting Symptoms and Clinical Course

The clinical presentation varied, as shown in Table 1, and was independent of the cerebral sinus affected. Presenting symptoms consisted most frequently of seizures ($n=29$ [55.8%]) and developed after a median time interval of 1.5 days postnatally (range, 0 to 28 days).

Of the 42 neonates who experienced seizures at presentation ($n=29$) or during clinical course ($n=13$), 38 had cerebral parenchymal lesions. In these patients, seizures were difficult to control; on average, 2 antiepileptic drugs were needed (range, 0 to 4). Only 5 of 43 neonates with parenchymal lesions did not have clinical seizures. The extent of parenchymal injury could not be correlated with seizure activity. Eighteen patients (35%) needed ventilatory support because of respiratory insufficiency due to seizures or their treatment.

Laboratory Results

Biochemical evaluation was nonconspicuous in all cases. There were no laboratory signs of dehydration. Median hemoglobin count at time of presentation was 10.2 mmol/L (range, 5.7 to 13.9 mmol/L). No statistically significant difference ($P=0.384$) was found in median platelet count at presentation ($197 \times 10^9/L$; range, 55 to $573 \times 10^9/L$) and at the time of diagnosis ($183 \times 10^9/L$; range, 28 to $821 \times 10^9/L$).

Prothrombotic screening results are summarized in Table 2. In all patients with proven methylene tetrahydrofolate reductase mutation ($n=13$), homocysteine plasma levels were within normal range. Plasma levels of protein C, S, and antithrombin were in the age-specific reference ranges in the neonates tested.

Anticoagulation Therapy

Twenty-two neonates were treated with low-molecular-weight heparin (LMWH) ($n=20$) or unfractionated heparin ($n=2$), including neonates with thalamic hemorrhage ($n=10$), 7 of which have been described in a previous report.¹⁹ Bleeding complications during treatment were not encoun-

Table 3. Sinus Involved and Associated Cerebral Lesions in 52 Neonates With SVT

Sinus Involved	No. (%)	Associated Lesions*
Multiple sinuses	26 (50%)	Thalamic hemorrhage (12) Diffuse cytotoxic edema (4) IVH (6) Basal ganglia infarction (5) No lesions (3) Hydrocephalus (2) Small single parenchymal infarction (2: frontal 1, occipital 1)
Superior sagittal sinus	13 (23.1%)	Parasagittal infarction (6) Thalamic hemorrhage (4) Basal ganglia infarction (3) No lesions (2)
Straight sinus	8 (15.4%)	Bilateral frontal infarction (3) IVH (3) Thalamic hemorrhage (2) Diffuse cytotoxic edema (2) Basal ganglia infarction (1)
Transverse sinus	3 (5.8%)	No lesions (2) Cerebellar hemorrhagic infarction (1)
Other	2 (3.8%)	Thalamostriatal vein: Unilateral periventricular infarct Internal cerebral vein: Unilateral infarct head caudate nucleus

*In some neonates, multiple associated lesions were present. IVH indicates intraventricular hematoma.

tered. Heparin was started immediately after diagnosis and LMWH was generally continued for 3 months.

Neuroimaging

Diagnosis of SVT was confirmed in all neonates by combined MRI/MRV performed with differential diagnosis of SVT, ischemic arterial stroke, or possible congenital cerebral malformation. In 19 of 52 cases (37%) diagnosis was made by screening color Doppler investigation. In 33 of 52 infants (63%), SVT was solely diagnosed on MRI/MRV and not recognized on initial ultrasound (Figure 1). Median time to diagnosis (ultrasound or MRI/MRV) after admission was 4.0 days (range, 0 to 26 days).

Associated lesions ($n=43$) like thalamic hemorrhage, intraventricular hemorrhage, or parenchymal hemorrhagic infarction were seen in 25 (48%), 29 (56%), and 41 (79%) neonates, respectively. Table 3 provides an overview of affected sinuses and associated cerebral lesions. Straight sinus thrombosis or complex multiple-sinus thrombosis was most frequently associated with severe hemorrhagic infarction of basal ganglia and/or thalamus. In patients with multisinus thrombosis without associated cerebral lesions (3 of 26), the straight sinus was not involved. Multisinus thrombosis was present in 9 of 10 newborns who died.

Table 4. Seizures During the Clinical Course and Neurophysiology Results at Presentation in 52 Neonates With SVT (EEG Combined With aEEG Results)

	No. (%)
Clinical seizures	
At presentation	29 (56%)
At presentation + during clinical course	42 (80.8%)
No. of AEDs needed (median, range)	1 (0–4)
Neurophysiology results/seizures	
Single seizure	5 (9.6%)
Recurrent seizures	18 (34%)
Status epilepticus	7 (13.5%)
No seizures	14 (26.9%)
No data	8 (15%)
Neurophysiology results/background	
Background activity	
Normal for age	24 (46.2%)
Moderately depressed	10 (19.2%)
Severely depressed	7 (13.5%)
No data	11 (21%)

AEDs indicates antiepileptic drugs.

aEEG Monitoring

All patients were frequently monitored by full lead EEG, and 39 of 52 received continuous amplitude integrated EEG monitoring, the results of which are displayed in Table 4.

Long-Term Outcome

Follow-up protocols differed per center. Table 1 shows follow-up data. Neurodevelopment was uncomplicated in 45%, although 36% of our patients were still <9 months of age when last seen. A severely abnormal outcome was documented in 8 of 42 survivors (19%), 7 of whom had multisinus thrombosis.

Visual deficits, like strabismus or uncoordinated eye movements, occurred in 5 patients. Four developed posthemorrhagic hydrocephalus requiring ventricular peritoneal shunting. Postneonatal epilepsy was noted in 9 infants, of whom 7 needed long-term antiepileptic treatment. Mortality was high (10 of 52 [19%]).

Discussion

This study confirms neonatal SVT is rare and usually presents with seizures. Although differential diagnosis of neonatal seizures is extensive, a history of complicated delivery, perinatal asphyxia, or infection followed by a symptom-free period should raise suspicion of SVT. This observation is in accordance with previous reports.^{3,4,8,15,20}

Neonatal and perinatal complications were present in over three fourths of our neonates and may prove to be more important than maternal risk factors. The high occurrence of complicated or assisted deliveries was remarkable. A plausible etiology for the association of traumatic birth and SVT could be severe changes in cerebral sinus venous flow during peripartum skull molding,^{21,22} predisposing the neonate to

SVT by disruption of venous endothelium and activation of the coagulation cascade, resulting in thrombus formation.

In agreement with other studies, a male predominance was found.¹⁴ This observation is as yet unexplained. In a recent publication, gender differences in pediatric thromboembolic arterial ischemic stroke and venous thromboembolism were associated with elevated testosterone levels in both male and female affected patients.^{23,25} Gender-related differences in testosterone levels may also play a role in neonatal SVT.²⁴

The observed incidence of neonatal SVT is higher than previously reported and could be due to increased awareness and improved perinatal care resulting in increased survival of neonates at risk. Thanks to extensive obstetric databases in The Netherlands, our estimate seems reliable. Because no active screening for SVT was performed, less severely affected neonates may have remained undiagnosed. Prospective studies are desired and may disclose an even higher incidence.

Neonatal brain lesions due to SVT found on MRI corresponded with known drainage territories of dural venous sinuses¹¹ and were comparable to other reports,^{11,26,27} as was the incidence of thalamic hemorrhage and intraventricular hemorrhage.^{1,4,28} Deep white matter and basal ganglia are drained by the internal cerebral and basal veins of Rosenthal, which join to form the great vein of Galen, eventually draining into the straight sinus. Either direct obstruction of thalamic venous drainage or the internal cerebral vein leads to hemorrhagic thalamic infarction.²⁷ In our series, multiple-sinus and straight sinus thrombosis invariably produced severe lesions in the thalamus and basal ganglia. Intraventricular hemorrhage during SVT is thought to result from germinal matrix or choroid plexus hemorrhage caused by obstructed venous flow at the vulnerable junction of 3 veins (venous angle): the thalamostriatal vein, septal vein, and choroidal vein.^{11,29}

The value of prothrombotic screening still needs to be determined. Because the content of screening protocols varied among neonatal intensive care units and not all patients were tested, no conclusions can be drawn regarding the significance of prothrombotic risk factors in the development of neonatal SVT. Protein S, C, and antithrombin examinations were usually not repeated after the neonatal period and none of the parents were tested. Therefore, congenital deficiencies could not be ruled out. FV G1691A mutation was present in 4.9%. FII G20210A mutation prevalence was 11% in our tested patients, which is higher than in the white population. The increased prevalence of FII G20210A mutation found might be due to selection bias, because only 18 of 52 neonates were tested. Previous studies demonstrated presence of FII G20210A mutation predicts recurrent thrombosis in children with SVT and/or deep venous thrombosis.^{30,31} Because homocysteine levels were not elevated in any of the patients with methylene tetrahydrofolate reductase mutations, their relevance seems negligible.

Discussion remains regarding optimal treatment for neonatal SVT. Kenet and colleagues suggest anticoagulation should be given on a patient-to-patient basis in children with newly identified SVT and high risk of recurrence.³² In our study, choice for treatment highly depended on clinician

preferences in the absence of guidelines. Severely affected neonates with deep or multisinus thrombosis, complicated by intracerebral hemorrhage, usually received none for fear of hemorrhagic complications (Figure 2). Therefore, treatment effect on outcome cannot be reliably evaluated in our cohort. In a recent extensive international prospective study, multivariate analysis of factors influencing treatment decisions in neonatal SVT failed to demonstrate presence of intracranial hemorrhage as a major reason to withhold treatment.³⁰ Clot propagation has been reported in 25% of affected infants. Although not based on clinical trials, unfractionated heparin or low-molecular-weight heparin administration is therefore advised in patients with SVT for a minimum period of 6 weeks and no longer than 3 months.^{31,33}

There are substantial differences in reported neonatal SVT neurodevelopmental outcome data.^{1,4,5,28,34} In our cohort, outcome in survivors was normal in 45%, neurological deficits were seen in 47%, and persistent epilepsy in 16%. These results are comparable with those of deVeber et al.⁵ In the only other study focusing solely on neonatal SVT, more adverse sequelae occurred.³⁵ Because of our relatively short follow-up period (36% of patients being younger than 9 months), no definite conclusions regarding final outcome can be drawn. Lack of a standardized neurodevelopmental follow-up protocol may have influenced outcome data. Mortality in our cohort (19%) is higher than previously reported^{1,4} and may reflect identification of the most severely affected neonates with extensive parenchymal damage.

In conclusion, neonatal SVT is a multifactorial disease with a significant risk of serious adverse neurological sequelae. It is increasingly diagnosed and incidence proved higher in our population than previously reported. Complicated delivery seemed the major risk factor and most infants presented with seizures. Although treatment with low-molecular-weight heparin in neonatal SVT appears safe, international collaboration should be sought for in documentation and evaluation of these patients to develop evidence-based treatment guidelines.

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Disclosures

None.

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