Cerebral Sinovenous Thrombosis in the Neonate

Karima C. Fitzgerald, MSc; Linda S. Williams, MD; Bhuwan P. Garg, MBBS; Karen S. Carvalho, MD; Meredith R. Golomb, MD, MSc

Background: There are few studies on neonatal cerebral sinovenous thrombosis (SVT).

Objectives: To describe the presentations, treatments, and outcomes of neonatal SVT and to assess infarction as a predictor of outcome.

Design: Retrospective chart study.

Setting: A tertiary pediatric hospital in Indianapolis, Ind.


Interventions: None.

Main Outcome Measures: Cognitive impairment, motor impairment, and epilepsy at last clinic visit.

Results: Gestational or delivery complications or risk factors and comorbid conditions such as dehydration, sepsis, and cardiac defects were common (gestational/delivery factors in 82% [31 of 38 with available maternal data]; comorbid conditions in 62% [26 of the 42]). Twenty-four (57%) presented with seizures. Twenty-five (60%) had infarcts, which were hemorrhagic in 22. Only 27 (64%) of 42 received prothrombotic evaluations; none had persistent deficiencies of protein C, protein S, or antithrombin III. Three (7%) received heparin sodium. All other children received only supportive care. One child died. Outcome data were available for 29 (71%) of the 41 survivors; of these, 23 (79%) had impairment(s). Two were known to be in early intervention, and no further information was available. Of the remaining 27, 16 (59%) had cognitive impairment, 18 (67%) had cerebral palsy, and 11 (41%) had epilepsy. Infarction was associated with the presence of later impairment ($P = .03$).

Conclusions: The presentation of neonatal SVT is often nonspecific, the diagnosis can be difficult to make, treatment beyond supportive care is rarely used, and outcomes can be severe. Further work is needed to develop standardized guidelines for the evaluation and treatment of neonatal SVT.

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INOVENOUS THROMBOSIS (SVT) is rare in the neonate but may cause cognitive impairment, motor impairment, and epilepsy.1 2 It can cause stroke, and neonates with stroke tend to have a worse prognosis than older children with stroke.3 Few studies have been published that present information on more than 20 cases or discuss in detail the factors that predict outcome in neonates with SVT. We identified 42 children who presented with SVT during the neonatal period and were seen in our hospital. This study describes clinical presentations, risk factors, outcomes, and factors that may predict outcome.

DATA COLLECTION

Chart reviews were performed to collect the following data: maternal risk factors during gestation; patient sex; gestational age at birth; ethnic background; age at onset of symptoms; initial presentation; age at diagnosis; length of stay in the neonatal intensive care unit; underlying disorders such as dehydration, sepsis, and heart defects; radiographic findings; and the results of testing for any prothrombotic risk factors, which included testing for protein C, protein S, antithrombin III, factor V Leiden mutation, prothrombin 20210GA gene mutation, and methylene tetrahydrofolate reductase (MTHFR) mutations C677T and A1298C. Outcomes were determined by the presence or absence of cognitive or motor sequelae (cerebral palsy) or seizures at the last inpatient or outpatient visit. Children with mild cognitive impairment were...
Table 1. Maternal Gestational Details*

<table>
<thead>
<tr>
<th>Gestational Details</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia/hypertension</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Gestational diabetes/diabetes</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Meconium aspiration/meconium-stained plaцenta</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Other†</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Urgent/emergency cesarean section</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Normal</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Postdate delivery</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Premature delivery</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Positive for group B streptococcus</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Breech position</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*Data were available for 38 patients. Some mothers had more than 1 gestational complication or risk factor.
†Includes preterm labor and fetal distress.

Table 2. Presentation in 42 Neonates

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>24 (57)</td>
</tr>
<tr>
<td>RDS</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Apnea</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Poor feeding/weight loss</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Multiple*</td>
<td>28 (67)</td>
</tr>
</tbody>
</table>

*Some children were included in more than 1 category.

MATERNAL RISK FACTORS

Gestational data were available on 38 (90%) of the 42 neonates in the study. Thirty-one (82%) of the 38 had complications or risk factors during gestation or delivery (Table 1).

PATIENT POPULATION AND PRESENTATION

The group included 42 patients: 24 boys and 18 girls. Six were premature. Thirty-six were white, 3 were African American, 2 were Hispanic, and 1 was classified as “other.” Median age at presentation was birth (range, 0-20 days). Twenty-three (55%) of the 42 neonates presented at birth. An additional 11 presented in the first week of life. Symptoms were often nonspecific and included seizures, apnea, and weight loss. Most of the neonates with SVT presented with 1 or more of these symptoms (Table 2). Comorbidities that may also have been risk factors were present in 26 (62%) and included dehydration, sepsis, meningitis, and cardiac malformations or defects. Eleven (26%) of the 42 children were dehydrated. Three patients (7%) had sepsis. Twenty-one (50%) had suspected sepsis but negative cultures. Four (10%) had meningitis. Eleven (26%) of the 42 patients had 1 or more cardiac malformation or defect, including 5 (45%) of the 11 with atrial septal defect, 4 (36%) with patent ductus arteriosus, 3 (27%) with complex congenital heart disease, 3 (27%) who had had open heart surgery, 2 (18%) with ventral septal defect, and 1 (9%) with both patent ductus arteriosus and atrial septal defect. Several children had more than 1 cardiac defect or issue. Four patients (10%) received extracorporeal membrane oxygenation.

Seizures were the most common presentation and occurred in 24 patients (57%). Children with early presentation (before 1 week of age) were just as likely to present with seizures as children with later presentation: seizures were present in 19 (56%) of 34 children with early presentation (95% CI, 38%-73%) and 5 (63%) of 8 children with later presentation (95% CI, 24%-91%). Two patients were asymptomatic and identified during screening radiographic studies performed for a skull bump (1 patient) or follow-up for oral lesions and low-grade fever during the first week of life (1 patient).

RADIOGRAPHIC FINDINGS

Twenty-one patients (50%) had involvement of a single sinus, most commonly the sagittal sinus, while 21 (50%) had involvement of multiple sinuses. The specific locations were as follows:

<table>
<thead>
<tr>
<th>Sinus</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sagittal</td>
<td>28 (67)</td>
</tr>
<tr>
<td>Transverse</td>
<td>23 (55)</td>
</tr>
<tr>
<td>Straight</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Torcular</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Jugular</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Vein of Galen</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

*Some children were included in more than 1 category.

Twenty-five (60%) had infarction on first imaging, which was hemorrhagic in 22. Eight of these had intra-
ventricular hemorrhage. Children’s conditions were diagnosed by means of computed tomography without contrast (1 patient), computed tomography with contrast (4 patients), computed tomographic venogram (1 patient), or magnetic resonance imaging (36 patients; 18 of these included magnetic resonance venogram).

Radiographic findings in those lost to follow-up were compared with findings in those with follow-up. Of the 12 patients lost to follow-up, 5 (42%; 95% CI, 15%-72%) had multiple sinuses involved, 7 (58%; 95% CI, 28%-84%) had infarct, and 5 (71% of infarcts; 95% CI, 29%-96%) had infarct with hemorrhage. Of the 29 patients with follow-up data available, 17 (59%; 95% CI, 39%-76%) had multiple sinuses involved, 18 (62%; 95% CI, 42%-79%) had infarct, and 17 (94% of infarcts; 95% CI, 73%-100%) had infarct with hemorrhage. There was no statistically significant difference between the 2 groups.

**PROTHROMBOTIC FINDINGS**

Information on prothrombotic testing was recorded for 27 (64%) of the 42 patients. Not all children received all tests. None of those tested had persistently low protein C or S levels (25 tested) or antithrombin III levels (24 tested). Three (13%) of 24 tested were heterozygous for factor V Leiden; 4 (40%) of 10 tested carried the MTHFR C677T mutation (3 heterozygous and 1 homozygous); 4 (44%) of 9 tested carried the MTHFR A1298C mutation (3 heterozygous and 1 homozygous); and none of the 16 tested carried the prothrombin 20210GA mutation.

**THERAPY**

Eleven neonates (26%) required correction of dehydration, which was hypernatremic in 2. A saline bolus, dopamine hydrochloride, or dobutamine hydrochloride, or a combination of these was used to provide pressor support to 5 children, 4 of whom had clinical dehydration.

Three neonates were treated for confirmed sepsis, and 4 were treated for meningitis. Twenty-one initially received antibiotics but had negative cultures; their antibiotic regimens were discontinued after 2 to 10 days.

Three of the 11 children with cardiac malformations had surgical intervention. One received a heart transplant, 1 had open heart surgery for repair of a ventral and atrial septal defect, and 1 had open heart repair of tetralogy of Fallot.

The 24 patients who presented with seizures were treated with phenobarbital, phenytoin, or fosphenytoin sodium. One of the premature children had intractable seizures, which were partially controlled with phenytoin.

Three children (7%) received therapy with heparin sodium. Two of these had clots outside the cerebral venous system in addition to SVT; 1 of the 2 had clots in an arm that led to amputation, and the other had a cardiac clot.

One patient was completely asymptomatic and did not require treatment. One neonate was treated with antiviral therapy for oral lesions but received no other therapy as she was otherwise asymptomatic.

**OUTCOMES**

One (2%) of the 42 patients died of complications of meningitis. He had hemorrhagic infarcts from SVT. Outcome data past the initial neonatal intensive care unit admission were available for 29 (71%) of the 41 surviving patients. Median age of survivors at last follow-up was 2 years (range, 2 months to 15 years). Twelve patients were lost to follow-up, most commonly because they lived far away from our hospital. Six (21%) of the 29 (95% CI, 8%-40%) had normal development at last visit, with no cognitive or motor sequelae and no seizures. The remaining 23 (79%; 95% CI, 60%-92%) had some sort of impairment at last follow-up.

Two (7%) of the 29 patients were known to have disabilities, as they were followed up in our state’s First Steps early intervention programs, but additional clinical details could not be accessed because of regulations of the Health Insurance Portability and Accountability Act. Data on the other 27 patients are summarized in Table 3. Of the 3 patients treated with heparin, 2 were lost to follow-up. The third had normal examination results at 19 months of age.

Two patients had congenital disorders that predisposed them to significant long-term disability: trisomy 8 in one and cerebral polymicrogyria in the other. We repeated our analyses after excluding those children (n=25) and still found impairments in 19 (76%) of our cohort (95% CI, 55%-91%): cognitive in 15 (60%; 95% CI, 39%-79%), motor in 16 (64%; 95% CI, 43%-82%), and epilepsy in 10 (40%; 95% CI, 21%-61%). (Some children had >1 impairment.) Infarction was associated with the presence of disability at last follow-up (P=.03).

**COMMENT**

We found that neonates experience significant morbidity and long-term impairments caused by SVT. We found long-term sequelae in 23 (79%) of the 29 children with...
any available follow-up data, and in the 27 with detailed follow-up data we found cognitive impairment in 16 (59%), motor impairment (“cerebral palsy”) in 18 (67%), and epilepsy in 11 (41%). Twelve (44%) had at least 1 moderate to severe impairment.

Few studies have focused on the presentation and outcome of SVT in neonates. The largest study, that by deVeber and colleagues,1 described 160 children with SVT, including 69 neonates. They calculated an SVT incidence of 0.67 cases per 100 000 children per year, with neonates the most commonly affected age group. Wu and colleagues8 described maternal risk factors, clinical presentations, and radiographic findings in 30 neonates with SVT. Most of the literature describes groups of fewer than 20 neonates. The limited literature on neonates makes patient care and counseling of families difficult.

Maternal gestational risk factors may play a role in some cases of neonatal SVT, particularly in children who present in the first week of life. In our study, 10 (26%) of the 38 women had preclampsia or hypertension. In the study by Wu and colleagues,6 10% of the mothers had hypertension. Preeclampsia is a hypercoagulable state; preeclampsia may contribute to thrombotic cascades in neonatal SVT. There is limited literature describing the correlation between gestational diabetes and the development of SVT. Diabetes leads to vascular injury, which may lead to thrombosis; diabetic mothers appear to be at increased risk for placental infarctions.9 Ten (26%) of 38 mothers in our study had gestational diabetes or chronic diabetes; 2 of these also had preeclampsia. In the study by Wu and colleagues,6 10% of the mothers had diabetes. However, in the cohort described by deVeber and colleagues,1 gestational diabetes was reported in the mothers of only 2 (3%) of 69 neonates with SVT. Gestational diabetes increases the risk of developing maternal preeclampsia or hypertension, premature rupture of membranes, preterm delivery, and giving birth to infants of higher birth weight.8 In Indiana in 2002, 2757 infants (3.2% of total births) were born to diabetic mothers, 1503 (1.8% of total births) to women with gestational diabetes, and 1254 (1.5% of total births) to women with preexisting diabetes.10 The elevated rates of maternal diabetes in our cohort and in that of Wu and colleagues8 suggest that it may be a risk factor for neonatal SVT. The maternal complication most commonly found in the series described by Wu and colleagues was choioamnionitis; unfortunately, data on placental pathological findings and cultures were not available for most of the children in our study.

We did note a predominance of male infants in this group, with a male-female ratio of 1.3:1. A male preponderance in neonatal SVT has been noted previously, with an even higher male-female ratio.11 The ethnic population of our group reflects the population of Indiana; no one group appeared to be at an increased risk.12 Many of our patients (62%) had acute illnesses or clinical conditions at the time of diagnosis, including dehydration (26%), sepsis (7%), cardiac defects (26%), and meningitis (10%). deVeber and colleagues also found high rates of illness; 84% of neonates in their cohort had an acute illness at the time of diagnosis. Perinatal complications and dehydration were the most common.1 Several patients carried factor V Leiden or MTHFR mutations, but these mutations are common in populations of European background13,14 and the frequency in our cohort was not significantly elevated. Almost half (48%) of our cohort had multiple risk factors. Wu and colleagues8 also described neonates presenting with 2 or more risk factors. Combinations of risk factors may have contributed to the development of SVT and may place these children at risk for recurrent thrombosis.

Twenty-four (57%) of the 42 patients included in our study presented with seizures; patients also presented with apnea or respiratory distress, poor feeding, lethargy, and hypotonia. Twenty-eight (67%) of the 42 neonates had multiple symptoms. Other authors15-18 have also described seizures as the presenting symptom in up to 70% of patients. It was often difficult to confirm exactly when the symptoms of SVT began; many of the patients in our study had nonspecific neurologic symptoms at birth.

We observed clot most commonly in the sagittal and transverse sinuses. Twenty-eight (67%) of the 42 patients had a clot in the sagittal sinus. In Volpe’s meta-analysis,17 more than 85% of thromboses affected the superior sagittal sinus. We noted thrombosis in the transverse sinus in 23 (55%) and involvement of multiple sinuses in 21 (50%). This correlates with the findings of Sebire and colleagues18 and deVeber and colleagues9 in both neonates and older children, who found the sagittal and transverse sinuses to be the most commonly affected sinuses in their cohorts. More than 40% of the children in the study by Sebire and colleagues18 had involvement of multiple sinuses.

Twenty-five (60%) of our patients had infants. In the series described by deVeber and colleagues,4 41% had infants. Eight of our patients had intraventricular hemorrhage. Sinovenous thrombosis is a known cause of symptomatic intraventricular hemorrhage in the term neonate.19 Treatment of neonatal SVT is highly controversial. Children with thrombophilia are at greater risk for clot recurrence.20 The most common treatment measures for neonates with SVT are supportive;21 they typically receive rehydration therapy, antibiotics for suspected sepsis, and antiepileptic drugs, usually phenobarbital. A pilot study looked at the use of heparin or low-molecular-weight heparin to treat these children and found low rates of symptomatic hemorrhage,22 but there are no randomized controlled trials. In our study, only 3 (7%) of the 42 patients were given anticoagulants. Two of those had vascular clots outside the brain and appeared to have hypercoagulable states. The third had multiple thrombosed sinuses.

There is limited literature describing outcomes and predictors of outcomes in neonates with SVT. In our study, 23 (79%) of the 29 children with any available follow-up data were left with some sort of impairment. Of the 27 patients in our study with detailed follow-up data, more than half (16 [59%]) had some degree of cognitive impairment, more than half (18 [67%]) had motor impairment, and 11 (41%) had seizures. Our outcomes are worse than those in previous reports, which have described learning disabilities in 5%, developmental delay in 28% to 58%, motor impairment in 26%,23 and seizures in 20% of children with neonatal SVT. Two small studies described “abnormal outcome” in 18% to 44%.10
but both studies had a median follow-up of less than 1 year. In older children with SVT, the rate of subsequent disability has been reported at 38% to 62%.\(^1,2,18\) deVeber and colleagues\(^1\) described the presence of infaracts as a predictor of poor outcome after SVT in both neonates and older children. Golomb and colleagues\(^24\) found that bilateral infarcts resulting from neonatal SVT raised the risk of delayed walking or not walking. We also found an association between infarction and the presence of impairment at last follow-up (\(P = .03\)).

Our study has several limitations. We may not have captured all patients with SVT. Our selection criteria probably biased our cohort toward those with worse outcomes, as we included only children with clear-cut SVT. We excluded 9 children with "possible" SVT on imaging; they had lesser degrees of thrombosis, if they actually had thrombosis, and probably had good outcomes. Our cohort was more than 80% white and reflective of the population of Indiana; these results might vary in genetically different populations. This was a retrospective chart study, and we were limited by the degree of documentation available. It is possible that the patients lost to follow-up had better or worse outcomes than those with follow-up data. However, when we compared radiographic findings of children with follow-up with those lost to follow-up, there was no statistical difference, suggesting that the groups were comparable. Analysis of outcomes was also clouded by the presence of comorbidities such as meningitis and cardiac defects, which themselves may cause long-term disability. A prospective study of children with neonatal SVT has been initiated by our group. In the future, when we have a larger cohort, we will be able to adjust for the presence of comorbidities in our analysis.

We found that neonates usually developed SVT in the setting of maternal risk factors and/or acute systemic illness, and that making the diagnosis was often difficult. Children with SVT frequently progressed to infarction, and more than half of the children with SVT were left with some degree of chronic morbidity. Further work is needed to develop standardized guidelines for the evaluation and treatment of SVT in neonates.

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Author Contributions: Study concept and design: Williams, Garg, Carvalho, and Golomb. Acquisition of data: Fitzgerald and Golomb. Analysis and interpretation of data: Fitzgerald, Williams, and Golomb. Drafting of the manuscript: Fitzgerald, Garg, Carvalho, and Golomb. Critical revision of the manuscript for important intellectual content: Fitzgerald, Williams, Garg, Carvalho, and Golomb. Statistical analysis: Williams and Golomb. Obtained funding: Golomb. Administrative, technical, and material support: Garg, Carvalho, and Golomb. Study supervision: Williams and Golomb.

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REFERENCES