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# Cerebral Venous Sinus Thrombosis in Children: A Multicenter Cohort From the United States

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This study presents a large multicenter cohort of children with cerebral venous thrombosis from 5 centers in the United States and analyzes their clinical findings and risk factors. Seventy patients were included in the study (25 neonates, 35%). The age ranged from 6 days to 12 years. Thirty-eight (55%) were younger than 6 months of age, and 28 (40%) were male. Presenting features included seizures (59%), coma (30%), headache (18%), and motor weakness (21%). Common neurological findings included decreased level of consciousness (50%), papilledema (18%), cranial nerve palsy (33%), hemiparesis (29%), and hypotonia (22%). Predisposing factors were identified in 63 (90%) patients. These included infection (40%), perinatal complications (25%), hypercoagulable/hematological diseases (13%), and various other conditions (10%). Hemorrhagic infarcts occurred in 40% of the patients and hydrocephalus in 10%. Transverse sinus thrombosis was more common (73%) than sagittal sinus thrombosis (35%). Three children underwent thrombolysis, 15 patients received anticoagulation, and 49 (70%) were treated with antibiotics and hydration. Nine (13%) patients (6 of them neonates) died. Twenty-nine patients (41%) were normal, whereas 32 patients (46%) had a neurological deficit at discharge. Seizures and coma at presentation were poor prognostic indicators. In conclusion, cerebral venous thrombosis predominantly affects children younger than age 6 months. Mortality is high (25%) in neonatal cerebral venous thrombosis. Only 18 (25%) patients were treated with anticoagulation or thrombolysis.

**Keywords:** thrombosis; venous; stroke; magnetic resonance imaging

Cerebral venous thrombosis in children is rare, with an incidence less than 1 per 100 000 children per year.[1] However, venous thromboses are increasingly recognized in children due to advances in imaging. Most published papers related to pediatric or neonatal cerebral venous thrombosis are reported from Europe, Canada, and other countries.[1-9] Cases reported from the United States are typically single-center series or case reports (see Table 1).[10-14] This study was done to analyze clinical and imaging features, risk factors, treatment options, and outcome of cerebral venous thrombosis in children at various US centers. We compared our findings to other studies reported in Europe or Canada to identify regional differences in predisposing factors, treatment strategies, and outcome of these patients.

## Methods

We retrospectively analyzed children with cerebral venous thrombosis from 5 centers in the United States, University of Texas Southwestern Medical Center, Dallas, Texas; 19 patients, State University of New York at Buffalo, New York; 16 patients, Metro Health Medical Center, Cleveland, Ohio; 8 patients, University of Michigan, Ann Arbor, Michigan; 13 patients, Vanderbilt University, Nashville, Tennessee; 14 patients) from 1992 to 2001. All patients had radiographic confirmation of cerebral venous thrombosis by cranial ultrasound, computerized tomography (CT) scan, or magnetic resonance imaging (MRI). Diagnosis of cerebral venous thrombosis was established by MRI and magnetic resonance venography (MRV) in 55 patients, Cranial CT and cerebral angiography in 2 patients, and CT head and cranial ultrasound in 13 patients. These 13 patients were all neonates.

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**Table 1.** Comparison of Published Studies Related to Pediatric and Neonatal Cerebral Venous Thrombosis

| Author | Country | Number of Patients | Predisposing Factor | Clinical | Labs | Location | ICH | Complete Recovery | Mortality |
|---|---|---|---|---|---|---|---|---|---|
| Byers and Hass (1933)[10] | United States | 50 | Infections 53% | | | SSS 24%<br>TS 19%<br>Deep veins 19% | 25% | | |
| Shevell et al (1989)[2] | Canada | 17 neonates | Perinatal complications 25% | Seizures 90% | | | | 58% | |
| Barron et al (1992)[11] | United States | 25 | Hypercoaguable state 25%<br>Sepsis/dehydration 25% | Seizures 45%<br>Headache 34% | | | | 75% | 4% |
| Lee et al (1995)[3] | Taiwan | 25 | | Seizures 100%<br>Headache 37% | | | | 50% | 8% |
| Carvalho et al (2001)[12] | United States | 31 | Mastoiditis 30%<br>Cardiac malformation 27%<br>Dehydration 21% | | | | 25% | 35% | 6% |
| Huisman et al (2001)[4] | Switzerland | 19 | Trauma 50%<br>Infection 35%<br>Coagulation defects 15% | | | | | | |
| deVeber et al (2001)[1] | Canada | 160 | Prothrombotic state 32%<br>Dehydration 25%<br>Perinatal complications 24%<br>Infections 18% | Seizures 58%<br>Headache 34%<br>Hemiparesis 13%<br>Papilledema 12% | Anemia | SSST 55%<br>TS 51%<br>Deep cerebral venous thrombosis 38% | 43% | 48% | 8% |
| Wu et al (2002)[13] | United States | 30 neonates | Extracorporeal membrane oxygenation 29%<br>Heart malformation 23% | Seizures 57% | Genetic 12% | | 50%<br>IVH 33% | | |
| Heller et al (2003)[5] | Germany | 149 | Prothrombotic state 56%<br>Infections 29% | Headache 32%<br>Seizures 38%<br>Motor 3% | Lipoprotein a 41%<br>Genetic 18% | SSS 62%<br>TS 14%<br>Sigmoid 7% | | | |
| Barnes et al (2004)[6] | Australia | 16 | Infections 88% | Headache 45%<br>Seizures 25%<br>Motor 6% | | | | | |
| Kenet et al (2004)[7] | Israel | 46 | Infections 47%<br>Prothrombotic state 38% | AplA 10%<br>Genetic 20% | | | | | 4% |
| Sebire et al (2005)[8] | Europe | 42 | Mastoiditis 47%<br>Other infections 24%<br>Dehydration 21%<br>Prothrombotic state 16%<br>Recent surgery 9% | Seizures 40%<br>Headache 68%<br>Hemiparesis 33% | Anemia 55%<br>High factor VIII 54% | SSST 40%%<br>TS 48%<br>Sigmoid 26%<br>Deep cerebral venous thrombosis 20% | 28% | 26% | 12% |
| Bonduel et al (2006)[9] | Argentina | 38 | Prothrombotic 34% | | | | | | None |
| Fitzgerald et al (2006)[14] | United States | 42 neonates | Dehydration 26%<br>Cardiac malformation 26%<br>Infections 17% | Seizures 57%<br>Respiratory 19%<br>Apnea 19%<br>Poor feeding 12% | Genetic 27% | SSST 67%<br>TS 55%<br>Sigmoid 14%<br>Deep cerebral venous thrombosis 45% | 52%<br>IVH 20% | 12% | 2% |

NOTE: Apl A = Anti phospholipid antibody; SSS = superior sagittal sinus; TS = transverse sinus; SSST = superior sagittal sinus thrombosis; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage.

Children younger than 12 years of age were included. Children younger than 1 month of age were classified as neonates. Some of the patients were identified because one of the authors was involved in these children's care, and others were identified by searching for the appropriate *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes at the medical records departments of participating centers. Data were collected on a standardized data collection form. Data was analyzed using SPSS 13.0. Logistic regression analysis was performed to identify predictors of outcome.

**Table 2.** Clinical Presentations, n (%)

| | |
|---|---|
| Seizures | 41 (59) 20 neonates, 21 others |
| Focal | 26 (37) |
| Generalized | 15 (21) |
| Coma | 21 (30) |
| Drowsy/stuporous | 37 (51) |
| Headache | 12 (18) |
| Generalized weakness | 20 (29) |
| Focal weakness (hemi/monoparesis) | 16 (21) |
| Jitteriness (neonates) | 12 (18) |
| Agitation/behavioral symptoms | 6 (10) |
| Fever | 23 (33) |

**Table 3.** Neurological Findings, n (%)

| | |
|---|---|
| Decreased level of consciousness | 37 (50) |
| Papilledema | 12 (18) |
| Cranial nerve palsy | 23 (34) |
| Dysarthria | 9 (13) |
| Hemiparesis | 20 (29) |
| Aphasia | 3 (5) |
| Monoparesis | 3 (5) |
| Ataxia | 6 (9) |
| Hypotonia (neonates) | 16 (22) |
| Neck stiffness | 3 (5) |
| Ear infection | 10 (15) |

**Table 4.** Predisposing Factors, n (%)

| | |
|---|---|
| Identified | 63 (90) |
| Not identified | 7 (10) |
| Infection | 28 (40) |
| Otitis/mastoiditis/sinusitis | 17 (25) |
| Meningitis | 2 (3) |
| Sepsis | 9 (12) |
| Perinatal complications | 18 (25) |
| Hypoxic ischemic encephalopathy | 16 (22) |
| Birth trauma | 2 (3) |
| Hypercoagulable/hematological | 13 (20) |
| Protein C deficiency | 1 |
| Protein S deficiency | 2 |
| Anti-thrombin-III deficiency | 1 |
| Lupus anticoagulant | 2 |
| Factor V mutation | 1 |
| Homocystinuria | 3 |
| Disseminated intravascular coagulation | 1 |
| Thrombotic thrombocytopenic purpura | 1 |
| Sickle cell disease | 1 |
| Other conditions | 17 (25) |
| Nephrotic syndrome | 1 |
| Systemic lupus erythematosis | 2 |
| Cancer (lymphoma, leukemia) | 2 |
| Cancer chemotherapy | 1 |
| Severe dehydration | 3 |
| Oral contraceptives | 1 |
| Anemia | 7 |

## Results

Seventy-nine charts were reviewed, and 9 individuals were excluded due to lack of imaging confirmation of a cerebral venous thrombosis or because of other incomplete information. Of the 70 children who were included, 25 (35%) were neonates, and 38 (55%) were younger than 6 months of age. The age range was 6 days to 12 years, and 28 (40%) were male. The male-to-female ratio was 1:1.5 for both neonates and nonneonates.

Clinical features at presentation (Table 2) included seizures (59%), fever (33%), coma (30%), drowsiness (21%), motor weakness (21%), and headache (18%). Headache was present in 12 of 25 patients (45%) ages 6 to 12 years. Common neurological abnormalities (Table 3) included decreased level of consciousness (50%), papilledema (18%), cranial nerve palsy (33%), hemiparesis (29%), and, in neonates, hypotonia (22%).

Predisposing factors were identified in 63 (90%) children. These included infection (otitis, mastoiditis, meningitis, and sepsis) in 40%, perinatal complications (hypoxic-ischemic injury, birth trauma) in 25%, hypercoagulable/hematological diseases (eg, protein C or S deficiency, systemic lupus erythematosus, and homocystinuria) in 13%, and various other conditions (eg, nephrotic syndrome, cancer, chemotherapy, dehydration) in 10%. However, testing for a hypercoagulable state was only performed in 39 patients (55%). This workup was not standardized and differed from one center to another. Only 16% patients had multiple predisposing factors (Table 4).

Most children (79%) had at least 2 diagnostic studies (cranial ultrasound, CT, MRI) for confirmation. Ultrasound was done only in neonates, and cerebral venous thrombosis was confirmed by CT or MRI in all patients where ultrasound suggested a diagnosis of cerebral venous thrombosis. Hemorrhagic infracts were present in 40% of patients, and hydrocephalus was present in 10% of patients. Five patients underwent cerebral venography (Table 5).

Transverse sinus thrombosis was more common (73%) than sagittal sinus thrombosis (35%). The superficial and deep venous system was involved in 10 (15%) children, and multiple sinuses were involved in more than 70% of patients (Table 6).

Three patients (5%) were treated with direct thrombolysis with urokinase, 15 (20%) patients received anticoagulation with unfractionated heparin or low molecular weight heparin, 49 (70%) patients were treated with antibiotics and hydration, and 7 patients (10%) underwent surgery (decompression and/or shunt placement). These patients were not randomized, and treatment was based entirely on the clinical situation. Nine patients were discharged on warfarin, and 22 patients were discharged on aspirin.

Nine (13%) patients died, including 6 neonates (25%) and 3 other children (7%). One patient who underwent thrombolysis died, 1 died in the anticoagulation treatment group, and 7 children in the antibiotic/hydration group died.

**Table 5.** Neuroimaging Findings

| | |
|---|---|
| Cranial ultrasound | 18/25 neonates |
| Abnormal | 10 |
| Sinus thrombosis alone | 2 |
| Hemorrhage | 5 |
| Sinus thrombosis + hemorrhage | 3 |
| Head CT scan: Done | 43/70 (neonates, 18; children, 25) |
| Normal | 8 |
| Thrombosed sinus | 11 |
| Hemorrhage | 15 |
| Infarct | 6 |
| Hydrocephalus | 3 |
| Brain MRI/MRV: Done | 55/70 (neonates, 10; children, 45) |
| Thrombosed sinus | 54 |
| Hemorrhage | 23 |
| Infarct | 10 |
| Hydrocephalus | 3 |
| Cerebral angiogram: Done | 5/70 |
| Sinus thrombosis | 5 |
| Hemorrhagic infarct on CT or MRI | 28 (40%) |

NOTE: CT = computed tomography; MRI = magnetic resonance imaging; MRV = magnetic resonance venography.

**Table 6.** Location of Thrombosis, n (%)

| | |
|---|---|
| SSS | 7 (10) |
| TS alone | 8 (12) |
| SS alone | 0 |
| Sigmoid sinus | 0 |
| JV | 0 |
| Internal cerebral vein/vein of Galen | 2 (3) |
| Cortical vein | 2 (3) |
| SSST + TS | 16 (24) |
| TS + sigmoid sinus | 9 (13) |
| TS + SS + JV | 7 (10) |
| Bilateral TS | 13 (18) |
| Superficial + deep venous system | 6 (9) |

NOTE: SSS = superior sagittal sinus; TS = transverse sinus; SS = straight sinus; JV = jugular vein; SSST = superior sagittal sinus thrombosis.

The outcome was assessed at discharge: 29 (41%) patients were normal, and 32 patients (46%) had a neurological deficit at discharge. Thirty-day outcome or a longer follow-up was not available due to the retrospective nature of study. Univariate analysis revealed that predictors of mortality were coma at presentation, age less than 1 month of age, presence of intracerebral hemorrhage, and seizures. On multivariate analysis, the best predictors of mortality were coma at presentation (odds ratio 3.9 [95% confidence interval (CI): 0.0-7.6]) and seizures (odds ratio 2.1 [95% CI: 0.8-5.5]).

## Discussion

Although cerebral venous thrombosis is uncommon in children, it occurs more often during the first 6 months of life. In our series, 55% of the children belonged to this age group. Similarly, 54% of the children in the Canadian cerebral venous thrombosis registry were younger than 1 year old.[1] Why children in this age group are more susceptible to cerebral venous thrombosis than older children is not clear. Previous reports have suggested the presence of multiple risk factors as the potential cause of cerebral venous thrombosis in neonates.[13] Reported risk factors contributing to cerebral venous thrombosis in infants and neonates include dehydration, infections, extracorporeal membrane oxygenation treatment, and a variety of maternal factors.[5,7,8,13] At least 1 risk factor was identified in 90% of patients in our series, comparable to published reports from European and Canadian studies. The frequency of prothrombotic states would no doubt have been higher in our series had a uniform procedure for their evaluation been in place. Prothrombotic factors are increasingly recognized as a cause of cerebral venous thrombosis in pediatric patients as in adults.[15,16] Anemia, lipoprotein a, and high factor VIII have been suggested as predisposing factors for pediatric cerebral venous thrombosis.[1,5,8,17] The role of these factors in adult cerebral venous thrombosis has not been established.

Contrary to some previous studies reporting male predominance, our patient population was predominantly female.[18] Most of the large series dealing with adult patients with cerebral venous thrombosis reported female predominance.[19]

Clinical features in neonatal and nonneonatal cerebral venous thrombosis vary, but seizures remain the most common presentation in both groups. Hypotonia and irritability were more common in neonates, whereas headache and motor symptoms predominated in the nonneonatal group. These symptoms are nonspecific, and diagnosis of cerebral venous thrombosis is challenging in these patients. A low threshold for neuroimaging is required for early diagnosis. Cranial ultrasound may be helpful in neonatal cerebral venous thrombosis, but its findings often need to be confirmed by MRI and magnetic resonance venography.[20,21]

Treatment of pediatric cerebral venous thrombosis is controversial. Treatment of cerebral venous thrombosis was more aggressive in our patients than in previous reports. Three patients (previously reported) were treated with thrombolytic therapy,[22] and 7 patients underwent surgical decompression and shunt placement. Experience with thrombolytic therapy in pediatric cerebral venous thrombosis is limited to a few case reports.[23-25] Griesmer et al[23] reported a 10-year-old boy with superior sagittal sinus thrombosis, transverse sinus thrombosis, straight sinus, and sigmoid sinus thrombosis. Due to progressive neurological deterioration, he was treated with local urokinase thrombolysis and improved dramatically. Wong et al[24] reported a 1-day-old neonate with parasagittal hemorrhage due to cortical vein thrombosis. This baby recovered completely after locally applied urokinase. Gebara et al[25] reported a 9-week-old girl with dural sinus thrombosis secondary to subclavian vein catheterization. She had complete recovery after local

urokinase thrombolysis. One study compared direct thrombolysis to heparin therapy for treatment of adult cerebral venous thrombosis in a nonrandomized manner and showed that thrombolysis was both safe and effective in comparison to anticoagulation with heparin.[26] Despite its effectiveness in achieving recanalization or patency of thrombosed intracranial sinuses, safety and availability are the main limitations of thrombolysis.[27]

The evidence regarding anticoagulation in adult cerebral venous thrombosis is conflicting. Many reports suggest its safety and efficacy in patients with puerperal cerebral venous thrombosis and in patients with intracerebral hemorrhage and hemorrhagic infarction.[28-30] The most recent randomized, placebo-controlled trial of anticoagulant treatment with low molecular weight heparin for cerebral sinus thrombosis failed to show a significant benefit.[31] Despite this fact, anticoagulation remains the mainstay of treating adult cerebral venous thrombosis. There are no randomized trials related to anticoagulation in pediatric cerebral venous thrombosis. Anticoagulation with heparin, low molecular weight heparin, and warfarin is reported to be safe in pediatric patients with cerebral venous thrombosis.[32,33] The use of anticoagulants was less common in our patients (20%) as compared to 34% to 70% in other reports.[1,32,33] Anticoagulation is used less commonly in neonates than in older children.[1,14] Most of these patients are treated with hydration and antibiotics. Surgical treatment of cerebral venous thrombosis is generally reserved for intracerebral hematomas with mass effect and for hydrocephalus. Seven patients underwent surgery, one of whom was a neonate. A more conservative approach in neonatal cerebral venous thrombosis is applied.

The mortality was high in our series, especially among neonates, although the prognostic indicators were similar in our series to those in previous reports.[1] Our findings add to the current state of knowledge related to pediatric cerebral venous thrombosis, but our data are subject to the same limitations as other retrospective studies. There is a chance that cases have been missed during the coding process. An evaluation for hypercoagulable states was not done at some centers and varied from one center to another. All participating centers, being tertiary care centers, tend to care for sicker patients, perhaps explaining the high mortality. We think that these 70 patients from 5 US centers only present a fraction of pediatric cerebral venous thrombosis. Retrospective reviews based on the ICD coding system may miss a number of patients. A recent study pointed out that coding accuracy ranges from 37% to 88% for acute ischemic stroke.[34] The North American pediatric stroke registry and some of the European pediatric stroke registries have made an extraordinary contribution in the understanding of pediatric stroke, especially pediatric cerebral venous thrombosis. A large, prospective, global, multinational registry for pediatric patients with cerebral venous thrombosis is warranted to understand the entity and plan intervention for managing this condition. Large, multicenter, online registries are feasible due to advances in information technology and international collaboration. These may be helpful in identifying regional differences in cerebral venous thrombosis and as well as enrolling patients for future randomized trials.[35]

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