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Antithrombotic Treatment in Neonatal Cerebral Sinovenous Thrombosis: Results of the International Pediatric Stroke Study

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Abstract

Objective—To identify predictors of antithrombotic treatment in neonates with cerebral sinovenous thrombosis (CSVT) in a large multi-national study.

Study Design—Neonates with CSVT from 10 countries were enrolled in the International Pediatric Stroke Study from 2003-2007. Term neonates with CSVT who presented with neurologic symptoms or signs of systemic illness and neuroimaging evidence of thrombus or flow interruption within cerebral venous system were included.

Results—Of 341 neonates enrolled, 84 had isolated CSVT. Neuroimaging findings, available in 67/84 neonates, included: venous ischemic infarction in 5, hemorrhagic infarction or other intracranial hemorrhage in 13, both infarction and hemorrhage in 26, and no parenchymal lesions in 23. Treatment data, available in 81/84 neonates, included antithrombotic medications in 52% (n=43), comprising heparin (n=14), low molecular weight heparin (n=34), warfarin (n=1) and aspirin (n=2). By univariate logistic regression analysis, deep venous system thrombosis (p=0.05) and location in the United States (p=0.001) predicted non-treatment. Presence of infarction, hemorrhage, dehydration, systemic illness, and age did not predict treatment or non-treatment. In multivariate analysis only geographic location remained significant.

Conclusions—In neonatal CSVT, regional antithrombotic treatment practices demonstrate considerable variability and uncertainty about the indications for antithrombotic therapy. Additional studies to determine appropriate treatments are warranted.

Keywords

Cerebral sinovenous thrombosis; neonatal; stroke; treatment

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INTRODUCTION

Studies to address the treatment and monitoring of neonates with cerebral sinovenous thrombosis (CSVT) are lacking and as a result, there is a great deal of practice variability. Published consensus-based guidelines for antithrombotic treatment of neonatal CSVT are discordant. The American College of Chest Physician guidelines, published in 20041 and updated in 20082 suggest anticoagulation for neonates without significant intracranial hemorrhage, while the American Heart Association (AHA) guidelines published in 20083 recommend anticoagulants only when there is evidence of thrombus propagation, multiple cerebral or systemic emboli or a severe prothrombotic state is present.

In one of the largest series of neonates with CSVT (n=69), published from the Canadian Pediatric Ischemic Stroke Registry, only 25/69 neonates (36%) diagnosed between 1992 and 1998 were anticoagulated.[4] Most treated neonates received low molecular weight heparin (LMWH; 20/25). None had hemorrhagic complications associated with death or neurologic deterioration. Hemorrhagic infarction was reported in 24/69 neonates (35%), while ischemic infarction was reported in 5/69 (7%). In a European collaborative study of childhood CSVT, 75 neonates were included. Specific data for neonates were not reported in detail, but there was no significant difference in treatment for children younger versus those older than age 2 years.5

In the present study, we determined current treatment practices and outcomes in neonates with CSVT enrolled in the International Pediatric Stroke Study (IPSS) registry. We also assessed predictors of treatment versus non-treatment. We hypothesized that regional differences in the use of antithrombotic medications may exist.

METHODS

Study Design

The IPSS is an ongoing multi-national registry that prospectively enrolled 1,187 children with arterial ischemic stroke (AIS) and CSVT between 1/2003 and 7/2007 (https://app3.ccb.sickkids.ca/cstrokestudy/).[6] Children were enrolled if they were diagnosed between birth (gestational age >=37 weeks) and 19 years-of-age. Participants were from 30 hospitals in 10 countries (or regions); Australia, Canada, Chile, Georgia, Germany, Hong Kong, Malaysia, Thailand, the United Kingdom, and the United States (U.S.).

The study was approved by the institutional review board (IRB) at each enrolling center. The IPSS site investigator obtained informed parental or caregiver consent according to institutional IRB requirements. Our primary analysis focused on neonatal CSVT and excluded children older than 28 days-of-age and all study participants with AIS including 8 neonates with AIS and CSVT.

Case identification and confirmation

Potential inpatient and outpatient subjects were identified at each center. Neonatal CSVT diagnosis was confirmed by the enrolling investigator (a pediatric neurologist or hematologist) using consensus-based, published clinical and radiologic criteria.[7] Inclusion criteria were all 3 of the following: (1) age ≤ 28 days at diagnosis of CSVT; (2) clinical symptoms of either seizure(s), altered consciousness, focal neurologic deficit, or signs of systemic illness; and (3) neuroimaging showing thrombus or flow interruption within cerebral veins or dural venous sinuses with or without venous infarction by either magnetic resonance imaging (MRI), magnetic resonance venography (MRV), computed tomographic venography (CTV) or conventional angiography (CA). Although case submission was based on a priori imaging criteria as described above, there were 2 individuals in whom imaging confirmation of CSVT

was by CT alone without venography. Images for these 2 neonates were obtained from the site study investigators and confirmed the CSVT.

Data abstraction

Participating centers recorded detailed medical and laboratory data on a standardized IPSS data collection form, including information about patient demographics (age, gender, race/ethnicity, geographic location), clinical presentation, neuroimaging features, risk factors for CSVT, treatment (antithrombotic, antibiotic or anticonvulsant), outcome at discharge (normal, death, neurologic deficit) and discharge destination (home, rehabilitation hospital, other hospital). Location of CSVT was classified as (i) superficial system (superior sagittal or lateral sinus, and cortical or jugular vein), (ii) deep system (inferior, sagittal, and straight sinus, internal cerebral vein, vein of Galen) or (iii) both. Age at diagnosis was classified by post-natal week at CSVT onset. De-identified data were collected by the study coordinating center in Toronto, either by fax or using a secure web-based data entry system designed for the IPSS. Full methods for the IPSS are published.[8]

Evaluation and Treatment

Local providers determined the evaluation and treatment of neonates with CSVT based on individual practices, published guidelines,[1] or institutional protocols. Thrombophilia testing and antithrombotic dosing regimens were not prescribed by the IPSS.

Statistical Analysis

For univariate analysis, proportions were compared utilizing Fisher's exact test for cell sizes<5 and Chi-square for all others (including predictors of treatment and outcome). Variables having a p-value of <0.10 on univariate testing were assessed for co-linearity and entered into a multivariate model. The presence of intracranial hemorrhage at diagnosis in neonates as a predictor of treatment was analyzed as a 2-part variable, hemorrhage versus no hemorrhage. To evaluate for regional differences in treatment practices, we compared treatment practices in 6 international regions, and also in U.S. versus other countries. All statistical analyses were performed using Stata 9.0 (College Station, TX). A p-value <0.05 was considered significant for all analyses. The authors had full access to the data and take responsibility for its integrity. All authors read and agreed to the manuscript contents.

RESULTS

There were 341 neonates enrolled; 246 with AIS, 84 with isolated CSVT and 8 with both conditions. There were 162 children (non-neonates) concurrently enrolled with childhood CSVT. The 84 neonates with isolated CSVT comprising our study population represent 34% of all pediatric patients with CSVT and 24% of neonates with ischemic stroke. Among the 84 neonates with CSVT, 62 (74%) were male, similar to the proportion reported for the entire cohort.[8] The median gestational age was 40 weeks, range 37-42 weeks. The median birth weight was 3515g, range 2610 -4713 grams.

Clinical Presentation

The majority (61%) of neonates with CSVT presented during the first post-natal week. Additional 15, 10 and 8 neonates presented within the 2nd, 3rd and 4th post-natal weeks. The most common presenting symptoms were seizure(s) in 56/84 (67%), altered consciousness (48 of 74, 65%) and focal motor deficits (5/84, 6%). Eleven neonates only had systemic signs of illness (apnea, irritability, hypotonia, poor feeding, vomiting or other signs of concern to the treating physician). All included neonates had symptomatic CSVT.

Radiographic Features

Neuroimaging confirmation was required for study inclusion. Initial confirmation of CSVT was via MRI in 81 of 84 neonates, via CT combined with CTV in 1 neonate, and by CT alone in 2 neonates. Overall, 68 (80%) had venography, either acutely or in follow-up. MRV was performed in 56 neonates, CTV in 29, and 17 of these neonates had both MRV and CTV. Conventional angiography was performed in 4 neonates. Follow-up neuroimaging 2 or more days after diagnosis was documented in 42 (50%) neonates, median 5.5 days, range 2-63 days for first follow-up image. Of those with follow-up imaging, 10 (24%) had complete recanalization of CSVT, 4 (10%) had partial recanalization, and 1 (2%) had thrombus extension.

Among 67 neonates with full data on associated parenchymal lesions, 23 (34%) had no hemorrhage or infarct, 13 had hemorrhage alone (hemorrhagic infarct or other hemorrhage), 5 had isolated ischemic infarct, and 26 had both ischemic infarct and hemorrhage. Hemorrhages were reported prior to treatment with antithrombotic therapy. For the other 17 neonates with incomplete data, 8 had missing data for the presence or absence of both infarct and hemorrhage, while the other 9 had data on one variable but not the other. Of these 17 children who were excluded for missing data, 4 had infarct, 1 had hemorrhage.

Risk Factors for CSVT

Risk factor data were available for 81/84 neonates (96%), (Table 1). There were 18 neonates with cardiac disease that was congenital in 17 and acquired in 1. Peripartum risk factors including presence of meconium, hypoxia, sepsis, acidosis, and newborn resuscitation were frequent (42/60; 70%). Mode of delivery was spontaneous vaginal in 45%, induced vaginal in 12%, elective cesarean (c)-section in 15% and urgent c-section in 28%. Instrumental assistance (forceps or vacuum) was attempted in 20%. Anemia was recorded in 1 neonate, and platelet count at the time of diagnosis was not available. Family history of thrombosis or bleeding was present in 3 neonates. All had maternal history of major thrombosis (pulmonary embolism, deep venous thrombosis, and portal vein thrombosis). No details on maternal thombophilia testing or medications during pregnancy were available. A maternal history of miscarriage was present in 18 of 64 (28%) with 4 women reported to have more than one lost pregnancy. As this is a prospective registry, there was no thombophilia testing protocol for neonates.

Investigators noted when a neonate was found to have a prothrombotic risk factor, but the details of testing for each neonate were not recorded by most participating centers. Prothrombotic risk factors were recorded in 8/81 (10%) neonates, although some abnormalities were minor.

Antithrombotic Treatment

Treatment data were available in 81 of 84 neonates (96%) with CSVT. Overall, 43/81 (53%) were treated with an anticoagulant or antiplatelet medication. Fourteen received unfractionated heparin (UFH) (5 received UFH alone, 8 received UFH followed by LMWH, 1 received UFH followed by warfarin), 34 received LMWH (24 received LMWH alone, 8 received LMWH after UFH, 2 received LMWH followed by aspirin), 1 received warfarin (preceded by UFH), and 2 received aspirin (both preceded by LMWH). No neonate received clopidogrel or a thrombolytic agent. Eleven received more than one antithrombotic medication. Regional differences in the use of antithrombotic medication were observed as follows: U.S. 8/32 neonates received antithrombotic treatment, Canada 23/34, Europe 8/10, Australia 1/2, South America 2/5, and Asia 0/1. The most common antithrombotic treatment was LMWH. In Canada 19/23 treated neonates received LMWH, 8/23 received UFH, and none received aspirin or warfarin. In the US, of 8 treated neonates, 7 received LMWH, 4 received UFH and 2 received aspirin. In Europe, 7 neonates received LMWH and 2 neonates were treated with UFH. No

acute complications of antithrombotic treatment were reported. Among the 50% of treated neonates with follow-up imaging, thrombus extension occurred in only one neonate 49 days post-CSVT after anticoagulation with LMWH was discontinued.

Predictors of Antithrombotic Treatment

In univariate analysis (Table 2), geographic location of the patient was predictive of treatment. Neonates from the U.S. were significantly less likely to be treated with anticoagulant or antiplatelet drugs (25%) than neonates from other countries (68%) (OR 0.2, 95% CI:0.1-0.5, p=0.001). Thrombus limited to the deep venous system reduced the chances of treatment by 70%, (OR 0.3, 95% CI:0.1-0.9, p=0.05). The presence of hemorrhage was not a predictor of treatment (OR 0.7, 95% CI:0.3-2.0, p=0.55). Risk factors including dehydration, acute systemic illness, sepsis, age <7 days at diagnosis, family history of thrombosis and maternal history of pregnancy loss did not predict treatment or non-treatment.

Based on univariate screening we included the following variables in our multivariate logistic regression model to determine predictors of antithrombotic treatment: thrombus limited to the deep venous system and geographic location. The presence of any intracranial hemorrhage compared with no hemorrhage was also included in the multivariate model as this factor seems to guide treatment recommendations according to recently published international guidelines. (1) Only geographic region, e.g. location in the U.S. versus other regions remained significant in the multivariate analysis. The odds of U.S. children being treated versus other regions were reduced by 70% (OR 0.3, 95% CI:0.1-0.9, p=0.03).

Since treatment selection was significantly different in U.S. versus non-U.S. centers, additional analyses were performed to determine if risk factors or distribution of bleed / no bleed at these centers also differed, thereby explaining the regional treatment differences (see Table 2). In neonates from non-U.S. centers, anoxia was a significantly more common risk factor (p=0.006). There were no other significant differences in risk factors. Finally, presence of hemorrhage did not differ between U.S. and non-U.S. centers with 15/27 (55%) neonates at U.S. centers and 24/40 (60%) neonates at non-U.S. centers found to have intracranial hemorrhage (p=0.5).

Neurologic outcome and predictors of poor outcome or death

Outcome data at hospital discharge were available for 73/84 (87%) neonates with CSVT. Overall, 47 neonates (64%) were described as normal, 24 (33%) had a neurologic deficit, and 2 infants (3%) died. There were no significant differences in neurologic outcome at the time of hospital discharge in infants from the U.S. versus other regions. Among U.S. infants, 11/25 (44%) had a neurologic deficit and 1/25 (4%) died, compared with infants from other countries where 13/48 (27%) had a neurologic deficit and 1/48 (2%) died; there was no significant difference between groups (data not shown). There were no univariate predictors of death. Surviving neonates with any neurologic deficit were categorized as having a poor outcome, others were considered to have a good outcome. There were no univariate predictors of poor outcome. In particular, antithrombotic treatment did not predict poor outcome (OR 1.16, 95% CI:0.51- 2.71, p=0.72) or death (OR 0.67, 95% CI:0.15-2.92, p=0.59). Since discharge to a location other than home could be a surrogate for poor neurologic outcome, discharge location was also explored. Discharge location was available for 68/84 neonates (81%); there were no significant differences in discharge location between neonates treated in the U.S. and elsewhere; 81% of both groups were discharged to home.

DISCUSSION

Our data show that there is wide practice variability and uncertainty about treatment of neonatal CSVT. Physicians in the U.S. were less likely to treat neonates with CSVT with antithrombotic medications compared to physicians at non-U.S. centers, 25% versus 69% of neonates. There was no significant difference in the percentage of neonates with parenchymal hemorrhage in the U.S. compared to non-U.S. centers where anticoagulation was more commonly used. There were no reported complications of antithrombotic therapy, but we may not have complete reporting of such complications. Complications related to lack of treatment such as progressive thrombosis were not reported, though follow-up imaging was only documented in 50% of neonates. Screening for progressive thrombosis was not systematic. In this series, we did not observe a difference in short-term outcomes between treated and untreated neonates. Since neonates with brain injury frequently show the sequelae years later, outcome at hospital discharge likely underestimates the burden and degree of disability. In this very young population, useful information on neurologic outcome must be acquired over many years. The regional practice differences we observed may reflect the lack of evidence for or against neonatal CSVT treatment or uncertainty about whether treatment improves outcome, emphasizing the need for further studies.

Physicians might be less likely to treat with antithrombotic medication in the presence of parenchymal hemorrhage; however, hemorrhage was not a significant predictor of non-treatment. This finding is either due to small sample size and limited power to detect an association or familiarity with the adult CSVT literature in which anticoagulation to treat thrombosis was shown not to worsen outcome even in the presence of cerebral hemorrhage.[9] A meta-analysis of the 2 small randomized controlled trials of anticoagulation in adult CSVT, one that randomized 20 patients,[10] and one that randomized 49 patients,[9] showed a trend towards benefit in terms of absolute risk reduction in death or dependency, but did not achieve statistical significance.11 However, when two additional randomized studies were included in the meta-analysis, a statistically significant benefit was found.12،13 Based on this trend for improved outcome after anticoagulation and evidence for its safety, anticoagulation is recommended for adults with uncomplicated CSVT.[14] Neonates with CSVT are clearly a different population with different risk factors and treatment considerations, so the decision to treat neonates based on the available adult data remains problematic. Developmental changes in hemostasis may impact antithrombotic treatment decisions in neonates. Studies have shown that healthy newborns have prolonged activated partial thromboplastin time (APTT) values compared to older children and adults,[15,] 16 and perhaps due to a larger volume of distribution, neonates anticoagulated with UFH often need higher doses to achieve a therapeutic level.2 Likewise, in neonates, vitamin-K-dependent cofactors are approximately 50% of adult values, 15،[16] but levels change rapidly and are near normal adult values by 6 months of age.[15] These factors make UFH and warfarin dosing in neonates particularly difficult; patient size also complicates frequent monitoring. Low molecular weight heparins are often preferred in neonates given that monitoring is less frequent and there are few dietary or drug interactions. [3] Higher doses are generally required in very young children, particularly those less than 3 months of age, perhaps due to lower antithrombin levels.[3]

There were minor differences in risk factors between U.S. and non-U.S. centers, namely, the increase in anoxic injury in the non-US centers. Therefore, differences in risk factors could not explain regional differences in treatment practices. As multiple comparisons were undertaken to assess for differences in risk factors, it is possible that one or more of these associations was found by chance alone. Correction for multiple comparisons in this small sample was felt to be overly strict; our findings require confirmation in a larger group of patients. Based on the data available, no conclusions may be drawn regarding the effect of a prothrombotic state in this cohort.

The frequency of parenchymal brain injury with CSVT is high in this study. Of 67 neonates with full imaging data on the presence of ischemic infarct and hemorrhage, only 23 (34%) had neither infarct nor hemorrhage, thus 66% had a parenchymal lesion. This is considerably higher than the 42% rate found in the Canadian Pediatric Ischemic Stroke registry,[4] but similar to the 59% rate found in a retrospective study of neonatal CSVT.16 A limitation in the current study that might explain this discrepancy is that imaging studies were not available for centralized review. In addition, severely affected neonates with CSVT-related brain injury may preferentially have been referred to neurologists and thus entered into the registry. Likewise, since parenchymal imaging showing lesions is theoretically more likely to result in venous imaging than a 'normal' appearing brain, a CSVT diagnosis may have been made more frequently in neonates with initial imaging showing infarct or hemorrhage. It has also been suggested that brain injury is possible after venous infarction without demonstrable imaging abnormalities.17-20

All neonates in the study had symptomatic CSVT and hence had brain imaging and neurological assessment. There may be many additional neonates who had mild symptoms and were not identified. The treatment of incidentally identified "asymptomatic" neonatal CSVT was not evaluated in this study.

Both referral and volunteer bias may limit our registry-based study. As consent was required, investigators may have enrolled more study subjects with good outcomes as approach for consent may have been easier and willingness to participate may have been greater.

These limitations are outweighed by the strengths of this study including: a highly motivated group of investigators all of whom have special expertise in pediatric cerebrovascular disease, case confirmation via neuroimaging by the site investigators, and a population of children from a broad geographic region, similar to those who might be recruited for future RCTs in neonatal CSVT.

There is wide practice variability and uncertainty about the treatment of neonatal CSVT. Of three published guidelines, one does not address neonatal CSVT,[21] one suggests treatment[2] and the other suggests antithrombotic treatment for selected neonates with CSVT.[3] Thus, practice variability is understandable. In our series of 84 neonates with CSVT, the presence of brain hemorrhage did not predict whether or not antithrombotic agents were used. Instead, the decision to treat seemed guided by regional practices, with physicians in the U.S. treating far fewer neonates than non-U.S. physicians. Conclusions regarding the effectiveness of treatment cannot be made from this observational work. Clearly the safety and efficacy of antithrombotic treatment in neonatal CSVT deserves further study. Standardized outcome measures and long-term follow-up are needed as part of future observational studies or randomized controlled trials.

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Appendix (For On-Line Publication)

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ABBREVIATIONS

CSVT	cerebral sinovenous thrombosis
MRI	magnetic resonance imaging
CT	computed tomography
IPSS	International Pediatric Stroke Study

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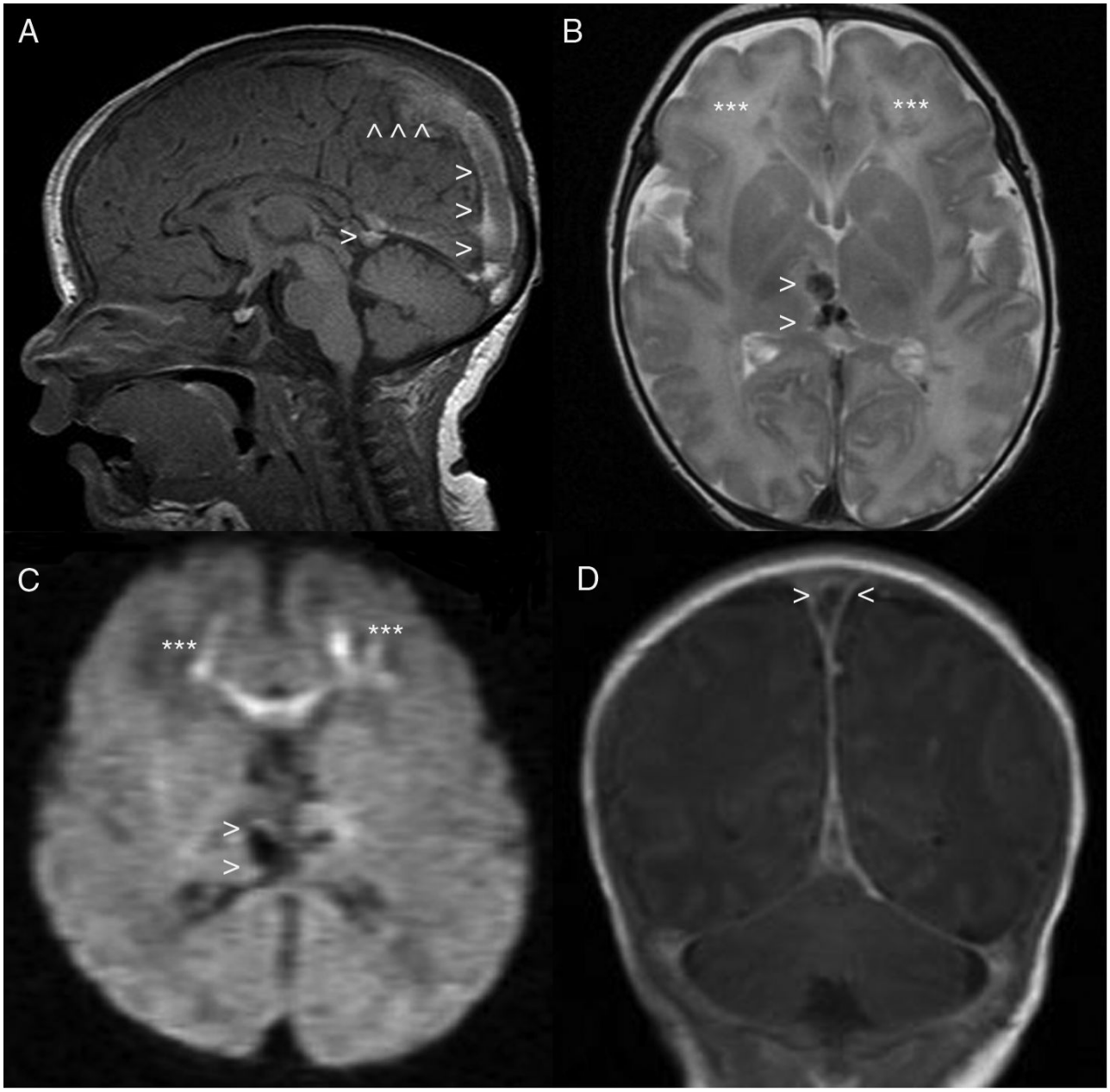

Figure 1 (A-D). MRI of the brain in neonatal cerebral sinovenous thrombosis

A) Sagittal T1 image showing hyperintense signal abnormality, suggestive of clot in the superior sagittal and straight sinus (arrowheads) B) Axial T2 image showing signal abnormalities in the bilateral frontal white matter suggestive of hemorrhagic transformation of ischemic infarcts (indicated by asterisks). Similarly, there is hemorrhage in the medial thalamus (arrowheads), suggestive of thrombosis in the deep venous system C) Diffusion-weighted sequence reveals restricted diffusion in bilateral frontal subcortical regions (asterisks), confirming ischemic infarction and hemorrhage in the medial thalamus (arrowheads) D) Gadolinium-enhanced coronal image shows filling defects in superior sagittal sinus (arrowheads), confirming clot in this region.

TABLE 1

Risk Factors in Neonates with CSVT Compared by Region

Risk Factors	United States (N=32)	Canada (N=34)	Europe (N=10)	Other* (N=8)	Total for Non-U.S. Regions (N=52)	P-value for Comparison**
Maternal						
PROM	0/20	3/32	1/8	0/6	4/46	0.42
PROSSL	1/18	7/31	1/8	0/6	8/45	0.31
Instrument assisted delivery	4/18	6/27	1/7	0/5	7/39	0.73
Maternal hypertension	3/20	11/31	2/10	0/6	3/47	0.47
Maternal fever	1/22	1/31	0/8	0/6	1/45	0.04
Meconium	4/22	7/28	0/8	2/6	9/42	0.77
Neonatal						
Acute systemic illness	14/26	19/34	4/10	6/8	29/52	0.55
Anoxia	0/31	7/34	1/10	3/8	11/52	0.006
Resuscitation at birth	8/23	20/31	2/9	1/6	23/46	0.16
Dehydration	6/31	3/34	1/10	1/8	5/52	0.32
Prothrombotic state	5/31	2/34	3/10	1/8	6/52	0.74
Congenital heart disease	8/31	5/34	0/9	6/8	14/51	1.0
Stroke†						
Infarct alone	4/27	1/31	0/3	0/6	1/40	0.04§
Hemorrhage alone	2/27	10/31	1/3	0/6	11/40	
Infarct & hemorrhage	13/27	10/31	1/3	2/6	13/40	
None	8/27	10/31	1/3	4/6	15/40	
Any hemorrhage	15/27	20/31	2/3	2/6	24/40	0.57^

PROM=premature rupture of membranes, PROSSL=prolonged second stage of labor

*Other=Asia, Australia, South America

**Comparison is U.S. versus all other regions, Canada, Europe, Asia, Australia, South America

†Data available on 67/84 neonates

§p-value is for the comparison of all 4 stroke groups with “none” as the reference

^p-value is for the comparison of 2 groups “any hemorrhage” compared with none as the reference

TABLE 2

Univariate Predictors of Antithrombotic Treatment in Neonatal Cerebral Sinovenous Thrombosis

Predictors	ATT	(%)	No ATT	(%)	Total N	OR*	(95% CI)	P-value
Age greater than 7 days	18/30	(60)	12/30	(40)	77	1.3	(0.5-3.1)	0.56
Infarct alone	2/4	(50)	2/4	(50)	67	0.7	(0.1-5.6)	0.727
Intracranial hemorrhage**	17/38	(45)	20/38	(53)	67	0.7	(0.3-2.0)	0.55
Neither infarct nor hemorrhage	13/22	(59)	9/22	(41)	67	0.4	(0.1-1.3)	0.124
Prothrombotic state	7/9	(78)	2/9	(22)	77	2.6	(0.6-10.6)	0.184
Dehydration	7/10	(70)	3/10	(30)	77	2.6	(0.6-10.6)	0.184
Acute systemic illness†	24/42	(57)	18/42	(43)	77	1.2	(0.3-4.9)	0.834
Deep thrombus only	6/18	(33)	12/18	(67)	73	0.3	(0.1-0.9)	0.05
Occlusive thrombus	6/13	(46)	7/13	(54)	66	0.7	(0.2-2.2)	0.516
Family history of thrombosis	2/3	(67)	1/3	(33)	7	2.0	(0.1-44.3)	0.661
Maternal history of pregnancy loss	8/16	(50)	8/16	(50)	64	0.8	(0.5-1.2)	0.302
Treated in U.S. (vs. elsewhere)	6/26	(23)	19/26	(73)	77	0.2	(0.1-0.5)	0.001

ATT= Antithrombotic treatment (anticoagulant or antiplatelet drug), data available for 81 of 84 neonates

*Odds ratio for use of ATT among neonates with this predictor (e.g. age over 7 days) vs. neonates without this predictor

**Compared to no hemorrhage

†Includes fever, sepsis, and other systemic illnesses