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A Prospective Outcome Study of Neonatal Cerebral Sinovenous Thrombosis

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Abstract

Neonatal cerebral sinovenous thrombosis is a frequent contributor to neonatal mortality and morbidity. Treatment is controversial and reported clinical outcomes vary widely. Newborns with radiologically confirmed neonatal cerebral sinovenous thrombosis from 1992–2009 were prospectively followed in our Children's Stroke Clinic for standardized outcomes, including the Pediatric Stroke Outcome Measure. Outcomes were available in 90/104 (87%) neonates. Early outcomes included cerebral sinovenous thrombosis-associated death (5) and thrombus propagation [15 (6 associated with new venous infarcts)]. Lack of anticoagulation predicted propagation (RR = 13, $P = .0007$). Complete thrombus recanalization occurred in 90% by 3 months. Late outcomes (median, 2.5 years) were epilepsy (15) and neurological disability (50), which included moderate-severe language (43), sensorimotor (38), and cognitive/behavioral (24) deficits. Overall, 61% had poor outcome (death/any deficit). Concurrent neurological comorbidity at diagnosis (odds ratio = 2.8, $P = .029$) predicted poor outcome. Clinical trials are urgently needed to establish more effective treatment strategies.

Keywords

Newborn; cerebral sinovenous thrombosis; outcome

Introduction

The incidence of neonatal cerebral sinovenous thrombosis ranges from 2.6 to 12/100,000 term neonates/year.^{1,2} Neonates are at a high risk for this condition and represent 18% to 51% of all reported pediatric cases.^{1,3–5} However, until recently outcome studies have consisted primarily of case reports and small case series.^{6–9} In recent years, systematic studies of neonatal cerebral sinovenous thrombosis (neonatal cerebral sinovenous thrombosis) outcome have been published.^{2,10,11} However, these are retrospective studies with only short-term or non-standardized outcomes. Outcome from neonatal cerebral sinovenous thrombosis is important to determine to justify both screening of neonates with dedicated cerebral venous imaging¹² and the development of neonatal treatment trials. As

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there are no clinical trials yet, anticoagulant treatment decisions in neonatal cerebral sinovenous thrombosis are based on adult^{13,14} and pediatric practice.⁵ In the absence of age-specific data, anticoagulant use for neonatal cerebral sinovenous thrombosis varies widely around the world¹¹ and across consensus-based pediatric stroke treatment guidelines.^{15,16} The high frequency of spontaneous intracranial hemorrhage associated with neonatal cerebral sinovenous thrombosis underlies the concern about anticoagulant treatment.^{5,17} However, emerging data suggest that anticoagulant treatment in neonatal cerebral sinovenous thrombosis is safe,⁵ perhaps even in the presence of intracranial hemorrhage.² There is an increasing awareness that adverse outcomes are frequent in neonatal cerebral sinovenous thrombosis and that the use of more aggressive therapies may be warranted.^{2,5,10,18} The growing need to study this condition in a systematic fashion^{19–22} arises from an acknowledgment that age-related differences in sinovenous, hematological, and neurological systems prevent extrapolation of treatment data from older children and adults to neonates. The current study aimed to provide prospective, standardized outcome data in a large cohort of neonates with cerebral sinovenous thrombosis.

Methods

Patient Selection

Neonates (birth to 28 days, term, and preterm) with radiographically confirmed cerebral sinovenous thrombosis were prospectively enrolled at diagnosis from 1992–2009. Subjects were identified through the Canadian Pediatric Ischemic Stroke Registry (Toronto site) and referral to our institutional Children's Stroke Service from 1995. The diagnosis was confirmed by independent retrospective review of clinical and imaging data by 2 investigators (MM, MS). Anticoagulation-related data from 83 neonates in the current study were previously reported in a pediatric cerebral sinovenous thrombosis study.⁵ The neonates in that study were diagnosed with neonatal cerebral sinovenous thrombosis from 1992–2005 and outcome data were available in 63/83 neonates. Therefore, for the current study we expanded the study sample to include additional neonates enrolled in the Registry from 2006–2009 for a greater breadth of outcome data and a longer duration of follow-up to 2010. Methods of data collection were otherwise similar to those detailed in the previously published study.⁵

Study Definitions

The diagnosis of neonatal cerebral sinovenous thrombosis required both clinical (seizures or encephalopathy during the first 28 days of postnatal life) and radiological evidence (computed tomography or magnetic resonance (MR) venography demonstrating absence of flow in venous channels). We defined neonatal encephalopathy as altered consciousness (irritability, confusion, lethargy, and coma) and neurological comorbidity as neurological condition(s) preceding or concurrent with cerebral sinovenous thrombosis potentially impacting neurological recovery (e.g., hypoxic-ischemic encephalopathy, concurrent meningitis), and further defined hypoxic-ischemic encephalopathy based on the published American College of Obstetrics and Gynecology criteria.²³ A “hypercoagulable state” was defined as abnormal laboratory testing for prothrombotic disorders or cerebral sinovenous thrombosis associated with concurrent systemic thrombosis.

Clinical Data Collection

Clinical and laboratory data were collected by review of the health record and standardized interviews of all parents available during the inpatient or outpatient phase. These included age, gender, neurological presentation, neurological co-morbidity, risk factors, and treatment details. Anticoagulant therapy was provided by protocols established in 1995. These protocols are detailed in the related publication.⁵ Neonatal cerebral sinovenous thrombosis

was treated with anticoagulant therapy unless contraindications were present (including significant intracranial hemorrhage). Anticoagulant therapy consisted of low molecular weight heparin or unfractionated heparin at full treatment dosing in the initiation phase followed by maintenance low molecular weight heparin until the end of planned therapy (usually 3 months for neonates).

Radiographic Data Collection

The study neurologist (MM) and neuroradiologist (MS), the latter blinded to clinical data, including treatment and outcome, independently reviewed each initial and available follow-up CT/CT venography and MR/MR venography for cerebral sinovenous thrombosis location, extent (single/multiple sinus, occlusive/non-occlusive), venous infarction (bland/hemorrhagic), intracranial hemorrhage, thrombus propagation (increased/new thrombus), and recanalization (decreased thrombus). Propagation was defined as a new thrombus detected in a sinovenous channel distant or adjacent to the initial thrombus occurring within 14 days following diagnosis. Recanalization at 3 months was dichotomized as favorable (full/almost full) or unfavorable (partial/none).

Study Outcomes

We studied the frequency and predictors of early (cerebral sinovenous thrombosis - associated deaths, thrombus propagation), and late (recanalization, epilepsy, and neurological deficits) outcomes. Epilepsy and neurological deficits were assessed at serial outpatient visits to our Stroke Clinic. At each visit (3 to 6 months, annually, or biannually thereafter to age 18 years) parents were questioned about the presence of seizures and impression of recovery, and the study neurologists (MM, GD, RA, and DM) and nurse practitioner (IY) examined children using the Pediatric Stroke Outcome Measure. The Pediatric Stroke Outcome Measure is a previously published validated standardized neurological assessment tool.²⁴ It assesses 5 spheres of neurological function: R sensorimotor (including motor, visual, hearing, and somatosensory), L sensorimotor, language production, language comprehension, and cognitive/behavioural performance. Each sphere is given a score as follows: 0 (none), 0.5 (mild), 1.0 (moderate), and 2 (severe) deficits. The patient is assigned an overall score out of 10 based on a combination of scores in the 5 individual spheres. For this study, we dichotomized overall clinical outcome as 'favorable/good' (survival with no neurological deficits, Total Pediatric Stroke Outcome Measure score = 0) or 'unfavorable/poor' (cerebral sinovenous thrombosis -related death or any neurological deficit at last follow-up assessment, Total Pediatric Stroke Outcome Measure score ≥ 0.5).

Statistical Analysis

We used SAS statistical software (Version 9.1.3, SAS Institute, Cary, North Carolina). On the basis of the number of events for all outcomes, we planned predictor testing with univariable (Fisher's or chi-square for dichotomous variables) and multivariable logistic regression. For multivariable analyses we included variables with P value $\leq .2$ on univariable testing. P values $< .05$ were considered significant and $.05$ – $.10$ as trend. We selected the following *a priori* variables for predictor testing: Cerebral Sinovenous Thrombosis Propagation—gender, presence of perinatal risk factors, presence of hypercoagulable state, lack of anticoagulant therapy and multiple sinus involvement; Recanalization Outcome—gender, hypercoagulable state, lack of anticoagulant therapy, multiple sinus and deep sinovenous system involvement; Clinical Outcome—gender, neurological comorbidity, intracranial hemorrhage at diagnosis, deep sinovenous system involvement, cerebral sinovenous thrombosis propagation, hemorrhagic complication, lack of anticoagulant therapy, and length of follow-up interval from cerebral sinovenous thrombosis diagnosis to

the last available clinical follow-up. The outcomes cerebral sinovenous thrombosis-related deaths and epilepsy were descriptively analyzed.

RESULTS

Study Population

We enrolled 104 neonates with cerebral sinovenous thrombosis. Male gender predominated (72%). Table 1 summarizes patient characteristics.

Clinical Features

Seizures (69%) and encephalopathy (53%) were the main presenting symptoms. Initial symptoms occurred in the initial postnatal week in 47, and the subsequent 3 weeks in 53. Acquired neonatal (65%) and perinatal risk factors (46%) were frequent. Almost all (88%) had at least one risk factor and many (40%) had multiple risk factors. Hypoxic-ischemic encephalopathy (20%), complicated delivery (20%), complicated pregnancy (16%), dehydration (13%), prematurity (13%), congenital heart disease (10%), and sepsis (10%) were relatively common risk factors. Laboratory-defined prothrombotic abnormalities were documented in 10/56 (20%) neonates with complete testing. These included anti-cardiolipin antibody, low protein C and low antithrombin (1 each, none persistent on repeat testing), Factor V Leiden mutation (3), and *MTHFR* heterozygous mutation (4). Systemic thrombosis was documented in 19% of neonates concurrent with the cerebral sinovenous thrombosis.

Radiographic Features

The most common sites of cerebral sinovenous thrombosis were superior sagittal sinus (57%), transverse/lateral sinuses (one or both) (75%), and torcular (46%). Thirty-four percent had deep system involvement (only 2 neonates had isolated deep system involvement, all the others had additional superficial system involvement). Seventy-six percent had fully occlusive cerebral sinovenous thrombosis in at least one of the affected sinuses. Thrombosis in multiple sinuses/veins was frequent (82%). Venous infarcts, present in 42 (40%), were frequently hemorrhagic (62%). Intraventricular hemorrhage occurred in 28%. Extra-parenchymal hemorrhage (subdural, subarachnoid) occurred in 26%. A total of 71% had some variation of intracranial hemorrhage. Twenty-two percent had parenchymal abnormalities unrelated to the cerebral sinovenous thrombosis [diffuse cerebral edema not in keeping with the extent of cerebral sinovenous thrombosis (9), arterial ischemic stroke (3), congenital hydrocephalus (3), skull fracture (2), malformation of cortical development (1), delayed myelination (1), periventricular leukomalacia (1), and watershed infarction (1)]. Only 15% had no parenchymal abnormalities.

Anticoagulant Therapy

Four neonates were managed prior to anticoagulant therapy protocols that were established in 1995. Overall, 53/104 (51%) neonates received anticoagulant therapy. Anticoagulant therapy was initiated at diagnosis in 41/104 (39%) neonates and only after cerebral sinovenous thrombosis propagation was documented in 12. Among 71 neonates with intracranial hemorrhage at diagnosis, 42 (60%) did not receive anticoagulant therapy due to significant extent of intracranial hemorrhage. However, 29 (30%) did receive anticoagulant therapy despite intracranial hemorrhage because of insignificant/minor intracranial hemorrhage (15), systemic thrombosis (14), cerebral sinovenous thrombosis propagation (11), radiologically extensive cerebral sinovenous thrombosis (5), and symptomatic deterioration with persistent non-resolving cerebral sinovenous thrombosis (1). Anticoagulant therapy consisted primarily of low molecular weight heparin either alone

(64%) or following unfractionated heparin (36%). The median treatment duration was 12 weeks (4 days to 35 weeks).

Nine neonates without initial intracranial hemorrhage did not receive anticoagulant therapy because of physician preference (6) and severe cerebral edema, meningitis, or non-occlusive cerebral sinovenous thrombosis (1 each). No anticoagulant therapy-related deaths or major systemic hemorrhage occurred. All 53 treated neonates had follow-up imaging. Major anticoagulant therapy-related intracranial hemorrhage was documented in 3/53 (5.6%) neonates. Mean interval from anticoagulant therapy initiation to detection of increased/new major intracranial hemorrhage was 42 days (median, 45 days; range, 3 days to 12 weeks). Anticoagulant therapy did not increase the risk ($P = .536$) of new or increased hemorrhage post-diagnosis, which was documented in 1/35 (3%) untreated neonates as well. None of the 14 neonates with significant pre-treatment intracranial hemorrhage who were treated with anticoagulant therapy had hemorrhagic complications. Anticoagulant therapy-related intracranial hemorrhage was classified as major in the 3 patients due to decreased hemoglobin (2) and large intracranial hemorrhage size (3). None required blood transfusion or were fatal. Anticoagulant therapy was stopped in all after detection of hemorrhage. All patients had risk factor(s) for hemorrhage, including pre-treatment intracranial hemorrhage in 3 (although insignificant parenchymal petechial hemorrhage); one had a supra-therapeutic anticoagulant therapy. Outcome in the 3 patients with major anticoagulant therapy-related intracranial hemorrhage was favorable in 1 and unfavorable in 2 (0 deaths, both moderate-severe deficits).

Early Study Outcomes (Table 2)

Cerebral Sinovenous Thrombosis Propagation

This was documented overall in 15/88 patients, including 1/41 (2%) anticoagulant therapy-treated and 14/47 (30%) untreated neonates. Propagation was asymptomatic in all but 1 neonate (worsening of seizures), was documented on routine follow-up imaging at mean 8 days post-diagnosis (median, 7; range, 1–14), and was associated with new venous infarction in 6/15 neonates (40%). Predictors of propagation included lack of anticoagulant therapy use (univariable $P = .0007$; RR = 12.2; 95% confidence interval [CI]: 2.0–89.0) and absence of perinatal risk factors (univariable $P = .0263$; RR=3.5, 95% CI: 1.0–11.0), while a trend was noted for multiple sinus involvement at diagnosis and propagation ($P = .1062$; RR= 4.4, 95% CI: 1.0–31.0). Gender and hypercoagulable state did not predict propagation. Outcome in 15 neonates with cerebral sinovenous thrombosis propagation was unfavorable in 10 (0 deaths; 4 mild and 6 moderate-severe deficits). Predictor testing by multivariable analyses for cerebral sinovenous thrombosis-propagation was not done due to small number of outcome events.

Cerebral Sinovenous Thrombosis -Related Deaths

Five neonates (4 males) died due to cerebral sinovenous thrombosis in the initial month after diagnosis (11–37 days). All were term infants with cerebral sinovenous thrombosis diagnosed after first week of age (range, 8–26 days). All had extensive cerebral sinovenous thrombosis involving both superficial and deep venous systems with significant intracranial hemorrhage and parenchymal intracranial hemorrhage. Risk factors included severe dehydration (3), Group B Streptococcal meningitis (1), and nephrogenic diabetes insipidus (1). One neonate had no identifiable risk factors. One neonate had an autopsy confirmation of cerebral sinovenous thrombosis-related death. None were treated.

Late Study Outcomes (Table 2)

Neurological Deficits

Neurological follow-up information was available in 90/104 (87%) patients. Mean and median follow-up duration was 2.5 years (range, 6 months to 15 years). Overall, neurological outcome was normal in 39% and abnormal in 61% (including the 5 neonates with cerebral sinovenous thrombosis -related deaths). Among 85 surviving neonates with Pediatric Stroke Outcome Measure assessment during follow-up visits in the Stroke Clinic, 35 were normal, 12 had mild deficits, and 38 had moderate-severe deficits. The spectrum of the neurological deficits was varied but all spheres of function were involved (Table 3). All 50 neonates with abnormal outcome had some degree of sensorimotor deficits (moderate/severe in 38), receptive language problems (moderate/severe in 19), expressive language issues (moderate/severe in 24), and cognitive and behavioral concerns (moderate/severe in 24). The range of sensorimotor deficits varied from subtle to severe and included weakness and tone abnormalities (hemiparesis, hemiplegia, diplegia, and quadriplegia), global developmental delay, isolated motor delay, and visual impairment. The main predictor of unfavorable outcome by multivariable testing was the presence of neurological comorbidity (observed in 45/104 neonates) at diagnosis ($P = .03$; OR = 2.8, 95% CI: 1.0–7.0) while longer follow-up interval ($P = .08$; OR = 1.2, 95% CI: 1.1–1.5) showed a trend toward unfavorable outcome. Gender, intracranial hemorrhage at diagnosis, lack of anticoagulant therapy, cerebral sinovenous thrombosis propagation, and deep sinovenous system involvement did not predict adverse outcome on univariable testing.

Epilepsy

Epilepsy was documented in 16/90 (18%) of survivors. None of the patients with a normal outcome had epilepsy. All 16 patients with epilepsy had neurological deficits. Four of these 16 patients had infantile spasms and have been published previously.²⁵ Unfortunately, inadequate information was available in the remainder 12 patients in terms of the type, frequency, and severity of their seizures and anticonvulsant medications. Predictor testing was not performed due to small number of outcome events.

Thrombus Recanalization

Cerebral sinovenous thrombosis recanalization was assessed in 88/104 neonates who had at least one follow-up imaging study. Maximum extent of recanalization was documented in most neonates (nearly 90%) by 3 months of diagnosis. Gender, hypercoagulable state, lack of anticoagulant therapy, multiple sinus involvement, and deep system involvement did not predict incomplete recanalization at 3 months following diagnosis, by univariable analysis. Multivariable analysis was not possible due to small outcome event size (14 neonates with no or partial/incomplete recanalization at 3 months). No episodes of recurrent cerebral sinovenous thrombosis were documented in any neonate in this cohort throughout the entire follow-up duration in our Stroke Clinic.

Discussion

We report short-term (early) and long-term (late) outcomes of cerebral sinovenous thrombosis in a prospectively enrolled single-center cohort of neonates. Mortality observed in 6% emerged as an important determinant of early outcome, while neurological disability was seen in 61% and epilepsy in 19% of survivors despite complete thrombus recanalization in 90%. Death directly attributable to cerebral sinovenous thrombosis was documented in 6% of neonates (all untreated), clearly indicating that neonatal cerebral sinovenous thrombosis is a life-threatening neurological disorder. Cerebral sinovenous thrombosis propagation is a frequent event (1 in 3) in the acute phase in anticoagulant therapy-untreated

neonates and appears to increase the risk of brain injury; 40% of the neonates who propagated their thrombus developed new associated venous infarction. Anticoagulant therapy prevented thrombus propagation ($P = .0007$) without increasing the bleeding risk (only 5.6% of neonates had anticoagulant therapy-related bleeding complications, none fatal). Full recanalization was observed in nearly all (89%) neonates by 3 months. However, neurological outcome was poor in a large percentage (61) of neonates, with substantial risk of long-term epilepsy (nearly 1 in 5 survivors). Descriptive analysis of the neonates with abnormal outcome revealed a wide range of sensorimotor, language, and cognitive deficits, which were significant enough in the majority to adversely impact function and quality of life. Neurological comorbidity at diagnosis (seen in nearly half of all neonates) predicted worse neurological outcome, suggesting that cerebral sinovenous thrombosis should be suspected and sought in all sick newborns with neurological symptoms. However, even in neonates without comorbidity, the rate of unfavorable outcome was high at 50% (27 out of 55 neonates with unfavorable outcome had no associated neurological comorbidity), indicating that adverse outcome specifically attributable to cerebral sinovenous thrombosis is important.

Our observations add to the recently published data on outcomes from neonatal cerebral sinovenous thrombosis and confirm poor outcome from this condition.^{2,10,11} The incidence of mortality from cerebral sinovenous thrombosis in neonates is unknown. The 6% mortality rate in our study is similar to that reported in 2 other studies^{10,11} but much lower than the 19% reported in a recent Dutch study.² Abnormal neurodevelopmental outcomes in reported literature have ranged from 40% to 80%, similar to our study.^{2,10,18} The spectrum of neurological disabilities reported in these studies is also varied but is suggestive of global impairment of function with more severe impairments in individual domains. Our observation of longer follow-up duration predicting poorer outcome suggests that “neonates tend to grow into their deficits,” reflecting the need for adequate long term follow-up period before accurate outcome predictions can be made. The risk of epilepsy following neonatal cerebral sinovenous thrombosis is similar to that reported in a recent outcome study of neonatal cerebral sinovenous thrombosis² although much lower than a study from 2006.¹⁰

Table 4 presents a review of main literature surrounding outcomes in neonatal cerebral sinovenous thrombosis. It is evident that most of the neonatal data lie embedded within larger all-age pediatric cerebral sinovenous thrombosis datasets. Four observations can be made from these data about neonatal cerebral sinovenous thrombosis: (1) between 40% and 80% of neonates have poor outcome, (2) neonatal cerebral sinovenous thrombosis has a high frequency of intracranial hemorrhage at diagnosis (30% to 80%), (3) between 33% and 50% of neonates reported since 2007 have received anticoagulant therapy, and (4) reported anticoagulant therapy-related bleeding complication rates are low (0% to 8%).

The controversy surrounding treatment of neonatal cerebral sinovenous thrombosis with anticoagulant therapy arises from the following concerns: (1) perceived lack of safety data, (2) a high frequency of spontaneous intracranial hemorrhage, (3) lack of recanalization data to decide the duration of anticoagulant therapy, and (4) absence of long-term efficacy studies. Our study findings as well as 2 recent reports support the safety of anticoagulant therapy in neonatal cerebral sinovenous thrombosis^{2,18} similar to childhood^{5,18,26} and adult^{13,14,27} cerebral sinovenous thrombosis. We observed a high rate of spontaneous intracranial hemorrhage at diagnosis similar to rates reported by others.^{2,10,17} Intracranial hemorrhage in cerebral sinovenous thrombosis is an expected comorbidity to cerebral sinovenous thrombosis as part of the natural pathophysiology of the disease process,^{28–30} supporting the notion that anticoagulant therapy could be theoretically safe even in presence of pre-existing intracranial hemorrhage. Intracranial hemorrhage is usually not deemed to be a contraindication for anticoagulant therapy in adults with cerebral sinovenous

thrombosis.^{13,14} This is likely the case in children^{18,26} and also neonates given recent data in the latter to support the anticoagulant therapy -safety even in presence of intracranial hemorrhage from our study and Berfelo and colleagues.² In the pediatric age group, 2 studies, one of which included neonates, have suggested improved clinical outcome in anticoagulant therapy-treated children.^{18,26} It is interesting to note that in studies, including ours and Berfelo and colleagues, where neonates received anticoagulant therapy relatively frequently, rates of normal outcome (39% to 50%) are increased compared with the large study by Fitzgerald and colleagues, where more than 90% of neonates received no anticoagulant therapy and outcomes were normal in only 20%.

As far as recanalization is concerned, based on our previous study⁵ and the current study, nearly all neonates have fully recanalized sinuses by 3 months after diagnosis. Future prospective studies in neonatal cerebral sinovenous thrombosis can use this information in deciding treatment duration and endpoints. Finally, robust efficacy data remains lacking in neonatal cerebral sinovenous thrombosis. Such information cannot be obtained without clinical trials. Retrospective and registry-based consecutive cohort studies cannot reliably determine the effect of anticoagulant therapy on the long-term clinical outcome. It is clear that a prospective clinical trial is absolutely vital to ultimately determine the effect of anticoagulant therapy on the long-term outcome from neonatal cerebral sinovenous thrombosis. We certainly have the safety and outcome data to proceed in this direction.

Our study has limitations intrinsically associated with analysis of datasets from a registry due to incomplete/missing information and the retrospective nature of data analysis, even though the study subjects were prospectively enrolled and followed. The main strengths of the study lie in the large sample size of the cohort, prospective enrollment of the study subjects, protocol-based treatment, meticulous analysis of the imaging data, and standardized outcome measures.

Our study and a review of emerging literature in neonatal cerebral sinovenous thrombosis confirm the safety of anticoagulant therapy and the high frequency of adverse neurodevelopmental outcomes. Our previous observations of thrombus propagation with resultant increased risk of brain injury in untreated neonates are further strengthened by this study. We have recanalization outcomes to help define treatment endpoints in future studies. This study demonstrates the wide range of neurological disabilities, including epilepsy in survivors of neonatal cerebral sinovenous thrombosis. These observations highlight an urgent need to proceed with multicenter clinical trials in neonatal cerebral sinovenous thrombosis.

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Table 1

Profile of Neonates with CSVT

Clinical Features at Diagnosis			Neonates (N = 104)	
Age: median (range)			6 days (0–27)	
Sex	Male		72%	
Clinical Presentation	Seizures		69%	
	Encephalopathy		53%	
	Other/None		9%	
Risk Factors	None		12%	
	Single risk factor		48%	
	Multiple risk factors		39%	
	Acquired neonatal risk factors		65%	
	Perinatal		46%	
Prothrombotic work-up	HIE		20%	
	Complete testing done		56 (54%)	
	Abnormal*		10/56 (20%)	
Concurrent systemic thrombosis			19%	
Neurocomorbidity			43%	
Radiographic Features at Diagnosis				
Intracranial abnormalities	None		15%	
	Venous Infarct(s)	Total	42(40%)	
		Bland	16/42 (38%)	
		Hemorrhagic	26/42 (62%)	
	Intraventricular bleed(s)		28%	
	Extra-parenchymal bleed(s)		26%	
	Total intracranial bleed(s), including hemorrhagic venous infarcts		71%	
	Other intracranial lesions§		22%	
	Venous System	Multiple sinuses		80%
	Abnormalities	Superficial venous system only		67%
Superficial+Deep venous system		28%		
Transverse sinuses (one or both)		75%		
Superior sagittal sinus		57%		
Straight sinus		34%		
Anticoagulant Therapy				
Initially treated at diagnosis			41 (39%)	
Subsequently treated for CSVT propagation			12 (12%)	
Total # treated			53 (51%)	
ACT type	Initial Std Heparin+Maintenance Low Mol Wt Heparin		19 (36%)	
(N = 53)	Initial+Maintenance Low Mol Wt Heparin		34 (64%)	

Abbreviations: CSVT, cerebral sinovenous thrombosis; HIE, hypoxic-ischemic encephalopathy; Mol, molecular; Std, standard (unfractionated) heparin wt, weight.

Table 2

Outcomes from Neonatal CSVT*

Outcome		N (%)
CSV T Propagation		
	All patients with at least one f/u imaging study	15/88 (17%)
Early	Patients imaged within first 2 weeks of diagnosis	14/71 (20%)
	CSV T-related Deaths	5/90 (6%)
	Normal (PSOM score = 0)	35/90 (39%)
Neurological	Mild (PSOM score = 0.5)	12/90 (13%)
Deficits	Moderate-Severe (PSOM score 1.0-3.0)	38/90 (42%)
Late	Epilepsy	16/90 (18%)
	Full recanalization by 3 months	55/62 (89%)
	Recurrence of CSV T	0

Abbreviations: CSV T, cerebral sinovenous thrombosis; f/u, follow-up; PSOM, Pediatric Stroke Outcome Measure.

* The reader is kindly requested to review the Results section in the text to understand the denominators in this table.

Table 3

Spectrum of Neurological Deficits in Survivors of Neonatal CSVT

Outcome Sphere*	Mild Functional Impairment (PSOM = 0.5)	Moderate-Severe Functional Impairment (PSOM 1.0)
Left sensorimotor	14/90 (15%)	19/90 (21%)
Right sensorimotor	9/90 (10%)	19/90 (21%)
Language production	6/90 (7%)	24/90 (27%)
Language comprehension	3/90 (3%)	19/90 (21%)
Cognitive/Behavioral abnormalities	0	24/90 (27%)

Abbreviations: CSVT, cerebral sinovenous thrombosis; PSOM, Pediatric Stroke Outcome Measure.

* Many patients had abnormal outcome in more than 1 sphere of PSOM, the numbers are not mutually exclusive.

Neonatal CSVT Literature Over the Years: Intracranial Hemorrhage, Anticoagulant Therapy, ACT-Related Bleeding Complications, Outcome *

Table 4

Author/Year	Study Type	Number of Neonates	ICH at Diagnosis	Neonates Treated With ACT	Major Bleeding Complications	Abnormal Neurological Outcome
Hanigan et al, 1988 ⁶	Case series	5	?	0	-	60%
Shevell et al, 1989 ⁷	Case series	17	6%	0	-	16%
Barron et al, 1992 ⁸	Case series	10	?	0	-	50%
Rivkin et al, 1992 ⁹	Case series	7	28%	0	-	14%
deVeber et al,2001 ³	Multicenter registry	69/160	30%	36%	0	?
Heller et al, 2003 ¹	Consecutive cohort	40/149	?	~80%	0	?
Fitzgerald et al, 2006 ¹⁰	Consecutive cohort	42	52%	7%	?	80%
Kenet et al, 2007 ⁴	Multicenter registry	75/396	?	?	? 1/75(1%)	?
Wasay et al, 2008 ³¹	Multicenter cohort	25/70	?	?	?	?
Jordan et al, 2010 ¹¹	International Pediatric Stroke Study	84	58%	53%	0	40% (outcome at discharge only)
Vieira et al, 2010 ³²	Multicenter cohort	6/53	?	0	-	?
Grunt et al,2010 ¹⁸	Multicenter registry	21/65	~50%	33%	0	50%
Berfelo et al, 2010 ²	Multicenter cohort	52	80%	42%	0	50%
Moharir et al, 2010 ⁵	Consecutive cohort	83/162	70%	46%	8%	60% (outcome data in 63 neonates)

? = data not mentioned/specified

Abbreviations: ACT, anticoagulant therapy; CSVT, cerebral sinovenous thrombosis; ICH, intracranial hemorrhage.

* Only studies that have reported at least 5 neonates have been included in this Table.