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CLINICAL RESEARCH ARTICLE

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Magnetic resonance venography to evaluate cerebral sinovenous thrombosis in infants receiving therapeutic hypothermia

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BACKGROUND: The incidence of cerebral sinovenous thrombosis (CSVT) in infants receiving therapeutic hypothermia for neonatal encephalopathy remains controversial. The aim of this study was to identify if the routine use of magnetic resonance venography (MRV) in term-born infants receiving hypothermia is associated with diagnostic identification of CSVT.

METHODS: We performed a retrospective review of 291 infants who received therapeutic hypothermia from January 2014 to March 2020. Demographic and clinical data, as well as the incidence of CSVT, were compared between infants born before and after adding routine MRV to post-rewarming magnetic resonance imaging (MRI).

RESULTS: Before routine inclusion of MRV, 209 babies were cooled, and 25 (12%) underwent MRV. Only one baby (0.5%) was diagnosed with CSVT in that period, and it was detected by structural MRI, then confirmed with MRV. After the inclusion of routine MRV, 82 infants were cooled. Of these, 74 (90%) had MRV and none were diagnosed with CSVT.

CONCLUSION: CSVT is uncommon in our cohort of infants receiving therapeutic hypothermia for neonatal encephalopathy. Inclusion of routine MRV in the post-rewarming imaging protocol was not associated with increased detection of CSVT in this population.

Pediatric Research; https://doi.org/10.1038/s41390-022-02195-5

IMPACT:

- Cerebral sinovenous thrombosis (CSVT) in infants with NE receiving TH may not be as common as previously indicated.
- The addition of MRV to routine post-rewarming imaging protocol did not lead to increased detection of CSVT in infants with NE.
- Asymmetry on MRV of the transverse sinus is a common anatomic variant.
- MRI alone may be sufficient in indicating the presence of CSVT.

INTRODUCTION

Cerebral sinovenous thrombosis (CSVT) is characterized by complete or partial occlusion of a venous sinus in the brain by a thrombus, which can prevent proper drainage of the sinuses and can lead to hemorrhagic infarction and intraventricular hemorrhage.[1–4] Risk factors for CSVT are numerous and include maternal factors, such as preeclampsia, gestational diabetes, and fever, as well as neonatal events during the peripartum period, such as meconium aspiration, hypoxia, or the need for resuscitation.[1] The consequences of CSVT in infants can be severe and include neurological and motor impairments, epilepsy, or death.[2,5,6]

The incidence of CSVT in children is about 0.67/100,000 children each year, with approximately 43% of these cases occurring in newborn infants.[5] The clinical presentation of CSVT in infants can be non-specific and ranges from asymptomatic to presenting with neonatal encephalopathy (NE) and seizures.[7] Since factors predisposing to CSVT can overlap with those predisposing to hypoxic–ischemic encephalopathy (HIE), both conditions can coexist. Moreover, in severe cases of CSVT, it might be challenging to differentiate whether encephalopathy is due to CSVT or due to HIE, and these infants may be started on a therapeutic hypothermia (TH) protocol. This similarity could lead to a higher incidence of CSVT in infants receiving TH.

Data regarding the incidence of CSVT in newborn infants with NE receiving TH are conflicting.[8,9] The differences reported could be related to the imaging protocol used in different studies. Time of flight magnetic resonance venography (MRV) allows for visualization of the cerebral veins and the blood flow within these veins.[10] Thus, MRV is the gold standard for diagnosing and confirming CSVT.[11] A recent study by Radicioni et al. indicated that 27% of newborn infants receiving TH for encephalopathy developed CSVT, diagnosed by MRV.[8] This finding raised concern in our center that a high number of infants with NE may be developing undetected CSVT. Therefore, routine MRV was added

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Received: 2 April 2022 Revised: 14 June 2022 Accepted: 28 June 2022
Published online: 19 July 2022

Table 1. Demographic and clinical data of the study cohort.

	Total $n = 291$	Before routine MRV $n = 209$	After routine MRV $n = 82$	p value
Sex (male)	165 (56.7%)	122 (58.4%)	43 (52.4%)	0.36
Gestational age (weeks)[a]	38.9 ± 1.74	39.0 ± 1.7	38.7 ± 1.9	0.25
Apgar 1 min[b]	2 (2–4)	2 (1–4)	2 (2–4)	0.83
Apgar 5 min[b]	6 (5–7)	6 (4–7)	7 (5–7)	0.42
Apgar 10 min[b]	7 (6–8)	7 (6–8)	8 (6–8)	0.12
Electrographic seizures	20 (6.9%)	13 (6.2%)	12 (14.6%)	0.45
Stage of NE	$n = 232$	$n = 152$	$n = 80$	
Mild	105 (45.3%)	74 (48.7%)	31 (38.8%)	0.22
Moderate	116 (50.0%)	72 (47.4%)	44 (55.0%)	0.22
Severe	11 (4.7%)	6 (3.9%)	5 (6.3%)	0.52
Umbilical blood fases				
UA pH ($n = 226$)[a]	7.04 ± 0.14	7.04 ± 0.15	7.06 ± 0.13	0.36
UA BD ($n = 210$)[a]	11.5 ± 4.7	11.6 ± 4.8	11.3 ± 4.4	0.57
UV pH ($n = 249$)[a]	7.12 ± 0.15	7.12 ± 0.16	7.13 ± 0.13	0.98
UV BD ($n = 240$)[a]	10.1 ± 4.4	10.1 ± 4.6	9.9 ± 3.8	0.60
Length of hospital stay (days)[b]	8 (6–13)	8 (6–12)	8 (6–16)	0.53
Death	5 (1.7%)	4 (1.9%)	1 (1.2%)	1

Data are presented as *n* (%). A total of 59 cases had incomplete documentation and thus did not have a stage of NE available.
NE neonatal encephalopathy, *UA* umbilical artery, *UV* umbilical venous, *BD* base deficit.
[a]Mean ± SD.
[b]Median (interquartile range).

to the post-rewarming MRIs of all babies who received TH at our center. The goal of this study was to determine if the routine use of MRV improved the diagnosis of CSVT in infants with encephalopathy who underwent TH.

METHODS

This is a retrospective clinical study that includes infants who received TH for NE between January 2014 and March 2020 at a single tertiary-level neonatal intensive care unit (NICU) at Brigham and Women's Hospital (BWH). In our center, eligibility criteria for cooling are expanded to include infants with mild encephalopathy, in addition to those receiving cooling for the standard moderate and severe grades of encephalopathy. Details of the cooling criteria in our center have been previously published.[12] Routine MRV was added to post-rewarming MRI beginning in April 2018.

Patient population

A retrospective chart review was conducted to gather demographic, clinical, and diagnostic information of infants born during the study period. Institutional Review Board approval was obtained to conduct this analysis.

Infants were separated into two groups. Group I: those who were born before the implementation of routine MRV; Group II: those who were born during the period of routine MRV. Demographic, clinical data, MRI, and MRV data were compared between these two groups. The stage of NE was assigned based on the NICHD criteria.[13] We utilized the worst exam prior to the initiation of hypothermia to determine the stage of encephalopathy.

MRI assessment

The clinical MRI/MRV reports were used to identify the presence of CSVT. CSVT was scored if there was a loss of flow-related enhancement on MRV and congruent structural MRI findings. Asymmetry was designated for cases with segmental attenuation of flow-related enhancement without vessel expansion or intraluminal signal abnormality. MRIs were obtained after rewarming and prior to discharge. MRI scans were performed on a 3-T Siemens scanner (Siemens, Erlangen, Germany). The standard clinical imaging protocol includes sagittal motion-corrected magnetization prepared rapid gradient–echo T1-weighted images, axial turbo spin-echo T1-weighted images, axial turbo spin-echo T2-weighted images, coronal turbo spin-echo T2-weighted images, and axial susceptibility-weighted images. Diffusion-weighted imaging used multidirectional diffusion-weighted measurements. Because of concerns about undetected CSVT diagnoses, routine MRV was implemented in the BWH NICU in April 2018.

Statistical methods

Descriptive statistics are presented as proportions for categorical variables, mean ± standard deviation for continuous parametric variables and median (interquartile range) for continuous non-parametric variables. Comparisons between study groups were done using *t*-test for continuous parametric variables, Mann–Whitney *U* tests for continuous non-parametric variables and χ^2/Fisher's exact test for categorical variables. Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

RESULTS

This study included 291 infants with NE who were cooled during this study period. Of these, 45.3% were mild, 50% were moderate and 4.7% were severe stages of NE. Demographic and clinical data are summarized in Table 1.

Prior to the routine use of MRV in post-rewarming MRIs, 209 babies were cooled (Group 1), and 25 (12%) of them had MRV performed. Only one infant was diagnosed with CSVT during this period. The CSVT was initially noticed on MRI and was subsequently confirmed with MRV. After the addition of routine MRV to the imaging protocol in April 2018, 82 infants underwent cooling (Group II). Of these 82, 74 (90%) had MRV performed. None of these infants were diagnosed with CSVT. Demographic and clinical data were compared between groups and no statistically significant differences were seen (Table 1).

Thus, during the study period, only one infant (0.3%) that received TH for NE was diagnosed with CSVT. This infant was born prematurely at 35 weeks, 6 days gestation to a gravida 1 para 1 mother, with a history of hypothyroidism and gestational diabetes. Delivery was via urgent caesarean section under general anesthesia following decreased fetal movements and non-reassuring fetal tracing. The infant was born depressed and required positive pressure ventilation and intubation in the delivery room. Apgar

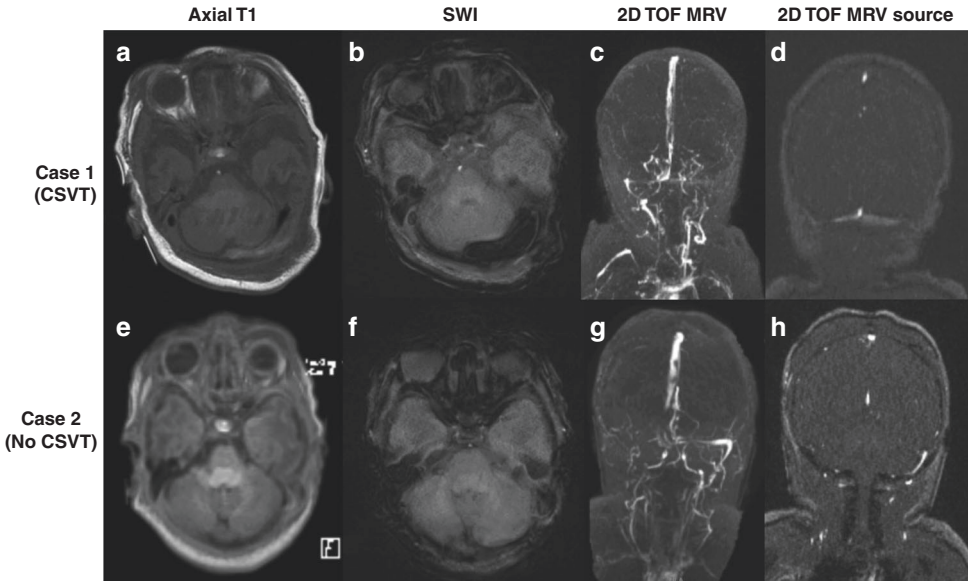


Fig. 1 Representative MRI and MRV images for the infant with CSVT and an infant with cerebral vein asymmetry. MRI and MRV images of Case 1 (the baby diagnosed with CSVT, **a**–**d**) and Case 2 (a baby with asymmetry on MRV but no CSVT, **e**–**h**). Case 1: demonstration of linear hyperintensity on axial T1 (**a**) and susceptibility on SWI (**b**) in the region of the left transverse sinus not associated with significant asymmetry on MRV (**c**, **d**). Case 2: demonstration of the absence of flow in the right transverse and sigmoid sinuses on MRV (**g**, **h**) in the absence of clear corresponding thrombosis in T1 and SWI sequences (**e**, **f**). SWI susceptibility-weighted imaging, TOF time of flight.

scores were 2, 4, and 6. The infant's medical course was complicated by NE that was treated by TH. Electroencephalography showed excessive discontinuity for age, asynchrony, excess multifocal sharp waves and poor reactivity and state change. This infant had severe pulmonary hypertension which required high-frequency ventilation, nitric oxide, and inotropic support. In addition, this infant was diagnosed with right renal vein thrombosis that improved spontaneously. The first MRI was performed on day of life (DOL) 10, as the baby was critically ill. This first MRI did not include MRV. It showed no evidence of hypoxic injury but showed a non-occlusive venous thrombus in the left transverse sinus. Follow-up imaging on DOL 15 included MRV and showed the evolution of the thrombus (Fig. 1a–d). A comprehensive coagulopathy work-up was completed, and all tests were negative. Placental pathology was unremarkable. The patient was not treated with anticoagulant medications. He was discharged after 4 weeks and was followed in the stroke clinic.

Overall, 99 infants (34%) out of the 291 cooled during our study period received MRV. Of these 99 infants, the MRV was unremarkable in 84. The remaining 15 (15%) had cerebral vein asymmetry on MRV. None of these 15 infants had a Doppler ultrasound performed after rewarming to confirm this absence of flow visualized on MRV. This asymmetry was not associated with the expansion of the sinus or underlying signal abnormality to indicate thrombus. An example of this finding is demonstrated in Fig. 1e–h. We evaluated the incidence of MRI abnormalities associated with MRV asymmetry and their relation to the side of decreased flow (ipsilateral or contralateral). Of these 15 infants with cerebral vein asymmetry, three (20%) had intraventricular hemorrhage (1 bilateral, 2 contralateral), four (26.7%) had parenchymal hemorrhage (all contralateral), and six (40%) had extra-axial hemorrhage. In addition, five infants (33.3%) had an acute injury on MRI in the form of diffusion restriction (2 ipsilateral, 1 bilateral, 2 contralateral) and one infant (6.7%) had evidence of chronic injury in the form of an abnormal signal without diffusion restriction (bilateral).

DISCUSSION

This study demonstrates a low incidence of CSVT in newborn infants receiving TH for NE (0.3%). The addition of MRV to routine imaging following TH was not associated with an increased incidence of diagnosis when compared to previous research about the incidence of CSVT.

The incidence of CSVT in the HIE population is still debated. A recent study indicated that hypoxia was a strong independent risk factor for CSVT, with 52.1% of infants with CSVT having one or more indicators of hypoxia, including an umbilical artery pH ≤7.1, 5-min Apgar score <7, perinatal asphyxia, or intubation/ventilation in the delivery room.[14] The paper by Radicioni et al. found that 27% (10/37) of infants receiving TH for asphyxia were diagnosed with CSVT on MRV.[8] Eligibility for cooling in their center was based upon criteria fulfilling moderate to severe encephalopathy.[13] Interestingly, this group identified partial or complete absence of flow on MRV with or without associated parenchymal lesions as diagnostic of thrombosis, without specifically describing if a true thrombus needed to be visualized on MRI.[8] In contrast to this definition, we classified these babies with an absence of flow of the transverse sinus on MRV, but with no thrombus on MRI, as having cerebral vein asymmetry. In closer agreement with the incidence of CSVT in our review, the TOBY trial found that only 3/131 (2.3%) encephalopathic infants (2 who received cooling, 1 who did not) developed CSVT in their population.[9] The TOBY trial diagnosed CSVT in infants with abnormal signal intensity in a venous sinus with associated lesions in the sinus' draining area due to the hemorrhagic venous infraction. Differences in these definitions may lead to differences in the incidence of CSVT.

It is notable that there are common risk factors for HIE and CSVT, including both maternal and peripartum factors. Maternal conditions such as gestational diabetes, preeclampsia, maternal fever, and chorioamnionitis are overlapping factors that predispose infants to develop a thrombus, and that may predispose infants to intrapartum hypoxic injury/asphyxia.[1,7,15–17] Peripartum complications such as acidosis, need for resuscitation, presence of meconium-stained fluid, and a prolonged/difficult labor also put infants at risk for both CSVT and hypoxic injury.[1,7,16,18]

Perinatal asphyxia could also be associated with development of CSVT through its effect on cerebral circulation and coagulation. During the latent phase of hypoxia, a period of hypoperfusion and associated hypometabolism occurs. This period is followed by a

relative hyperperfusion in the secondary phase of injury.[19,20] Hypoxia has also been linked to coagulopathy.[14] The effect of perinatal asphyxia on coagulation includes consumptive coagulopathy defined by an increase in fibrin degradation products, prolonged clot formation and decreased platelet counts.[21] Conversely, thrombophilia due to a significant reduction in many anticoagulation factors in the hypoxic infant including protein S, protein C, and antithrombin III has been described in infants with NE.[21–23]

The overall impact of TH on incidence of CSVT in hypoxic infants is unknown. TH might alter this risk through its effect on cerebral hemodynamics as well as its effect on coagulation. TH is associated with an increase in vascular tone and a reduction in cardiac output.[24–27] Moreover, TH has been shown to reduce cerebral blood flow in asphyxiated infants.[28,29] On the other hand, TH is associated with decreased activity of enzymes involved in the coagulation cascade, as well thrombocytopenia and platelet dysfunction.[30] However, TH related thrombocytopenia does not cause clinically significant cerebral hemorrhage in this population.[21,31] Whether TH predisposes encephalopathic infants to a higher or lower risk for CSVT needs further investigation.

This study did not demonstrate specific value for adding routine MRV to the post-rewarming MRI. In fact, the singular case of CSVT in our population was in Group I, where MRV was not part of the routine post-rewarming MRI, and thus the thrombus was initially noted with routine MRI and subsequently confirmed by MRV. The implementation of routine MRV to a post-rewarming MRI is likely unnecessary due to the very low incidence of CSVT in this population, especially given the visibility of subacute thrombus on structural MRI alone.

While the financial cost for an intervention or imaging technique should not guide the care an infant receives, it is still important to consider the cost of implementation of routine MRV compared to the potential benefits. Of note, cranial ultrasound (cUS) can assist in the diagnosis of CSVT. As infants undergoing TH do not typically receive MRI until after rewarming is complete, cUS at the bedside can aid in early CSVT diagnosis in the first few days of life. Examination of the transverse sinus through the mastoid fontanelle has been successful in diagnosing neonatal CSVT.[32] In our center, the use of cUS is limited to the period before beginning TH to evaluate the presence of intracranial hemorrhage.[33]

The prevalence of asymmetry on MRV in the cerebral veins in the absence of a clear thrombus was approximately 5% in our cohort. None of these infants had an associated intracranial hemorrhage, which could have indicated the presence of an undetected thrombus on MRV. Alper et al. demonstrated that such asymmetry occurs in 24% of the normal population.[34] Their research showed that cerebral vein asymmetry in the absence of an identifiable thrombus is not necessarily of clinical significance and may represent a typical anatomic variant; however, identification of asymmetry should warrant further investigation and closer inspection of MRI for anatomic and physiologic explanations.[34,35] Infants with loss of flow visualized on MRV may benefit from a color Doppler ultrasound scan to further investigate the flow within the non-dominant sinus.[36,37]

The limitations of our study include its retrospective nature, and the proportionally large number of mild cases cooled in our center. Since 45% of infants with staging available were mildly encephalopathic, this may partially explain the low incidence of CSVT in our cohort.

The prevalence of CSVT in our cohort of newborn infants with NE receiving TH is low. The addition of routine MRV to the post-rewarming MRI did not improve its diagnostic utility. Future research is needed to identify risk factors for the development of CSVT in infants with encephalopathy, which may allow for a more focused evaluation of those at the highest risk.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

C.B.M. participated in data acquisition, performed data analysis, drafted the initial manuscript, and reviewed and revised the manuscript. H.E.-S. participated in data acquisition and reviewed and revised the manuscript. E.S. participated in data acquisition, data interpretation, and reviewed and revised the manuscript. E.Y. performed data interpretation and reviewed and revised the manuscript. B.H.W. and T.E.I. provided guidance around study design and reviewed and revised the manuscript. M.E.-D. conceptualized and designed the study, helped to draft the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was not required. This was a retrospective data study and institutional review board approval waived consent.

ADDITIONAL INFORMATION

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