Association between portal vein thrombosis after umbilical vein catheterization and neonatal asphyxia

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Research Article

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Abstract

Background

Neonatal portal vein thrombosis (PVT) is frequently related to umbilical venous catheterisation (UVC) but risk factors remain unclear.

Objective

To analyse the variables associated to PVT in near to full term newborns with UVC, with a focus on newborns exposed to controlled therapeutic hypothermia (CTH) for hypoxic ischemic encephalopathy (HIE).

Methods

Retrospective cohort study of infants delivered at or after 36 weeks and with a birthweight over 1500g. All infants were assessed for UVC location and PVT using ultrasonography performed between day 5 and day 10 after catheterisation.

Results

Among 213 eligible patients, PVT was diagnosed in 57 (27%), among them 54 (95%) were localized in the left portal vein branch and 28 (49%) were of grade 1. With all significant factors in univariate analysis considered, higher gestational age at birth (adjusted OR 1.35; 95%CI: 1.12–1.64, P = .002) and duration of UVC placement (adjusted OR 1.36; 95%CI: 1.11–1.67, P = .004) were the main risk factors of PVT. Among 87 infants who were cooled for HIE, 31 (36%) had PVT compared to 26 (21%) in infants without CTH. Using a multivariate model including variables linked to treatment procedures only, an increased PVT incidence was statistically associated with UVC duration (adjusted OR 1.33; 95%CI: 1.08; 1.63, P = .01) and CTH (adjusted OR 1.94; 95%CI: 1.04–3.65, P = .04).

Conclusion

Left PVT was frequently observed in near to full term neonates with UVC. Among factors linked to treatment procedures, both duration of UVC and CTH exposure for HIE were found to be independent risk factors of PVT.

What is known

Neonatal portal vein thrombosis (PVT) may lead to severe long-term complications.

The most reported risk factors are umbilical venous catheterization (UVC) and neonatal asphyxia.

There is a lack of evidence-based guidelines for the use of anticoagulation in PVT.

What is new

Controlled therapeutic hypothermia for perinatal asphyxia and duration of umbilical venous catheterisation placement were found to be independent risk factors of portal vein thrombosis in near to full term neonates.

Our results encourage to limit the duration of umbilical venous catheterisation and to screen for PVT all patients cooled for perinatal asphyxia.

Introduction

Portal vein thrombosis (PVT) is a relatively rare event in newborns, frequently diagnosed as an incidental ultrasonography finding [1, 2]. Its incidence ranges from 0.7-1/100 000 live births [3] to 36 per 1000 neonatal intensive care unit (NICU) admission [4, 5]. Central venous catheter (CVC) placement has been reported as the main risk factor for PVT in neonates [6, 7]. However, several other factors related to CVCs can contribute to the thrombus formation, including injury of the vessel wall, infusion of hypertonic solutions, disrupted blood flow, and CVCs components that can be thrombogenic [8].

According to a Canadian registry, 89% of venous thrombosis were CVC-related [4]. Another prospective study of neonates with UVC demonstrated a 22% incidence of UVC-associated thrombosis [9].

PVT incidence is likely to be underestimated due to the paucity of clinical symptoms [4, 7], the absence of systematic screening, and the frequent spontaneous resolution [10–12]. Nevertheless, it is potentially associated with high morbidity, and it represents the principal extrahepatic cause of portal hypertension and gastrointestinal bleeding in children, as PVT may transform into a cavernoma, with dilatation of pancreaticoduodenal and prebiliary veins [4, 6, 7]. Moreover, screening and management of PVT in neonates are limited by the lack of clinical guidelines, consensus treatment, and long-term follow-up.

Risk factors for UVC-related PVT remain currently unclear and rarely documented in prospective well-designed studies. In addition to UVC, adverse conditions including sepsis, hemodynamic instability, perinatal asphyxia leading to hypoxic ischemic encephalopathy (HIE) [9, 13] are recognised as risk factors for neonatal thrombosis but their contribution to neonatal PVT development is not as well established. These factors can be contemporary present in term infants with HIE, a clinical consequence of acute perinatal asphyxia. To date, controlled therapeutic hypothermia (CTH) is the only proven treatment enable to reduce the risk of death or disability in infants with HIE [14, 15], with well-recognized entry criteria according to international and national guidelines. Infants exposed to CTH for HIE have an increased risk for coagulation disorders and cerebral thrombosis [13], but the incidence of PVT prospectively screened remains unknown.

Here, we analysed risk factors associated with neonatal PVT associated with UVC and hypothesized that CTH, a frequent therapy in term neonates requiring UVC, could independently increase the incidence of PVT.

Methods

We performed a retrospective study of a cohort of patients recruited from January 2012 to December 2017 at NICU of Robert Debré University Children's Hospital, Paris, France.

The local clinical research committee approved the study (N° 2019/424). As the study was observational on collected data, and according to French regulations on research, information note for parents was not required or no written consent was required by the institutional review board. Only deidentified information was used in data analysis to preserve confidentially.

Patients

All infants with a gestational age at birth ≥ 36 weeks, a birthweight ≥ 1500 g, admitted in NICU, and with UVC were considered eligible for this study. Abdominal Doppler imaging of the portal and hepatic veins was routine screening to detect PVT in all near- or fullterm infants with UVC. Infants with congenital malformations or chromosomic aberrations were excluded from analysis.

Data collection and definitions of clinical events

For each patient clinical data referred to pregnancy (gestational diabetes, preeclampsia, antenatal steroids), birth (gestational age at birth, birth weight, gender, Apgar score at 5 minutes, pH, lactates and haemoglobin from cord blood or venous blood in the first hour of life) and clinical status within the first week in NICU were prospectively recorded into the medical chart.

Infants were classified as small for gestational age (SGA) if they were born with a birth weight < 10th percentile on customized AUDIPOG curves for male and female neonates [16].

CTH was started in infants with HIE according to international guidelines [15, 17]. Infants aged ≤ 6 hours with neonatal HIE who met the 2 following criteria: (1) a severe perinatal asphyxia (defined by a metabolic acidosis (pH ≤ 7.0 or lactates ≥ 11 mmol/L on umbilical cord blood or any postnatal blood sample within 1 hour of age) or a history of an acute perinatal event with necessity of reanimation initiated at birth and continued for at least 5 minutes (a 5-minute Apgar score ≤ 5) and (2) a clinical stage based on Sarnat score [18] and classified as 1 (normal/mild HIE), 2 (moderate) or 3 (severe). Infants who met these criteria with a Sarnat score ≥ 2 were cooled for 72 hours using a cooling blanket (CritiCool™ with CliniLogger, MTRE Mennen medical group) and maintaining the rectal temperature controlled at 33.5°C.

Based on national French consensus guidelines, early-onset sepsis (EOS) was *a posteriori* defined by a positive culture of central (blood or cerebrospinal fluid) samples or by the association of postnatal

biological and clinical signs of sepsis and antibiotic treatment for more than 72 hours [19]. Late onset sepsis (LOS) was defined by the detection of a bacterial pathogen in the blood after 72 hours of life requiring antibiotic treatment for more than 72 h [20].

The need of vasoactive drugs for hemodynamic instability during the first week of hospitalisation was also recorded.

Platelet count < 150'000/mm^3 was used to define thrombocytopenia and categorized in two classes: mild (range 50'000 and 150'000/mm^3) and severe (< 50'000/mm^3).

All UVC tip positions were assessed on abdominal radiographs, the UVC location was classified as appropriate if the catheter tip was in the right atrium or in the suprahepatic portion of the inferior vena cava, or inappropriate if it was placed below the umbilical-portal confluence [7]. The duration of catheter use in days was also recorded.

*PVT classification*Abdominal Doppler was performed for all neonates included in the study to identify PVT and reviewed by an expert pediatric radiologist between 5 and 10 days of life, at least 2–3 days after UVC was removed.

As proposed by Morag et al. [4], PVT was classified into 3 grades: grade 1 for non-occlusive PVT with normal liver parenchyma, grade 2 for occlusive PVT with normal parenchyma, grade 3 for occlusive PVT with ultrasonography abnormalities of the liver parenchyma.

The exact location of the thrombus (right portal vein branch, left branch, or before portal vein division) was recorded. The decision of anticoagulation was based on thrombus location, extend of vessel occlusion, bleeding risk, and thrombus progression in accordance with our standardized NICU practice. Patients treated with anticoagulant were followed in the outpatient neonatology service until the thrombus showed signs of resolution by ultrasonography.

Statistical Analysis

Descriptive data are presented as medians [interquartile range (Q1-Q3)] for quantitative variables and as frequencies (percentages) for qualitative variables. Differences in proportions between groups were analysed with χ^2 test and Wilcoxon-Mann–Whitney test was used to compare differences in median values between the groups.

Logistic regression analyses were used to calculate unadjusted odds ratio (OR) with 95%CI for PVT associated with possible risk factors, including as CTH, gestational diabetes, early onset sepsis (EOS), umbilical venous catheterisation (UVC) position, UVC duration, inotropes, and gestational age at birth.

In the multivariate analysis, variables significantly associated with PVT in univariate analyses at the 20% level were included following a stepwise approach whereby each potential confounder was added one by one in the model; only variables identified as independent risk factors were kept in the final model. A

second model was performed to consider the factors linked to care procedures only, including UVC position, UVC duration, CTH, and inotropes.

All the statistical analyses were performed using the statistical software SAS 9.4, ©2002–2012 SAS Institute Inc., Cary, NC, USA, for Windows version 9.4. Graphs were performed with GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Statistical analyses were carried out with a two-sided alpha level of 0.05.

Results

Among the 213 studied infants, 57 (27%) developed PVT, including 54 (95%) in the left portal vein branch and 3 (5%) in the main portal vein; no thrombosis in the right branch was observed. According to Morag classification (4), 28 (49%) patients had PVT of grade 1, 22 (39%) of grade 2 and 7 (12%) of grade 3. The central location of the UVC tip (junction of the inferior vena cava and right atrium) was found appropriate in 33/57 (58%) infants with PVT and in 97/156 (62%) infants without PVT.

Characteristics related to pregnancy, birth and neonatal outcomes are summarized in the Table 1 in infants with and without PVT. The variables significantly associated with PVT in univariate analysis included CTH (adjusted OR 2.13; 95%CI: 1.15–3.94, P = .02), higher gestational age at birth (adjusted OR 1.35; 95%CI: 1.12–1.64, P = .002), SGA (adjusted OR 1.35; 95%CI: 1.12–1.64, P = .002), EOS (adjusted OR 1.86; 95%CI: .92 – 3.80, P = .09), and the duration of UVC placement (adjusted OR 0.38; 95%CI: 0.26–1.06, P = .03) (Table 2). Apgar score, cord pH, cord lactates, and hemoglobin at birth were not significantly associated with PVT detection in univariate analysis. Thrombocytopenia was found in 30 cases (64%), among them 6 (13%) were recorded with a platelet count below 50000/mm^3. This variable was not significantly associated with PVT, as for LOS and vasoactive drugs use.

A total of 87 infants (41%) were admitted for HIE and treated with CTH. Among them, 62 (71%) had moderate HIE (Sarnat 2) and 25 (29%) severe HIE (Sarnat 3). Among the 87 infants who were cooled, 31 (36%) had PVT compared to 26 (21%) in infants without CTH. Characteristics of PVT in infants with and without cooling for HIE are described in Table 3. No significant difference was observed between the two subpopulations regarding either the location or the severity of PVT.

To further identify variables independently associated with PVT, two multivariate regression models were performed: model 1 including all variables with a p-value < 0.20 in univariate analysis and model 2 including only factors linked with care. Variables included in each model are listed above in the statistical section. While duration of UVC was found to significantly associated with PVT in both models (Table 4), the model 2 revealed a statistical association between CTH and PVT (OR 1.94; 95%CI: 1.04–3.65, P = 0.04).

Discussion

PVT was diagnosed in a high proportion (27%) of near/full term included in the study, and even higher (36%) in infants cooled for HIE. Consistently, after adjustment for confounding co-variates, PVT was found to be significantly more frequent in infants treated with CTH for HIE compared to infants unexposed to HIE. To our knowledge, this study is the first one reporting the incidence of PVT in cooled infants.

Umbilical vein catheterization is considered as the most important risk factor for neonatal PVT development [4, 6, 7, 10–12]. In our study, the incidence of UVC-associated PVT was 27%, lower than other reported series [4, 7, 10, 12]. Discrepancy between reported incidences can be related to population characteristics, diagnosis delay, and variability due to spontaneous recovery and asymptomatic course in most cases. The lower incidence in our study may be related to the exclusion of very low birthweight or premature infants and potential variation in the severity of illness.

Similarly, to previous studies and consistently to anatomic configuration [7, 10, 21], we found that most of UVC-related PVT were localized in the left portal vein branch (95%). Position of catheter tip and prolonged catheterization have been identified as risk factors for neonatal PVT [7]. However, in the present study, the most appropriate position for an UVC tip position, considered as the junction of the inferior vena cava and right atrium, was reported in 58% of cases and in 62% of controls, and this difference was not statistically significant in univariate analysis. In contrast, the duration of UVC was found associated with the risk of PVT, both in unadjusted analysis and multivariate models.

Theoretically, reduction in heart rate and blood flow during CTH could increase the risk of venous thrombosis, as demonstrated for cerebral thrombosis [13]. Conversely, there are also evidences about risks of bleeding and disseminated intravascular coagulation in neonates with HIE, potentiated by CTH. Competitive alterations of hemostasis (i.e. bleeding *versus* thromboembolic events) can be both present in asphyxiated infants and CTH may potentiate microvascular thrombosis formation [24]. Our data support this hypothesis, although CTH did not correlate with a particular location or with the severity grade of PVT.

HIE has been identified as a risk factor for neonatal thrombosis (similarly to sepsis, dehydration, or metabolic acidosis [10]), in observational studies [21, 22] and in a recent review [23]. In the present study, metabolic acidosis, a constant indicator for HIE was not found to be significantly associated with PVT. All infants with HIE included in our study were treated by CTH, according to the French guidelines [17]. While clear benefits of CTH in HIE are now widely recognized, a causal link between PVT as a potential side effect of either HIE (the disease itself) or CTH (treatment of this disease) remains to be confirmed. However, because CTH is only initiated in infants with HIE in NICU, this treatment should lead to a systematic screening for PVT.

The other reported risk factors for neonatal PVT reported in the literature include transfusion of blood products through the UVC, HIE, dehydration, polycythaemia, sepsis, congenital cardiac malformation and maternal diabetes [4, 7, 21–24]. Here, we found no significant differences for maternal diabetes, birth weight, perinatal metabolic acidosis, Apgar score, hemoglobin at birth, hemodynamic instability and

respiratory distress, and EOS. According to our local guidelines, blood products are not administrated through the UVC, reason for excluding this risk factor in our description, as well as the condition of thrombophilia, as its role in neonatal PVT remains controversial.

All babies included in our study were asymptomatic for PVT, as reported previously [4, 21]. Consistently with our results, thrombocytopenia was reported as a relatively common sign at diagnosis [4].

Clinical relevance of anticoagulation for PVT remains still unclear since a significant proportion resolve spontaneously [5, 25]. Low-molecular-weight heparin was often used to treat PVT in our cohort. Because our study was not designed to describe the effect of this therapy on PVT evolution, definitive recommendations cannot be made.

A limitation of this study is its relatively small sample size (57 cases). Although comparable with most previous studies, further prospective investigations to confirm associations between PVT and HIE with and without CTH is needed. The retrospective study design and the lack of information on long-term follow up, including US control or effect of anticoagulant therapy, are also other substantial limitations.

In conclusion, left portal venous thrombosis is often observed also in nearly term neonates who need an UVC placement and asphyxiated cooled infants appear particularly at risk to develop PVT.

Pending further confirmation in a larger population, our study suggests to reduce the duration of UVC placement as short as possible, and to screen for PVT all patients cooled for HIE.

Declarations

Ethics approval: The study was approved by the hospital system institutional review board of Robert Debré Hospital (N° 2019/424).

Patient consent for publication: Not required.

Competing interests: None declared.

Contributors: MC was the executive researcher of this study. She performed literature search, data collection, data analysis, data interpretation, writing and submitting of the report. AZ was involved in study design, data collection and writing of the report. were involved in study design, data collection and critical revision of the content of the report. AT, AB, NL, SK, SGC were involved in writing and critical revision of the content of the report. MA was involved in study design, data collection and interpretation and critical revision of the content of the report. VB and OB were the project leaders and performed literature search, coordinated data analysis, data interpretation and writing and editing of the report. All authors gave approval for the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of a part of the work are appropriately investigated and resolved. No honorarium, grant or other form of payment was given to anyone to produce the manuscript.

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Tables

Table 1
Perinatal characteristics of infants with and without portal vein thrombosis (PVT).

	PVT	
	Yes (n = 57)	**No (n = 156)**
Preeclampsia, n (%)	15 (26)	42 (27)
	n = 57	n = 156
Gestational diabetes, n (%)	18 (32)	69 (44)
	n = 57	n = 156
Antenatal steroids, n (%)	0	5 (3)
	n = 57	n = 156
Male, n (%)	36 (63)	92 (59)
	n = 57	n = 156
Gestational age at birth,	39.5 ± 1.7	38.6 ± 1.6
mean +/- SD (weeks)	n = 57	n = 156
Birthweight,	3125 (± 549)	2968 (± 743)
mean +/- SD (g)	n = 57	n = 156
SGA, n (%)	13 (23)	56 (36)
	n = 57	n = 156
Apgar < 5 at 5 minutes	13 (23)	39 (25)
	n = 56	n = 155
Cord blood pH < 7	17 (30)	39 (27)
	n = 56	n = 146
Cord blood lactate > 11 mmol/L	21 (50)	44 (42)
	n = 42	n = 104
CTH, n (%)	31 (54)	56 (36)
	n = 57	n = 156
Thrombocytopenia, n (%)	30 (64)	69 (58)
	n = 47	n = 118

	PVT	
	Yes (n = 57)	**No (n = 156)**
Hemoglobin level at birth, mean +/- SD, (g/dl)	16.1 (± 2.8) n = 49	15.9 (± 3.3) n = 130
Appropriate UVC, n (%)	33 (58) n = 57	97 (62) n = 156
UVC duration, mean +/- SD (days)	4.0 (± 1.4) n = 57	3.3 (± 1.5) n = 156
Inotropes, n (%)	23 (40) n = 57	51 (34) n = 151
Early onset sepsis, n (%)	16 (28) n = 57	27 (17) n = 156
Late onset sepsis, n (%)	17 (30) n = 57	46 (31) n = 150

SGA means small for gestational age below 10th centile; CTH means controlled therapeutic hypothermia; UVC means umbilical venous catheterisation.

Table 2
Variables associated with portal vein thrombosis (PVT) in univariate analysis.

Variable	N	OR* [IC95%]	p-value
Preeclampsia	213	0.97 [0.49 ; 1.93]	0.93
Gestational diabetes	213	0.58 [0.31 ; 1.11]	0.10
Gender: male	213	1.19 [0.64 ; 2.23]	0.58
Gestational age at birth, in weeks	213	1.35 [1.12 ; 1.64]	**0.002**
Birthweight, in g	213		
< 2500 g		0.38 [0.16 ; 0.91]	**0.03**
> 4000 g		0.47 [0.13 ; 1.70]	0.25
SGA	213	0.53 [0.26 ; 1.06]	**0.07**
Apgar < 5 at 5 minutes	211	0.90 [0.44 ; 1.85]	0.77
Cord blood pH < 7	202	1.20 [0.61 ; 2.35]	0.60
Cord blood lactate > 11 mmol/L	146	1.36 [0.66 ; 2.80]	0.40
CTH	213	2.13 [1.15 ; 3.94]	**0.02**
Thrombocytopenia	165	1.25 [0.62 ; 2.52]	0.53
Hemoglobin level at birth ≥ 12 g/dL	179	0.98 [0.33 ; 2.90]	0.97
Appropriate UVC	213	0.84 [0.45 ; 1.55]	0.57
UVC duration, in days	213	1.36 [1.11 ; 1.67]	**0.004**
Inotropes	208	1.33 [0.71 ; 2.48]	0.38
Early onset sepsis	213	1.86 [0.92 ; 3.80]	**0.09**
Late onset sepsis	207	0.96 [0.49 ; 1.87]	0.91

Univariate analysis with antenatal steroid was not possible to carry out because the model did not converge. It is therefore impossible to produce an IC95% or a p-value.

CI means interval confidence; CTH means controlled therapeutic hypothermia; SGA means small for gestational age below 10th centile; UVC means umbilical venous catheterisation.

*Odd ratio and 95% confidence interval of Wald.

Table 3
Characteristics of portal vein thrombosis (PVT) in relation to controlled therapeutic hypothermia for hypoxic-ischemic encephalopathy (HIE).

	Therapeutic hypothermia for HIE		**p value**
	Yes **n = 31**	**No** **n = 26**	
Location of PVT			> 0.99
Right portal vein branch PVT, n (%)	0	0	
Left portal vein branch PVT, n (%)	29 (94)	25 (96)	
Main portal vein, n (%)	2 (6)	1 (4)	
Grade			0.68
Grade 1, n (%)	16 (52)	12 (46)	
Grade 2, n (%)	12 (39)	10 (39)	
Grade 3, n (%)	3 (10)	4 (15)	

Table 4
Multivariate analyses to assess associations between portal vein thrombosis (PVT) and risk factors using two logistic models.

Variable	**OR* [IC95%]**	**p-value**
Model 1		
UVC duration, in days	1.34 [1.08 ; 1.66]	**0.01**
Gestational age at birth, in weeks	1.34 [1.10 ; 1.62]	**0.003**
Model 2		
CTH	1.94 [1.04 ; 3.65]	**0.04**
UVC duration, in days	1.33 [1.08 ; 1.63]	**0.01**

- Model 1 includes gestational diabetes, controlled therapeutic hypothermia (CTH), early onset sepsis, umbilical venous catheterisation (UVC) position, UVC duration, inotropes and gestational age at birth.

- Model 2 includes only the factors linked to care procedures: UVC position, UVC duration, CTH and inotropes.

CI means interval confidence;

*Odd ratio and 95% confidence interval of Wald.