

Central venous catheter-associated thrombosis in children with congenital hyperinsulinism

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Summary

Congenital hyperinsulinism (CHI) is an important cause of severe hypoglycaemia in infancy. To correct hypoglycaemia, high concentrations of dextrose are often required through a central venous catheter (CVC) with consequent risk of thrombosis. We describe a series of six cases of CHI due to varying aetiologies from our centre requiring CVC for the management of hypoglycaemia, who developed thrombosis in association with CVC. We subsequently analysed the incidence and risk factors for CVC-associated thrombosis, as well as the outcomes of enoxaparin prophylaxis. The six cases occurred over a 3-year period; we identified an additional 27 patients with CHI who required CVC insertion during this period ($n = 33$ total), and a separate cohort of patients with CHI and CVC who received enoxaparin prophylaxis ($n = 7$). The incidence of CVC-associated thrombosis was 18% (6/33) over the 3 years, a rate of 4.2 thromboses/1000 CVC days. There was no difference in the frequency of genetic mutations or focal CHI in those that developed thromboses. However, compound heterozygous/homozygous potassium ATP channel mutations correlated with thrombosis ($R^2 = 0.40$, $P = 0.001$). No difference was observed in CVC duration, high concentration dextrose or glucagon infused through the CVC. In patients receiving enoxaparin prophylaxis, none developed thrombosis or bleeding complications. The characteristics of these patients did not differ significantly from those with thrombosis not on prophylaxis. We therefore conclude that CVC-associated thrombosis can occur in a significant proportion (18%) of patients with CHI, particularly in severe CHI, for which anticoagulant prophylaxis may be indicated.

Learning points:

- CVC insertion is one of the most significant risk factors for thrombosis in the paediatric population.
- Risk factors for CVC-associated thrombosis include increased duration of CVC placement, malpositioning and infusion of blood products.
- To our knowledge, this is the first study to evaluate CVC-associated thrombosis in patients with congenital hyperinsulinism (CHI).
- The incidence of CVC-associated thrombosis development is significant (18%) in CHI patients and higher compared to other neonates with CVC. CHI severity may be a risk factor for thrombosis development.
- Although effective prophylaxis for CVC-associated thrombosis in infancy is yet to be established, our preliminary experience suggests the safety and efficacy of enoxaparin prophylaxis in this population and requires on-going evaluation.



Background

Congenital hyperinsulinism (CHI) is an important cause of persistent and severe hypoglycaemia in infancy due to excess insulin secretion (1, 2). In cases where a genetic aetiology is identified, mutations in the ATP-sensitive potassium (K_{ATP}) channel genes, *ABCC8* and *KCNJ11*, are the most frequent. Homozygous and compound heterozygous mutations in *ABCC8/KCNJ11* cause diffuse CHI with severe and often refractory hypoglycaemia. A cardinal feature of CHI is increased glucose demand, often requiring central venous catheter (CVC) insertion to achieve euglycaemia and prevent permanent neurologic injury. Although CVCs are recognised as a significant risk factor for thrombosis in children (3, 4, 5, 6), this has not been described in patients with CHI. We describe six cases of CVC-associated thrombosis in CHI patients, presented in chronologic order, and quantified the incidence and examined for potential risk factors. We additionally examined a separate cohort of patients with CHI and CVC who were placed on enoxaparin prophylaxis.

Case presentation

Patient 1 was a term male infant (birth weight 4.05 kg) who presented with a hypoglycaemic seizure at 3 days of life. CHI was confirmed (glucose 1.6 mmol/L, insulin 132 pmol/L, C-peptide 1050 pmol/L) and genetic testing revealed diffuse disease due to a homozygous mutation in *ABCC8*. Glycaemic stability could only be achieved through high dextrose (up to 20%) and glucagon (up to 12.5 µg/kg/h) via CVC, delivering a maximal glucose infusion rate of 25 mg/kg/min. His initial CVC, inserted in the right internal jugular vein (IJV), became dislodged after 8 days and ultrasound (US) later performed to assess for sites for intravenous access showed evidence of non-occlusive thrombus at this site. He had an extremely complicated treatment course. After his initial CVC, three further CVCs dislodged, and at the time of insertion of the fifth CVC, severe occlusion of the superior vena cava by thrombus was found with further thrombi identified in the inferior vena cava, common iliac and right common femoral veins on ultrasound scanning. Treatment with low-molecular-weight heparin was commenced on advice from haematology specialists. Other complications included several episodes of sepsis secondary to central line infections, necrolytic migratory erythema from glucagon infusion and raised transaminases from octreotide. Pancreatectomy was performed at 3 months of age due to refractoriness to medical therapy but hypoglycaemia

persisted. After the sixth CVC dislodged secondary to further thrombi, it was not possible to secure additional central venous access. Temporary access was obtained via intraosseous and a peripheral venous cannula. However, he developed *Candida albicans* sepsis complicated by disseminated intravascular coagulation and died. The presence of an inherited thrombophilia could not be ascertained.

Patient 2 was born at 41 weeks with birth weight 3.08 kg and presented with jitteriness at 4 h of age followed by hypoglycaemic seizures. CHI was biochemically confirmed (glucose 1.7 mmol/L, insulin 5 pmol/L, c-peptide 457 pmol/L) and testing for mutations in *ABCC8*, *KCNJ11* and *HNF4A* was negative. Maximum dextrose and glucagon infusions of 20% and 17.5 µg/kg/h respectively were required to achieve euglycaemia. A peripherally inserted central catheter (PICC) was placed at the referring hospital, and removed 10 days later after transfer to our centre when a tunnelled catheter was inserted into the right IJV. A routine echocardiogram performed 2 days after removal of the PICC demonstrated a right atrial thrombus and the patient was promptly commenced on enoxaparin therapy. He was responsive to low-dose diazoxide and follow-up imaging demonstrated thrombus resolution with normal cardiac structure and function.

Patient 3 presented with hypoglycaemic seizures at 105 days of life after uneventful term delivery. A hypoglycaemia screen demonstrated CHI (glucose 2 mmol/L, insulin 58 pmol/L, c-peptide 400 pmol/L), and he was found to have a paternal *ABCC8* mutation and ^{18}F DOPA PET CT scan demonstrated a focal lesion in the distal body of the pancreas. He required 15% dextrose, but not glucagon, delivered via a right IJV tunnelled catheter which was removed 13 days later due to infection and leakage. Non-occlusive thrombus was noted at the site of the previous CVC, and he was treated with enoxaparin. The CHI was successfully treated with focal lesionectomy.

Patient 4 presented on day 1 with hypoglycaemic seizures after emergency caesarean section for non-reassuring fetal heart rate at 37 weeks with birth weight 3.83 kg. She required 25% dextrose with glucagon infusion up to 15 µg/kg/h and was unresponsive to diazoxide, octreotide and sirolimus. Genetic testing revealed a homozygous *ABCC8* mutation. Prior to subtotal pancreatectomy, a PICC was inserted in the left femoral vein followed by a tunnelled CVC in the right IJV. Malfunction and infection of the right IJV catheter was noted after 118 days, and the CVC was removed.



Ultrasound scanning revealed thrombus in the right IJV and therapeutic enoxaparin was commenced.

Patient 5 was born at 35 and 6-week gestation with a macrosomic birth weight of 4.64 kg. He required moderate respiratory support after birth and was noted on day 1 to be hypoglycaemic due to CHI (glucose 0.2 mmol/L, insulin and c-peptide both elevated). Owing to the significant birth weight, mutation testing for *ABCC8*, *KCNJ11*, *HNF4A* and Beckwith-Wiedemann were performed and negative. He initially required up to 50% dextrose and glucagon at 20 µg/kg/h to achieve glycaemic stability. This was initially delivered via umbilical venous catheter and PICC in both femoral veins. For long-term access, a tunneled right IJV was inserted at the referring hospital, which dislodged after 17 days. A femoral line was placed for temporary access and when the patient was brought to theatre for further CVC insertion, swelling was noted at the previous CVC site and USS confirmed the presence of non-occlusive thrombus in the right IJV. Treatment with enoxaparin was commenced and a trial of diazoxide, initially postponed due to respiratory issues and significant ventricular hypertrophy, was successful.

Patient 6 presented at 3 days of life after an uneventful term delivery in cardiorespiratory collapse and was found to be severely hypoglycaemic due to CHI (glucose 0.2 mmol/L, insulin 163 pmol/L, c-peptide 560 pmol/L). Glucose stabilisation was achieved with 12.5% dextrose and glucagon infusion at 3 µg/kg/h via right femoral CVC. Right leg swelling was noted 2 days after CVC insertion, which persisted despite CVC removal. Ultrasound scanning demonstrated thrombus from the right femoral to the popliteal vein. The patient was responsive to diazoxide and intravenous support could be discontinued.

Genetic testing by targeted next-generation sequencing for known CHI genes was negative.

Investigation

Doppler ultrasound demonstrated thrombosis in association with the CVC in patients 1, 3–6 as detailed above. Thrombus was noted incidentally in patient 2 in the right atrium on routine echocardiogram.

Treatment

All six cases were treated with enoxaparin for 6 weeks or until thrombosis resolution by USS. Doses were titrated to maintain an anti-factor Xa level between 0.5 and 1.0 U/mL. With the exception of case 1, follow-up ultrasound demonstrated resolution and enoxaparin was discontinued.

Outcome and follow-up

Given the occurrence of these cases, we aimed to analyse the incidence and identify the potential risk factors. These six cases of CVC-associated thrombosis occurred from August 2014 to 2017 at a specialist centre for CHI. All admitted cases of CHI requiring CVC during this time period were retrospectively reviewed. CHI was diagnosed according to well-established criteria (1, 2). Data were collected on CHI characteristics, CVC features, dextrose and glucagon-containing fluids, enoxaparin dose for those on anticoagulation prophylaxis and bleeding events. Venous thrombosis detection was based on clinical signs (i.e. swelling, erythema, warmth, reduced limb mobility, CVC occlusion) and confirmed by ultrasound. Occlusive and

Table 1 Characteristics of CHI patients with and without thrombosis.

	Thrombosis (n = 6)	No thrombosis (n = 27)	Prophylaxis (n = 7)
Males, n (%)	5 (83)	18 (67)	5 (71)
Any mutation in <i>ABCC8</i> or <i>KCNJ11</i> , n (%)	3 (50)	12 (44)	4 (57)
Homozygous/compound heterozygous K_{ATP} mutation, n (%)	2 (33%)	5 (19%)	–
Catheter duration, days (range)	17 (2–120)	24 (2–216)	52 (19–80)
Number requiring high dextrose, n (%)	5 (83)	23 (85)	7 (100)
Maximum high dextrose concentration, % (range)	20.0 (15–50)	20.0 (15–50)	50 (17.5–50)
Duration of high dextrose, days (range)	13 (7–58)	13 (2–107)	30 (9–43)
Number requiring glucagon, n (%)	5 (83)	20 (74)	7 (100)
Maximum glucagon, micrograms/kg/h (range)	15 (3–20)	10 (4–25)	15 (5–20)
Duration of glucagon, days (range)	6 (1–34)	7 (1–67)	27 (5–42)

Thrombosis was associated with a marginally higher proportion of patients with compound heterozygous and homozygous K_{ATP} mutations. There were no significant differences in CHI characteristics, CVC features, high concentration dextrose (defined as >15%) or glucagon-containing solutions among the groups with and without thrombosis. The characteristics of the patients on enoxaparin prophylaxis were similar to those with thrombosis.



non-occlusive thromboses were included. Fisher's exact test and Student's *t*-test were used to test for significance in categorical and continuous variables, respectively, using SPSS.

During this period, 33 inpatients with CHI required CVC including those who developed thrombosis, an incidence of 18% (6/33) over 3 years or 4.2 thromboses per 1000 catheter days. Thrombosis occurred at a median of 12 (range 2–118) days after CVC insertion at 24 (6–139) days of life.

Patient, CVC and treatment-related factors were examined for associations with thrombosis development. There was no difference in the frequency of K_{ATP} channel mutations in those with and without thrombosis (Table 1). However, the frequency of homozygous and compound heterozygous K_{ATP} channel mutations, associated with severe diffuse CHI, tended to be higher but not statistically significant in those with thrombosis (Table 1). In a stepwise backward logistic regression model, compound heterozygous and homozygous mutations correlated with thrombosis ($R^2=0.40$, $P=0.001$), while sex, glucagon dose, CVC duration and focal CHI were excluded.

There was no association between thrombosis development and CVC characteristics (CVC type (i.e. tunnelled vs non-tunnelled), location or lumen number) or the maximum concentration of dextrose or glucagon infused via the CVC (Table 1). The duration of CVC placement was marginally shorter in those with thrombosis reflecting earlier withdrawal following thrombosis detection (Table 1). No patient had blood products infused via the CVC prior to thrombosis development, a previously identified risk factor in neonates (7).

Following the recognition of CVC-related thrombosis in CHI patients, seven patients with severe CHI were commenced on enoxaparin prophylaxis. Clinical parameters to consider prophylaxis were severe hypoglycaemia requiring high concentration ($\geq 15\%$) dextrose infusion for the majority of fluid intake and/or sustained glucagon infusion. Baseline, CVC and treatment characteristics were similar for this group compared to those with thrombosis (Table 1). None of these patients developed thrombosis or bleeding manifestations, suggesting the safety and efficacy of anticoagulation prophylaxis in our cohort of patients with severe CHI.

Discussion

We observed a clinically relevant incidence of CVC-associated thrombosis in patients with CHI, 18% over

3 years or 4.2 events/1000 catheter days. The incidence is twice that reported in the neonatal literature (9.2%) (7) and is the first report in patients with CHI. No direct association was identified with CVC characteristics, dextrose or glucagon dosage. Thrombosis was associated with a marginally higher proportion of patients with compound heterozygous and homozygous K_{ATP} mutations, suggesting a greater risk in patients with severe and persistent CHI. In response to thrombotic events, we introduced anticoagulation prophylaxis with no development of thrombosis or bleeding complications. Awareness of the heightened thrombosis risk and consideration of prophylaxis are therefore important in severe CHI.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent was obtained from the patients' parents/guardians for publication. For the deceased case described, however, it was not possible to contact the family. The study was approved by the local research ethics committee.

Author contribution statement

I B conceived of the study. D Y, M S E and I B designed the study; D Y, M S E and A C collected the data; D Y and I B analysed the data; D Y drafted the manuscript, which was edited by all authors. J G provided guidance and input on the haematological aspects of the study.

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