CASE REPORT

Delayed presentation of prolonged hyperinsulinaemic hypoglycaemia in a preterm small-for-gestational age neonate

Jin Ho Chong, Suresh Chandran, Prathibha Agarwal, Victor Samuel Rajadurai

Department of Neonatology, KK Women's and Children's Hospital, Singapore

Correspondence to
Dr Suresh Chandran, schandran1312@yahoo.co.uk

SUMMARY

Hyperinsulinaemic hypoglycaemia in small-for-gestational age infants usually presents in the first two postnatal days. We present a preterm, small-for-gestational age infant who had hyperinsulinaemic hypoglycaemia on day 13 of life. A female twin infant weighing 1390 g was born at 32^{+6} weeks of gestation. Her glycaemic profile was normal till day 13 of life, after which she was noted to be lethargic and hypoglycaemic and had hyperinsulinism, hypoketonaemia and hypofattyacidaemia, requiring high glucose infusion rate to maintain normoglycaemia, while negative for septic markers and metabolic screen. Initially, there was no response to diazoxide and the genetic studies for *ABCC8* and *KCNJ11* gene mutations were negative. Delayed response to diazoxide was followed by complete resolution of hypoglycaemia in 5 months. This case highlights the importance of glucose monitoring in small-for-date infants for hypoglycaemia till they achieve full feeds and gain weight. Early recognition and appropriate management of hypoglycaemia in this group of infants have important implications for neurodevelopmental outcome.

BACKGROUND

Poor glycogen stores, impaired gluconeogenesis and hyperinsulinism are the most common causes of hypoglycaemia in the neonatal and infancy periods. Hyperinsulinaemic hypoglycaemia (HH) occurs as a consequence of unregulated insulin secretion from pancreatic β cells. Three forms of HH have been recognised. The transient form, seen in infants of diabetic mothers, presents soon after birth and responds well to increasing glucose administration until the β-cell insulin secretion is normalised. Persistent HH, more often known as congenital hyperinsulinism (CHI), is increasingly being reported with identifiable genetic mutations, especially in populations with high degree of consanguinity.[1] Prolonged HH, typically seen in small-for-gestational age (SGA) infants, usually presents within 48 h of life and most of them respond well to high glucose infusion rate (GIR). Some of these infants need diazoxide and hypoglycaemia resolves over a few weeks to months.[2] Rapid diagnosis and appropriate management of infants with HH are essential to prevent brain injury due to hypoglycaemia. We describe an SGA infant with HH, symptomatic on day 13 of life and required diazoxide for 5 months to maintain normoglycaemia. Delayed onset of hypoglycaemia in this group of SGA infants may go unnoticed in special care areas where glucose monitoring is not mandatory while on feeds.

CASE PRESENTATION

A baby girl weighing 1390 g was born to a 35-year-old primigravida mother at 32^{+6} week gestation by caesarean section for non-reassuring fetal status. She was the first twin of a dichorionic diamniotic natural conception, of non-consanguineous parents. There was no family history of diabetes or hypoglycaemia. Antenatal ultrasound scan showed growth restriction but Doppler studies were normal. The Apgar scores were 7 and 9 at 1 and 5 min, respectively. She was not dysmorphic but was growth retarded with weight, head circumference and length below the third centile. The second twin was appropriate for gestational age.

She was admitted after birth to the intensive care unit with respiratory distress requiring surfactant and ventilation for 36 h. She attained a feed volume of 120 mL/kg/day by day 12 and the blood sugar levels (BSLs) were in normoglycaemic (3.5–5.5 mmol/L) range since birth. On day 13 of life, she became lethargic and was noted to be hypoglycaemic (1.9–2.1 mmol/L). The twin sister remained stable on feeds.

INVESTIGATIONS

During a hypoglycaemic episode, serum insulin and cortisol levels were 111 mU/L (normally undetectable with hypoglycaemia) and 370 nmol/L (46–389 nmol/L), respectively. Serum ketones were negative and acyl carnitine levels were low. Septic markers were unremarkable. The screening tests for inborn error of metabolism were negative. Serum ammonia and lactate levels were normal. Although transient, there was a rise in glucose levels following glucagon administration. In view of the initial diazoxide unresponsiveness, genetic studies were performed at Exeter, UK for the baby, the twin sister and the parents. Blood samples were negative for *ABCC8* and *KCNJ11* mutations. Karyotyping was normal, 46 XX.

TREATMENT

She required increasing GIR (maximum of 22 mg/kg/min) for maintaining normoglycaemia. Oral diazoxide (20 mg/kg/day), hydrochlorothiazide, hydrocortisone and glucagon infusion were given in an attempt to normalise BSL. A surgical opinion for possible pancreatectomy was made in light of

To cite: Chong JH, Chandran S, Agarwal P, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-200920

the high GIR requirement and initial diazoxide unresponsiveness while continuing with the aggressive medical management, pending genetic study report. However, BSL was controlled by day 22 and her medications except diazoxide were weaned over 3 days.

OUTCOME AND FOLLOW-UP

Her feed tolerance improved and was graded up to more than half of the fluid requirement as milk by day 30. Thereafter, her stay was uneventful. She was discharged on day 80 of life at a corrected age of 1 month with a weight of 2000 g, on a diazoxide dose of 10 mg/kg/day with home blood glucose monitoring. She was followed up by the neonatal team and was off diazoxide at the corrected age of 5 months. In the last neurodevelopmental follow-up at the age of 23 months, she was assessed to be doing well.

DISCUSSION

HH has an estimated incidence of 1 in 27 000–50 000 live-births.[3] HH is defined as a plasma glucose level of less than 3 mmol/L, with an inappropriately elevated plasma insulin concentration in a baby receiving a glucose-infusion rate of more than 8 mg/kg/min, suppressed ketone bodies and free fatty acids and a positive glycaemic response (rise in BSL > 1.5 mmol/L) to parenteral glucagon.[1]

The aetiology of prolonged HH in SGA infants could be due to a lack of exogenous substrate supply, depletion of hepatic glycogen stores, defective gluconeogenesis, hyperinsulinism and increased sensitivity to insulin or adrenocortical insufficiency.[4 5] In this reported case the infant had severe HH lasting for weeks and the mechanism could be a transient alteration in the β-cell regulation of insulin secretion. The underlying possible genetic or epigenetic aetiology of prolonged HH due to growth restriction in SGA infants is poorly understood.[6]

In infants with HH, diazoxide unresponsiveness is an absolute indication to perform genetic studies as seen in this reported case.[7] The aetiology of CHI can be due to two major defects known as channelopathies and metabolopathies. In channelopathies, the commonest genetic cause is recessive mutations in the genes *ABCC8* and *KCNJ11* encoding the SUR and Kir 6.2 of the pancreatic K_{ATP} channels. Once confirmed as congenital HH, identifying focal lesions using ^{18}F-fluoro-L-DOPA positron emission tomography to make the surgical decision is essential.[1 7] In metabolopathies, the commonest cause is Hyperinsulinism-Hyperammonaemia syndrome, a dominant missense mutation in glutamate dehydrogenase enzyme encoded by the *GLUD1* gene.[7] The inborn error of metabolism screen was negative and so the cause was unlikely to be a metabolopathy. Arya *et al*[6] recently published the genotypic characteristics of SGA babies with HH, where no mutations were identified in *ABCC8* and *KCNJ11* genes, supporting the non-genetic aetiology of prolonged HH in SGA infants.In our case, a non-genetic aetiology is supported by the normal genetic studies, response to diazoxide and spontaneous resolution with time.

Infants with hypoglycaemia most often present during the first 24–48 h of life. Holtrop[8] found that the average time for finding low glucose levels in SGA infants was 6.1 h (range 0.8–34.2 h). By contrast, Hoe *et al* reported a median age of presentation of 13 days (range 2–180 days) in a group of infants with prolonged HH. In neonates, typically the presentation of HH is more severe than in infancy requiring higher concentrations of glucose to maintain the BSL. Symptoms of hypoglycaemia are mostly non-specific such as lethargy, poor feeding, apnoea, seizures and coma.[9] Late presentation of hypoglycaemia as seen in our case could be missed as infants at these gestational ages are usually nursed in low dependency neonatal areas while on feeds with infrequent or no BSL monitoring.

Diazoxide, a K_{ATP} channel agonist, remains the mainstay of medical treatment in prolonged HH.[7] Prolonged HH resolves by 6 months as seen in this reported case as well. Rarely, it may persist up to 1 year of age.[2 6] Diazoxide is usually combined with hydrochlorothiazide in neonates to counteract its fluid retention side effects. Hypertrichosis seen in infants on diazoxide usually resolves on discontinuation.[7 10] Recent reports of large symptomatic pericardial effusion in infants on diazoxide warrant meticulous cardiovascular monitoring while on treatment.[11]

Neonates who are treated for HH need a long-term developmental and visual follow-up because of the high risk of neurodevelopmental delay.[12]

Learning points

- Small-for-gestational age (SGA) infants usually present with hypoglycaemia during the first 2 days of life. Late onset hypoglycaemia can be missed if blood sugar level (BSL) is not frequently monitored when these SGA infants are cared for in low-dependency areas.
- Hyperinsulinaemic hypoglycaemia (HH) is increasingly being diagnosed today. Differentiation of transient, prolonged and persistent HH is paramount, as unrecognised low BSL will lead to significant neurodevelopmental morbidity.
- If glucose infusion rate is above 8 mg/kg/min, basic workup for HH including serum insulin, ketones and acylcarnitine levels should be performed and a response to glucagon will help with the diagnosis.
- Prolonged HH seen in SGA infants are diazoxide responsive. Diazoxide unresponsiveness in a baby with HH warrants genetic studies for common mutations.
- There are no clear guidelines on how long to monitor BSL in SGA infants. Our experience and published literatures support to continue BSL monitoring for 2–3 weeks from birth to identify delayed onset of hypoglycaemia in SGA infants.

Acknowledgements The authors express their gratitude to Dr Khalid Hussain, Molecular Genetics Unit, Institute of Child Health, UCL, London for giving advice while this case was worked up and also to his genetics department team for getting the genetics study performed for the patient and family.

Contributors CJH wrote the case report. SC wrote the discussion section. PA edited the case report. VSR edited the discussion section.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Hussain K. Diagnosis and management of hyperinsulinemic hypoglycaemia of infancy. *Horm Res* 2008;69:2–13.
2 Hoe FM, Thornton PS, Wanner LA, *et al*. Clinical features and insulin regulation in infants with syndrome of prolonged neonatal hyperinsulinism. *J Pediatr* 2006;148:207–12.
3 Glaser B, Thornton PS, Otonskoski T, *et al*. Genetics of neonatal hyperinsulinism. *Arch Dis Child* 2000;82:F79–86.
4 Collins JE, Leonard JV, Teale D, *et al*. Hyperinsulinaemic hypoglycaemia in small for date babies. *Arch Dis Child* 1990;65:1118–20.
5 Collins JE, Leonard JV. Hyperinsulinism in asphyxiated and small for date infants with hypoglycemia. *Lancet* 1984;2:311–13.

6 Arya VB, Flanagan SE, Kumaran A, *et al*. Clinical and molecular characterization of hyperinsulinaemic hypoglycaemia in infants born small-for-gestational age. *Arch Dis Child Fetal Neonatal Ed* 2013;98:F356––8.
7 Senniappan S, Arya VB, Hussain K. The molecular mechanisms, diagnosis and management of congenital hyperinsulinism. *Indian J Endocrinol Metab* 2013;17:19–30.
8 Holtrop PC. The frequency of hypoglycemia in full-term large and small for gestational age newborns. *Am J Perinatol* 1993;10:150–4.
9 Aynsley-Green A, Hussain K, Hall J, *et al*. Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000;82:98–107.
10 Arnoux JB, Lonlay PD, Ribeiro MJ, *et al*. Congenital hyperinsulinism. *Early Hum Dev* 2010;86:287–94.
11 Avatapalle B, Banerjee I, Malaiya N, *et al*. Echocardiography monitoring for diazoxide induced pericardial effusion. *BMJ Case Rep*. Published online: 3 Jul 2012. doi:10.1136/ bcr.03.2012.6110
12 Kumaran A, Kar S, Kapoor RR, *et al*. The clinical problem of hyperinsulinemic hypoglycemia and resultant infantile spasms. *Pediatrics* 2010;126: e1231–6.