CASE REPORT

Prematurity, macrosomia, hyperinsulinaemic hypoglycaemia and a dominant *ABCC8* gene mutation

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SUMMARY

Congenital hyperinsulinism (CHI) is a rare cause of hyperinsulinaemic hypoglycaemia (HH) and is due to an inappropriate secretion of insulin by the pancreatic β -cells. Genetic defects in key genes lead to dysregulated insulin secretion and consequent hypoglycaemia. Mutations in the genes *ABCC8/KCNJ11*, encoding SUR1/Kir6.2 components of the K_{ATP} channels, respectively, are the commonest cause of CHI. A 33⁺6 week gestation male infant weighing 3.38 kg (above 90th centile) presented with severe neonatal symptomatic hypoglycaemia. He required a glucose infusion rate of 20 mg/kg/min to maintain normoglycaemia (blood glucose levels at >3.5 mmol/l). Investigations established the diagnosis of HH (blood glucose 2.2 mmol/l with simultaneous insulin of 97.4 mU/l). Subsequent molecular genetic studies identified a heterozygous pathogenic *ABCC8* missense mutation, p.R1353H (c.4058G>A), inherited from an unaffected mother. His HH was diazoxide responsive and resolved within 3 months of life.

BACKGROUND

Hypoglycaemia is the most common biochemical problem observed in neonates and if untreated can have a major impact on normal brain development.^{1–2} Congenital hyperinsulinism (CHI) is a rarer but important cause of hypoglycaemia (1 in 50 000 live births) and is due to different genetic defects, some of which confer an increased risk of early onset diabetes mellitus. The most common cause of CHI is recessive and dominant mutations in the genes *ABCC8/KCNJ11* which encode the two components (SUR1 and Kir6.2, respectively) of the pancreatic β -cell K_{ATP} channels.^{3–4} While the majority of recessive *ABCC8/KCNJ11* mutations show no response to medical therapy, dominant mutations are very variable in clinical presentation and response to therapy.^{5–6} Dominant *ABCC8/KCNJ11* may present with mild-to-severe CHI and adults may present with diabetes mellitus. Clinicians must bear in mind the possibility of CHI when faced with an infant with prolonged hypoglycaemia while also diligently treating hypoglycaemic episodes as both have potential long-term consequences. We describe an interesting case of macrosomia and transient CHI due to dominant *ABCC8* mutation.

CASE PRESENTATION

A Caucasian male infant presented with severe neonatal hypoglycaemia. He was born at 33⁺6 weeks gestation by spontaneous vaginal delivery weighing 3.38 kg (above the 99th centile) to non-consanguineous parents. The pregnancy was uncomplicated with normal antenatal scans. There was no history of gestational diabetes mellitus or perinatal asphyxia. He required high concentrations of intravenous glucose infusions (maximum glucose infusion rate—20 mg/kg/min) through central venous access to maintain normoglycaemia. There was no clinical or laboratory evidence of sepsis.

INVESTIGATIONS

A hypoglycaemic screen revealed elevated serum insulin of 97.4 mU/l when the blood glucose concentration was 2.1 mmol/l, with undetectable serum non-esterified fatty acids and ketone bodies. The serum ammonia level was <50 μ mol/l. The rest of the investigations including serum cortisol, plasma amino acids, acylcarnitine profile and urine organic acids were within normal range. The increased glucose infusion rate with the above biochemical findings have the metabolic 'foot print' of hyperinsulinaemic hypoglycaemia (HH).

To investigate the cause of HH, molecular genetic testing for *ABCC8* and *KCNJ11* was requested, as there was no evidence to suggest secondary cause of HH (intrauterine growth restriction, maternal or gestational diabetes, or perinatal asphyxia).

Molecular genetic testing identified a previously reported maternally inherited heterozygous *ABCC8* missense mutation, p.R1353H (c.4058G>A), which confirmed the diagnosis of CHI due to dominant *ABCC8* mutation.⁷ Dominant *ABCC8* mutations have been previously reported to increase the risk of diabetes mellitus in adulthood. There was no history of hypoglycaemia in the mother and her fasting blood glucose was normal (5.6 mmol/l).

TREATMENT

Initial management of hypoglycaemia

In view of the increased risk of brain injury with HH, our patient was managed with concentrated glucose infusions, while investigations to look for the cause of neonatal hypoglycaemia were carried out.

Management of the underlying hyperinsulinism

Once the biochemical diagnosis of HH was confirmed, diazoxide (5 mg/kg/day) and chlorothiazide

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(7.5 mg/kg/day) were started. Diazoxide acts by binding onto an intact SUR1 protein in the K_{ATP} channel and helps to open the K_{ATP} channels. One of the major side effects of diazoxide is fluid retention hence a diuretic is also administered.

OUTCOME AND FOLLOW-UP

The infant showed an excellent response to therapy with diazoxide and chlorothiazide. Within 48 h of treatment, he was successfully weaned off intravenous glucose and established on oral feeds. Prior to discharge he had a 6 h fast, at the end of which his blood glucose was 3.4 mmol/l. He was discharged on 4 hourly feeds with a plan for prefeed blood glucose monitoring at home 2–3 times/day.

During next 6 weeks, his HH was extremely well controlled on diazoxide and his dose of diazoxide reduced to 4 mg/kg/day as his weight increased to 3.78 kg (50th–75th Centile). He underwent a 24 h blood glucose profile and a controlled fast after stopping diazoxide for 3 days. His 24 h blood glucose profile revealed no episodes of hypoglycaemia. He fasted for 8 h, with a blood glucose of >3.5 mmol/l at the end of the fast with an appropriate increase in the non-esterified fatty acid and ketone bodies, suggesting that his hyperinsulinism had resolved. He stayed off diazoxide and chlorothiazide, with no further episodes of hypoglycaemia.

DISCUSSION

HH is characterised by unregulated secretion of insulin and can present in a variety of ways, depending on severity and age of patient.¹ In the neonatal period, it can present with severe symptomatic (ranging from poor feeding to seizures) hypoglycaemia. Clinicians must keep a high index of suspicion of diagnosing HH due to the resulting risk of brain damage and long-term complications such as epilepsy, mental retardation and cerebral palsy.² Most affected new-borns are macrosomic with a mean birth weight of 3.7 kg.⁸ Our patient weighed 3.38 kg despite being born premature at 33⁺⁶ weeks.

The diagnostic criteria for HH are as follows¹:

- ▶ An infusion rate of dextrose >8 mg/kg/min required to maintain blood glucose levels above 3.5 mmol/l.
- ▶ Detectable levels of serum insulin and or C-peptide during times of hypoglycaemia (there is no correlation between the serum insulin level and the severity of hypoglycaemia).
- ▶ Inappropriately low ketone bodies and low non-esterified free fatty acids during hypoglycaemia.
- ▶ An increase in blood glucose level >1.5 mmol/l within 30 min of an intramuscular or intravenous glucagon injection.

Our patient required a high glucose infusion rate (20 mg/kg/min) and had raised serum insulin and inappropriately low β -hydroxybutyrate and non-esterified fatty acids for the blood glucose levels, which is characteristic of HH.

Once a diagnosis of HH is established the aetiology must be identified. Apart from genetic defects, HH has been reported secondary to maternal diabetes mellitus, intrauterine growth restriction and perinatal asphyxia.⁹ Though born premature at 33⁺⁶ weeks, our patient was not intrauterine-growth restricted, nor was there any evidence of perinatal stress. He was in fact very large for his gestational age but his mother did not have gestational diabetes mellitus. These features pointed away from a secondary cause of hyperinsulinism.

Consequently, the most likely cause of the HH in our case was CHI, a clinically heterogeneous disorder in which there is inappropriate insulin secretion secondary to genetic defects in the key genes involved in regulating insulin secretion.¹⁰ It can be classified

histologically into two forms: a focal form, in which a small area of the pancreas shows adenomatous hyperplasia and the diffuse form where β -cells throughout the pancreas oversecrete insulin. Its incidence is up to 1:2500 in areas of increased consanguinity and in non-consanguineous regions it is about 1:50 000. The genetic aetiology is only known in about 50% of cases.

The most common cause of CHI is recessive and dominant mutations in the genes *ABCC8/KCNJ11* which encode the two components (SUR1 and Kir6.2, respectively) of the pancreatic β -cell K_{ATP} channels which control insulin secretion.^{3–4} While recessive *ABCC8/KCNJ11* mutations show no response to medical therapy, dominant mutations are very variable in clinical presentation and response to therapy. Dominant *ABCC8/KCNJ11* mutations may present with mild-to-severe CHI and adults may present with diabetes mellitus.^{5–6} These cases tend to be diazoxide responsive. Our patient had CHI due a dominant *ABCC8* mutation and was diazoxide responsive.

Dominant mutations in SUR1 were first described by Huopio *et al*⁶ who studied 38 paediatric cases of CHI in Finland and identified a missense mutation, p.E1507K (according to refseqU63421 and L78208, previously described as p.E1506K), within the second nucleotide binding fold of SUR1 in seven related patients with CHI. In our case, the patient had the missense mutation p.R1353H in the SUR1 component of K_{ATP} channels, which has previously been reported.⁷ However unlike the family reported before, in which the HH lasted till 4 years of age, HH in our patient resolved at 3 months of age.

The response to therapy in dominant mutations compared with recessive mutations is down to the molecular mechanisms of the mutations— K_{ATP} channel function is partially preserved in the dominant form. Pinney *et al*¹¹ showed that, unlike recessive mutations, dominantly inherited K_{ATP} mutant subunits trafficked normally to the plasma membrane but either show impaired responsiveness to channel agonists such as MgADP and diazoxide or result in complete loss of channel activity. This results in a milder hypoglycaemia phenotype that may escape detection in infancy and is frequently responsive to diazoxide medical therapy.

Other genetic mutations affect enzymes involved in glucose metabolism such as glucokinase and glutamate dehydrogenase or transcription factor defects such as HNF4A.^{12–15}

Frequently, biochemical investigations might give a clue to the underlying subtype of CHI. For example, CHI due to defects in the gene *GLUD1* is typically associated with a raised serum ammonia level and CHI due to defects in the *HADH* gene in some cases is associated with abnormal acylcarnitine and urine organic acids.^{12–16} Our patient had normal serum ammonia, urine organic acids and acylcarnitine profile. CHI might also be part of a syndrome (such as Beckwith-Wiedemann syndrome) but this patient had no clinical features suggestive of a syndrome.¹⁷

There is a clinical relevance to elucidating the genetic mutation involved in a patient with CHI. Kapoor *et al*⁵ studied the phenotype of 30 mutations carriers from nine families with dominant *ABCC8/KCNJ11* mutations and concluded that these mutations were an important cause of early onset diabetes mellitus. Genetic counselling can therefore be offered to families and long-term risks of developing early onset diabetes mellitus can be explained. This is pertinent to the patient in this case—he will now have his blood glucose monitored; the early diagnosis of diabetes mellitus will improve long-term outcomes.¹⁸ In addition, his mother, who is a carrier of this mutation, will have her blood glucose monitored and therefore will also benefit from this genetic analysis.

The management of hyperinsulinism is twofold: first, correct the hypoglycaemia as a matter of urgency and second, prevent the hypoglycaemia from happening, by treating the cause of the hyperinsulinism.

The first line treatment is the use of diazoxide, a K_{ATP} channel agonist that acts on pancreatic β -cells.¹ Its side effects include hypertrichosis, fluid retention and heart failure. In more severe cases which do not respond to diazoxide, somatostatin analogues such as octreotide can also be used and side effects include diarrhoea and vomiting and abdominal distension although necrotising enterocolitis remains the most serious.¹⁹ Medically unresponsive CHI would require near-total pancreatectomy or focal lesion resection depending on the subtype of CHI.

Learning points

- Neonatal hypoglycaemia (especially hyperinsulinaemic hypoglycaemia) has serious consequences—if ever in doubt measure a blood glucose level.
- Persistent and prolonged hypoglycaemia can be due to congenital hyperinsulinism.
- Genetic analysis of causes of hyperinsulinism is useful in predicting risk of early onset diabetes mellitus for both the patient and their relatives.

Contributors DK and VBA collected all the information and drafted the manuscript. SEF, SE and KH were involved in conceptualisation and reviewed the manuscript critically. DK and VBA contributed equally.

Competing interests None.

Patient consent Obtained.

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