Two Sri Lankan siblings with diazoxide responsive congenital hyperinsulinaemic hypoglycaemia due to a rare mutation in the *ABCC8* gene

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Introduction

Congenital hyperinsulinaemic hypoglycaemia (CHH) encompasses a spectrum of rare genetic disorders characterized by dysregulated insulin secretion by pancreatic β cells and is the most frequent cause of severe, persistent hyperinsulinism in newborn babies and infants[1-3]. CHH can occur due to mutations in several genes, including *KCNJ11* and *ABCC8*. Inactivating mutations in the *ABCC8* gene generally lead to unregulated insulin secretion, causing a severe form of CHH that is unresponsive to diazoxide. We present two Sri Lankan siblings born to non-consanguineous parents with a rare diazoxide responsive form of CHH, associated with a missense variant (c.2146G>A, p.(Gly716Ser) mutation in the *ABCC8* gene.

Case report

Baby girl was born to non-consanguineous parents after two 1st trimester miscarriages at 32 weeks of gestation with a birth weight of 2.5 kg (>+3SD on the preterm growth chart) via emergency lower segment caesarean section due to impending eclampsia and maternal diabetes. She was admitted to the special care baby unit (SCBU) due to moderate prematurity despite being born in good condition. She had an unrecordable capillary blood glucose (CBG) level on admission to the SCBU at 2 hours of life. She was immediately commenced on a dextrose bolus followed by an infusion of glucose at a rate of 4.1mg/kg/min in addition to expressed breastmilk (EBM). Subsequently, the glucose infusion rate (GIR) was gradually increased from 5.5mg/kg/min to 6.8mg/kg/min, to maintain the CBG values above 45mg/dl on day one. Her GIR increased to 13.6mg/kg/min (intravenous dextrose) on day 2 and 19.5mg/kg/min on day 4 (intravenous dextrose and expressed breastmilk) to maintain the CBG >45mg/dl. The dextrose infusion was gradually reduced from day 5 with increasing breast milk volumes to a minimum GIR of 15.2mg/kg/min by day 9 while maintaining a CBG >70mg/dl. GIR was increased once again to 20.87mg/kg/min on day 10 as CBG values decreased to 10 and 11mg/dl despite being on full feeds (150ml/kg/day) after which the CBG was between 46mg/dl–72mg/dl. She remained asymptomatic throughout.

A critical sample sent on day 14 (CBG = 41mg/dl) while on a GIR of 19mg/kg/min to maintain the CBG just above 50mg/dl, recorded a serum cortisol level of 303nmol/L (55–304nmol/L), a growth hormone level of 3.3µg/L (2–5µg/L), a serum insulin level of 37.2pmol/L (5.18µU/mL) (normal <2µU/mL), with no ketone bodies in the urine, confirming hyperinsulinaemic hypoglycaemia. She was started on oral diazoxide therapy at a dose of 5mg/kg/day in 3 divided doses, which was increased to 7mg/kg/day 24 hours later to maintain CBG consistently above 70mg/dL. The GIR was gradually reduced to 4mg/kg/min, and the dextrose infusion was omitted on day 17. Decrease of CBG to 56 mg/dL resulted in a further increase in diazoxide to 8mg/kg/day on day 27 after which the CBG remained above 75mg/dL until discharge while on exclusive breastfeeding. The diazoxide dose was tapered off and completely omitted at 2 months and 20 days of age during the clinic follow-up, due to normal CBG levels. Her blood glucose remained normal until 7 months of age until she presented again with an afebrile hypoglycaemic convulsion at which time, she was re-started on diazoxide to which she showed a good response.

She was confirmed to be heterozygous for an *ABCC8* missense variant, c.2146G>A, p.(Gly716Ser), at 11 months of age with the help of Exeter Genetic Laboratory in the United Kingdom. Her mother had the same *ABCC8* missense variant. Genetic testing could not be performed on the father, as he was working abroad, and further genetic testing and counselling was deferred till his return.

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Our patient is now 3 years of age and maintains normoglycaemia while on regular diazoxide therapy. Her developmental milestones are age appropriate with normal neurological examination.

They had not sought genetic counselling when the mother conceived her second child during the COVID-19 pandemic, when the father returned to Sri Lanka. A baby boy was born on 05th April 2022 at 32 weeks of gestation with a birth weight of 2.9kg (>+3SD on the preterm growth chart) via emergency lower segment caesarean section due to impending eclampsia and maternal diabetes just as in the index case. He too was born in good condition and was admitted to the SCBU since he was moderately preterm. Blood glucose on admission to the SCBU (at 2 hours of age) was 20mg/dL. This was followed by a 10% dextrose bolus, and infusion at a GIR of 4.2mg/kg/min. GIR was increased to 7mg/kg/min to maintain the CBG levels above 45mg/dl on day 2. GIR was maintained at 7-8 mg/kg/min while the dextrose infusion was tailed off from day 3 and omitted on day 9 when the GIR was 5.4mg/kg/min, while maintaining a CBG >60mg/dL with increasing amounts of expressed breast milk. However, 10% dextrose infusion was restarted on day 10 as the CBG decreased to 50mg/dL with a GIR of 9.6mg/kg/min which increased to 15.2mg/kg/min as the baby achieved full feeds (150mL/kg/day) 48 hours later. The baby was asymptomatic throughout this period and demonstrated no symptoms or signs of hypoglycaemia.

The diagnosis of CHH in the older child was only revealed at this stage. The endocrine team managing the first child was then consulted, and he too was commenced on diazoxide 10mg/kg/day in 3 divided doses after sending a critical sample when the CBG was 21mg/dL. Urine ketone bodies were negative while the serum cortisol level was 383nmol/L (55–304nmol/L), growth hormone level was 2.5µg/L (2–5µg/L) and serum insulin level was 22.9pmol/L (3.19µU/mL) (normal <2µU/mL) confirming hyperinsulinaemia. With this dose of diazoxide, the dextrose infusion was gradually tapered off and completely omitted in the next 48 hours. He was further observed for another 4 days for any hypoglycaemic episodes and discharged on day 17 with a plan to follow up at the clinic. At 36 days of age, developmental milestones were age appropriate and neurological examination did not reveal any abnormality. Both parents were counselled together regarding the condition and implications for future pregnancies explained. Genetic testing is planned for the second child, as well as the father, and long term follow up arranged for both children at the paediatric endocrine centre. Both children are on standard doses of diazoxide, together with thiazide to minimise fluid retention

Discussion

Congenital hyperinsulinaemic hypoglycaemia (CHH) is a cause of severe, persistent hypoglycaemia in newborn babies and infants[1]. CHH can occur due to one of several rare genetic disorders associated with dysregulated insulin secretion by the pancreatic β cells[1-3]. The incidence of CHH is estimated to be 1:50,000 live births but could be as high as 1:2500 in regions with high consanguinity rates[4]. Mutations in many genes have been described in relation to CHH[5,6]. Of these, mutations in *ABCC8* and *KCNJ11* genes affect K_{ATP} channel in pancreatic β cells, while other genetic mutations mainly alter the concentration of intracellular signalling molecules (ATP)[5]. Mutations in *ABCC8* and *KCNJ11* genes cause the most severe form of CHH, which is typically unresponsive to diazoxide treatment[5].

Pancreatic β cells have K_{ATP} channels. The key regulators of the K_{ATP} channels are intracellular ATP and ADP. An increase in the intracellular concentration of ATP results in closure of the K_{ATP} channel[1,5]. This in turn results in depolarization and activation of the voltage gated calcium channels causing calcium influx and exocytosis of insulin[5].

The *ABCC8* gene stands for ATP-Binding Cassette, Sub-Family C, Member 8, and codes for the SUR1 protein, which makes the K_{ATP} channel in the pancreatic β cells sensitive and responsive to sulfonylureas and channel activators such as diazoxide[5]. Inactivating mutations in any region of the *ABCC8* gene leads to persistent depolarization of the pancreatic β-cell membrane, which leads to unregulated insulin secretion and can cause a severe form of CHH that is unresponsive to medical therapy with diazoxide[5,7]. Diazoxide binds to the SUR1 subunit in the K_{ATP} channel, causing it to remain open thereby increasing its permeability to potassium ions resulting in hyperpolarization of the pancreatic β cells and inhibiting calcium dependent insulin secretion[6,8].

The ABCC8 missense variant, c.2146G>A, p.(Gly716Ser) identified in our index patient has been identified in three additional unrelated infants referred for congenital hyperinsulinism testing to the Exeter Genetic Laboratory. In two of these patients the variant was maternally inherited and in the third case the variant was *de novo*[9]. This variant has not been reported in the genome aggregation database. In our patient, the mutations could either have been inherited recessively with a non-coding paternal ABCC8 variant or could be an acquired ABCC8 variant on the paternal allele, or a dominant variant with variable penetrance from the unaffected mother[9]. This variant is recognised as being sensitive to diazoxide, and explains the good response noted in these two Sri Lankan siblings,

despite having CHH due to ABCC8 gene[10]. Additional genetic testing on the father and younger sibling is awaited.

Most newborns with CHH have macrosomia, as insulin acts as a growth stimulator *in utero*. The average birthweight is 3.7 kg at term[2]. The degree of hypoglycaemia in CHH can range from asymptomatic hypoglycaemia detected by routine blood glucose monitoring to life-threatening hypoglycaemic coma or status epilepticus[2]. CHH should be suspected when there is persistent hypoglycaemia beyond 48 hours of life, with increasing dextrose requirement to maintain normoglycaemia[2]. Further, hypoglycaemia can occur in fasting as well as post-prandial states[2]. In CHH, excessive insulin also blunts the normal counter-regulatory hormone response to hypoglycaemia and inhibits the normal protective mechanisms which occur during hypoglycaemia in the fasting state, such as glycogenolysis, gluconeogenesis, lipolysis and ketogenesis, thus depriving the brain of both glucose and alternative energy substrates[4,11,12]. Therefore, early diagnosis and treatment of patients with CHH are essential to avoid brain damage and long-term neurological sequelae[1].

The acute management of hyperinsulinaemic hypoglycaemia requires parenteral glucose infusion to maintain blood glucose above 3.5mmol/L[13,14]. The parenteral glucose requirements exceed 8mg/kg/min and can often be as high as 15-25mg/kg/min[9]. In case of emergency (e.g., symptomatic hypoglycaemia and seizures without a venous access), intramuscular administration of glucagon may be used[1,4,13,15,16]. Early initiation and frequent feeding is also a very important supportive method although it can be difficult due to the feeding disturbances, food aversion, gastro-oesophageal reflux disease and foregut dysmotility which has been observed in patients with CHH[13,17].

Long term treatment will be different in children who are responsive to diazoxide compared to those who are diazoxide unresponsive. The management of diazoxide responsive children is straightforward, while the management of diazoxide unresponsive children is challenging. In such cases, it is essential to find a suitable medical therapy or if necessary, in case of medically unresponsive cases, resort to surgical intervention[1,13,15,17,18]. The drugs that can be used in the long-term management of diazoxide unresponsive CHH include, octreotide, lanreotide, nifedipine, glucagon and sirolimus while surgical interventions include partial pancreatectomy for focal disease or near total pancreatectomy for diffuse disease[1,4,13].

In the case history described above, both siblings were large for the period of gestation, although macrosomia was not present due to the prematurity. Although blood glucose levels reach a physiologic nadir within 4 hours of birth, they were both identified to have hypoglycaemia on routine investigations done on admission to the SCBU within 2 hours of birth and were actively managed. Both had a glucose requirement greater than 15mg/kg/min to maintain normoglycaemia. Hyperinsulinaemia was confirmed biochemically in both, and both responded well to diazoxide, an unusual feature for CHH arising due to ABCC8 gene mutations[3,6]. Hypertrichosis was noted in the older sibling, but neither developed any other adverse effects. There is no evidence of neurodevelopmental delay in both children to date.

Conclusion

Persistent and/or recurrent hypoglycaemia beyond 48 hours with increasing requirement of dextrose should always raise the suspicion of CHH. With early diagnosis and treatment, satisfactory long term neurodevelopmental outcomes can be achieved in medically responsive CHH.

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