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V B Arya and others | *HNF4A* HH: diazoxide sensitivity

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Exceptional diazoxide sensitivity in hyperinsulinaemic hypoglycaemia due to a novel *HNF4A* mutation

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Summary

Diazoxide is the first-line treatment for patients with hyperinsulinaemic hypoglycaemia (HH). Approximately 50% of patients with HH are diazoxide resistant. However, marked diazoxide sensitivity resulting in severe hyperglycaemia is extremely uncommon and not reported previously in the context of HH due to *HNF4A* mutation. We report a novel observation of exceptional diazoxide sensitivity in a patient with HH due to *HNF4A* mutation. A female infant presented with severe persistent neonatal hypoglycaemia and was diagnosed with HH. Standard doses of diazoxide (5 mg/kg/day) resulted in marked hyperglycaemia (maximum blood glucose 21.6 mmol/L) necessitating discontinuation of diazoxide. Lower dose of diazoxide (1.5 mg/kg/day) successfully controlled HH in the proband, which was subsequently confirmed to be due to a novel *HNF4A* mutation. At 3 years of age, the patient maintains age appropriate fasting tolerance on low dose diazoxide (1.8 mg/kg/day) and has normal development. Diagnosis in proband's mother and maternal aunt, both of whom carried *HNF4A* mutation and had been diagnosed with presumed type 1 and type 2 diabetes mellitus, respectively, was revised to maturity-onset diabetes of young (MODY). Proband's 5-year-old maternal cousin, also carrier of *HNF4A* mutation, had transient neonatal hypoglycaemia. To conclude, patients with HH due to *HNF4A* mutation may require lower diazoxide than other group of patients with HH. Educating the families about the risk of marked hyperglycaemia with diazoxide is essential. The clinical phenotype of *HNF4A* mutation can be extremely variable.

Learning points:

- Awareness of risk of severe hyperglycaemia with diazoxide is important and patients/families should be accordingly educated.
- Some patients with HH due to *HNF4A* mutations may require lower than standard doses of diazoxide.
- The clinical phenotype of *HNF4A* mutation can be extremely variable.

Background

Hyperinsulinaemic hypoglycaemia (HH) is the most frequent cause of severe and persistent hypoglycaemia in infants and children (1). It is characterised by inappropriate secretion of insulin in the presence of low blood glucose (BG) concentrations. Mutations in a number of key genes (including *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A* and *HNF1A*) involved in the regulation of insulin secretion from pancreatic β-cells have been described as the underlying molecular mechanisms leading to congenital HH (2). The phenotype of dominant

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mutations in *HNF4A* is characterised by neonatal HH which evolves to diabetes mellitus in later life (3, 4). The first-line treatment in HH is diazoxide therapy, which at the doses of 5–20 mg/kg/day is effective in patients with heterozygous *HNF4A* mutations. We describe a novel finding of exceptional diazoxide sensitivity in an infant with HH due to a novel heterozygous *HNF4A* mutation.

Case presentation

The female proband was born at 37+1 weeks (birth weight 3610 g (+1.6 SDS)) by emergency Caesarean section (foetal decelerations) to non-consanguineous Caucasian parents. Apgar scores at 1 and 5 min were 9 and 10 respectively. The proband's mother had presumed type 1 diabetes mellitus since age 17 years, well controlled on continuous subcutaneous insulin infusion. The proband developed severe persistent hypoglycaemia soon after birth, requiring high glucose infusion (17.5 mg/kg/min). Apart from macrosomia, physical examination was unremarkable.

Investigations

A hypoglycaemia screen confirmed the diagnosis of HH (BG 2.6 mmol/L, serum insulin 40.3 mIU/L, non-esterified fatty acids 0.10 mmol/L, β-hydroxybutyrate <0.10 mmol/L). All other investigations including acylcarnitine profile, serum cortisol, serum lactate, serum ammonia and plasma amino acids were normal.

Treatment

The proband was commenced on standard doses of diazoxide (5 mg/kg/day in three divided doses) and chlorothiazide (7.5 mg/kg/day in two divided doses) on day 15 of life.

Outcome and follow-up

Within 48 h of commencing diazoxide, marked hyperglycaemia (highest bedside BG concentration 21.6 mmol/L) developed, which persisted despite weaning high-concentration glucose intravenous infusion to full enteral feeds (Fig. 1). Diazoxide was withheld and eventually stopped after 4 days. Following discontinuation, BG concentration gradually decreased followed by recurrence of hypoglycaemia. A repeat hypoglycaemia screen confirmed persistence of HH (BG 2.6 mmol/L and serum insulin 48.4 mIU/L). Additionally, high glucose

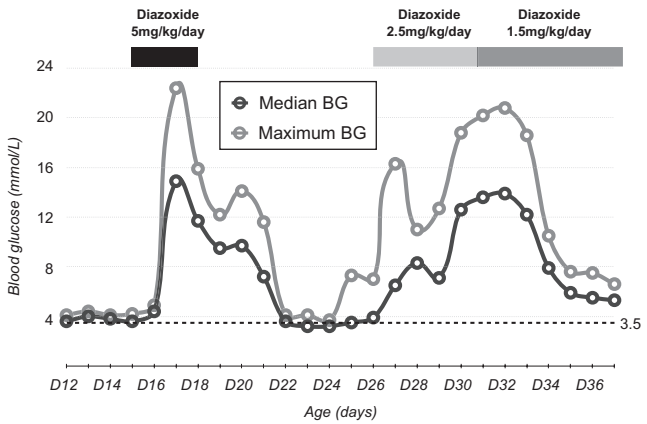

Figure 1
Blood glucose response to diazoxide in an infant with hyperinsulinaemic hypoglycaemia due to a novel *HNF4A* mutation. BG, blood glucose; D, day of life.

infusion rate (13.5 mg/kg/min) was required to maintain BG concentration greater than 3.5 mmol/L. Administration of glucagon (200 mcg/kg) raised the BG concentration from 2.3 mmol/L to 7.3 mmol/L, also in keeping with HH. Lower dose diazoxide (2.5 mg/kg/day) was started, after which glucagon infusion and intravenous fluids were quickly weaned. Despite lower doses, hyperglycaemia developed, necessitating further reduction in diazoxide (1.5 mg/kg/day). On this minimal diazoxide dose, BG concentration on demand feeds ranged between 3.9 and 7.5 mmol/L and were maintained after a 6-h fast. As body weight increased with age, the patient needed corresponding increase in diazoxide dose to maintain euglycaemia. At age 2.75 years, the patient required further increase in the dose of diazoxide due to occasional hypoglycaemic episodes implying persistence of HH. At last follow-up (age 3.1 years), the patient has normal development and remains on low-dose diazoxide (1.8 mg/kg/day) with stable BG profile and age-appropriate fasting tolerance.

Molecular genetic testing identified a maternally inherited heterozygous nonsense mutation (p. Ser419Ter; c.1256C>G) in *HNF4A* (NM_175914.4). The proband mother's diagnosis was revised from type 1 diabetes mellitus to maturity-onset diabetes of young (MODY). Family history revealed young-onset diabetes mellitus in maternal aunt and maternal grandfather who had been labelled type 2 diabetes mellitus and treated with metformin. Genetic analysis confirmed that maternal aunt was heterozygous for the same mutation, leading to change in her diagnoses and treatment (now on sulphonylurea therapy). Maternal grandfather unfortunately had died of complications secondary to diabetes mellitus at 76 years

before he could be tested for *HNF4A* mutation. A 5-year-old maternal cousin tested positive for same mutation. His birth weight was 3844 g (+1.4 SDS). He had transient neonatal hypoglycaemia that did not necessitate any intervention. He is currently asymptomatic, with normal HbA1C and glucose tolerance.

Discussion

Diazoxide is the first-line drug used in the management of HH, standard doses being 5–20 mg/kg per day in three divided doses (5). HH patients secondary to *HNF4A* mutations are diazoxide responsive (3, 6). Improda *et al.* described a case of *HNF4A* mutation who was managed on a lower dose of diazoxide (2 mg/kg per day) (7). However, the described patient had a fasting tolerance of 3.5 h and the authors did not specify reasons for using lower doses. Our patient is the first reported case of *HNF4A* mutation that required careful titration of diazoxide to a minimal dose of 1.5 mg/kg/day to avoid hyperglycaemia.

There are case reports in the literature of hyperglycaemic hyperosmolar coma with diazoxide (8, 9). Balsam *et al.* reported a 13-month-old infant who developed hyperosmolar hyperglycaemic coma on diazoxide (8). The patient presented with listlessness associated with severe hyperglycaemia (BG: 111 mmol/L) approximately 10 days after discharge from hospital on diazoxide 7.5 mg/kg per day and hydrochlorothiazide 12.5 mg per day. After initial management with intravenous insulin and intravenous fluids, hypoglycaemia recurred requiring reinstitution of diazoxide at lower dose (4 mg/kg per day). The authors reported that the BG concentration had been well controlled for 4 months on the lower doses of diazoxide. Mangla *et al.* recently reported a 16 month-old-child who developed severe hyperglycaemia (BG >22 mmol/L) and ketosis during intercurrent illness while receiving diazoxide (15 mg/kg per day) for HH diagnosed at 4 months of age (9). Cessation of diazoxide treatment and institution of insulin treatment was temporarily required. However, hypoglycaemia recurred within few days and the patient needed diazoxide 20 mg/kg per day, which he was on at 28 months of age, to maintain stable BG concentration. Mutation status of these patients was not known. Arguably, had our patient not had close BG monitoring, she would have been at a substantial risk of developing hyperglycaemic hyperosmolar coma. This case highlights the importance of awareness of risk of severe hyperglycaemia with diazoxide and to educate the family to observe for persistently high along with low BG readings.

The mechanism underling HH in early life and switch to MODY in *HNF4A* mutation carriers is not understood. Perhaps the same mechanisms underlie the predisposition to developing higher BG levels on diazoxide. To the best of our knowledge, marked hyperglycaemia on standard doses of diazoxide in a patient with *HNF4A* mutation has previously not been described. As this is a novel *HNF4A* mutation, it is plausible that this predisposition is mutation specific.

This case study also highlights the clinical heterogeneity well known to be associated with *HNF4A* mutation carriers, demonstrating the entire spectrum in the same family with asymptomatic neonatal periods to transient HH in proband's cousin and persistent HH in proband (4). The phenotype of DM is also varied with young-onset (17 and 22 years in proband's mother and proband's maternal aunt respectively) but subcutaneous insulin requirement in proband's mother to successful management with oral hypoglycaemic agents in maternal aunt and maternal grandfather. Maternal grandfather (likely carrier of *HNF4A* mutation) had later presentation of diabetes (30 years) with aggressive progression and complications leading to death at 76 years.

To conclude, awareness of risk of marked hyperglycaemia/hyperglycaemic hyperosmolar coma with diazoxide therapy is essential. Patients with HH due to *HNF4A* patients may require lower diazoxide than other group of patients with HH.

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 has been obtained from the patient's guardian for publication of the submitted article and accompanying images.

Author contribution statement
V B A researched data and wrote the manuscript. J K, S E F, A H and R K K reviewed the manuscript and contributed to discussion. R K K conceptualised the idea of the manuscript and is the named physician for the patient. The authors are grateful to the Department of Molecular Genetics at the Royal Devon and Exeter Hospital for performing the genetic studies.

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