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Congenital Hyperinsulinism Due to a Novel HNF4A Mutation

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Abstract

Congenital hyperinsulinism is the most common cause of persistent hypoglycemia in the newborn period. This case demonstrates an infant who was diagnosed with hyperinsulinism and responded to diazoxide treatment. Persistence of hypoglycemia led to genetic testing, which identified a novel de novo mutation in hepatocyte nuclear factor 4 alpha as the cause of the hyperinsulinism. Patients with this form of hyperinsulinism are noted to have variable clinical courses in terms of length of treatment needed with diazoxide. This gene mutation is also associated with the eventual development of maturity-onset diabetes of the young, so continued close clinical follow-up will be needed, even after the hypoglycemia resolves.

Keywords: Hyperinsulinism; HNF4A; Hypoglycemia; MODY

Abbreviations: HNF4A: Hepatocyte Nuclear Factor 4 Alpha; MODY: Maturity-Onset Diabetes of the Young; HI: Hyperinsulinism; SUR1: Sulfonylurea Receptor-1; LGA: Large For Gestational Age; POC: Point of Care; DOL: Day of Life.

Background

Hepatocyte nuclear factor 4 alpha (HNF4A), which is expressed in the pancreatic islets, liver, kidney, and intestine, is a member of the nuclear receptor family of ligand-activated transcription factors. HNF4A controls the expression of genes involved in glucose-stimulated insulin secretion in pancreatic islet cells. HNF4A gene mutations are a well-known cause of maturity-onset diabetes of the young (MODY). Mutations in HNF4A can also cause hyperinsulinemic hypoglycemia [1].

Congenital hyperinsulinism (HI) is the most frequent cause of persistent hypoglycemia in infants occurring with an incidence rate of 1 in 40000 live births. The diagnosis is made with a critical sample (serum glucose <50 mg/dL) that demonstrates a detectable insulin level, elevated C-peptide (>/= 0.5 ng/mL), suppressed beta-hydroxybutyrate (<1.8 mmol/L), suppressed free fatty acids (<1.7 mmol), and a positive glycemic response to a 1 mg glucagon injection (>/ = 30 mg/dL increase in plasma glucose) [2].

Diazoxide, which has been approved by the US Food and Drug Administration to treat HI, acts by binding to the sulfonylurea receptor-1 (SUR1) subunit in the KATP channel of pancreatic beta cells, causing the channel to open and increase its permeability to potassium ions, resulting in hyperpolarization of calcium-dependent insulin secretion [3]. The usual starting dose of this medication is 5-15 mg/kg/day divided into two to three doses. Genetic testing is important in the evaluation and management of infants with HI since diazoxide is usually effective in the forms of HI where the KATP channel function is intact [4]. Potential side effects of diazoxide may include pulmonary hypertension, edema, hypertrichosis, neutropenia, thrombocytopenia, and hyperuricemia.

A genetic cause is found in approximately 50% of cases of congenital hyperinsulinism with 11 known monogenic forms

currently identified [5]. The most common abnormalities identified are inactivating mutations in ABCC8 and KCNJ11, which encode the ATP-sensitive potassium channel. This accounts for approximately 85% of diazoxide-responsive forms of HI. Mutations in the previously mentioned HNF4A, as well as HNF1A, account for approximately 6% of diazoxide-responsive cases. Prior case series have demonstrated the variability of clinical presentations and outcomes in patients HNF4A mutations, including the association with macrosomia and variable diazoxide requirements and lengths of treatment [6-12]. This case demonstrates a new mutation in HNF4A presenting with diazoxide-responsive congenital hyperinsulinism.

Case Presentation

Patient was a well-appearing Caucasian male infant born at 38 6/7 weeks without consanguinity. His mother was diagnosed with gestational diabetes at 38 weeks of gestation. There was no other known family history of diabetes, though his paternal grandmother was noted to be pre-diabetic. He was large for gestational age (LGA) with a birth weight of 4.1 kg and length of 52.1 cm. During routine point of care (POC) glucose testing after the delivery, he was found to be hypoglycemic in the 20-40 mg/dL range. He was treated with breast milk, formula and D10 intravenous fluids (IVF). The hypoglycemia persisted, and a critical sample was drawn on day of life (DOL) 9 during POC glucose testing of 39 mg/dL that showed a serum glucose of 51 mg/dL, cortisol 12 mcg/dL (normal range >10 mcg/dL), GH 5 ng/mL (normal range >7 ng/mL), beta hydroxybutyrate 0.2 mmol/L (suppressed range <1.8 mmol/L) and insulin 9 mU/mL. He was started on diazoxide at a dose of 9 mg/kg/day. He was clinically stable with no signs of edema, so treatment with hydrochlorothiazide was not started with the diazoxide. His blood sugar started to increase to the 280-300 mg/dL range, so his dose was decreased by 50% at 3 wks of age. The medication was stopped at 4 weeks when his blood sugar was persistently in the 200 mg/dL range. A few days later, his blood sugar decreased again to 50-70 mg/dL, so a low dose of diazoxide (0.3 mg/kg/day) was re-started.

By 5 months of age, he required a diazoxide dose of 2.2 mg/kg/day to maintain his blood sugar in the target range (>70 mg/dL). Due to his persistent hypoglycemia and diazoxide requirement, genetic testing was completed. A gene panel looking at 21 genes associated with HI was completed at Fulgent, which revealed an autosomal dominant heterozygous gene mutation in HNF4A (c.147C>A, p.His49Gln) with unknown clinical significance. This variant is predicted to result in a single amino acid substitution (missense) of His to Gln at codon 49 in exon 2 of the HNF4A gene. Maternal and paternal genetic testing was then completed, which did not reveal any mutations in HNF4A. Thus, this patient has a novel de novo mutation in HNF4A, which was reclassified as likely pathogenic after familial known variant testing, resulting in HI.

The HNF4A gene is located on chromosome 20 and contains 13 exons. This gene encodes nine isoforms. Transcripts HNF4A7-9 are expressed from the pancreatic (P2) promoter and are the only isoforms expressed in the adult pancreas. The largest amounts of mutations in the HNF4A gene have been identified in exons 7 and 8 [13]. Mutations in "HNF4A have been shown to impair protein dimerization and DNA binding, impair the activity of transactivation domains, alter secondary structure and reduce protein stability, disrupt sub-cellular localization and impair translocation from the cytoplasm into the nucleus, inhibit the recruitment of coactivators and other transcriptional activators, and disrupt transcription factor binding sites in promoters" [14]. The reduction in transactivation activity is highly variable between different mutations, which makes predicting the pathogenicity of mutations very difficult. Despite this, some correlations have been made - such as later age of MODY onset with mutations in certain positions. MODY onset occurs by 24 years of age with mutations in exons 2-8, around 40 years of age with mutations in exons 9-10 that do not affect the P2 isoforms HNF4A3, 6, or 9, and around 31 years of age with mutations in the P2 promoter or exon 1D [14]. Since our patient was identified as having a variant predicted to result in an amino acid substitution in exon 2 of the HNF4A gene, we may anticipate the development of MODY by his 20's.

Patient has been monitoring his blood sugar at home, and has required increasing diazoxide dose changes. At 9 months of age, he was receiving 3.4 mg/kg/day. This was increased to 5 mg/kg/day at 13 months of age, 6.8 mg/kg/day at 17 months of age, and most recently 8.5 mg/kg/day at 22 months of age. He has been growing well with weight of 12.3 kg (63%) and length of 85 cm (33%). His gross motor skills are appropriate for his age, but he is not yet forming words. Throughout his treatment course with diazoxide, he did not develop significant persistent side effects, such as edema.

Discussion

This case details a patient with congenital hyperinsulinism due to a novel de novo mutation in HNF4A. His initial hypoglycemia and macrosomia were thought to be related to maternal gestational diabetes mellitus, but the persistence of his hypoglycemia led to diazoxide treatment. His case is unique in that the diazoxide temporarily caused hyperglycemia, leading to discontinuation of this medication. Hypoglycemia resumed and led to re-starting treatment with diazoxide and eventual genetic testing, which led to his diagnosis. Imaging studies of the pancreas were not pursued in this case since mutations in HNF4A are not associated with

focal disease, which could be treated with surgical resection.

Prior case reports have detailed the association between macrosomia and HNF4A mutation carriers [10]. These patients generally develop hypoglycemia within the first 24 hours of life-some requiring treatment with diazoxide, others requiring just intravenous glucose. HNF4A is required in the pancreatic beta cell for the maintenance of normal Kir6.2 mRNA and protein expression and is also a transcriptional activator of the Kir6.2 gene (one component of the KATP channel on pancreatic beta cells) [15]. This explains why HNF4A gene mutations may result in HI in infancy and are responsive to diazoxide treatment. Duration of diazoxide treatment is extremely variable in patients with HNF4A mutations with patients being treated for variable lengths of time - from one month to ongoing at 11 years of age [6,10]. One case series found the average age for discontinuing diazoxide treatment to be around 6.8 years [8]. This information is helpful to have when counseling families of patients with this form of hyperinsulinism so they are aware of how variable the duration of diazoxide treatment can be for this particular gene mutation. Since our patient has a novel HNF4A mutation we cannot predict how long he will require treatment with diazoxide, though as previously stated, he still requires this medication now that he is almost 2 years of age.

Patients with HI due to HNF4A mutations are expected to eventually develop MODY, though the exact mechanism for how the switch from hypoglycemia to hyperglycemia occurs has yet to be elucidated. One study showed patients with hypoglycemia eventually developed diabetes at a mean age of 12.4 years [10]. Due to the variability of this condition, these patients require close clinical follow-up. Our patient continues to monitor his blood sugar at home with diazoxide dose adjustments made to keep his blood sugar in the target range of >70 mg/dL. Long-term follow-up will also be needed and anticipatory guidance provided given his risk of developing MODY, which can then be managed with sulfonylureas. In the future, genetic counseling can also be offered to him, given his offspring will have a 50% risk of inheriting the same genetic mutation due to an autosomal dominant inheritance pattern.

Learning Points/Take Home Messages

- Congenital hyperinsulinism should be considered as a possible diagnosis when persistent hypoglycemia occurs in the newborn period.
- Genetic testing is important as part of the work-up for congenital hyperinsulinism, since this may reveal important information regarding response to treatment.
- Long-term follow-up of patients with congenital hyperinsulinism is essential since some of these patients may be at risk for future medical problems, such as MODY.

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