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Case Report

An Unexpected Cause of Hypoglycemia in a Neonate

Elise Martin, Rebecca Perry, Samuel Bradbrook, Mary Ann Thomas and Paola Luca*

Section of Pediatric Endocrinology, Department of Pediatrics, Alberta Children's Hospital, Calgary, Alberta, Canada

Abstract

Congenital hyperinsulinism (HI) is the most common cause of severe, persistent neonatal hypoglycemia resulting from unregulated secretion of insulin from pancreatic beta-cells. Neonates have diverse clinical presentations including varying genetics, response to medical treatment and need for surgery. Several genetic changes are known to cause congenital HI including *ABCC8, KCNJ11, GLUD1, CGK, SCL16A1* and *HADH*. It has long been known that changes in *HNF1A* and *HNF4A* cause maturity-onset diabetes of the young (MODY 3 and MODY1). More recently, they are also known to cause HI early in life before changing to diabetes later on, the pathophysiology of which is not clear. We report one patient with HI initially thought to be due to gestational diabetes, but after further review of the maternal and family history and investigations, HI was due to a change in *HNF4A*. The purpose of this paper is to increase awareness of a less common genetic cause of HI and when to suspect and test for *HNF4A*-related HI.

Keywords: Congenital hyperinsulinism; HNF4A; Hypoglycemia; Neonate

Case Presentation

A 4-week-old male presented to the Emergency department with feeding intolerance and emesis secondary to a urinary tract infection in association with hypoglycemia. Pediatric endocrinology recommended a diagnostic fast during which his point of care (POC) blood glucose (BG) was 2.7 mmol/L, serum BG of 3.2 mmol/L, insulin 49 pmol/L and negative ketones. Review of his medical history included late prematurity, large for gestational age (LGA), and maternal history of Type 2 diabetes (T2D). He developed hypoglycemia immediately after birth with POC BG of 1.1 mmol/L. Maximum glucose infusion rate was 16 mg/kg/min, and intravenous infusion of glucagon was required for 2 days. Feeds were fortified on day 5 of life. A critical sample showed serum BG 1.2 mmol/L, insufficient sample for insulin, and robust levels of cortisol, growth hormone and free T4. POC BG were normal on oral and nasogastric (NG) feeds at discharge. He was slow to bottle feed. On review of his mother's history, she was diagnosed with T2D 6 years prior based on elevated hemoglobin A1C (HbA1C). She subsequently had a decrease in body mass index. HbA1C since were 5.2-5.4%, without pharmacotherapy. The highest BG during the pregnancy was 10 mmol/L. The maternal grandmother was also reported to have T2D.

Discussion

The patient was diagnosed with hyperinsulinism (HI) and diazoxide and hydrochlorothiazide were started with immediate clinical response. Genetic testing returned positive for a heterozygous maternally inherited variant in the *HNF4A* gene, which encodes the hepatocyte nuclear factor (HNF) 4-alpha protein. This result provided the cause of the patient's congenital HI and is also consistent with a maternal diagnosis of maturity-onset diabetes of the young (MODY), subtype *HNF4A*. Variants in the human *HNF4A* gene are a known cause of MODY, with an autosomal dominant inheritance, resulting from impaired glucose-stimulated insulin release from pancreatic beta-cells [1].

Affected patients can often be treated with lifestyle modifications alone but are also very sensitive to sulfonylureas. Recommended screening includes monitoring for microvascular complications long-term. These variants have also been reported to cause transient and persistent HI associated with macrosomia. A large cohort study of children with HI identified *HNF4A* variants in 2.5% (5 of 204) of diazoxide- responsive patients and reported that the clinical phenotypes were variable. The affected patients were primarily born at term and 40% were LGA. The median age of presentation was 1.1 days although one child presented at 2.3 years with seizure and lethargy; this was the only patient with ketotic hypoglycemia, which the authors postulate could be due to resolving hyperinsulinism. In the 3 patients tested, there was an inappropriate glycemic response to glucagon. All were treated with diazoxide and two were able to stop diazoxide at 4 and 6.9 years. One child developed extra-pancreatic features with hepatomegaly, elevated transaminases at 3 months, and renal Fanconi syndrome at 1 year. None of the patients had developed diabetes mellitus at the time of study's analysis, although there was loss to follow up and the majority were younger than 10 years of age, whereas the mean age of developing diabetes in *HNF4A* is 25 years [2].

Similarly, in a separate cohort of 220 patients with diazoxide responsive HI, 11 or 5% of the patients were found to have a disease-causing variant in *HNF4A*. The majority of patients also showed macrosomia and early onset HI (within the first week of life). All of the patients required diazoxide and the duration ranged from 3 months to continuing at 8 years. One patient developed diabetes by the age of 12.

***Corresponding author:** Paola Luca, Section of Pediatric Endocrinology, Department of Pediatrics, Alberta Children's Hospital, Calgary, Alberta, Canada. Email: paola.luca@ahs.ca

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Interestingly, only 4 of the 11 patients had a parent with diabetes and two parents were found to have the variant but were not affected. The variant was de novo in 4 patients and one parent could not be tested as the child was conceived by ovum donation. Of the 10 genetically affected relatives (including extended family members) in this study, none were diagnosed with neonatal hypoglycemia. This demonstrates the variability in presentation of *HNF4A* variants in childhood, ranging from macrosomia to transient HI to more permanent HI in childhood [3].

The patient continues on diaxozide and hydrochlorothiazide and is wearing a continuous glucose monitor; BG are stable and above 4 mmol/L. He continued to require the support of NG feeds, attributed to poor oral feeding, and underwent a G-tube insertion at 7 months for overnight continuous feeds; he is otherwise primarily feeding orally in the daytime. His development has been normal and will continue to be monitored. The patient's mother is under the care of an adult endocrinologist and her family members were informed of the diagnosis and offered genetic testing. This demonstrates the benefit of an accurate diagnosis of HI in a neonate as it can impact the diagnosis and treatment of parents and extended family members.

Conclusion

Clinicians should explore the maternal and paternal history of diabetes in detail in infants and children presenting with HI. Clinicians should suspect HNF4A-related HI if there is a family history of youth-onset diabetes especially in an autosomal dominant pattern, macrosomia, or transient diazoxide-responsive HI without a clear history of risk factors. Genetic testing should start with the most common causes of HI (KCNJ11 and ABCC8) but if negative, should be followed by testing for other genetic etiologies including HNF4A, even in the absence of a family history of diabetes. A positive result will help inform risk of developing diabetes, its management, monitoring of complications and additional testing for family members.

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Informed Consent

Written informed consent was obtained from the patient's family.

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Potential Conflicts of Interest

The authors have no conflicts of interest to declare.

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