Case Report

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Congenital hyperinsulinism in a newborn presenting with poor feeding

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Abstract

Hyperinsulinemic hypoglycemia is a condition linked to several genetic, metabolic, and growth disorders in which there is dysregulated insulin secretion. In infants, an inappropriately persistent hypoglycemic and hypoketotic state can cause severe brain injury leading to epilepsy, cerebral palsy, and neurodevelopmental disabilities due to the lack of glucose and ketone substrate to serve as fuel for the developing brain. The most common cause of persistent hypoglycemia in neonates and children has been found to be congenital hyperinsulinism. Here, we report a child with a unique presentation, found to have a novel genetic variant as the underlying cause of hyperinsulinism. This case study highlights the importance of maintaining a broad differential and considering a diagnosis of congenital hyperinsulinism in a baby with poor feeding in the newborn period. Recognizing and treating congenital hyperinsulinism is essential to prevent potential neurological sequelae from recurrent, severe hypoglycemia.

Keywords

Diabetes/endocrinology, hyperinsulinism, pharmacoepidemiology/drug safety, poor feeding, women's health

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Introduction

Hyperinsulinemic hypoglycemia (HH) is a rare condition, linked to several genetic, metabolic, and growth disorders, in which there is dysregulated insulin secretion. Normally, pancreatic beta cells regulate serum glucose levels through tight control of insulin secretion. Glucose first enters the beta cell via a GLUT2 transporter and is converted to glucose-6-phosphate via glucokinase. Glucose-6-phosphate acts as the initial substrate for the complex metabolic and biochemical processes that produce ATP. When the ratio of ATP:ADP increases, the ATP-sensitive potassium channel on the cell closes causing depolarization of the cell. This cellular depolarization causes increased intracellular calcium levels, via voltage-gated calcium channels, that result in exocytosis of insulin.[1] There are several other mechanisms that facilitate this intricate mechanism, and any defect in one part may dysregulate the entire insulin secretion process.

Insulin plays a vital role in ensuring glucose homeostasis. When released, it promotes the peripheral consumption of glucose and activation of glycogenesis while also inhibiting glycogenolysis and gluconeogenesis. In addition, insulin upregulates lipogenesis while inhibiting the counterregulatory process of beta-oxidation, which is responsible for the production of ketones. In the case of HH, insulin secretion is inappropriately elevated and results in persistent hypoglycemic and hypoketotic states. In infants, recurrent hypoglycemia may cause severe brain damage, leading to epilepsy, cerebral palsy, and neurodevelopmental impairments due to the lack of glucose and ketone substrate to serve as fuel for the developing brain.[1] The most common cause of persistent hypoglycemia in neonates and children has been found to be congenital hyperinsulinism (CH). Other underlying causes include genetic, metabolic, or growth disorders. The focus of this case report is to explore possible genetic causes of hyperinsulinism that have yet to be studied and highlight the importance of early detection

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Table 1. Critical Sample Results.

Component	Latest reference range and units	8 October 2020
Ammonia	18–72 µmol/L	70
Insulin level	µIU/mL	6.0
Glucose	70–99 mg/dL	40 (L)
Cortisol	µg/dL	5.8
Growth hormone	<OR = 10.1 ng/mL	13.7 (H)
Beta hydroxybutyrate, whole blood	<0.6 mmol/L	0.2

of CH. In addition, this case report highlights the importance of maintaining a broad differential and considering a diagnosis of congenital hyperinsulinism in a baby with poor feeding in the newborn period.[2]

Case report

A 3-day-old ex-full term male presented to the emergency department (ED) with multiple episodes of apnea. He was born appropriate for gestational age (AGA) with a birth weight 3065 g (6 lb 12.1 oz) via normal spontaneous vaginal delivery to a 29-year-old G2P1 mother. Physical examination findings were normal except for caput succedaneum over the posterior scalp. The pregnancy was complicated by maternal polycystic ovarian syndrome that was being treated with metformin during the first trimester of pregnancy. There were concerns for borderline gestational diabetes due to several elevated glucose tolerance tests; however, the diagnosis was never made after a normal 3-h glucose test. Prenatal labs were otherwise notable for Group B Streptococcal infection (GBS), for which adequate antibiotics were provided before an uncomplicated delivery. The initial hospital course was notable for difficulty with breastfeeding and poor milk production on day of life 2. Feeds were supplemented with formula, which was tolerated well, and the mother and baby were discharged home.

At home, the mother noted continued poor feeding, which she attributed to poor colostrum production. Therefore, she continued to supplement with formula. Later that evening, the parents witnessed three apparent apneic episodes characterized as the baby turning ruddy in color and going limp with his eyes rolling back. Each episode lasted approximately 10 seconds and was not associated with feedings. The baby would return to baseline following stimulation. These events prompted the parents to take their son to the ED on day of life 3.

In the ED, the baby's vital signs were stable. A point-of-care glucose was obtained and revealed an undetectable glucose. He was immediately given a Dextrose (D) 10% bolus and started on a D 10% infusion. A repeat glucose of 18 mg/dL resulted in another D 10% bolus and he was placed on a glucose infusion rate of 13.85 mg/kg/min. A sepsis evaluation was initiated due to suspicion for possible infectious causes of hypoglycemia and included a urinalysis, urine culture, blood culture, and empiric treatment with ampicillin and gentamicin. After 48 h, all cultures remained negative and the antibiotics were discontinued. Chest X-ray was normal and did not show any signs of pneumonia. COVID-19 was also negative. A screening complete blood count (CBC) was unremarkable and a comprehensive metabolic panel (CMP) was remarkable for hyperkalemia of 5.9 and hypocalcemia of 7.2. The baby was transferred to the Cedars-Sinai Medical Center (CSMC) neonatal intensive care unit (NICU) for additional evaluation for persistent hypoglycemia requiring high glucose infusion rates. Prior to transport, the baby exhibited normal tone, color, and activity level with an improved blood glucose of 44 mg/dL.

Upon arrival to the NICU, the glucose was 66 mg/dL, and D 12.5% fluids were continued at a rate of 13.85 mg/kg/min. Physical examination demonstrated weight at the 30th percentile (Z=–0.52), length at the 25th percentile (Z=–0.40), and head circumference at the 55th percentile (Z=0.13). He had duplicated earlobes, but physical examination was otherwise unremarkable. After the glucose stabilized for 12 h, the glucose infusion rate was weaned to glucose infusion rate (12 mg/kg/min).

Final diagnosis

Pediatric endocrinology was consulted, and a comprehensive evaluation for persistent hypoglycemia was initiated. Notable critical lab results at the time of hypoglycemia less than 50 mg/dL included serum glucose level of 40 mg/dL, normal ammonia level of 70 µmol/L, a suppressed beta-hydroxybutyrate of 0.2 mmol/L, an equivocal cortisol of 5.8 µg/dL, and a serum insulin level of 6.0 µIU/mL (Table 1), which were consistent with a diagnosis of hyperinsulinism. Of note, a low-dose Adrenocorticotrophic Hormone (ACTH) stimulation test demonstrated a robust cortisol response excluding adrenal insufficiency.

Hospital course

Diazoxide (8 mg/kg/day) and Chlorothiazide (20 mg/kg/day) were subsequently initiated. After 36 h, his glucose infusion rate remained elevated at 11.11 mg/kg/min; therefore, his Diazoxide was increased from 8 to 12 mg/kg/day. Due to his hypoglycemic hyperinsulinemia, medical genetics was consulted, and a chromosomal microarray and CH panel was recommended.

Eight days after starting Diazoxide, he was noted to have intermittent tachypnea with oxygen desaturations to the 80s. Workup included a chest X-ray, which was concerning for pulmonary edema, a known side effect of Diazoxide. Cardiology was consulted and an echocardiogram was obtained revealing a small patent ductus arteriosus and patent foramen ovale with left-to-right shunting, as well as moderately elevated pulmonary artery pressures. Based on these findings, his Chlorothiazide dose was increased to 40 mg/kg/day resulting in the resolution of the pulmonary edema and normal repeat echocardiograms.

The CH gene panel came back negative for mutations in the following genes: *ABCC8, KCNJ11, GCK, GLUD1, HADH, HNF1A, HNF4A, SLC16A1*, and *UCP2*. It is important to note that our gene panel was missing the recently *FOXA2* identified gene involved in CH.[3,4] Interestingly, the chromosome microarray revealed a 1.46 Mb paternally inherited pathogenic duplication of chromosome 17q12 (arr[GRCh37] 17q12(34822465_36283612)×3).

His hyperinsulinism gradually improved, and Diazoxide was titrated down to 1.5 mg/kg/day with a concurrent decrease in Chlorothiazide dose to 20 mg/kg/day. He was discharged home on these doses and was followed closely by pediatric endocrinology and pediatric genetics as an outpatient. Serial cardiac examinations and echocardiograms remained normal, and he was successfully weaned off Diazoxide and Chlorothiazide at 3 months of life.

Discussion

CH presents with persistent hypoglycemia in the newborn and often requires high glucose infusion rates to maintain euglycemia. The diagnosis of CH is made by evaluating various markers of glucose homeostasis during hypoglycemia, most importantly insulin levels and ketone bodies. In order to solidify the diagnosis, other biochemical markers of insulin action can be found, including detectable and sometimes elevated insulin levels, elevated C-peptide, positive glycemic response to a glucagon injection, low fatty acid levels, and low 3-hydroxybutarate levels.[5,6] In our patient, the clinical diagnosis was made based on the infant's persistent hypoglycemia and increased glucose infusion rates up to 20 mg/kg/min coupled with biochemical evidence of inappropriately elevated insulin and low 3-hydroxybutarate during hypoglycemia.

After the diagnosis of CH is made, Diazoxide therapy is often the first line of treatment in conjunction. As pulmonary edema is a well-known side effect of Diazoxide therapy, it is not uncommon to empirically start a diuretic, usually Chlorothiazide. Diazoxide helps activate the pancreatic beta cell potassium channel, which leads to the cascade of hyperpolarizing the cell, closing of the calcium channel, and inhibition of insulin secretion. If a patient is Diazoxide-responsive, they can continue medical therapy. However, in Diazoxide-unresponsive patients, which our patient originally appeared to be, a genetic analysis is warranted.[5]

There are several causes of CH, both genetic and non-genetic, including perinatal distress, Beckwith–Wiedemann syndrome, Turner syndrome, Kabuki makeup syndrome, and congenital disorders of glycosylation.[6,7] However, extensive research has been done linking genetic causes to CH. The genes associated with CH correlate to several components in the pancreatic beta cell that are involved with insulin production. The most common genetic anomaly is a mutation in the *ABCC8* and *KCNJ11* genes, which corresponds to the production of the beta cell potassium ATP channel. These genetic mutations often result in a form of CH that is non-responsive to Diazoxide, since the mechanism of action of the drug is to enhance the opening of non-mutated potassium ATP channels. Other genetic mutations can include abnormalities in beta cell enzymes and transporters, including the *GCK, GLUD1, HADH1, SLC16A1*, and *UCP2* genes, as well as transcription factors, including HNF4A and HNF1A. CH due to these mutations is often responsive to Diazoxide since the defect does not affect the potassium ATP channels on which Diazoxide acts upon.[8]

In our patient, a postnatal chromosomal microarray showed a duplication of 17q12, which is a region that tends to have highly variable clinical manifestations with incomplete penetrance. In approximately 90% of patients with this duplication, it is found to be inherited from a parent who is minimally affected or phenotypically normal. Clinical manifestations include intellectual disabilities ranging from normal to severe disability, speech delay, gross motor delay, seizures, and vision problems. To date, there have been no reports of patients with 17q12 duplications who have CH although a variety of endocrine abnormalities have been observed, including growth hormone deficiency, hypoglycemia, hyponatremia, hypercalcemia, and pseudohypoaldosteronism.[9,10]

Interestingly, the specific 17q12 duplication observed in our patient includes 15 protein coding genes, of which 11 are *OMIM* genes. One gene within this duplicated region is the *HNF1B* gene. It is noteworthy to mention that loss of function mutations in the *HNF1B* gene have been associated with a diagnosis of maturity-onset diabetes of the young type 5 (MODY5).[11]

Conclusion

The purpose of this case report is threefold. First, genetics is an ever-advancing field. Even though extensive research has been done to identify genetic causes of CH, there are likely other causes that have yet to be studied, such as the 17q12 duplication. Second, research in this area is crucial because the outcomes of CH can be detrimental, including brain damage, neurodevelopmental delay, epilepsy, and

insulin-dependent diabetes. A cohort study had shown that it is the frequency of hypoglycemia, rather than the lower glucose levels, that can lead to abnormal magnetic resonance imaging (MRI) in infants with neonatal hypoglycemia. Third, this case report highlights the importance of fully evaluating the "normal newborn" in the well-baby nursery. Poor feeding is common after birth due to a variety of reasons, such as inappropriate latching and poor colostrum production. A broad differential for subtle nuances in the newborn period, such as poor feeding, is important to consider before sending the mother and baby home, as a missed diagnosis can lead to adverse consequences. As a result, we must be cautious: Instead of dismissing a newborn with poor feeding due to poor colostrum production, we may be inclined to evaluate for hypoglycemia as a cause for poor feeding.

In mothers with gestational diabetes, screening for hypoglycemia in the newborn is routinely done. In this case, although there were concerns for gestational diabetes during the pregnancy, the mother never fulfilled full criteria and was never formally diagnosed with diabetes. Throughout the years, there have been several adjustments made in maternal blood glucose cutoff values, which alters the number of pregnant women diagnosed with gestational diabetes and, therefore, changes the number of infants who should be routinely screened for hypoglycemia. This discrepancy in the numbers should warrant hypoglycemia screenings in infants who may not fall under this category and present with subtle symptoms of hypoglycemia, such as poor feeding.

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