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Case Report

Recurrent hypoglycaemic seizures and suppressed ketogenesis in a child with heterozygous ABCC8 mutation: a case of delayed presentation of familial hyperinsulinemia hypoglycemia

S. L. Akhila Swaraj*, A. T. Anirudh

Department of Paediatrics, Vydehi Institute of Medical Sciences and Research Centre, Whitefield, Bangalore, Karnataka, India

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***Correspondence:**
Dr. S. L. Akhila Swaraj,
E-mail: akhila.swaraj@gmail.com

ABSTRACT

Familial hyperinsulinemic hypoglycemia (FHH) is a rare genetic disorder characterized by inappropriate insulin secretion, resulting in persistent hypoglycemia. We report the case of a 3-year-8-month-old girl who presented with recurrent seizure-like episodes following a history of refractory neonatal hypoglycemia. Biochemical evaluation during hypoglycemic episodes revealed inappropriately normal insulin levels and significantly suppressed beta-hydroxybutyrate levels. Genetic analysis identified a heterozygous missense mutation in the ABCC8 gene. This case underscores the importance of recognizing low ketone levels during hypoglycemia as a critical diagnostic clue for hyperinsulinism. It also highlights that heterozygous ABCC8 mutations, traditionally associated with recessive inheritance, can present with clinically significant disease. Early recognition and intervention are crucial to preventing long-term neurodevelopmental impairment.

Keywords: FHH, Persistent hypoglycemia, Refractory hypoglycemia, ABCC8 mutation

INTRODUCTION

Congenital hyperinsulinism (CHI), also known as familial hyperinsulinemic hypoglycemia (FHH), is the most common cause of persistent hypoglycemia in infancy.[1] It results from mutations in genes that regulate insulin secretion, most frequently ABCC8 and KCNJ11, which encode the SUR1 and Kir6.[2] subunits of the pancreatic beta-cell KATP channel, respectively.

Excessive insulin from the pancreas is the main and most serious cause of lasting low blood sugar in babies and young children.[2] These mutations cause unregulated insulin secretion even during fasting, leading to hypoglycemia accompanied by suppressed ketone and free fatty acid levels. Although most cases present in the neonatal period, a delayed or biphasic presentation may occur in certain genotypes, especially those with partial sensitivity or heterozygous variants. The disease occurs in approximately 1 in 50,000 newborns[3]. We report a case of FHH in a child with a heterozygous ABCC8 mutation who returned with recurrent hypoglycemic seizures around the age of 4, highlighting the importance of long-term follow-up and the diagnostic significance of inhibited ketogenesis.

CASE REPORT

A 3-year-8-month-old girl, born to non-consanguineous parents, presented with stereotypical episodes of behavioral arrest, limb stiffening, and postictal confusion lasting 1–2 minutes, occurring every 7–10 days. Capillary blood glucose (CBG) measured during these episodes ranged between 30–50 mg/dl. She had a significant

neonatal history of refractory hypoglycemia requiring NICU admission for 22 days. Her birth weight was 4.65 kg. During the neonatal period, she experienced convulsions and was treated for late-onset sepsis. There was no family history of endocrine or metabolic disorders.

Developmentally, she exhibited delays in gross motor and language milestones. Her weight and height were between the 3rd and 10th percentiles, and her head circumference measured 46 cm (−2 to −3 SD). She appeared toxic during episodes, but systemic examination and physical features were otherwise unremarkable.

Investigations

Biochemical and endocrine evaluation

Parameter result reference range

CBG during episode- 30–50 mg/dl (>70 mg/dl), C-peptide- 0.66 ng/ml (0.8–3.8 ng/ml), Fasting insulin 2.79 µU/ml (<3 µU/ml) (inappropriately normal during hypoglycemia). Beta-hydroxybutyrate 0.11 mmol/l (>0.6 mmol/l during fasting), Cortisol 15.1 µg/dl (Normal), Ammonia- 55 µmol/l (Normal).

Urinalysis

Glucose and ketones present, Glycosuria uncommon in normal fasting,

CBC

Microcytic hypochromic anemia. The key biochemical findings included:

Hypoglycemia with inappropriately normal insulin and C-peptide levels.

Suppressed ketogenesis, with very low beta-hydroxybutyrate. Normal cortisol, ammonia, and absence of metabolic acidosis Genetic testing with next-generation sequencing revealed a heterozygous missense variant in exon 4 of the ABCC8 gene, confirming the diagnosis of familial hyperinsulinemic hypoglycemia.

Management

Acute management involved intravenous dextrose to maintain euglycemia and glucagon for severe episodes. Long-term management included- Nutritional therapy with frequent, carbohydrate-rich feeds, Initiation of diazoxide, a KATP channel opener.

Neurodevelopmental surveillance due to prior seizures, Surgical intervention (near-total pancreatectomy) was not required as the child responded to medical management.

The Table shows awareness about the care taking of wound shows cleaning with water 79 (54.8%), cleaning with water and soap 64 (44.4%).

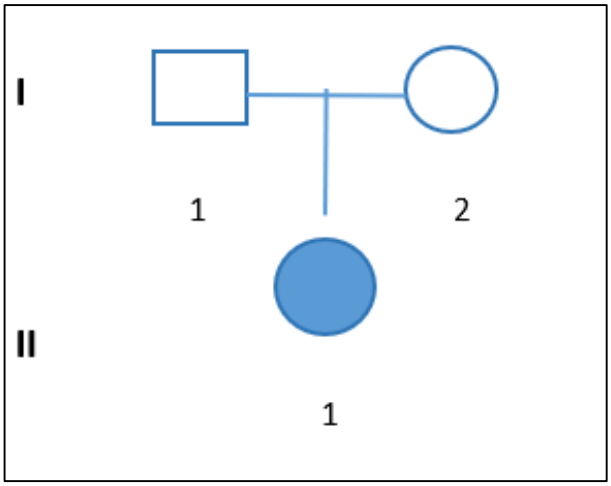

Figure 1: Lineage map. I-1Father: normal phenotype, I-2-. Mother: normal phenotype, II-1-Proband: Macrosmia and hypoglycemia, c 563G>G and (c) (3753+1-3754-1) (4411+1_4412-1) del.

Table 1: Investigations.

Investigations	Results
CBC	
Haemoglobin	10.5 gm/dl
White blood count	11,190 cells/microl
Differential count	N- 51.2%, L-38.3%, M- 4.5%
Platelet count	2.31 lakh/microl
Peripheral Smear	Microcytic hypochromic Anemia
Biochemical testing	
C-peptide	0.66 ng/ml
Fasting insulin	2.79 µU/ml
Beta-hydroxybutyrate	0.11 mmol/l
Cortisol	15.1 µg/dl
Ammonia	55 µmol/l

Continued.

Investigations	Results
Urine routine/ microscopy	
pH	6.5
Specific gravity	1.005
Colour	Pale yellow
Nitrite/leukocyte	Negative
Haemoglobin	0.75 mg/dl
Epithelial cells	0-1/HPF
Neutrophils	1-2/HPF
Erythrocytes (RBCs)	Nil
Ketones	+
Glucose	++
Genetic testing	
Next-generation sequencing	Heterozygous missense variant

DISCUSSION

This case exemplifies a delayed presentation of Familial Hyperinsulinemic Hypoglycemia (FHH), with symptomatic recurrence nearly four years after an initial neonatal diagnosis. Congenital hyperinsulinism (CHI) is characterized by inappropriate insulin overproduction and impaired regulation of blood glucose, leading to persistent and treatment-resistant hypoglycemia in infants and young children, which can result in permanent brain damage.[5] While CHI typically presents in the neonatal period, delayed or biphasic manifestations can occur, particularly in children with heterozygous mutations or partially responsive forms of the disease.

A central diagnostic clue in this case was the suppressed ketogenesis during hypoglycemia, evidenced by markedly low beta-hydroxybutyrate levels. This finding is characteristic of hyperinsulinemia and helps differentiate FHH from other causes of hypoglycemia, such as ketotic hypoglycemia, glycogen storage disorders, or fatty acid oxidation defects. Diffuse disease, which involves all pancreatic β-cells, comprises about 60% of cases and is caused by either biallelic recessive mutations or partial monoallelic dominant mutations in ABCC8 or KCNJ11.[5] Mutations in the ABCC8 gene are the most frequent cause of the disease, accounting for approximately 40% of cases, while KCNJ11 gene mutations contribute less frequently.[3]

Though FHH is traditionally considered an autosomal recessive condition, this case supports the growing evidence that heterozygous ABCC8 mutations can have pathogenic potential, likely due to variable expressivity or dominant-negative effects. Potassium channel defects are often refractory to medical therapies, with near-total pancreatectomy typically indicated; however, as seen in this case, genetic mutations causing metabolic dysregulation within the beta-islet pancreatic cells are often responsive to medical therapy.[4] The absence of consanguinity further emphasizes the need for a high index of suspicion in all children with unexplained hypoglycemia.

Mutations in the ABCC8 gene are also associated with the development of type 2 diabetes, which some members of the patient's family are experiencing. It is possible that these mutations are inherited within the family. Genetic screening can aid not only in selecting appropriate medical and surgical treatments but also in guiding both prenatal and postnatal care.[5]

CONCLUSION

This case highlights key insights into Familial Hyperinsulinemic Hypoglycemia (FHH), demonstrating that delayed recurrence of hypoglycemia can mimic seizure disorders in older children. Suppressed ketogenesis during hypoglycemia is a critical diagnostic marker for hyperinsulinism and should be routinely evaluated. Even a heterozygous ABCC8 mutation can lead to significant disease, broadening the phenotypic spectrum of FHH, with recurrent hypoglycemic seizures and developmental delay.

The case underscores the variability in treatment responses, with some mutations responsive to diazoxide and dietary interventions, while others may require near-total pancreatectomy. Early diagnosis, long-term monitoring, and genetic evaluation are essential for personalized care to prevent neurological damage. This case advances our understanding of congenital hyperinsulinism, highlighting the need for genetic screening and prenatal diagnosis to guide timely intervention and improve outcomes.

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