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Recurrent Hypoglycaemia in a 7-Year-Old with Genetically Complex, Diazoxide-Responsive Congenital Hyperinsulinism

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Abstract

Background:
Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in children, most frequently caused by pathogenic variants in *ABCC8* or *KCNJ11*, encoding subunits of the pancreatic KATP channel (1,3).

Case presentation:
A previously healthy 7-year-old boy presented with recurrent early morning hypoglycaemia associated with lethargy, sweating and confusion. Biochemical evaluation confirmed hyperinsulinaemic hypoglycaemia with suppressed ketones and free fatty acids. He responded completely to diazoxide, indicating functional KATP channel involvement. Whole-exome sequencing identified no clearly pathogenic variants but several variants of uncertain significance (VUS) in *ABCC8*, *KCNJ11*, and *HNF1A*, including a homozygous deep intronic variant (*ABCC8*: c.2256-50T>C) potentially affecting splicing (2,3).

Outcome:
The patient achieved full remission with diazoxide therapy, frequent carbohydrate intake, and bedtime cornstarch supplementation.

Conclusion:
This case illustrates the diagnostic complexity of CHI with multiple VUS and highlights the clinical utility of diazoxide responsiveness as a functional marker of KATP channel dysfunction. Functional studies of deep intronic variants and polygenic interactions remain essential for accurate molecular diagnosis (2,3).

Keywords

Congenital hyperinsulinism; ABCC8; KCNJ11; diazoxide-responsive hypoglycaemia; whole-exome sequencing; variants of uncertain significance

Background

Congenital hyperinsulinism (CHI) is the leading cause of persistent hypoglycaemia in neonates and children (3). It results from inappropriate insulin secretion despite low plasma glucose levels, most often due to mutations in *ABCC8* and *KCNJ11*, encoding the SUR1 and Kir6.2 subunits of the pancreatic ATP-sensitive potassium (KATP) channel (3). Dysfunction of this channel causes unregulated insulin release and recurrent hypoglycaemia.

Although typically monogenic, CHI can arise from genetically complex mechanisms. Variants of uncertain significance (VUS) in CHI-related genes pose diagnostic and therapeutic challenges (1). We report a diazoxide-responsive case of recurrent childhood hypoglycaemia with multiple VUS identified on exome sequencing.

Case Presentation

Patient Information

A 7-year-old boy (weight 22 kg; 10th percentile) presented with recurrent early morning episodes of lethargy, confusion and sweating for three months. Two episodes involved transient loss of consciousness with plasma glucose <40 mg/dL.
He was born full term with normal growth and development. Family history was unremarkable, and there was no consanguinity.

Clinical Findings

The child was alert, well nourished, and haemodynamically stable. Growth parameters were normal. No hepatosplenomegaly or neurological abnormalities were detected.

Investigations

Critical sample during hypoglycaemia (plasma glucose 36 mg/dL):

- Insulin: 7 µU/mL (inappropriately detectable)
- C-peptide: 2.1 ng/mL
- β-hydroxybutyrate: suppressed
- Free fatty acids: suppressed
- Cortisol and growth hormone: normal
- Liver enzymes, ammonia, lactate: normal
- Urine toxicology: negative

Fasting study: symptomatic hypoglycaemia after 8 hours with detectable insulin and suppressed ketones, consistent with endogenous hyperinsulinism (3).

Abdominal ultrasound: no pancreatic focal lesion.

Genetic Testing

Whole-exome sequencing (DNAGTxLAB FZ LLC, Dubai) revealed:

Gene	Variant	Zygosity	Predicted effect	Classification	Source
ABCC8	c.2256-50T>C	Homozygous	Deep intronic, possible splicing alteration	VUS	(2,4,5)
KCNJ11	c.801C>G (p.Leu267Leu)	Heterozygous	Synonymous, possible splicing impact	VUS	(1,4)
ABCC8	c.1947G>A (p.Lys649Lys)	Heterozygous	Synonymous	Likely benign	(4)
HNF1A	c.864G>C (p.Gly288Gly)	Heterozygous	Synonymous	Likely benign	(4)

No pathogenic or likely pathogenic variants were identified. The homozygous *ABCC8* intronic variant near a splice acceptor site was considered the most plausible contributor to disease (2).

Differential Diagnosis

- Congenital hyperinsulinism (KATP-channel type)
- Fatty acid oxidation disorder (excluded biochemically)
- Cortisol or GH deficiency (excluded)
- Exogenous insulin or sulphonylurea exposure (excluded)

Treatment

Diazoxide 8 mg/kg/day was commenced, with hydrochlorothiazide to prevent fluid retention. Dietary management included frequent meals and uncooked cornstarch at bedtime.

Outcome and Follow-Up

Within four weeks, hypoglycaemic episodes resolved completely. Fasting tolerance improved, and the patient remained symptom-free at six-month follow-up. Growth and neurodevelopment were normal. Family segregation analysis and RNA studies are planned to assess variant pathogenicity.

Discussion

This diazoxide-responsive CHI case demonstrates genetically complex aetiology with multiple VUS in *ABCC8* and *KCNJ11*. The biochemical signature—detectable insulin, suppressed ketones and free fatty acids, and diazoxide responsiveness—indicates KATP channel dysfunction (3).

The deep intronic *ABCC8* variant (c.2256-50T>C) may alter pre-mRNA splicing, similar to previously described non-coding *ABCC8* mutations causing CHI (2). However, confirmation requires RNA or minigene functional assays. The coexistence of additional synonymous variants raises the possibility of oligogenic or modifier effects (3).

Current ACMG-AMP guidelines classify such variants as "uncertain significance" pending further evidence (1). This case underscores the diagnostic limitations of exome sequencing alone and supports integrating clinical, biochemical, and therapeutic response data for variant interpretation.

Diazoxide responsiveness remains a valuable bedside indicator of KATP channel functionality and helps guide management when genetic results are inconclusive (3).

Learning Points

- Persistent or recurrent hypoglycaemia in children should prompt evaluation for CHI.
- Suppressed ketones and free fatty acids during hypoglycaemia indicate hyperinsulinaemic physiology.
- Absence of pathogenic variants on sequencing does not exclude CHI, particularly when non-coding or synonymous variants are present.
- Diazoxide responsiveness provides a practical clinical clue to KATP channel–related CHI.
- Functional assays and family studies are essential to reclassify variants of uncertain significance.

Patient's Perspective

"I used to feel dizzy and sleepy in the mornings. After starting the medicine and eating snacks before bed, I haven't had any more episodes. I feel normal again." — Patient (via parent)

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