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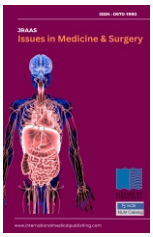

*Case Report*

**Section: Obstetrics & Gynecology**

# Congenital Hyperinsulinaemic Hypoglycaemia

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## HIGHLIGHTS

- Congenital hyperinsulinism causes persistent hypoglycaemia.
- ABCC8, KCNJ11 mutations commonly implicated.
- Neonate presented with recurrent seizures.
- Diazoxide achieved stable glycaemic control.
- ABCC8 VUS complicates genetic interpretation.

**Key Words:**
Congenital hyperinsulinism
*ABCC8* gene
Variant of uncertain significance (VUS)
Neonatal hypoglycaemia
Diazoxide responsiveness
Genetic counselling

## ABSTRACT

**Background:** Congenital hyperinsulinism (CHI) is the leading cause of persistent hypoglycaemia in neonates and infants. It is most often associated with *ABCC8* and *KCNJ11* mutations, and early recognition is vital to prevent neurodevelopmental sequelae. Although genetic testing has improved diagnosis and management, the detection of variants of uncertain significance (VUS) presents challenges for interpretation and counselling. **Case Presentation:** We describe a male neonate, delivered at 36 weeks by emergency cesarean section for oligohydramnios and abnormal CTG. Soon after birth, he developed respiratory distress requiring NICU admission and ventilatory support. During his stay, he experienced recurrent hypoglycaemic seizures. Biochemical evaluation confirmed hyperinsulinaemic hypoglycaemia. He was treated with diazoxide and hydrochlorothiazide, achieving good glycaemic control. Clinical exome sequencing revealed a heterozygous *ABCC8* variant (c.4078G>A; p.Val1360Met), classified as a VUS, associated with leucine-sensitive hypoglycaemia of infancy. **Discussion & Conclusion:** This case highlights the clinical relevance of integrating genetic results with phenotype and therapeutic response in CHI. The identification of an *ABCC8* VUS underscores the limitations of current genetic interpretation and the importance of careful follow-up. Preconception counselling, family testing, and ongoing variant reclassification are critical to guide recurrence risk and optimize future pregnancy outcomes.

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## INTRODUCTION

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in neonates and infants, characterized by inappropriate insulin secretion despite low plasma glucose concentrations [1]. Although rare, it is regarded as the most severe form of neonatal hypoglycaemia due to its potential to cause irreversible neurological sequelae if not promptly recognized and treated. The reported incidence is approximately 1:28,000–1:50,000 live births in Western populations, but in regions with high consanguinity, prevalence may be as high as 1:2,500 [2]. Such epidemiological variation highlights the genetic basis of CHI and underscores the role of preconception genetic counselling in high-risk populations, where early identification of carrier status can inform reproductive decision-making and reduce recurrence risk [3].

Glucose is the principal energy substrate for the developing brain, and even brief episodes of hypoglycaemia can result in neuroglycopenia. Recurrent or prolonged hypoglycaemia is associated with seizures, developmental delay, epilepsy, and long-term neurocognitive impairment [1,4]. Early recognition is often challenging because neonatal symptoms are subtle and nonspecific, necessitating proactive monitoring in infants with a family history of CHI or known carrier status. Counselling before conception or pregnancy enables families to anticipate inheritance patterns and seek early neonatal screening, facilitating rapid intervention [3].

Molecular genetics has transformed the understanding of CHI. Pathogenic variants in *ABCC8* and *KCNJ11*, encoding the two subunits of the pancreatic K ATP channel, are the most common causes [2]. These mutations disrupt channel activity, leading to inappropriate β-cell depolarization and unregulated insulin secretion. However, detection rates vary, and newer mechanisms continue to emerge, including mutations in *GLUD1* and *HADH*, as well as regulatory noncoding variants such as those in HK1 that expand the genetic spectrum [5]. Moreover, genetic testing often yields variants of uncertain significance (VUS), which complicate both diagnosis and counselling. Case reports of infants with mosaic ABCC8 VUS illustrate that clinical management cannot be delayed while awaiting reclassification, and immediate therapy should be based on phenotype [6]. Families must be counselled in advance that inconclusive results may occur and that such variants require functional studies, segregation analysis, and periodic re-evaluation for reclassification [5,7].

Management of CHI requires balancing medical therapy with surgical options. Initial stabilization typically involves intravenous glucose infusion, while diazoxide remains the only licensed first-line pharmacological agent [1]. Its efficacy depends on intact K ATP channel function, and resistance is common in K ATP channel mutations. Somatostatin analogues and calcium channel blockers can be used when diazoxide fails, though with variable success. In a large multicenter cohort, diazoxide was prescribed in over 80% of patients, somatostatin analogues in 16%, and calcium channel blockers in fewer than 2%; the mean time to remission exceeded four years [8].

Long-term outcomes in CHI are heterogeneous. Conservatively treated patients may achieve normal development, yet a significant proportion experience motor, speech, or cognitive delays [9]. Early recognition, strict metabolic control, and integration of family-based genetic evaluation are critical to optimizing prognosis. Beyond clinical aspects, families face major psychosocial and economic burdens, including anxiety about recurrent hypoglycaemia, frequent hospitalizations, and uncertainty about future offspring [3,10].

In summary, despite progress in genetics, imaging, and therapy, CHI remains a complex disorder. Integrating preconception genetic counselling and transparent communication about VUS is central to modern management, ensuring families make informed reproductive choices while clinicians deliver timely, individualized care to minimize neurological sequelae.

## REVIEW OF LITERATURE

Velde et al., 2025 analysed 98 probands with suspected CHI across Norway over two decades and identified pathogenic or likely pathogenic variants in 60% of cases, with ABCC8 mutations being most frequent. Importantly, the study also reported heterozygous dominant variants associated with milder, later-onset hypoglycaemia and several novel variants whose clinical significance was uncertain. This highlights how genetic testing not only confirms diagnosis but also stratifies severity and guides long-term expectations for families. For genetic counselling, the data emphasize that carrier status may not always translate into severe disease but still carries recurrence risk, making preconception counselling critical to inform reproductive choices and family planning [11].

Sanders et al., 2025 presented two detailed family case vignettes illustrating how preconception and reproductive counselling can influence family outcomes. In one family, delayed identification of an ABCC8 variant meant that the parents were unaware of recurrence risk, resulting in multiple affected children. The authors argue that genetic testing should not end with the proband but should extend to parents and siblings, ideally before future pregnancies, to enable informed reproductive decisions. They stress that families must be counselled about inheritance patterns (recessive vs dominant) and the distinction between focal and diffuse disease, since this directly impacts recurrence risk and management strategies. This reference powerfully underscores the preventive value of preconception counselling in CHI [3].

Bennett et al., 2025 identified novel noncoding cis-regulatory variants in HK1 in patients with otherwise genetically unexplained CHI. These regulatory variants disrupted normal

gene silencing in β-cells, leading to inappropriate HK1 expression and hypoglycaemia. Such findings expand the mutational spectrum beyond coding exons, meaning that standard sequencing may miss clinically relevant lesions. These variants often fall into the VUS category until functional assays confirm pathogenicity. The study highlights the importance of broad genetic evaluation and research-level testing in unsolved cases, and for counselling, it underscores the message that a "negative" genetic test does not eliminate hereditary risk. Families should be counselled that future pregnancies may still be at risk even if only a VUS or noncoding variant is identified, reinforcing the value of updated testing and research collaboration[5].

Bell-Sambataro et al., 2024 described an infant presenting with recurrent hypoglycaemia who was found to have a de novo mosaic ABCC8 variant of unknown significance (VUS). Although the genetic classification was uncertain, the clinical and biochemical profile was highly consistent with CHI, and the patient initially responded to diazoxide therapy. This case illustrates the clinical dilemma of VUS in CHI: while genetic confirmation aids in diagnosis, uncertain variants cannot delay life-saving treatment. The authors highlight the importance of family studies, functional assays, and ongoing reclassification of VUS, while clinicians must base immediate decisions on phenotype. This report demonstrates how VUS must be interpreted cautiously but pragmatically in clinical practice[6].

Rosenfeld et al., 2019 reviewed the spectrum of genetic causes of CHI and noted that in a substantial proportion of patients, variants remain unclassified (VUS) or no mutation is found. They stressed the limitations of current testing, particularly in detecting deep intronic or regulatory variants. The review advocates for segregation analysis, in vitro functional studies, and longitudinal re-evaluation of uncertain variants, as many VUS may later be reclassified. From a counselling perspective, families must be informed pre-test about the possibility of inconclusive results, and post-test about the uncertainty a VUS carries avoiding both false reassurance and undue alarm. This highlights the need for genetic counsellors to prepare families for indeterminate outcomes and explain follow-up strategies [12].

Together, these references emphasize that genetic counselling in CHI must begin before conception, especially in high-risk populations, to clarify inheritance patterns and recurrence risk. At the same time, the increasing detection of variants of unknown significance requires transparent counselling, careful integration of clinical and biochemical data, and readiness to adapt management as variant classification evolves. This dual focus ensures both accurate reproductive planning and optimal real-time clinical care.

## CASE PRESENTATION

A 28-year-old primigravida was admitted at 36 weeks of gestation with oligohydramnios (amniotic fluid index 5). Her antenatal course was otherwise uneventful apart from treated hypothyroidism. In view of a category 3 cardiotocograph (CTG), she underwent an emergency lower segment cesarean section.

The neonate was delivered with a birth weight of 2.67 kg. The baby cried immediately after birth, with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. Soon after delivery, the infant developed respiratory distress (Silverman–Anderson score 3) and was admitted to the neonatal intensive care unit (NICU). He was initially managed with continuous positive airway pressure, followed by mechanical ventilation for one week in the setting of septic shock requiring inotropic support.

During the NICU stay, the baby experienced recurrent hypoglycaemic seizures. Biochemical evaluation confirmed hyperinsulinaemic hypoglycaemia. The infant was started on diazoxide and hydrochlorothiazide, with subsequent clinical improvement. He remained under regular endocrinology follow-up.

Exome sequencing revealed a heterozygous ABCC8 gene variant of uncertain significance (VUS), c.4078G>A (p.Val1360Met), associated with familial hyperinsulinaemic hypoglycaemia type 1 and leucine-sensitive hypoglycaemia of infancy. No significant copy number variations (CNVs) were detected. Based on clinical presentation, biochemical findings, and genetic results, a diagnosis of congenital hyperinsulinaemic hypoglycaemia, leucine-sensitive type was made.

The child continues on diazoxide and hydrochlorothiazide therapy with stable glycaemic control and regular developmental monitoring under paediatric endocrinology care.

## DISCUSSION

Congenital hyperinsulinism (CHI) is the leading cause of persistent and severe hypoglycaemia in neonates and infants, and prompt recognition is crucial to prevent long-term neurological sequelae such as developmental delay, epilepsy, and intellectual impairment [1]. The disorder is genetically heterogeneous, with more than a dozen implicated genes including ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF1A, HNF4A, UCP2, HK1, PGM1, PMM2, and FOXA2 [2,12]. Among these, *ABCC8* mutations are most frequently encountered, accounting for nearly 50–60% of molecularly diagnosed cases[13].

Our patient's exome sequencing identified a heterozygous ABCC8 variant (c.4078G>A; p.Val1360Met), reported as a variant of uncertain significance (VUS). While ABCC8 is a well-established CHI gene, the uncertain pathogenicity of this particular variant illustrates a major limitation of current genetic testing: the frequent detection of variants lacking sufficient evidence for definitive classification [6,11]. Such results necessitate careful integration of genetic findings with clinical

management. In our case, the patient's responsiveness to diazoxide was reassuring, supporting a conservative therapeutic approach and avoiding invasive interventions.

Recent advances in molecular diagnostics have revolutionized the management of CHI, enabling rapid identification of mutations predictive of diazoxide responsiveness, differentiating focal from diffuse disease, and guiding surgical decision-making [8]. Similarly, $^{18}$F-DOPA PET/CT imaging plays a pivotal role in localizing focal pancreatic lesions, permitting targeted resection with curative intent [14]. Nevertheless, nearly half of CHI patients remain without a definitive genetic diagnosis or present with a VUS, highlighting the need for functional validation studies, segregation analysis, and collaborative genotype–phenotype registries[5].

The detection of a VUS also has implications for genetic counselling and reproductive planning. Families must be informed that a VUS neither confirms nor excludes disease and may be reclassified as pathogenic or benign with emerging evidence [7]. Counselling should emphasize inheritance patterns, recurrence risk, and the importance of parental testing. Preconception counselling and prenatal diagnosis are particularly relevant in high-risk families, providing reproductive options such as preimplantation genetic testing and ensuring preparedness for neonatal monitoring in subsequent pregnancies [3].

Reports from India provide additional context. Goel et al. described a term infant with a paternally inherited *ABCC8* splicing variant, where imaging suggested diffuse disease despite genetic prediction of focal CHI, ultimately managed medically with diazoxide and octreotide [15]. An OAText review reported an Indian case with a heterozygous *ABCC8* p.(Gly111Arg) mutation, in which $^{18}$F-DOPA PET confirmed a focal lesion requiring tailored management [16]. More recently, Handu et al. documented a diazoxide-unresponsive case with an ABCC8 missense mutation (p.Ser1385Cys), successfully stabilized on combined medical therapy over nine months [17]. These reports underscore the heterogeneity of ABCC8 mutations in Indian patients, the variability in diazoxide responsiveness, and the indispensable role of genetic counselling in family management.

Taken together, our case highlights both the strengths and limitations of current CHI diagnostics. While genetic sequencing provides important clues, the presence of a VUS requires cautious interpretation. Integration of molecular findings with clinical phenotype, advanced imaging, therapeutic response, and structured genetic counselling remains the cornerstone of individualized CHI care.

## CONCLUSION

Congenital hyperinsulinism remains a significant neonatal challenge with high risk of neurological sequelae if not promptly treated. *ABCC8* is a well-established CHI gene, but the heterozygous variant detected in our patient was reported as a VUS, underscoring the limitations of genetic interpretation. Careful clinical correlation and long-term follow-up are essential in such cases. Genetic counselling including preconception counselling should be offered to families to clarify recurrence risk, guide reproductive decisions, and improve outcomes in future pregnancies.

## ABBREVIATION

**CHI**: Congenital Hyperinsulinism
**VUS**: Variant of Uncertain Significance
**NICU**: Neonatal Intensive Care Unit
**CTG**: Cardiotocography
**ABCC8**: ATP Binding Cassette Subfamily C Member 8

## LIMITATIONS & FUTURE PERSPECTIVES

The study was limited by its single-centre design, relatively small sample size, and short duration, which may restrict generalizability. Future research could focus on multicenter studies with larger cohorts to validate findings, evaluate long-term outcomes, and explore innovative diagnostic and management strategies for appendicular perforation, improving patient prognosis and reducing complications.

## CLINICAL SIGNIFICANCE

Timely detection and management of acute appendicitis are crucial to prevent perforation, reducing morbidity and mortality. The study identifies high-risk groups, such as males and individuals at age extremes, highlighting the need for targeted preventive strategies and clinical vigilance. Delayed presentation significantly increases perforation risk, underscoring the importance of early healthcare access and awareness campaigns. Postoperative complications, including surgical site infections and prolonged ileus, emphasize the need for thorough preoperative risk assessment and tailored postoperative care. Recognizing the distal third of the appendix as the most common perforation site aids surgeons in effective intraoperative planning and management.

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## AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation.

They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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**CONFLICT OF INTEREST**

Authors declared that there is no conflict of interest.

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All necessary consent & approval was obtained by authors.

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**DATA AVAILABILITY**

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

**USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)**

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

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