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Case Report

A 13-Year-Old Girl with Congenital Hyperinsulinemic Hypoglycemia Due to an *ABCC8* Mutation and Recent Onset of Diabetes Mellitus: A Case Report and Literature Review

Kantzavelou A et al. Dual Phenotype in *ABCC8* Mutation: Hypoglycemia and Diabetes

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What is already known on this topic?
Congenital hyperinsulinism (HI) is most commonly caused by inactivating mutations in the *ABCC8* and *KCNJ11* genes, leading to dysregulated insulin secretion and persistent hypoglycemia in infancy and childhood.
Individuals with KATP channel gene mutations may develop diabetes mellitus later in life, although this progression is more commonly documented in adulthood.

What this study adds?
We report the first documented case of the *ABCC8* p.Gly716Asp variant associated with the transition from congenital hyperinsulinism to insulinopenic diabetes mellitus during adolescence.
This case expands the phenotypic spectrum of *ABCC8*-related disease and underscores the importance of long-term metabolic follow-up in patients with KATP channel mutations, as early hyperinsulinism may evolve into late-onset diabetes.

Abstract
Congenital hyperinsulinism (HI) is the most prevalent cause of persistent hypoglycemia in infancy and childhood and comprises a heterogeneous group of genetic disorders affecting insulin secretion. The most common etiology involves inactivating mutations in the *ABCC8* and *KCNJ11* genes, which encode the SUR1 and Kir6.2 subunits of the pancreatic β-cell ATP-sensitive potassium (KATP) channel. Variants in these genes are associated with a broad phenotypic spectrum, ranging from asymptomatic macrosomia and mild diazoxide-responsive disease to severe, persistent hyperinsulinemic hypoglycemia unresponsive to medical therapy. In some individuals, the clinical course may evolve over time, with progression from early hyperinsulinism to impaired glucose regulation and eventual diabetes mellitus. We describe a 13-year-old girl with diazoxide-unresponsive congenital hyperinsulinism caused by a heterozygous de novo *ABCC8* variant (c.2147G>A, p.Gly716Asp) who later developed insulin-deficient diabetes mellitus. She was treated with octreotide from 2 months until 7 years of age, when therapy was discontinued after gradual remission of hypoglycemia. At 11 years, evaluation revealed impaired fasting glucose and impaired glucose tolerance, and glibenclamide was initiated. After being lost to follow-up, she presented at 13 years with hyperglycemia and was diagnosed with antibody-negative, insulin-deficient diabetes mellitus. Basal insulin therapy led to progressive normalization of glycemic levels. To our knowledge, this is the first report linking the *ABCC8* p.Gly716Asp variant to transition from congenital hyperinsulinism to adolescent-onset diabetes, underscoring the phenotypic continuum of ABCC8-related disorders and the necessity for lifelong metabolic surveillance.
Keywords: congenital hyperinsulinism, diabetes mellitus, dominant inheritance, *ABCC8* gene

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Introduction

Congenital hyperinsulinism (HI) represents the most common cause of persistent hypoglycemia in infants and children[1]. HI is most frequently linked to inactivating mutations in the *ABCC8* or *KCNJ11* genes, which are located on chromosome 11p15.1 in close proximity to each other[1,2]. They encode the sulfonylurea receptor 1 (SUR1) and Kir6.2 proteins, respectively, which together constitute the hetero-octameric β-cell plasma membrane adenosine triphosphate-sensitive potassium (KATP) channel in pancreatic β-cells[1]. KATP channels are vital for regulating insulin secretion in pancreatic β-cells, maintaining blood glucose levels within a tight range of 3.5–5.5 mmol/L (63-99 mg/dL)[3,4]. Low glucose keeps these channels open, while higher circulating glucose levels (eg. after a meal) increase ATP production within the pancreatic β-cells leading to KATP channel closure, with ensuing membrane depolarization and calcium influx, which in turn triggers insulin release through granule exocytosis[3,4].
Depending on the type of mutation and the resultant dysfunction of the KATP channel, HI or monogenic diabetes can develop, presenting during the neonatal period, childhood or even in adulthood[5–8]. More specifically, HI occurs when KATP channels are either absent from the cell membrane or fail to close in response to low glucose concentrations. In contrast, diabetes develops when KATP channels remain abnormally open despite elevated blood glucose levels, leading to defective insulin production[4,5].
KATP mutations are inherited either dominantly or recessively[1,2]. Individuals with dominant mutations in the KATP channel genes, *ABCC8* and *KCNJ11*, can present with a wide spectrum of phenotypes ranging from asymptomatic macrosomia and mild diazoxide-responsive HI to severe, persistent hyperinsulinemic hypoglycemia (HH)[6,7]. Neonatal-onset HI followed by progression to diabetes later in life has been documented in patients with heterozygous inactivating variants in the *HNF4A* and *HNF1A* genes[9–11], as well as in a number of cases with inactivating variants in the *ABCC8* and *KCNJ11* genes[4,7,10–19].

We describe a case of a female, who initially presented with HI due to a *de novo* heterozygous variant in *ABCC8* gene and at the age of 13 years, developed insulinopenic diabetes. This case represents a rare example of HI progression to diabetes mellitus during adolescence, emphasizing the importance of long-term follow-up for individuals with *ABCC8* gene variants. Routine monitoring, including periodic oral glucose tolerance tests (OGTT), is essential for the early detection and effective management of potential diabetes onset.

Case presentation

A 13-year-old girl with a known history of diazoxide-unresponsive HI due to a a *de novo* heterozygous inactivating *ABCC8* gene pathogenic variant, c.2147G>A, p.Gly716Asp) was admitted to the Pediatric Department of the University Hospital of Ioannina, Ioannina, Greece for the initiation of basal insulin therapy due to persistent hyperglycemia.

The patient's history dates back to the neonatal period when, at the age of 9 days, she was hospitalized following two episodes of seizures (Figure 1). Upon admission, a dextrostick measurement revealed a capillary glucose level of 1.1mmol/L (20 mg/dL). After initial emergency management of hypoglycemia, and despite the continuous intravenous infusion of glucose, episodes of hypoglycemia persisted. During one such episode, with a plasma glucose level of 0.8mmol/L (15 mg/dL), a critical sample was collected, followed by a glucagon stimulation test. Laboratory findings were consistent with hyperinsulinemic hypoglycemia. Specifically, urinary ketones were negative, insulin levels were detectable, and the glucagon test was positive, with an increase in glucose concentration of 2.9mmol/L (53 mg/dL) at 15 minutes post-administration. No functional imaging with ^{18}F-DOPA PET/CT or histological confirmation was performed. Therefore, the distinction between diffuse and focal disease could not be definitively established. Treatment with diazoxide was initiated and titrated up to the maximum recommended dose of 15 mg/kg/day under inpatient monitoring. However, hypoglycemia persisted, confirming lack of therapeutic response. The neonate was therefore referred to a specialized Pediatric Hospital for further evaluation and management. Octreotide therapy was initiated subcutaneously at a starting dose of 5 μg/kg/day and gradually titrated according to glycemic response up to 20 μg/kg/day. Treatment was administered in divided daily subcutaneous doses. No significant adverse effects were documented during therapy. A partial clinical response was achieved, with reduction in the frequency and severity of hypoglycemic episodes, although intermittent events persisted, with an episode of status epilepticus occurring at the age of 6. Treatment continued until the age of 7 years, when it was discontinued by parental decision following gradual reduction in hypoglycemic episodes (Figure 1).

Genetic analysis at the age of 5 years revealed the presence of the heterozygous c.2147G>A, p.Gly716Asp variant in the *ABCC8* gene (NM_000352.6) employing a Next Generation Sequencing Targeted gene panel as previously reported[20]. Segregation analysis revealed that the p.Gly716Asp variant was a *de novo* variant and considered as Pathogenic according to the American College of Medical Genetics (ACMG) criteria[21].

At age 11, following a prolonged period without medical follow-up, the patient was re-evaluated at the Pediatric Endocrinology Department. Clinical examination revealed central obesity, with a body mass index (BMI) at the 95th percentile for age and sex (BMI SDS approximately +1.65). No acanthosis nigricans or other clinical stigmata of insulin resistance were observed. Blood pressure (BP) was within normal limits for age (systolic BP 106 and diastolic BP 78 mmHg, respectively). Laboratory evaluation demonstrated impaired fasting glucose (6.1 mmol/L or 110 mg/dL), impaired glucose tolerance at 2 hours during OGTT (9.9 mmol/L or 178 mg/dL), and elevated glycated hemoglobin (HbA1c 6.6%). Fasting insulin was 7.2 μU/mL and fasting C-peptide 0.8 ng/mL, with a calculated HOMA-IR of 1.96. A comprehensive diabetes autoantibody panel was performed and was negative: anti-insulin antibodies 0.2 U/mL (negative <0.4), anti-glutamic acid decarboxylase antibodies (GAD65) 0.4 U/mL (negative <1), anti–IA-2 antibodies 0.1 U/mL (negative <2), and anti–ZnT8 antibodies 0.5 U/mL (negative <2). Liver function tests were within normal limits (AST 28 U/L, ALT 31 U/L, normal for age <40). Fasting lipid profile was within age-appropriate reference ranges (total cholesterol 172 mg/dL, triglycerides 68 mg/dL, HDL 49 mg/dL, LDL 109 mg/dL). Treatment with oral glibenclamide (glyburide) was initiated and titrated up to 5 mg/day. A structured reassessment and further dose optimization were planned. However, the patient did not attend follow-up, and treatment was discontinued by the family. Therefore, formal assessment of sulfonylurea responsiveness could not be completed.

Repeated attempts to evaluate the patient were unsuccessful. Approximately two years later, at age 13, she returned to our Pediatric Endocrinology Department for evaluation and possible initiation of basal insulin therapy. In the interim, she had received no medical follow-up or treatment (Figure 1). Clinical examination was remarkable for persistent obesity but without any signs of acanthosis nigricans. Laboratory results showed a fasting glucose level of 8.4 mmol/L (152 mg/dL), a fasting insulin level of 5.3μIU/mL, a fasting c-peptide level of 0.7ng/mL, an HbA1c of 6.9%, and antibodies related to type 1 diabetes were once again negative. During a 75 gr OGTT, 2-hour plasma was 16.2 mmol/L (292 mg/dL), insulin was 19.8 μIU/mL, and c-peptide was 1.2 ng/mL. Continuous glucose monitoring over a 14-day period demonstrated mild fasting hyperglycemia and moderate postprandial glucose excursions, without marked glycemic variability or significant nocturnal hypoglycemia. Mean glucose was 160 mg/dL (GMI 7.4%), with 66% time in range (TIR) and 34% time above range (TAR). The overall pattern was consistent with early insulin deficiency. Based on these findings, basal insulin therapy was initiated at a dose of 0.2 IU/kg/day administered at night. The patient has since been followed regularly with CGM monitoring and gradual titration of basal insulin, achieving improved glycemic control without the need for prandial insulin to date.

Regarding neurological progression, the patient, as described above, had neonatal hypoglycemic seizures and subsequent episodes of afebrile seizures during infancy and childhood, for which she received valproate therapy that was discontinued at 9 years of age. Recent electroencephalography was normal. Brain magnetic resonance imaging (MRI) demonstrated occipital cystic leukomalacia and gliosis, consistent with a previous ischemic-type injury. At the time of the latest evaluation, neurological examination revealed no focal deficits, normal muscle strength and coordination, and no gait instability. She attends school regularly without reported cognitive impairment. No ongoing antiepileptic treatment is required.

Discussion

This report describes a 13-year-old girl with diazoxide-unresponsive congenital hyperinsulinism in the neonatal period due to a heterozygous p.Gly716Asp *ABCC8* pathogenic variant, who later developed insulin-deficient diabetes during puberty. Congenital hyperinsulinism is most commonly caused by inactivating mutations in the *ABCC8* and *KCNJ11* genes encoding the subunits of the pancreatic β-cell KATP channel[1,2]. Depending on the functional impact of the mutation, KATP channel dysfunction may result in persistent hyperinsulinemic hypoglycemia or, less commonly, progression to diabetes later in life[1,2,8]. Both recessive and dominant inactivating *ABCC8* mutations have been associated with severe neonatal disease, and the clinical phenotype of diazoxide-unresponsive KATP-related hyperinsulinism may be indistinguishable regardless of inheritance pattern[1–4]. This case further illustrates the phenotypic continuum of *ABCC8*-related disorders and highlights the potential for transition from early hyperinsulinism to subsequent β-cell failure.

Although many monoallelic dominant *ABCC8* variants are associated with milder, diazoxide-responsive phenotypes, several dominant-negative mutations, particularly those affecting critical functional domains such as the nucleotide-binding domains, have been shown to cause severe diazoxide-unresponsive HI, with preserved membrane trafficking but markedly impaired activation by MgADP and diazoxide [22].

The *ABCC8* gene variant c.2147G>A, p. Gly716Asp, identified in our patient has been reported in diazoxide unresponsive patients with diffuse HI[23] and a damaging negative effect on channel function was demonstrated by functional studies[22]. It is a very rare variant not present in gnomAD population databases and it is reported as likely pathogenic by ClinVar (Variation ID: 1702802). Three different aminoacid changes have been reported at the same codon p.Gly716, p.(Gly716Ser), p.(Gly716Val) pathogenic, p.(Gly716Cys) all associated with HI[24].

This variant is localized in the Nucleotide Binding Domain 1 (NBD) of the ABCC8 gene, a critical component of the KATP channel in pancreatic β-cells. Loss of function mutations in the NBDs can impair the function of KATP channels, resulting in the uncontrolled insulin secretion and persistent hypoglycemia characteristic of HI[25]. While *ABCC8* mutations are most often inherited either recessively or dominantly, *de novo* mutations are well-documented, especially in cases with no family history of the disorder, as the case presented herein. Individuals carrying inactivating mutations in the *ABCC8* and *KCNJ11* genes may exhibit a diverse spectrum of clinical phenotypes during the neonatal period, childhood, adolescence, or even adulthood[5–8]. These can range from asymptomatic macrosomia and mild diazoxide-responsive HI to severe persistent HH, with a likelihood of progressing to diabetes mellitus later in life[6,7]. Such cases of transition from HH to diabetes mellitus are well-documented in the literature in adults and, more rarely, in children, as this progression typically takes several years to manifest. This is more common in individuals with heterozygous inactivating mutations in the *HNF4A* and *HNF1A* genes[10,11], but various reports also describe cases involving *ABCC8* inactivating mutations[4,7,10–15]. Indeed, both biallelic (homozygous or compound heterozygous), and heterozygous mutations of the *ABCC8* gene, as observed in our patient, have been reported to be associated with neonatal HH and subsequent progression to diabetes before adulthood (Table 1). It is noteworthy that biallelic *ABCC8* mutations usually result in severe diazoxide-unresponsive HH which often necessitates surgical intervention for effective management, limiting the opportunity for long-term monitoring of pancreatic function[26]. The p.Gly716Asp (c.2147G>A) variant identified in our patient has previously been reported in association with diazoxide-unresponsive diffuse congenital hyperinsulinism. However, to our knowledge, available reports of this specific variant have not documented progression to diabetes or multiplex families exhibiting a combined hyperinsulinism–diabetes phenotype. In our case, the variant occurred de novo, and therefore family segregation does not provide additional information regarding diabetes risk associated with this pathogenic variant.

Regarding the mechanisms underlying the transition from hyperinsulinemic hypoglycemia to insulin-deficient diabetes, increasing evidence supports a loss-of-function model in which inactivating ABCC8 variants result in chronic β-cell membrane depolarization, persistent calcium influx, and sustained insulin hypersecretion during early life. Prolonged intracellular calcium elevation may promote β-cell stress, mitochondrial dysfunction, and progressive β-cell loss, ultimately leading to relative insulin deficiency[6]. This "crossover" phenotype has been described in patients with inactivating KATP channel mutations and differs mechanistically from gain-of-function variants, in which impaired channel closure leads primarily to reduced insulin secretion from the beginning. In the present case, the p.Gly716Asp variant has been functionally associated with marked impairment of KATP channel activation. Although detailed long-term functional studies specific to diabetes progression are not available, the severe neonatal presentation and diazoxide unresponsiveness are consistent with a loss-of-function mechanism. Within this context, sulfonylurea therapy would not be expected to restore physiological channel regulation, as these agents act by closing KATP channels. In loss-of-function variants with constitutively reduced channel activity, their efficacy may be limited. Therefore, the observed evolution toward insulin-deficient diabetes in adolescence likely reflects progressive intrinsic β-cell dysfunction rather than a primary defect in insulin secretion typical of gain-of-function monogenic diabetes. Specifically in our patient, additional metabolic stressors, including pubertal insulin resistance and obesity, may have accelerated β-cell failure in this genetically susceptible background. However, the underlying *ABCC8*-related channel dysfunction remains the most plausible primary driver of the observed transition.

Further to the above, prolonged exposure to somatostatin analogues may affect glucose homeostasis through inhibition of insulin secretion and modulation of counter-regulatory hormones [27]. Although dysglycemia (including hypo- or hyperglycemia) has been reported during octreotide therapy, available pediatric CHI data do not clearly demonstrate a causal link between long-term octreotide exposure and the development of permanent insulin-deficient diabetes [28]. In our patient, the temporal evolution and the underlying ABCC8 pathogenic variant support intrinsic β-cell dysfunction as the primary mechanism."

Conclusion

In conclusion, this case emphasizes the critical need for lifelong follow-up in individuals with HI, particularly those carrying *ABCC8* gene mutations dominantly inherited. While prompt diagnosis and management of HI are vital to mitigate the risks of severe hypoglycemia and its complications, including seizures and developmental impairments, the importance of continued surveillance cannot be overstated, since possible progression to hyperglycemia and insulinopenic diabetes remains a significant possibility. Routine glucose monitoring and periodic diabetes screening, including assessment of fasting plasma glucose and HbA1c, are essential components of long-term care. OGTT should be reserved for individuals with impaired fasting glucose, borderline HbA1c values, or clinical suspicion of evolving diabetes.

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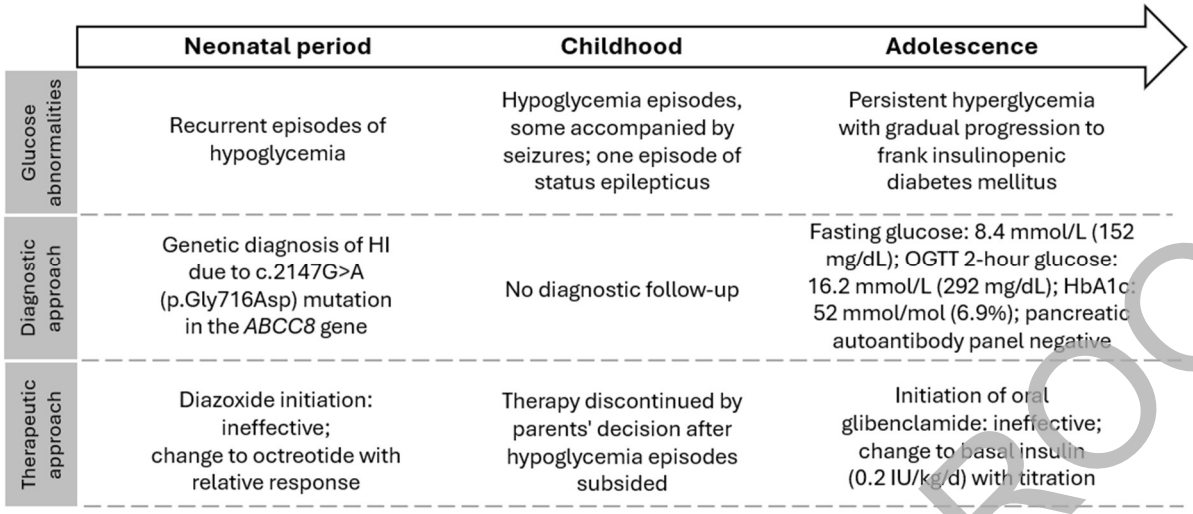

Figure 1. Timeline of clinical events and corresponding diagnostic and therapeutic approach, HI: congenital hyperinsulinism, HBA1c: glycated hemoglobin

Table 1. Case reports describing progression from hyperinsulinemic hypoglycemia to insulinopenic diabetes mellitus in children and adolescents (<18 years) with *ABCC8* gene mutations.

Reference	***ABCC8* gene variant**	**Age at diagnosis of hypoglycemia**	**Hypoglycemia treatment**	**Age at diabetes diagnosis, sex**	**Diabetes treatment**
Abdulhadi-Atwan, 2008[12]	p.Arg370Ser	2nd day of life	Glucose infusions, sweet drinks at home	10.5 yo f	Repagninide, glibenclamide
Gussinyer, 2008[13]	p.Leu1191Leufs*1207/ p.Arg1251* p.Leu1148Arg/p.Arg1251*	Neonatal period-not specified Neonatal period-not specified	Continuous enteral nutrition Continuous enteral nutrition	10 yo m 16 yo m	None None
Saito-Hakoda, 2012[15]	p.Arg1420His/p.Phe591fs*604	2nd day of life	Glucose infusions	11 yo f	Voglibose, nateglinide
Işık , 2019[18]	p.Leu171Phe	2nd day of life	Octreotide	9 yo m	Insulin, glibenclamide
Casertano, 2020[19]	p.Gly1479Arg (2 cases) p.Thr1045fs p.Glu654*/p.Leu1520Pro	1-3nd day of life 1-3nd day of life 1-3nd day of life	Not specified Not specified Not specified	Not specified Not specified Not specified	Not specified Not specified Not specified
Ref: reference; yo: year-old; m: male; f: female					