Abdulghfar *et al.*
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Hyperinsulinism–hyperammonemia syndrome associated with *GLUD1* gene mutation: a case series

Miral M. Abdulghfar[1], Afaf Alsagheir[1*], Ismail A. Abdullah[2] and Raghad Alhuthil[1]

Abstract

Background Congenital hyperinsulinism is a rare disorder characterized by inappropriate insulin secretion, leading to persistent hypoglycemia. One genetic subtype, hyperinsulinism–hyperammonemia syndrome, results from activating mutations in the *GLUD1* gene. This study aimed to describe the clinical spectrum, genetic variants, and outcomes of patients with GLUD1-related hyperinsulinism–hyperammonemia syndrome treated at a tertiary care center in Saudi Arabia.

Methods This retrospective case series included five patients of Saudi ethnicity diagnosed with *GLUD1*-associated hyperinsulinism–hyperammonemia syndrome between September and November 2023 at King Faisal Specialist Hospital and Research Centre. Clinical, biochemical, imaging, and genetic data were collected from medical records. Descriptive statistics were used to summarize the findings.

Results All five patients (four pediatric, one adult) presented with hypoglycemia, elevated insulin levels, and persistent hyperammonemia. Genetic testing confirmed *GLUD1* mutations in all cases, with two patients sharing the c.1493C > T (p.Ser498Leu) variant. Diazoxide therapy effectively controlled hypoglycemia in most patients. Two patients experienced significant neurological complications, including seizures and developmental delay. One adult patient underwent pancreatectomy with improvement in hypoglycemia control but retained chronic neurological sequelae. Brain magnetic resonance imaging abnormalities and secondary genetic variants were identified in two cases.

Conclusion *GLUD1*-related hyperinsulinism–hyperammonemia syndrome presents with a wide clinical spectrum, often with early onset and risk of neurological impairment if not promptly treated. Early diagnosis and individualized management—including genetic testing and diazoxide therapy—are essential to prevent irreversible complications. Further multicenter studies are warranted to better understand long-term outcomes in affected populations.

Keywords Congenital hyperinsulinism, *GLUD1*, Hypoglycaemia, Hyperammonemia, Case series, Saudi Arabia

Introduction

Congenital hyperinsulinism (CHI) is a rare disorder that is genetically, clinically, and histologically diverse. It is characterized by excessive secretion of insulin from pancreatic β cells, which leads to hypoglycemia [1]. Newborns and infants with this syndrome experience recurring episodes of chronic hypoglycemia. Moreover, CHI has been linked to pathogenic or likely pathogenic variants in the *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*,

*Correspondence:
Afaf Alsagheir
ASagheir@kfshrc.edu.sa
[1] Department of Pediatrics, King Faisal Specialist Hospital & Research Centre, Al Takhassousi & 12713, 11211 Riyadh, Saudi Arabia
[2] College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

HNF4A, and *SLC16A1* genes, which have been identified in 68% of patients. Mutations in the KATP channel subunit genes (*ABCC8* and *KCNJ11*) are the most common cause of CHI, accounting for the majority of cases [2, 4].

Glutamate dehydrogenase hyperinsulinism (GDH-HI), also known as hyperinsulinism–hyperammonemia (HI/HA), is the second most prevalent form of CHI [15]. Studies have shown that GDH-HI is caused by mutations in the glutamate dehydrogenase 1 (*GLUD1*) gene, accounting for between 5% and 13% of all CHI cases [3, 4]. Notably, around 50–60% of HI/HA causing *GLUD1* mutations arise *de novo*, with the remainder inherited in an autosomal dominant pattern [4].

GDH-HI is distinguished by a hypoglycemic response that is sensitive to specific proteins, particularly those triggered by leucine, coupled with a moderate and persistent increase in plasma ammonia levels. The enzyme glutamate dehydrogenase (GDH) occupies a pivotal position in the metabolic processing of amino acids and the secretion of insulin; mutations that activate *GLUD1* disrupt the regulatory mechanisms of GDH, resulting in an overproduction of insulin in reaction to amino acid stimuli [5, 6, 15, 17]. Clinically, children with GDH-HI typically present with fasting hypoglycemia, neuroglycopenic symptoms such as seizures, and plasma ammonia levels roughly 2–3 times the upper limit of normal [15, 17]. Unlike the severe hyperammonemia noted in urea cycle disorders, the hyperammonemia linked to hyperinsulinism–hyperammonemia (HI/HA) syndrome typically remains mild and does not exhibit clear clinical symptoms [15]. The prompt recognition and administration of CHI, especially the variant associated with GLUD1, are critically significant, given that prolonged episodes of hypoglycemia can result in irreversible neurodevelopmental deficits [13]. To our knowledge, no studies in Saudi Arabia have investigated the association between hyperinsulinism and *GLUD1* gene mutations. Thus, we report a series of HI/HA cases due to *GLUD1* mutations, with the aim of expanding existing literature on this syndrome and emphasizing the importance of prompt diagnosis and intervention.

Materials and methods

This case series study retrospectively analyzed five Saudi ethnicity cases diagnosed with hyperinsulinemia associated with *GLUD1* gene mutations who are currently being followed up at the endocrine clinic at the King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia. Data on demographics, history, clinical presentations, treatment, laboratory tests, and radiology findings were extracted from our database from September to November 2023. This study included both pediatric and adult patients who tested positive for *GLUD1* gene mutations following genetic testing. Carriers of *GLUD1* gene mutations were excluded.

Genetic testing

Genetic testing was performed as part of routine clinical practice. After obtaining patient consent, DNA was extracted from peripheral blood samples, and whole-exome sequencing was conducted at the Molecular Diagnostic Laboratory of the Clinical Genomic Department Center for Genomic Medicine at KFSH&RC.

Results

Case 1

Case 1 involved a 6-year-old boy who was born full-term via normal vaginal delivery with a normal birth weight and no perinatal complications (Table 1). His mother had gestational diabetes mellitus that was treated with insulin; however, no history of neonatal intensive care unit (NICU) admission was noted. His health was unremarkable, and he was feeding well until the age of 6 months when he started developing abnormal movements characterized by tonic posturing of the upper limbs and uprolling of the eyes. Subsequent testing revealed hypoglycemia (2.4 mmol/L; normal range, 3.9–6.9 mmol/L) (Fig. 1) with elevated insulin levels (192 pmol/L; normal range, 12–150 pmol/L). Other laboratory findings were

Table 1 Demographic data of the five cases and their management and complications

Case	Sex	Age at presentation	Seizure	Family history of mutation	Diazoxide treatment (dose)	Neurological complications
1	M	6 months	Positive	Negative	Yes (7.5 mg/kg/day)	Negative
2	F	3 months	Positive	Negative	Yes (8 mg/kg/day)	Negative
3	F	35 days	Positive	Negative	Yes (13.9/kg/day)	Positive
4	M	6 months	Positive	Negative	Yes (5 mg/kg/day)	Negative
5	M	39 years	Positive	Positive	Others*	Positive

M male, *F* female

* Had pancreatic surgery and is currently on other medications, including pancreatic enzymes, antiepileptic drugs, arginine, and pyridoxine for hyperammonemia

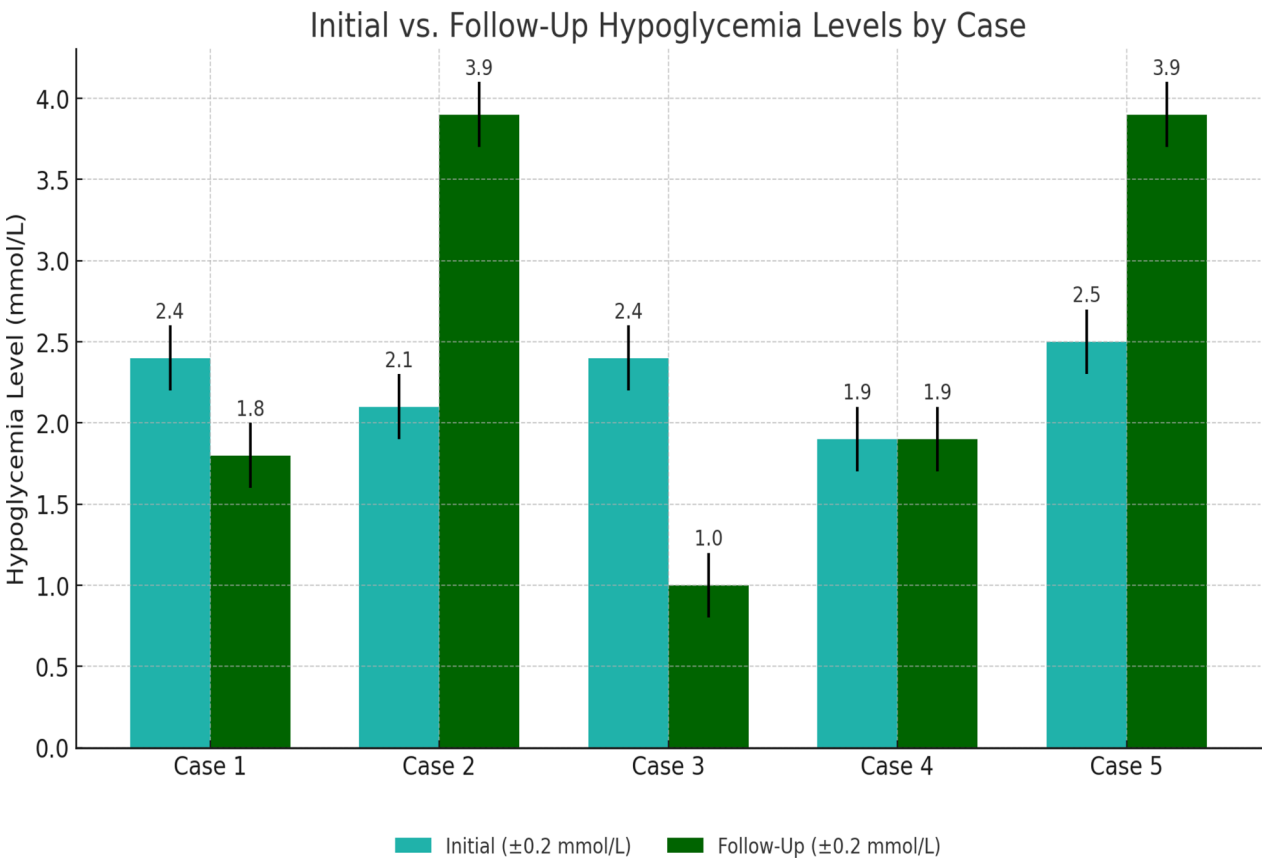

Fig. 1 The bar graph compares the initial and follow-up hypoglycemia levels (blood glucose in mmol/L) for each case. For case 2, we assumed an improvement to the normal range (3.9 mmol/L) as a demonstration, indicating no recurrent episodes after treatment. Case 5 is shown with placeholder values to illustrate potential improvement after pancreatectomy

within normal limits. The patient was started on diazoxide therapy. During the safety fast test, he was able to fast for a few hours before developing hypoglycemia again (1.8 mmol/L), with insulin levels at 26.70 pmol/L and C-peptide insulin levels at 0.465 nmol/L (normal range, 0.26–0.62 nmol/L). Ammonia levels fluctuated between 147 and 157 µmol/L (normal range, 0–55 µmol/L) with negative urine ketones (Table 2). Metabolic screening and cortisol, adrenocorticotropic hormone (ACTH), and parathyroid hormone (PTH) levels returned normal, and he responded to the glucagon test within 30 minutes.

Both of his asymptomatic parents were nonconsanguineous, and none of his siblings were known to have hypoglycemia or pancreatic diseases. However, the patient had a family history of epilepsy on his maternal side. Developmentally, the boy has been meeting milestones appropriate for his age with no delays and dysmorphic features having been noted. He presented with hyperpigmented skin on the abdomen but no organomegaly; otherwise, his examination showed normal findings.

Management with diazoxide has been largely successful. However, the patient did experience a few seizure episodes in his life, with the first leading to his diagnosis and subsequent seizures occurring during periods of noncompliance with treatment or concurrent illness (Table 3). His mental and physical growth proceeded normally despite these obstacles.

Case 2

Case 2 involved a 2-year-old girl who was the only child born to consanguineous parents and was delivered at term weighing 2.4 kg through normal vaginal delivery with no history of any perinatal complications or NICU admission. Examination revealed no family history of similar illnesses or pancreatic diseases (Table 1). Her medical history commenced at the age of 3 months when her mother witnessed episodes of tiredness, lethargy, and brief losses of consciousness lasting about 3 seconds, which initially occurred once or twice per week but escalated to three incidents in a single day. A critical sample taken

Table 2 Initial investigations and gene mutations:

Case	Insulin, pmol/L (ref.: 12–150 pmol/L)	Ammonia, µmol/L (ref.: 0–55 µmol/L)	C-peptide, nmol/L (ref.: 0.26–0.62 nmol/L)	Blood glucose, mmol/L (ref.: 3.9–6.9 mmol/L)	Genetic findings and ACMG class
1	26.7	147–157	0.465	2.4	• ***GLUD1*** (NM_005271.5):c.1493C > T p.(Ser498Leu) (pathogenic)
2	High	117	High	2.1	• ***GLUD1*** (NM_005271.5):c.1493C > T p.(Ser498Leu) (pathogenic) • *PAH* (NM_000277.3):c.688G > A p.(Val230Ile) (likely pathogenic)
3	147.8	214	9.08	2.4	• ***GLUD1*** (NM_005271.5):c.1496G > T p.(Gly499Val) (pathogenic) • *ALDOB* (NM_000035.4):c.448G > C p.(Ala150Pro) (pathogenic) • *SLC26A4* (NM_000441.2):c.1198del p.(Cys400ValfsTer32) (pathogenic)
4	64	137–109	0.65	2.1	• ***GLUD1*** (NM_005271.5):c.965G > A p.(Arg322His) (pathogenic)
5	47	300	0.5	3.2	• ***GLUD1*** (NM_005271.5):c.956A > G p.(Tyr319Cys) (pathogenic)

Ref. reference range

ACMG American College of Medical Genetics

during an episode, when her blood glucose level was at 2.1 mmol/L (normal range, 3.9–6.9 mmol/L) (Fig. 1), indicated elevated insulin and C-peptide levels, low ketones, and high ammonia levels at 117 µmol/L (normal range, 0–55 µmol/L) (Table 2). Following these findings, the patient was started on diazoxide and hydrochlorothiazide.

Further workup, including magnetic resonance imaging (MRI), revealed marked thinning of the corpus callosum and cystic changes in the basal ganglia, with no additional brain abnormalities. Clinically, although her weight was below the third percentile, her height was normal for her age at time of diagnosis. No developmental delays, dysmorphic features, organomegaly, or midline defects were observed, and her examination was otherwise normal. Genetic testing confirmed HI/HA syndrome due to a mutation in the *GLUD1* gene and identified her as heterogeneous for a secondary gene *PAH* mutation class 2, which has been associated with recessive and early onset Mendelian diseases.

She was managed with diazoxide and hydrochlorothiazide, to which she responded effectively, with no recurrent hypoglycemia episodes having been reported since the last incident at the age of 3 months. Initially, she experienced multiple hypoglycemic attacks during 3 hours of fasting or when ill. A safety fast test revealed that the patient could now fast for up to 10 hours. Her physical and mental development continued normally without any neurological conditions (Table 3).

Case 3

Case 3 involved a 2-year-old girl with a history of frequent hospital admissions due to hypoglycemia and noncompliance with medication. Born via vaginal delivery after a pregnancy complicated by oligohydramnios, her perinatal history was otherwise unremarkable. Her parents were healthy, with no known consanguinity or family history of metabolic diseases (Table 1). At 35 days old, she exhibited an episode of abnormal movement characterized by stiffness of the hands that lasted for less than 5 minutes. Although no tonic–clonic seizures were observed, she was lethargic and difficult to arouse. Subsequent examination revealed low blood glucose (2.4 mmol/L; normal range, 3.9–6.9 mmol/L), high insulin levels (147.8 pmol/L; normal range, 12–150 pmol/L), elevated C-peptide (9.08 nmol/L; normal range, 0.26–0.62 nmol/L), and consistently high ammonia levels (214 µmol/L; normal range, 0–55 µmol/L), with negative urine ketones and low beta-hydroxylase levels (Table 2). Furthermore, blood gases and hormone levels were within normal ranges. Initial treatment included octreotide, later transitioning to diazoxide and hydrochlorothiazide. Echocardiography revealed mild left ventricular hypertrophy and pulmonary stenosis, while MRI showed significant brain abnormalities, including atrophic changes and ischemic signs.

At 1 year old, she experienced a severe hypoglycemic event leading to a seizure and subsequent diagnosis of hypoxic-ischemic encephalopathy, with

Table 3 Long-term outcomes and hypoglycemia resolution

Case	Age at last visit	Blood glucose, mmol/L (ref.: 3.9–6.9 mmol/L)	Basic labs (CBC, RP, HP, BP)	Management	Hypoglycemia resolution	Seizure frequency after treatment	Functional and developmental status	Comorbidities	Follow-up and compliance	Clinical outcome
1	7 years	4.8	WNL	Diazoxide responsive; on Keppra	Initially improved; recurrence during non-compliance or illness	Several episodes linked to non-compliance or illness	Developmentally appropriate; no deficits	Seizure (not hypoglycemia-related)	Every 3–6 months, annual safety fast (compliant)	Alive and well
2	3 years	4.2	WNL	Diazoxide + hydrochlorothiazide	Resolved by 3 months; stable since	No seizures after treatment	Developmentally appropriate; no deficits	Hyperuricemia (353 µmol/L, diazoxide-related)	Every 3–6 months, annual safety fast (compliant)	Alive and well
3	2 years	7.2	WNL	Diazoxide responsive; off HCTZ; on antiseizure meds	Controlled after improved compliance	One severe seizure at 1 year due to hypoglycemia	Global developmental delay	HIE, seizure disorder	Every 3–6 months (compliant)	Alive with poor outcomes
4	9 years	4.5	WNL	Diazoxide responsive	Resolved after starting diazoxide	One seizure at 22 months during illness; none since	Developmentally appropriate; no deficits	None	Every 3–6 months (compliant)	Alive and well
5	40 years	Not done	WNL	Not on medication; post-pancreatectomy	Improved significantly post-surgery	Chronic seizure disorder from earlier uncontrolled hypoglycemia	Neurological impairment	Severe intellectual disability, spasticity, dystonia	Non-compliant; no follow-up	Alive with poor outcomes

Ref. reference range, *WNL* within normal limits, *CBC* complete blood count, *RP* renal profile, *HP* hepatic profile, *BP* bone profile, *HCTZ* hydrochlorothiazide, *HIE* hypoxic-ischemic encephalopathy

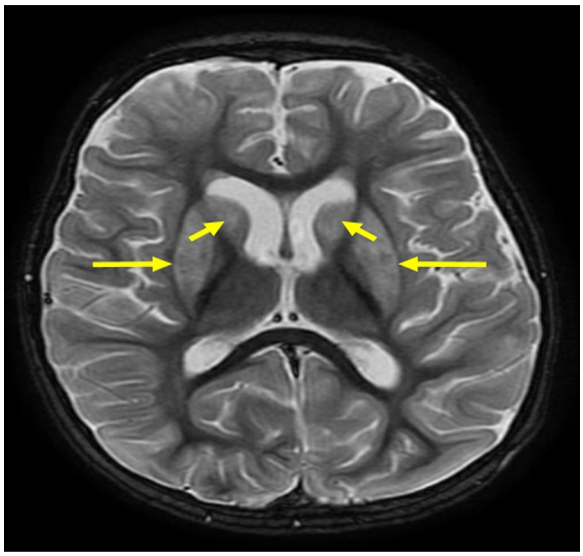

Fig. 2 Axial T2-weighted brain MRI showing bilateral symmetrical hyperintense signal abnormalities (yellow arrows) involving the posterior limbs of the internal capsules and adjacent periventricular white matter. These findings may reflect demyelination, gliosis, or metabolic white matter involvement

electroencephalography (EEG) showing cerebral dysfunction and brain magnetic resonance imaging (MRI) strongly indicating severe acute/subacute hypoglycemic encephalopathy (Fig. 2). Genetic testing confirmed HI/HA syndrome (*GLUD1* gene mutation) and heterozygosity for secondary genes (*ALDOB* and *SLC26A4* mutations class 1) associated with severe early onset Mendelian diseases. Currently, she is being treated with diazoxide and hydrochlorothiazide, which have effectively controlled her hypoglycemia and seizures. Clinically, her weight and height were below the third percentile for her age. Moreover, she showed significant developmental regression, currently presenting with global developmental delays, including loss of head control, inability to sit, spasticity predominantly in the lower limbs, and limited responsiveness to visual stimuli.

Case 4

Case 4 involved a 5-year-old boy, born full-term with a birth weight of approximately 3 kg following an uneventful vaginal delivery and regular antenatal follow-up, who had no record of NICU admission. The boy's health remained normal until the age of 6 months when his mother witnessed him convulsing without losing consciousness. These episodes recurred several times, prompting medical consultation. Initial investigations, including EEG, ecogradiograhpy, and comprehensive blood workup, returned normal results.

However, a safety fast test revealed low serum glucose levels at 1.9 mmol/L (normal range, 3.9–6.9 mmol/L). The critical samples showed low beta-hydroxylase levels and negative urine ketones, along with increased ammonia levels ranging from 137 to 109 μmol/L (normal range, 0–55 μmol/L), C-peptide levels of 0.651 nmol/L (normal range, 0.26–0.62 nmol/L), and an insulin level of 64 pmol/L (normal range, 12–150 pmol/L) (Table 2). Metabolic screening revealed no abnormalities, and hormone levels were within normal ranges.

He began to demonstrate abnormal movements after an illness at 22 months of age. These motions included drooling saliva and perioral cyanosis, along with generalized clonic movements and eye rolling. He went into a postictal state of sleepiness as the episode ended on its own. His blood glucose level was 1.9 mmol/L at this time (normal range, 3.9–6.9 mmol/L). The results of a subsequent EEG revealed normal findings. Hyperinsulinism nesidioblastosis (diffuse pancreatic uptake) was revealed on positron emission tomography (PET).

Although the patient had healthy siblings and no family history of endocrine disorders or similar illnesses, the patient's parents are first-degree cousins. His weight and height were clinically below the third percentile. However, no midline deformities, dysmorphic characteristics, developmental delays, or organomegaly had been noted, with his evaluation largely revealing normal findings.

Diazoxide treatment has been effective, with the patient having no further seizure events or repeated hypoglycemia episodes for the past 2 years. His progress, both mentally and physically, has proceeded normally (Table 3).

Case 5

Case 5 involved a 39-year-old male who had been diagnosed with HI/HA syndrome secondary to nesidioblastosis following pancreatectomy at the age of 7 years for the management of pancreatic hyperplasia. The patient had a fasting insulin level of 47 pmol/L (normal range, 12–150) and a C-peptide value of 0.5 nmol/L (normal range, 0.26–0.62 nmol/L), which were particularly indicative of a history of recurrent hypoglycemia episodes (Table 2). His hypoglycemia, which was frequently uncontrollable, improved considerably after pancreatic surgery. Furthermore, the patient experienced recurring episodes of hypoglycemia-related increase in ammonia levels up to 300 μmol/L (normal range, 0–55 μmol/L) and the development of a seizure disorder as a secondary consequence. MRI revealed no anomalies. Genetic testing revealed a *GLUD1* gene mutation in both the patient and his father.

The patient was managed through pancreatic enzymes, antiepileptic drugs, arginine and pyridoxine for hyperammonemia, and a specific diet. Regretfully, due to a genetic

disorder, the patient has a severe intellectual handicap and static encephalopathy with lifelong neurological consequences, including cognitive impairment and a mix of spasticity and dystonia.

Discussion

The diagnosis and treatment of CHI remains extremely difficult owing to its genetic complexity and clinical management, particularly when *GLUD1* mutations are involved [3, 4]. Notably, HI/HA syndrome has been explicitly associated with *GLUD1* gene mutations as a major etiological component underlying CHI, highlighting the complex interaction between genetic variables and clinical manifestations of the disease [16]. The variety of mutations affecting pancreatic β cells and their glucose-sensing pathways demonstrates the heterogeneity of CHI, requiring focused genetic testing for accurate diagnosis and therapeutic planning [16].

The differential diagnoses associated with congenital hyperinsulinism (CHI) ought to encompass mutations in other recognized genetic loci beyond *GLUD1*, which include *ABCC8*, *KCNJ11*, *GCK*, *HNF4A*, and *SLC16A1*. The predominant etiology of CHI is attributed to a dysfunction in the *KATP* channel, frequently leading to diazoxide-unresponsive CHI. Mutations in *GCK*, *HNF4A*, and *HADH*, which are less prevalent, constitutes significant etiological factors with unique clinical manifestations. It is now advisable to employ comprehensive multigene panel testing or exome sequencing in cases of persistent neonatal hypoglycemia to ascertain the underlying etiology and inform therapeutic strategies [3, 6, 10]

A multidisciplinary approach is necessary for the management of CHI, particularly in cases suspected to have *GLUD1* mutations. This emphasizes the significance of early and precise diagnosis through genetic screening. Preventing neurodisability associated with prolonged hypoglycemia is imperative [17]. Mutations in the *ABCC8*, *KCNJ11*, and *GLUD1* genes have been reported in Saudi patients, highlighting the necessity of thorough genetic screening in this population to enable early intervention and individualized treatment regimens [18].

Our diagnostic approach is anchored on the clinical features of children and their biochemical markers during hypoglycemic episodes. Specimens are collected at the onset of hypoglycemia and before any treatment intervention. Detectable C-peptide levels, increased insulin release at low blood glucose levels, and nonketogenic hypoglycemia are usually critical findings. Our diagnostic criteria are consistent with those reported by Ferrara *et al*. [7], which suggests that all our cases will have exhibited genetic alterations during DNA testing. Four of the five patients included herein ranged in age from 1 to 6 months, with a median age of onset of 3 months. Only one case (case 5) was an adult with an age of onset of 39 years. The median age of onset was 5 years (interquartile range: 2, 23), with one adult case. This finding is consistent with that reported in another study, which found a median age of onset of 11 months and an average age of onset of 4 months [8], demonstrating the tendency of the condition to present at a young age.

All of our patients developed seizures, exhibited low serum glucose and increased plasma insulin levels, and initially presented with 100% hyperammonemia, which is typically observed with *GLUD1* mutations, as noted in previous research. Cases 2 and 3 (40%) showed cystic and atrophic alterations, thinning of the corpus callosum, etc. on MRI, with case 3 showing notable cardiac problems. Additional research is essential considering that these patients also had secondary gene mutations linked to Mendelian disorders with an early onset. Another study also observed abnormalities on brain MRI, including cerebral atrophy and left frontal encephalomalacia, in a smaller cohort of patients [8].

Two cases (cases 3 and 5) experienced significant neurological complications (40%), possibly due to several reasons, including *GLUD1* mutations, the severity of hypoglycemia attacks, late diagnosis in our adult patient, or poor medication compliance in case 3. Previous studies have indicated that multiple factors, including medication compliance and the age at which seizures and hypoglycemia first occur, can affect the neurological prognosis and likelihood of these events recurring. Another important factor is the frequency and severity of hypoglycemia episodes [5]. According to a 2019 study, children with GDH-HI had significant neurological complications, such as mental retardation and cognitive impairment [10].

In one example (case 4 pre-genetic testing), PET indicated hyperinsulinism nesidioblastosis (diffuse pancreatic uptake), which was associated with mutations in *GLUD1*. This finding is consistent with that reported in another research, which found that 12 out of 20 children undergoing PET/CT for hyperinsulinemic hypoglycemia had genetic variants associated with HI, with the majority exhibiting diffuse pancreatic uptake [11].

Interestingly, we note that 40% of our patients were born to consanguineous parents and that merely 20% of our patients had a positive family history. This aligns with the high rates of consanguineous marriages in Saudi Arabia, a factor that significantly increases the prevalence of autosomal recessive genetic disorders such as CHI [16]. Diazoxide (80%) was administered to four patients (cases 1, 2, 3, and 4) initially at lower doses, with adjustments being made depending on clinical symptoms and follow-up evaluations. Following up, 60% (cases 1, 2, and 4) responded effectively and showed improvements

with low-dose diazoxide (5–8 mg/kg/day), similar to the results from a 2020 study on *GLUD1* mutations and diazoxide responsiveness (100%). However, given the numerous difficulties and problems with compliance, case 3 needed an increased dosage of up to 13.9 mg/kg/day.

Furthermore, according to the guidelines from a 2020 literature review on diazoxide monitoring criteria, two cases (cases 1 and 3) received hydrochlorothiazide along with diazoxide to ameliorate cardiopulmonary side effects [12]. Our adult patient, who was diagnosed after undergoing pancreatectomy at the age of 7 years, showed notable progress, which is consistent with a 2022 study that highlighted new medical interventions and surgical advancements [13]. This patient followed a particular diet and managed hyperammonemia instead of receiving diazoxide, similar to another adult case with a *GLUD1* mutation and ornithine carbamoyl transferase deficiency [14].

Long-term management of *GLUD1*-HI requires regular follow-up to monitor glucose control, assess neurodevelopment, and adjust treatment. Diazoxide dosage may need to be modified with growth, and dietary counseling is essential to avoid protein-induced hypoglycemia. Periodic ammonia monitoring is also recommended. Current practices endorse the gathering of a cross-functional group comprising endocrinologists, neurologists, dietitians, and genetic counselors, aimed at optimizing clinical results [11, 15].

The *GLUD1* gene mutation c.1493C > T/p.Ser498Leu was found in 40% of our cases. One case had the c.965G > A/p.Arg322His mutation, which did not cause any neurodevelopmental problems. However, cases 3 and 5, who had distinct genetic disorders, experienced developmental regression and encephalopathy that caused long-term neurological consequences.

This study provides a comprehensive clinical overview of five pediatric cases of HI/HA syndrome associated with *GLUD1* mutations—a relatively rare genetic condition. While informative, the study is limited by its small sample size and single-center design, which may affect the generalizability of the findings.

Conclusion

Further research and vigilant monitoring are essential to provide a robust foundation to comprehensively elucidate the relationship between hyperinsulinism and *GLUD1* gene mutations. Additional studies are required to understand the neurological complications associated with *GLUD1* mutations. Early detection and diagnosis are pivotal in preventing disease progression and neurodevelopmental deterioration. Also, future studies with extended follow-up and multicenter collaboration are essential to better characterize the long-term prognosis and optimize the lifelong management strategies for patients with *GLUD1* mutations.

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Author contributions
Miral M. Abdulghfar drafted the original manuscript. Afaf Alsagheir and Ismail A. Abdullah aided in interpreting the results and worked on the manuscript. Raghad Alhuthil critically edited and drafted the final version of the manuscript. All authors discussed the results and commented on the final version.

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Availability of data and materials
The datasets used in the current study are available from the corresponding author upon reasonable request.

Declarations

Consent for publication
Written consent was obtained from all included cases and their families to publish this study and any accompanying information. In addition, the study was cleared for publication by the institutional review board in King Faisal Specialist Hospital and Research Centre (KFSHRC) (reference: 2245413). Written informed consent was obtained from the patients' legal guardians for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors state that they do not have any competing interests.

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