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CLINICAL BRIEF

Congenital Hyperinsulinemic Hypoglycemia and Hyperammonemia due to Pathogenic Variants in *GLUD1*

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Abstract

Congenital hyperinsulinism (CHI) is a clinically and genetically heterogeneous disorder, characterized by dysregulated insulin secretion. Pathogenic variants in at least twelve different genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A, UCP2, TRMT10A HK1,* and *PGM1*) are known to cause CHI. Pathogenic variants in the *GLUD1* gene, which encodes the enzyme glutamate dehydrogenase (GDH), account for 5% of the cases of congenital hyperinsulinemic hypoglycemia. Pathogenic variants in *GLUD1* typically present in late infancy, are diet and/or diazoxide-responsive and cause protein-induced hyperinsulinemic hypoglycemia as insulin secretion is triggered by allosteric activation of GDH by leucine. The authors are presenting three unrelated Indian children, who manifested with fasting as well as dietary protein induced hypoglycemia in late infancy, and were diagnosed to have hyperinsulinemic hyperammonemic hypoglycemia due to pathogenic variants in *GLUD1*. Although the hypoglycemia responded to diazoxide, delayed diagnosis and irregular treatment had resulted in neurological problems in two of the three children. Early identification, appropriate dietary modifications and regular treatment with diazoxide can prevent adverse neurological outcome.

Keywords Hyperinsulinism-hyperammonemia (HI/HA) syndrome · Leucine sensitive hypoglycemia · Neurological disabilities

Introduction

Congenital hyperinsulinism (CHI) typically presents in newborns or infants as persistent hypoglycemia. If not managed promptly and effectively, it often results in adverse neurodevelopmental outcomes. Among the twelve known genes, pathogenic variants in *ABCC8* and *KCNJ11* are responsible for about half the cases and > 80% of the severe, diazoxide-unresponsive CHI [1, 2]. Hyperinsulinism-hyperammonemia (HI/HA) syndrome is the next commonest cause, resulting from 'gain of function' pathogenic variants of the Glutamate dehydrogenase (*GLUD1)* gene, inherited in autosomal dominant manner [3, 4]. The authors are presenting three unrelated Indian children, who presented to them over the last 3 y, with fasting as well as protein-induced hypoglycemia in late infancy, and were diagnosed to have HI/HA syndrome due to pathogenic variants in *GLUD1*.

The patients presented with recurrent episodes of hypoglycemia from the age of 4–8 mo, had history suggestive of hypoglycemia following protein intake, had elevated serum insulin and low blood ketone in the critical sample taken during hypoglycemia, as well as mild hyperammonemia. Hence, a pathogenic variant in *GLUD1* or *HADH* gene was suspected. All three patients had dominantly expressed known activating missense pathogenic variants in *GLUD1* gene and responded to diet and diazoxide. Although, the dose of diazoxide can be reduced on follow-up, the children promptly develop hypoglycemia if it is missed. The clinical presentation, biochemical

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work-up, molecular diagnosis and the status on follow-up of the three patients is summarized in Table 1, and the salient points are presented below.

Case Reports

Patient 1

This baby started having episodes of hypoglycemic seizures around weaning at 6 mo of age. She was treated outside with hydrocortisone and antiepileptic drugs, and presented to authors at 5 y of age, with global developmental delay and uncontrolled hypoglycemia. The family was vegetarian, but history suggested that hypoglycemia was temporally related to intake of khichdi and pulses. Euglycemia was achieved with diazoxide. Pathogenic variant in *GLUD1* was identified on molecular testing undertaken at University of Exeter Medical School, UK. On follow-up, due to financial constraints and availability issues, the compliance with the medication has been erratic.

Patient 2

This baby was asymptomatic till 7.5 mo of age when he had the first episode of brief lethargy with fever. He had another such episode also accompanied by clonic seizure after 2 mo. He was seen at a private hospital, where blood sugar was documented as 31 mg/dl, with normal sepsis screen and electrolytes. He started having frequent recurrences of hypoglycemia at 15 mo and was referred to authors' hospital. The baby had firm hepatomegaly, 3.5 cm below the costal margin, and required glucose infusion rate of 8 mg/kg/min. On evaluation, hyperinsulinemia and hyperammonemia were documented with inappropriately suppressed ketones. There was history of hypoglycemic episodes following intake of meat. Liver function tests were normal and he had non-specific changes on liver biopsy. Targeted next generation sequencing performed at University of Exeter Medical School, UK revealed a pathogenic variant in *GLUD1*. Baby responded well to oral diazoxide and low protein diet.

Patient 3

This baby on exclusive breast feeding started having brief seizures with post-ictal drowsiness at 4 mo and presented to authors' hospital during the 4th episode when the drowsiness continued for more than 1 h. After starting diazoxide and frequent feeds, glucose infusion was discontinued. 18-F DOPA PET-CT revealed increased focal uptake at head, and junction of body and tail. The child as well as the mother was noted to have the same heterozygous pathogenic variant in exon 6 of *GLUD1*, on molecular testing undertaken at Madras Diabetes Research Foundation, Chennai. The mother had epilepsy from the age of 10 y, for which she had taken antiepileptic drugs for several years (and discontinued 3 y ago). However, there was no history or documentation of hypoglycemia in the mother, and no temporal association of her seizures with fasting or intake of protein-rich diet.

Table 1 Summary of clinical presentation, biochemical work-up, molecular diagnosis and follow-up of the three patients

	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Female
Birth weight	2.6 kg	3.1 kg	3.0 kg
Resident of	Bihar	Rajasthan	Rajasthan
Age at onset of symptoms	6 mo	7.5 mo	4 mo
Age at diagnosis	5 y	15 mo	5 mo
Symptoms and signs at presentation	Seizure, developmental delay	Lethargy, seizure, hepatomegaly	Seizure, hepatomegaly
Biochemical			
Blood sugar at presentation (mg/dl)	28	31	36
Serum insulin during hypoglycemia (mIU/L)	14.5	5.9	11
Serum ketones during hypoglycemia (mmol/l)	0.2	0.1	0.1
Serum ammonia (normal 30–86 μg/dl)	131	110.4	177
Molecular analysis in the patients	Heterozygous missense pathogenic variant in *GLUD1* in exon 11	Heterozygous missense pathogenic variant in *GLUD1* in exon 7	Heterozygous missense pathogenic variant in *GLUD1* in exon 6
Nucleotide	c.1493C > T	c.943C > T	c.820C > T
Protein	p.(Ser498Leu)	p.(His315Tyr)	p.(Arg274Cys)
Molecular analysis in parents	Neither parent had this pathogenic variant	Parents' samples could not be analyzed	Mother had the same heterozygous pathogenic variant as child
Treatment	Diazoxide 12 mg/kg/d Diet	Diazoxide 10 mg/kg/d Diet	Diazoxide 7 mg/kg/d Diet
Duration of follow-up	3.5 y	2 y	6 mo
Current glycemic and neurological status	Due to discontinuous use of medication, child has intermittent hypoglycemia. Global developmental delay with epilepsy, microcephaly and sensorineural hearing loss	Maintaining euglycemia on diazoxide Autistic spectrum disorder	Maintaining euglycemia on diazoxide Mild fine motor delay

Discussion

GLUD1 gene encodes the mitochondrial enzyme glutamate dehydrogenase (GDH), which is expressed in several organs including pancreatic β-cells. GDH catalyzes oxidative deamination of glutamate to α-ketoglutarate and ammonia. Excessive GDH activity in hepatocytes results in hyperammonemia. In β-cells, α-ketoglutarate enters the tricarboxylic acid cycle, leading to exocytosis of insulin. GDH is allosterically activated by leucine, and inhibited by GTP and ATP. 'Gain of function' pathogenic variants in *GLUD1* desensitize GDH to allosteric inhibition by GTP, while allosteric activation by leucine is uninhibited. This manifests as hypoglycaemia following protein-rich meals [5, 6]. Another rare genetic defect that presents as protein-sensitive hypoglycemia is caused by inactivating pathogenic variants in the *HADH* gene that encodes the enzyme short-chain 3-hydroxyacyl-CoA. The authors have previously reported pathogenic variants in *HADH* in two Indian siblings [7].

CHI resulting from pathogenic variants in *GLUD1* is typically reported to be milder compared to the more common forms related to pathogenic variants in *ABCC8* and *KCNJ11*. There is no macrosomia at birth, and presentation is in late infancy with recurrent seizures. The seizures are speculated to be either due to hypoglycemic brain injury or to decrease in the neurotransmitters like glutamate and gamma-aminobutyric acid in the brain due to raised GDH. Epilepsy is particularly common in children with mutation in exons 6 and 7, which encode major GTP binding sites of *GLUD1* gene. Kapoor et al. in a case series of 15 children with HI/HA syndrome described similar clinical manifestations and high risk of epilepsy (with or without hyperammonemia) [8]. In the present study, first patient had exon 11 mutation, but developed epilepsy because of delayed diagnosis.

Management includes adequate treatment with diazoxide and a diet restricted in protein (especially leucine). Although response to dietary management and/or diazoxide is good, neurological sequelae are common due to delayed diagnosis and poor compliance. Adverse neurodevelopmental outcomes ranging from specific cognitive deficits in early childhood, to visual-motor impairment, executive dysfunction, general cognitive impairment and scholastic problems in later childhood have been described [9]. The high cost and limited availability of diazoxide in our country contributes to a poorer outcome.

In conclusion, authors emphasize that evaluation and management of persistent hypoglycemia in newborns and infants is a priority, optimal glycemic control should be established at the earliest and maintained to prevent later neurological disabilities. Most cases of CHI presenting beyond the neonatal period are responsive to diet and/or diazoxide. Molecular diagnosis helps in identifying causative gene. This aids in management, understanding long term prognosis, and in being vigilant for associated co-morbidities like epilepsy. In addition, this allows for screening of other family members, who may be asymptomatic, and counseling regarding the risk for subsequent offspring and the next generation.

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Authors' Contribution KK and VJ prepared the manuscript. KK, AKS, RS and VJ managed the cases. SEF, JALH, VR and VM have helped in mutation studies. VJ has critically reviewed the manuscript and will act as a guarantor. All authors have given their inputs and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest None.

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