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CASE REPORT: CONGENITAL NEONATAL HYPOGLCEMIA ASSOCIATED WITH HOMOZYGOUS ABCC8 GENE MUTATION

Neonatology

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ABSTRACT

Background : Neonatal hypoglycemia is a common metabolic issue in newborns, particularly among at-risk infants. Congenital Hyperinsulinism (CHI), often caused by genetic mutations, leads to excessive insulin secretion, resulting in persistent hypoglycemia. Early diagnosis and intervention are crucial to prevent long-term neurological complications. **Case Presentation** : We report a case of a male infant born at 35+6 weeks gestation with severe hypoglycemia (glucose 14 mg/dL) at birth. Despite glucose infusion and pharmacological management, hypoglycemia persisted, requiring referral to a specialized neonatal unit. Genetic testing identified a homozygous mutation in the **ABCC8** gene, confirming CHI. The infant was managed with diazoxide, octreotide, and glucose infusion, leading to stabilization and eventual discharge on oral therapy. **Discussion :** CHI is a rare but severe condition often linked to mutations in **ABCC8** and **KCNJ11** genes, which disrupt pancreatic β-cell potassium channels. Treatment options include medical therapy (diazoxide, octreotide, nifedipine) and, in severe cases, pancreatectomy. Genetic testing plays a pivotal role in guiding diagnosis and treatment decisions. **Conclusion :** Early recognition and targeted genetic testing are essential for CHI diagnosis and management. Pharmacological interventions can effectively stabilize glucose levels, but individualized treatment strategies are necessary based on genetic findings. Long-term follow-up is crucial to monitor growth, neurological development, and treatment efficacy.

KEYWORDS

INTRODUCTION:

Hypoglycemia is the most common metabolic problem in neonates in the newborn nursery and neonatal intensive care unit (NICU). Neonatal hypoglycemia occurs most often (47%–52%) in at-risk infants who are small for gestational age (SGA) or large for gestational age (LGA), late preterm infants, or infants of diabetic mothers (IDM). It can occur in up to 10% of healthy term newborns. There is controversy surrounding neonatal hypoglycemia, including no absolute definition of hypoglycemia.

American Academy of Pediatrics defines hypoglycemia as:
In late preterm (34–36 6/7 weeks), term SGA infants, IDM, and LGA infants, hypoglycemia is defined as:

1. Symptomatic infants at any age and asymptomatic infants from birth to 4 hours of age: <40mg/dl
2. Asymptomatic infants (4–24 hours): <45mg/dl [(1)]

Congenital hyperinsulinism(CHI). Hyperinsulinism is seen in mutations of genes encoding the pancreatic beta-cell adenosine triphosphate (ATP)–sensitive potassium channel, such as ABCC8 and KCNJ11 which encode for SUR1 and Kir6.2. Elevated insulin levels are also associated with loss-of-function mutations in HNF4A gene.[(2)]

This condition is marked by uncontrolled insulin secretion from pancreatic β-cells, leading to sustained and severe hypoglycemia. Affected children might display reduced appetite, diminished crying, drowsiness, and poor responsiveness. In severe cases, neurological symptoms can emerge, potentially resulting in irreversible brain damage. Hence, prompt diagnosis and treatment are crucial to prevent neurological complications. CHI treatment options encompass diazoxide, growth inhibitor analogs, calcium channel blockers, and surgical interventions, all of which can enhance the prognosis for CHI patients [(3)]. In this study, we present a case of CHI featuring a homozygous ABCC8 mutation.

CASE DESCRIPTION:

We enrolled a newborn admitted to the Neonatal Intensive Care Unit (NICU) of MAX Super Speciality Hospital, Mohali on January 18, 2025, as the subject of our study. Here are the child's basic details: He is a 2nd Issue of a non-consanguineous marriage, Male, born at 35 + 6 weeks' gestation, on January 07, 2025. At birth, He had an Apgar score of 8 at 1 minute and 9 at 5 minutes, weighing 3750g (> 97th percentile). The child's mother underwent a cesarean section at outside hospital due to non-reassuring NST. The child was admitted at birth hospital due to severe hypoglycemia, with glucose levels as low as 14mg/dL after delivery. Neither parent had a family history of diabetes. 1st issue is a healthy female child at 3 years of age.

The child was managed at the birth centre for persistent hypoglycemia. The investigations showed

Laboratory inspection items		Results	
Complete Blood Count	HAEMOGLOBIN	20.1 g/dL	normal
	PCV	59.90 %	normal
	MCV	108.2 fL	normal
	MCH	36.3 pg	normal
	MCHC	33.5 g/dL	normal
	TOTAL LEUCOCYTE COUNT (TLC)	13,880 cells/cu.mm	normal
	PLATELET COUNT	373000 cells/cu.mm	normal
GLUCOSE, RANDOM , SODIUM FLUORIDE PLASMA (R)		14 mg/dl	low
KETONE (BETA HYDROXY BUTYRATE) – SERUM		0.09 mmol/L	normal
C-REACTIVE PROTEIN CRP (QUANTITATIVE) , SERUM		1.0 mg/l	normal
CORTISOL (RANDOM)		3.22 µg/dL	normal
INSULIN - RANDOM , SERUM		33.33 uIU/Ml	high
Urine - Ketone bodies		Negative	normal
Urine – Sugar		Negative	normal

There was no electrolyte imbalance with normal Renal function Tests and Liver Function Test over the course of stay. The child was on continuous glucose monitoring with incidences of hypoglycemia 4-6 times / day and treated with GIR (glucose infusion rate) reaching >12mg/kg/min and on Drugs including IV Hydrocortisone and Oral Diazoxide and refered to our centre for further evaluation and management.

The child was admitted at our NICU on 12th Day of Life. On Examination, there was no gross congenital anomaly with normal vitals and normal neonatal reflex and admission weight of 3800g and blood glucose value of 48mg/dl.

The child was continued on GIR @12mg/kg/min, Oral Diazoxide and IV Hydrocortisone. Octreotide s.c was added and glucose monitoring done and investigations done. The CBC was normal and sepsis screen negative, there was no electrolyte imbalance with normal Renal Function Tests and Liver Function Tests. The following abnormalities

were noted

Laboratory inspection items	Results	
C-Peptide,Serum	6.82 ng/mL	High
INSULIN - RANDOM , SERUM	39.70 µIU/mL	High

USG ABDOMEN/ PANCREAS : Normal Scan

performed to determine the presence of any pancreatic lesions such as adenoma, but no pancreatic problems could be detected.

17 - OH - Progesterone 2.657 ng/mL: Normal

NBS (7 PARAMETERS): Normal

Computed tomography and positron emission tomography of the pancreas were not performed because of the risk of radiation exposure.

The GIR was tapered slowly and stopped over the course of stay and feeds started, while monitoring the blood glucose levels. The dosages of octreotide and diazoxide increased while hydrocortisone was stopped. The child was discharged on 3 February on oral diazoxide and s.c octreotide and on full oral feeds (formula feeds made in Dextrose 5%).

The insulin levels before discharge was

INSULIN , SERUM	3.80 µIU/mL	normal

The Exome study showed

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classification
ABCC8 NM_000352.6	c.331G>A p.Gly111Arg	Exon 3	Homozygous	CADD: 23 SIFT: Deleterious	DIABETES MELLITUS, TRANSIENT NEONATAL, 2; TNDM2:610374 DIABETES MELLITUS, PERMANENT NEONATAL, 3; PNDM3:618857	Autosomal Recessive	Pathogenic

The child is on regular follow up, with no fresh incidence of hypoglycemia with normal growth and development and the medications are being tapered.

DISCUSSION:

Congenital Hyperinsulinemia (CHI) constitutes a group of syndromes characterized by persistent and profound hypoglycemia, displaying diverse histological, genetic, and clinical features. Onset typically occurs within the first two years of life, with approximately one-third of cases manifesting within 28 days after birth, varying in severity. [4,5]

Neonates with CHI exhibit varying clinical symptoms related to hypoglycemia, and severe cases can result in irreversible damage to the nervous system or even cerebral palsy due to inadequate glucose supply to the brain.[6]

Genetic analysis should be performed in suspected patients to guide treatment. For CHI patients, diazoxide therapy is the first-line treatment. Octreotide can be administered as second-line therapy for patients who do not respond to diazoxide. Genetic screening and 18F-L-DOPA-PET/CT are also recommended to guide treatment. The goal of CHI treatment is to maintain a blood glucose level >70 mg/dL[7]

Diazoxide, a KATP channel opener, is effective in CHI patients with intact KATP channels or autosomal dominant KATP mutations . KATP mutations accounts for 45–50% of CHI patients, while ~90% of diazoxide non-responsive patients have mutations in ABCC8 or KCNJ11. [8]

The inheritance patterns of ABCC8 and KCNJ11 genes are predominantly autosomal recessive, although there are instances of autosomal dominant inheritance and de novo mutations. Autosomal recessive mutations in ABCC8 and KCNJ11 genes cause persistent hypoglycemia due to structural and functional abnormalities of KATP. This results in continuous depolarization of the pancreatic β-cell membrane, activation of voltage-gated calcium channels, and influx of calcium ions into pancreatic β-cells, triggering insulin release. This type of inheritance is characterized by early onset and severe symptoms. Typically, autosomal recessive inheritance exhibits diffuse and focal disease histological types. Autosomal dominant inheritance of these genes usually leads to focal histological changes in the pancreatic islets, manifesting with late onset and milder symptoms. [9,10]

Nifedipine is a calcium channel blocker and has been reported as effective drug in regulating insulin secretion. [11] Glucagon stimulates glycogenolysis and gluconeogenesis. But it can cause paradoxical insulin secretion. When CHI patients fail to respond to medical and nutritional treatment, a pancreatectomy should be considered. The extent of surgery depends on CHI subtype, diffuse and focal. However, as pancreatectomy has several risks including the inherent risks of surgery, persistent hypoglycemia and risk of developing diabetes mellitus postoperatively, so surgery is carefully considered. [12]

Apoptotic death of insulin-oversecreting β cells and functional shutdown of insulin secretion were suggested as possible mechanisms for the spontaneous remission of CHI. [13]

CONCLUSION

In summary, congenital hyperinsulinemia and genetic mutations are closely related. Newborns with congenital hyperinsulinemia should be closely watched for recurrent hypoglycemic episodes. Accurate diagnoses require prompt genetic testing for both parents and infants. Prompt pharmacological intervention is essential to prevent damage to the neurological system. It is important to note that the effectiveness of medications varies greatly depending on the type of CHI gene mutation. Therefore, genetic testing plays a pivotal role in the early diagnosis of children with CHI, guiding the development of diagnostic and therapeutic protocols, and determining prognosis.

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