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Congenital Hyperinsulinemia: A Hidden Cause of Persistent Hypoglycemia in Newborns

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ABSTRACT

Persistent, recurrent hypoglycemia is considered when the newborn fails to maintain normal blood glucose despite a Glucose Infusion rate (GIR) of 12 mg/kg/min or if stabilization is not obtained after 7 days of medication, warranting high glucose infusion rates to establish euglycemia. Hyperinsulinism is the most prevalent cause of persistent hypoglycemia, but it can be acquired or congenital. We present a 35-week-old male newborn who presented on the day of life (DOL) 7 with symptomatic hypoglycemia (Random Blood Sugar 33mg/dL) in the form of lethargy, reduced oral acceptance, and seizure-like behavior, with repeated hypoglycemic episodes recorded since DOL 1. He started on GIR at 6mg/kg/min and subsequently raised to 10mg/kg/min and then 12 mg/kg/min since the baby's blood glucose levels were not stable. A critical sample was submitted, which revealed plasma insulin levels of 94.2 mIU/L. The baby was subsequently put on diazoxide, hydrocortisone, and octreotide. Once euglycemia was reached by DOL 11, GIR was gradually reduced, and meals were supplemented with dextrose in every feed. By DOL 15, the child was on full orogastric feeds enriched with dextrose and medium chain triglyceride (MCT) oil before being discharged at DOL 30 on injection octreotide. Ultrasonography of the whole abdomen and later F-DOPA PET scan indicated no localized pancreatic disease. The genetic test revealed a heterozygous single-base pair duplication in exon 1 of the KCNJ11 gene, suggesting congenital hyperinsulinism (CHI). The diagnosis process followed a stepwise approach: first, a critical sample was taken to establish hyperinsulinemia; then, all acquired causes were ruled out through history, examination, and investigations; and finally, the diagnosis was clinched using genetic testing.

Keywords: Octreotide; Congenital hyperinsulinism; KCNJ11; Persistent hypoglycemia; Neonatal hypoglycemia

INTRODUCTION

Persistent, recurrent hypoglycemia should be regarded if the baby is unable to maintain normal blood glucose levels despite a GIR of 12 mg/kg/min or if stabilization is not attained after 7 days of treatment, necessitating high glucose infusion rates to achieve euglycemia.[1,2] The most common cause of chronic hypoglycemia in newborns and children is hyperinsulinism (HI), causing persistent, recurrent hypoglycemia in neonates.[3] It is associated with an increased risk of brain injury because it lowers serum glucose levels and inhibits fatty acid release and ketone body synthesis, preventing the brain from using secondary fuel sources.[4] Some cases of hyperinsulinemic hypoglycemia are transient and recover within a few days, while others require more aggressive and prolonged treatment.[5] Certain conditions, including maternal diabetes, birth asphyxia, polycythemia, Rh incompatibility, severe intrauterine growth restriction, etc., can cause acquired hyperinsulinemic hypoglycemia. At the same time, congenital forms result from mutations that dysregulate the pancreatic release of insulin.[6] Diagnosis of hyperinsulinism is confirmed through critical sample analysis, where low levels of free fatty acids, low beta-hydroxybutyrate levels, low cortisol levels, increased insulin levels, low glucose levels, and low glucose-to-insulin ratio are expected.[7] Deviations from these normal values help distinguish hyperinsulinism from other causes of hypoglycemia.[8]

CASE PRESENTATION

A 35-week preterm male infant with a birth weight of 2.86 kg was admitted on DOL 7 due to symptomatic hypoglycemia, presenting with lethargy, poor feeding, and seizure-like activity. His initial Random Blood Sugar (RBS) was 33 mg/dL, consistent with hypoglycemia. Recurrent hypoglycemic episodes have been observed since DOL 1. The baby was started on a GIR of 6 mg/kg/min, which was gradually increased to 10 mg/kg/min on DOL 8 and further increased to 12 mg/kg/min, as blood glucose levels remained unstable despite the increasing GIR.

The clinical examination revealed that the child was large for gestational age (LGA), with no organomegaly. Investigations revealed normal hematocrit, as well as normal liver and kidney function tests. A critical blood sample was sent for further evaluation, which showed an elevated plasma insulin level of 94.2 mIU/L (normal <2 mIU/L) and an elevated C-peptide level of 0.8 ng/ml (normal <0.5 ng/ml), indicative of endogenous hyperinsulinism. Based on these findings, a diagnosis of congenital hyperinsulinism (CHI) was considered. (Table 1)

Treatment with diazoxide (15 mg/kg) and intravenous hydrocortisone was started to control insulin secretion. By DOL 10, despite the management with diazoxide and hydrocortisone, the infant continued to experience recurrent hypoglycemic episodes. Injection Octreotide was added at 25 mcg/kg/day, and IV hydrocortisone was discontinued. The GIR was maintained at 12 mg/kg/min with IV fluids and feeds until euglycemia was achieved.

Once blood glucose levels stabilized on DOL 11, the GIR was gradually reduced to 6 mg/kg/min, and the feeds were fortified with 1 ml of 10% dextrose per feed. An abdominal ultrasound was performed to rule out any pancreatic pathology, which was normal. By DOL 15, GIR was omitted, and the infant was transitioned to full oral feeds, fortified with 3 mL 10% dextrose and MCT (medium-chain triglyceride) oil every 2 hours.

At discharge on DOL 30, the infant received expressed breast milk fortified with MCT oil and 2 mL of 25% dextrose in alternate feeds and continued subcutaneous Octreotide injections (0.6 mL, thrice daily). (Figure 1)

To further evaluate the cause of CHI, on follow-up, an F-DOPA PET scan was conducted, which revealed no focal pancreatic lesions. Genetic testing was performed to investigate the possibility of neonatal monogenic diabetes, and Sanger sequencing revealed a heterozygous single-base pair duplication in exon 1 of the KCNJ11 gene (chromosome 11), which is suggestive of congenital hyperinsulinism (CHI). This genetic finding confirmed the diagnosis of CHI, which is typically associated with mutations in the KCNJ11 gene, encoding the Kir6.2 subunit of the ATP-sensitive potassium (K-ATP) channel in pancreatic beta-cells. (Table 2)

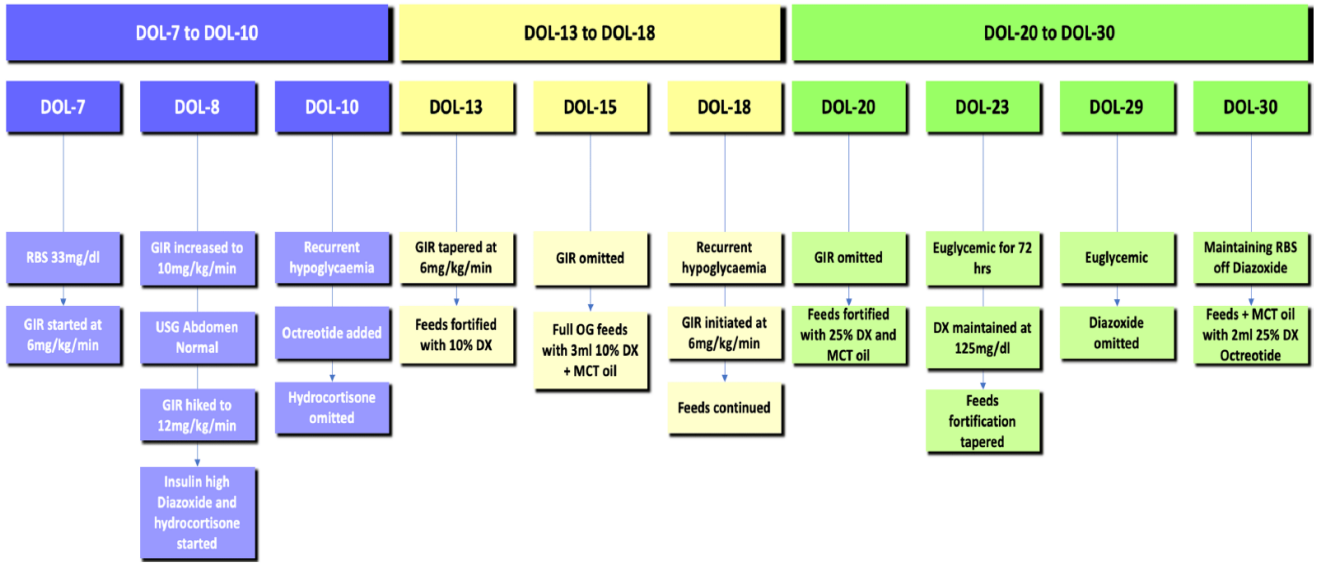

Figure 1: Clinical course during hospital stays. Abbreviations: DOL, day of life; RBS, random blood sugar; GIR, glucose infusion rate; USG, ultrasonography; Dx, dextrose; MCT, medium-chain triglyceride

Table 1: Laboratory investigations of the child

Parameter	Patient Value	Reference Range (SI Units)	Interpretation
Random Blood Sugar (RBS)	33 mg/dL (1.8 mmol/L)	>45 mg/dL (>2.5 mmol/L) in neonates	Severe hypoglycemia
Hematocrit	0.56	0.45–0.65 L/L (45–65%)	Within normal limits
Liver Function Tests	ALT: 35 U/L, AST: 60 U/L	ALT: ≤45 U/L, AST: ≤80 U/L	No hepatic dysfunction
Kidney Function Tests	Urea: 6.3 mmol/L, Creatinine: 0.4 mg/dL	Urea: 2.5–7.1 mmol/L, Creatinine: 0.3–1.2 mg/dL	Normal renal function
CSF Analysis	Pre-LP RBS – 60 mg/dL; 15 cells/hpf (100% polymorphs); Protein 155 mg/dL; Glucose 122 mg/dL; Culture – sterile	In term neonates: 0–30 cells/hpf (≤60% polymorphs); Protein 20–170 mg/dL; Glucose 34–119 mg/dL; Culture – sterile	Infective etiology: antibiotics initiated
Plasma Insulin	94.2 mIU/L	<2 mIU/L during hypoglycemia	Markedly elevated; confirms hyperinsulinism
C-Peptide	0.8 ng/mL (0.26 nmol/L)	<0.5 ng/mL (<0.17 nmol/L)	Elevated indicates endogenous insulin
Free Fatty Acids (FFA)	Low	>1.5 mmol/L during hypoglycemia	Suppressed; consistent with HI
β-Hydroxybutyrate	Low	>2 mmol/L during hypoglycemia	Suppressed – no ketosis
Abdominal Ultrasound	Normal pancreas	No focal lesion or organomegaly	No anatomical pancreatic abnormalities
F-DOPA PET Scan	No focal uptake	Focal lesion would show increased uptake	Diffuse form of CHI

Abbreviations: RBS – Random blood sugar; ALT – Alanine transaminase; AST – Aspartate transaminase; LP – Lumbar puncture.

Table 2: Results of Molecular Genetic Investigation

Genomic position	Gene (Strand)	c.DNA Position	Amino acid change	Location
chr11: 17387594dup 'C'	KCNJ11 (-)	c.498dup 'C' (ENST00000339994)	p. Ile167HisfsTer13	Exon 1

DISCUSSION

This case report highlights the complex management of a preterm infant with CHI. Despite initial GIR and subsequent increases, the infant's blood glucose levels remained unstable, necessitating a comprehensive diagnostic and therapeutic approach. The infant's presentation with lethargy, decreased oral acceptance, and seizure-like activity was consistent with severe hypoglycemia. Initial management with GIR at 6 mg/kg/min was insufficient, requiring escalation to 12 mg/kg/min. This highlights the challenge of managing hypoglycemia in CHI, where standard glucose administration often fails to maintain euglycemia.

The diagnostic workup included a critical sample revealing elevated plasma insulin and C-peptide levels, confirming hyperinsulinism. The absence of organomegaly and normal hematocrit, liver, and kidney functions ruled out other potential hypoglycemia causes.

Introducing diazoxide, a K-ATP channel opener, at 15 mg/kg and IV hydrocortisone aimed to reduce insulin secretion and stabilize blood glucose levels. However, recurrent hypoglycemic episodes required the addition of octreotide, a somatostatin analog, which further helped manage insulin levels. The gradual tapering of GIR and fortifying feeds with dextrose and medium-chain triglyceride (MCT) oil were crucial in achieving and maintaining euglycemia.

To distinguish between the diffuse and focal forms of the disease, an 18F-DOPA PET scan was performed, which ruled out a focal pancreatic lesion—a surgically correctable finding. The definitive diagnosis was then established through molecular analysis. Sanger sequencing revealed a heterozygous single-base pair duplication in exon 1 of the *KCNJ11* gene, confirming congenital hyperinsulinism. This pathogenic mutation is known to disrupt the function of K-ATP channels in pancreatic beta cells, resulting in unregulated insulin secretion.

Mutations in the genes ABCC8 and KCNJ11, which encode for SUR1 and Kir6.2, the pancreatic beta cell adenosine triphosphate (ATP)-sensitive potassium channel, result in hyperinsulinism.[9] Mutations in the HNF4A gene that cause loss of function are also linked to elevated insulin levels. In addition to many syndromic types, at least 12 recognized monogenic forms of HI exist.[10] The likelihood of surgically curable focal hyperinsulinism and response to medicinal therapy can both be predicted with genetic molecular diagnostics. As a result, prompt genetic mutation analysis is now considered the norm.[11,12]

CONCLUSIONS

This case underscores the importance of early recognition and aggressive management of hypoglycemia in infants with CHI. A multidisciplinary approach is vital for optimizing outcomes, including endocrinology, neonatology, and genetics. The diagnosis method was carried out in stages, beginning with a critical sample to confirm hyperinsulinemia, then ruling out all acquired reasons by history, examination, and investigations, and lastly concluding with genetic testing. Genetic testing plays a crucial

role in diagnosing CHI and guiding treatment strategies. Further research is needed to explore novel therapies and improve the prognosis for infants with this challenging condition.

DECLARATIONS

Informed Consent: Informed consent for treatment and publication was obtained.

Conflicts of Interest: The authors declare no conflicts of interest.

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REFERENCES

1. Paul S Thornton, Charles A Stanley, Diva D De Leon, Deborah Harris, Morey W Haymond, Khalid Hussain, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015;167:238-245.
2. Eichenwald EC, Hansen AR, Martin C. Hypoglycemia and Hyperglycemia. In: Castillero AB, Simmons R, eds. Cloherty and Stark's Manual of Neonatal Care. Philadelphia: Wolters Kluwer; 2023:319-327.
3. Lord K, De León DD. Hyperinsulinism in the Neonate. Pediatr Clin North Am. 2018;65(5):937-954.
4. Addisu Sertsu, Kabtamu Nigussie, Addis Eyeberu, Abel Tibebu, Abraham Negash, Tamirat Getachew, et al. Determinants of neonatal hypoglycemia among neonates admitted at Hiwot Fana Comprehensive Specialized University Hospital, Eastern Ethiopia: A retrospective cross-sectional study. SAGE Open Med. 2022;10:1-9.
5. Hussain K. Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. Horm Res. 2007;68(1):2-13.
6. Demirbilek H, Hussain K. Congenital Hyperinsulinism: Diagnosis and Treatment Update. J Clin Res Pediatr Endocrinol. 2017;9(Suppl 2):69-87.
7. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015;167(2):238-45
8. Kelly A, Tsalikian E. Hypoglycemia in Infants and Children. Pediatr Rev. 2021;42(6):296-308.
9. Rosenfeld E, Ganguly A, De Leon DD. Congenital hyperinsulinism disorders: Genetic and clinical characteristics. Am J Med Genet C Semin Med Genet. 2019;181:682-692.
10. Demirbilek H, Hussain K. Congenital Hyperinsulinism: Diagnosis and Treatment Update. J Clin Res Pediatr Endocrinol. 2017;9(Suppl 2):69-87.
11. Sims K. Congenital Hyperinsulinism. NeoReviews. 2021;22(4):e230-e240.
12. Velde C, Hansen E, Reigstad H, et al. Medfødt hyperinsulinisme. Tidsskr Nor Laegeforen. 2023;143:1.