Protein-induced Hypoglycemia Secondary To Hyperinsulinism-Hyperammonemia Syndrome: A Glud1 Gene Mutation

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♦ INTRODUCTION

Hyperinsulinemia-hyperammonemia (HI/HA) syndrome is a rare autosomal disease characterized by episodes of hypoglycemia related to consumption of high-protein containing foods or fasting with associated hyperammonemia secondary to activating mutation in the GLUD1 gene. The syndrome of HI/HA continues to remain often unrecognized until later in childhood because symptomatic episodes can be misinterpreted as epilepsy if patterns of hypoglycemia with fasting and protein-rich meals are not identified.

Here we present a case of a 9 months old male presenting with new onset seizures in the setting of hypoglycemia.

♦ CASE

9 month old full-term male with history of failure to thrive presents to the ED with seizure-like activity in the setting of severe hypoglycemia.

Clinical Course:

- Presentation → Vitals signs stable with blood glucose (BG) 33 mg/dl.
- Administration of apple juice → BG increased to 53 mg/dl.
- Placed on IV dextrose → maintains BG >50 mg/dl.
- Admitted to the PICU and made NPO, fluids stopped to induce hypoglycemia → maintains BG >50mg/dl for 10 hours.
- Two hours after protein rich meal → BG in 40s, resolves with juice. Critical labs obtained. (Table 1)
- BG monitoring initiated via sensor (Graph 1)

Genetic Testing:

- Heterozygous in GLUD1 gene for variant c.965>A (p.Arg322His) confirming HI/HA syndrome.

Intervention:

- Diet restricted to formula
- Started on Diazoxide 15 mg PO TID with resolution of hypoglycemia.
- Patient continues on Diazoxide, now 25 mg TID with a regular diet for age.

♦ DISCUSSION

Hyperinsulinemia-hyperammonemia syndrome:

- Activating mutation in GLUD1 gene.
- Second most common cause of congenital hyperinsulinism.
- Tends to be milder presentation.
- The GLUD1 gene, found on Chromosome 10, is responsible for expression of glutamate dehydrogenase (GDH) in pancreatic β-cells, liver, kidney and the brain.
- GDH plays an important role in regulating amino acid-induced insulin secretion.
- GDH is activated by ADP and leucine and inhibited by GTP and ATP.
- In particular, loss of inhibition by GTP in HI/HA leads to increased leucine-induced glutamate oxidation to alpha-ketoglutarate leading to leucine sensitivity manifested by hypoglycemia after protein-rich meals.

Clinical Suspicion:

- Unexplained hypoglycemia associated with and without hyperammonemia outside of the newborn period.
- Mild hyperinsulinemia not associated with neonatal macrosomia.
- Symptomatic episodes can be misinterpreted as epilepsy if patterns of hypoglycemia with fasting and protein-rich meals are not identified.

♦ GRAPHS

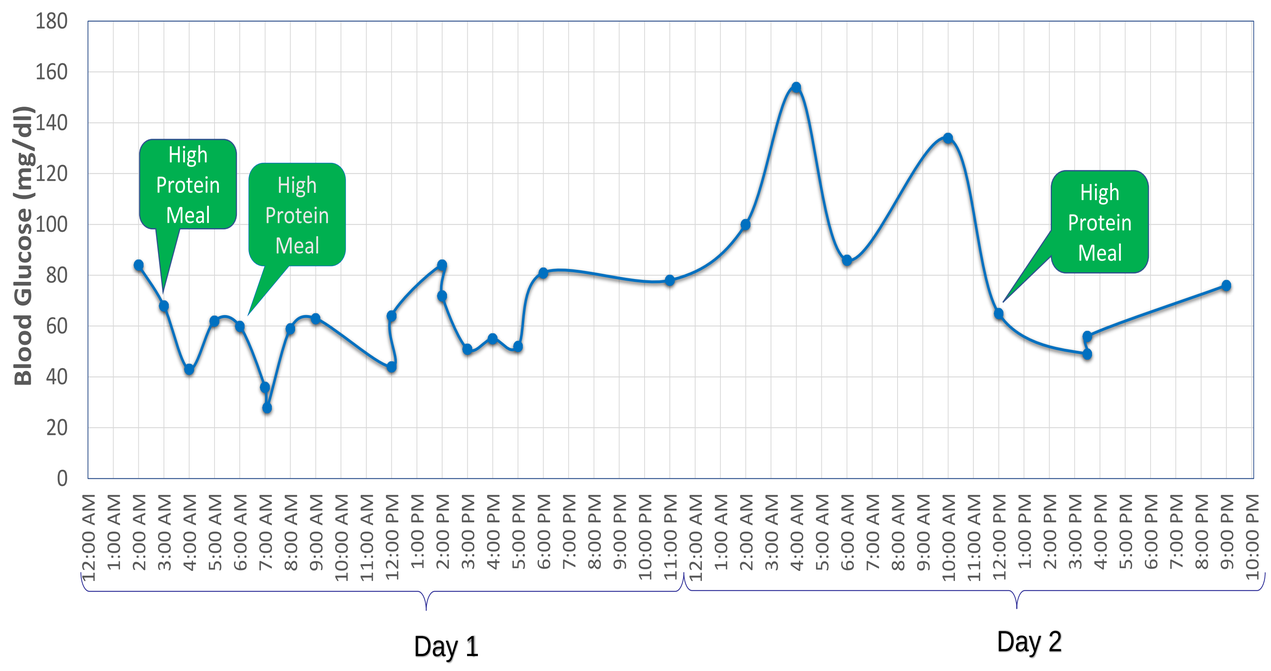
Table 1

HYPOGLYCEMIC EPISODES RELATED TO HIGH PROTEIN MEALS

	1st Hypoglycemia	2nd Hypoglycemia
POC blood Glucose	42 mg/dl	43 mg/dl
Serum glucose	31 mg/dl	40 mg/dl
Insulin	5.6 uIU/ml	
Ketones	Negative	
Cortisol	1.8 ug/dl	12.6 ug/dl
ACTH		48 pg/ml
Ammonia		178 ug/d
GH		9.0 ng/ml

Graph1

BLOOD GLUCOSE MONITORING



♦ CONCLUSION

- HI/HA syndrome secondary to GLUD1 defect should be considered in patients with unexplained hypoglycemia associated with and without hyperammonemia outside of the newborn period.
- Identifying timing of hypoglycemia episodes in relation to schedule of feeding and types of food consumed in meals is important. This can help to define a pattern for the hypoglycemic episodes and aid in the diagnosis.

♦ REFERENCES

- Genetics Home Reference https://ghr.nlm.nih.gov/gene/GLUD1
- Kapoor, Ritika R, et al. "Hyperinsulinism–hyperammonaemia syndrome: novel mutations in the GLUD1 gene and genotype–phenotype correlations." European Journal of Endocrinology, 1 Nov. 2009, www.eje-online.org/lookup/doi/10.1530/EJE-09-0615.
- Stanley, Charles A. "Two Genetic Forms of Hyperinsulinemic Hypoglycemia Caused by Dysregulation of Glutamate Dehydrogenase." Neurochemistry International, vol. 59, no. 4, 2011, pp. 465–472., doi:10.1016/j.neuint.2010.11.017.
- Stanley, Charles A., et al. "Hyperinsulinism and Hyperammonemia in Infants with Regulatory Mutations of the Glutamate Dehydrogenase Gene." New England Journal of Medicine, Massachussetts Medical Society, 5 Oct. 2015, experts.umich.edu/en/publications/hyperinsulinism-and-hyperammonemia-in-infants-with-regulatory-mut.
- W. A. COCHRANE,' W. W. PAYNE, M. J. SIMPKISS, AND L. I. WOOLF. "Familial hypoglycemia precipitated by amino acids". Journal of Clinical Investigation, 1956 Apr;35(4):411-22. PMID: 13306783, DOI: 10.1172/JCI103292

♦ DISCLOSURES

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