Protein-induced Hypoglycemia Secondary To Hyperinsulinism-Hyperammonemia Syndrome: A Glu1 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 GLU1 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 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 GLU1 gene.
- Second most common cause of congenital hyperinsulinism.
- Tends to be milder presentation.
- The GLU1 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.

Conclusion

- HI/HA syndrome secondary to GLU1 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


Disclosures

Funding source: No funding was secured for this study. Disclosures: None. Conflict of interest: None