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Hyperinsulinism-Hyperammonaemia syndrome: a dive into the rare presentation and diagnostic challenges encountered in adults

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Background: Hyperinsulinemic-hyperammonemia, a rare form of congenital hyperinsulinemia, can seldom present in adulthood if failed to be diagnosed during infancy, enabling it to be difficult to identify, and predisposing affected individuals to neurological complications. **Case:** A 20-year-old female with intellectual disability, seizure disorder and ornithine transcarbamylase deficiency was admitted for recurrent episodes of asymptomatic hypoglycemia. Her medications included risperidone, fluoxetine, levetiracetam, lacosamide, ferrous sulphate and acetaminophen. Physical examination including vital signs was unremarkable. Relevant labs included a fasting glucose of 46mg/dl [70-99]. Further work up of hypoglycemia revealed an IGF-1 of 215ng/dl [85-350] and AM Cortisol of 6.5mcg/dl [5-25]. Given a low AM cortisol level under stress, an ACTH stimulation test was done with appropriate response of cortisol of 24 following cosyntropin administration, ruling out adrenal insufficiency. The patient continued to have h ypoglycemia noted on several glucometer checks every 4 hours where she remained asymptomatic. She was further evaluated with a mixed meal study where no hypoglycemia was noted. A 72 -hour fast was performed which was terminated based on a venous blood sample glucose reading of 50 mg/dl confirmed after hypoglycemia was noted on a glucometer check. The labs showed elevated C-peptide levels of 4ng/ml [0.4-2], insulin of 4mIU/L [<25] and proinsulin level of 2.3pmol/l [3-20]. Levels of insulin and proinsulin were noted to be inappropriately normal in the setting of hypoglycemia. Beta hydroxybutyrate was low at 0.1mmol/L [<0.5] and glucagon inappropriately normal at 36pg/ml [50-100]. Sulfonylurea, meglitinide and autoimmune antibody screen were negative. CT abdomen and pelvis was negative for pancreatic abnormality. In the absence of evidence for acquired causes of hyperinsulinemic hypoglycemia, congenital cases were investigated. Based on that, further labs were obtained including ammonia levels which was elevated at 177.2 u/dl [15-45]. Accordingly, GLUD-1 gene mutation was sent, given high suspicion for hyperinsulinemic hyperammonemia syndrome, which resulted positive and confirmed the diagnosis. She was started on a protein restricted diet and diazoxide which regulated her blood glucose levels effectively. **Discussion:** Hyperinsulinism/hyperammonemia (HI/HA) syndrome is a form of congenital hyperinsulinism caused by activating mutations of the GLUD 1 gene which encodes Glutamate Dehydrogenase, a key enzyme in the beta cell pathway of amino acid-stimulated insulin secretion. The resultant syndrome is characterized by fasting and protein induced hypoglycemia, elevated serum ammonia levels without typical hyperammonemic symptoms. Management includes effective blood glucose control with an insulin inhibitor such as diazoxide and a protein restricted diet with consideration to predominantly include carbohydrates and fat. **Conclusion:** Hyperinsulinemia hyperammonemia is a rare form of congenital hyperinsulinemia typically diagnosed during infancy and should be considered as a possible differential diagnosis in patients presenting with new onset hypoglycemia, as timely diagnosis and intervention can prevent forthcoming neurological complications.

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