DELAYED DIAGNOSIS OF HYPERINSULINISM HYPERAMMONEMIA SYNDROME: A CASE REPORT

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Hyperinsulinism Hyperammonemia Syndrome (HI/HA syndrome) is an autosomal dominant disease caused by activating mutations in GLUD1, the gene responsible for encoding the mitochondrial enzyme glutamate dehydrogenase (GDH). This syndrome represents the second most common genetic form of congenital hyperinsulinism in infancy. Children with HI/HA syndrome typically experience hypoglycemic symptoms triggered by fasting or high-protein meals and persistently elevated ammonia levels. We report a case of HI/HA syndrome in a 7-month-old female who presented with cyanosis and hyperammonemia, along with an initial normal glucose level at the time of presentation. About one week after the child's admission to the hospital, we discovered that hypoglycemia was the cause of her irritability. The hypoglycemic episode was found to occur coincidentally with hyperammonemia. The combination of clinical findings, biochemical markers, and genetic sequencing identifying a GLUD1 pathogenic variant facilitated the correct diagnosis of HI/HA syndrome. As demonstrated by this case, the diagnosis of HI/HA syndrome requires a thorough clinical evaluation, comprehensive biochemical analysis, and genetic testing. With the correct diagnosis, a patient with HI/HA syndrome can receive ongoing monitoring and care with the goal of preventing adverse neurologic sequelae.

Keywords: Hyperinsulinism Hyperammonemia Syndrome, hyperammonemia, hypoglycemia, *GLUD1*.

I. INTRODUCTION

Hyperinsulinism Hyperammonemia (HI/HA) syndrome is a rare metabolic disorder characterized by recurrent episodes of hypoglycemia in association with persistently elevated plasma ammonia levels. First described as a familial hypoglycemia precipitated by amino acid intake, the syndrome is now understood to result predominantly from activating mutations in the *GLUD1* gene, which encodes glutamate dehydrogenase (GDH).[1-3] These mutations lead to enhanced GDH activity, resulting in increased insulin secretion, particularly after protein-rich meals, and overproduction of ammonia due to accelerated glutamate catabolism.[4,5] HI/HA accounts for approximately 10% of congenital hyperinsulinism (CHI) cases and is notable for its distinct clinical and biochemical profile, including protein-induced hypoglycemia and hyperammonemia in the absence of liver dysfunction.[6] The neurological phenotype varies, with some patients exhibiting developmental delays, learning disabilities, or epilepsy, likely due to recurrent hypoglycemia and the neurotoxic effects of ammonia.[7,8] Early diagnosis through genetic testing and biochemical evaluation is essential, as appropriate treatment-including diazoxide therapy and dietary protein moderation-can significantly reduce the risk of long-term neurological complications.[2,9]

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II. CASE REPORTS

Clinical manifestation

A 7-month-old girl, the first child, with a birth weight of 2800 grams (-1.1 SD), showed normal psychological and motor development, a normal medical history, and a negative family history for other individuals with HI/HA syndrome. At 6 months of age, she experienced cyanosis before and after meals (two episodes per month), and she returned to normal without any treatment.

The patient was transferred to a local hospital due to irritability without cyanosis. Initial laboratory tests at this hospital yielded the following findings: normal arterial blood gas, hyperammonemia (with an unknown initial value), serum glucose of 3.2 mmol/l, normal serum lactate, negative ketone urine, and normal results for her first brain MRI scan, electroencephalogram, and abdominal ultrasound. She was given natribenzoate at 250mg/kg/day every 8 hours orally, biotin 5mg/time every 12 hours orally, L-carnitine 330mg every 12 hours orally, and L-Arginine 300mg every 12 hours orally. However, the patient's symptoms did not significantly improve after the treatment for hyperammonemia, prompting transfer to the National Children's Hospital of Vietnam.

In our hospital, her symptoms include severe irritability and vomiting, but her hemodynamic status remains stable. A physical examination revealed a weight of 7,500 gram (-0,1 SD), a length of 63cm (-1.85 SD), and a head circumference of 45cm (+1.6 SD). Point-of-care testing for blood glucose shows a reading of 4.5 mmol/l. A preliminary examination produced the following results: a serum ammonia level of 294 mcg/dL (normal < 85.2 mcg/dL); a serum glucose level of 4.2 mmol/L (normal: 3.3 – 5.5 mmol/L); a serum lactate level of 1.9 mmol/L (normal: 0.8 – 1.5 mmol/L); normal serum transaminase (GOT: 35.3 U/L - GPT: 26.3 U/L), normal coagulation function; negative ketones in urine; and arterial blood gas showing respiratory alkalosis. Her metabolic panel was unremarkable, with normal MS/MS (Tandem Mass Spectrometry, including plasma amino acids and acylcarnitine profile) screening performed twice, and normal blood amino acid and urine organic acid levels. Brain MRI scan revealed suspicious abnormalities in the white matter signal beneath the brain's cortex and delayed myelination. We diagnosed her as hyperammonemia and a suspected metabolic disorder.

She was managed with dextrose and required a glucose infusion rate of 8 mg/kg/minute due to her vomiting status; she was given L-carnitine and natribenzoate, but her hyperammonemia was still elevated (Chart 1). We decided to switch to a non-essential amino acid-free formula (WND1) for milk.

After two weeks of treatment, her eyes rolled back into her head (we discontinued fluid infusion, and she had been eating entirely by mouth for one week), with her serum glucose during that time at 2.74 mmol/L. Afterward, we observed that her blood glucose continuously decreased throughout the day. The patient required a high glucose infusion rate (GIR: 4.4 mg/kg/min) necessary to maintain euglycemia.

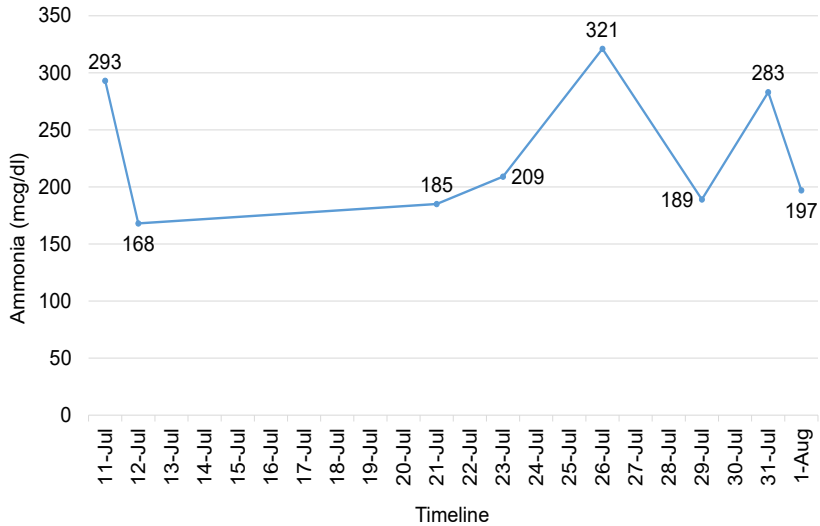

Chart 1. Changes in serum ammonia levels during treatment

Genetic results

Direct sequencing of the coding region of the *GLUD1* gene revealed that the patient was heterozygous for a missense mutation in exon 12, (c.1519 C>T; p.His507Tyr; (based on NCBI Accession Number NM_005271.5). Neither parent carried this variant (Figure 1), suggesting a “de novo” mutation, which could not be definitively confirmed because a paternity test was not performed. Currently, she is using diazoxide at a dosage of 10mg/kg/day to control her blood glucose levels.

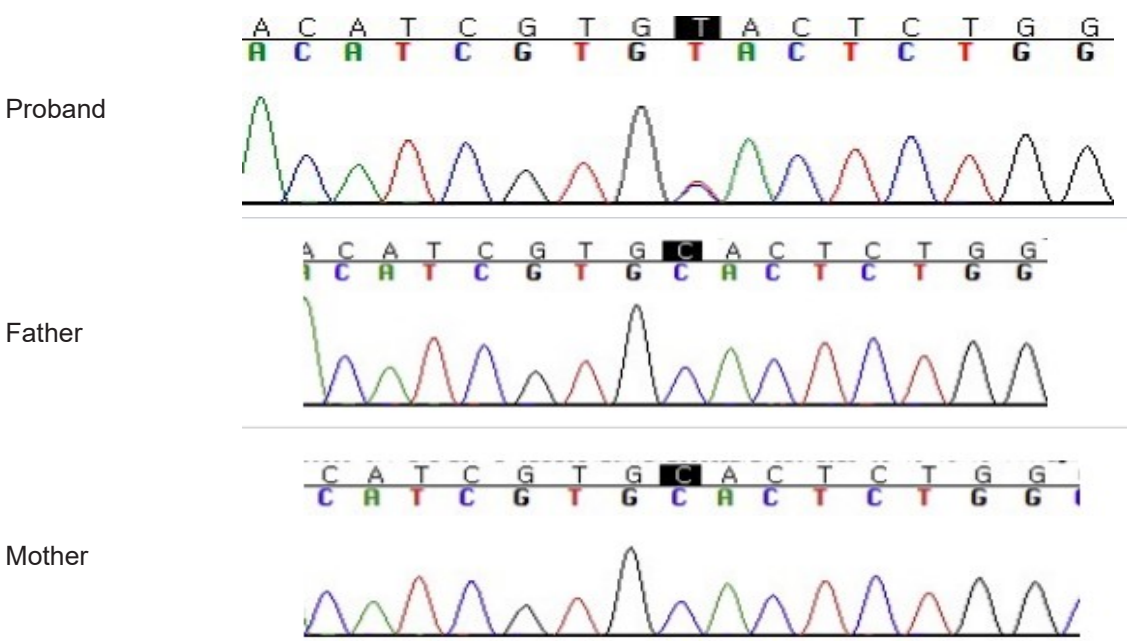

Figure 1. Electropherogram showing the reverse strand sequence of exon 12 of her family. In the proband, the substitution of C by T at nucleotide 1519 (c.1519 C>T) results in the replacement of Histidine by Tyrosine at codon 507 (p.His507Tyr) of the GLUD1 protein

Follow–up

The patient is still treated with diazoxide (10mg/kg/day) to control her glucose levels. After 2 months of discharge, cyanosis appeared, and point-of-care testing for blood glucose at that time showed 4.6 mmol/l. She has not had an electroencephalogram (EEG) or repeat brain MRI thus far.

IV. DISCUSSION

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infants and children. It is characterized by the inappropriate secretion of insulin during hypoglycemia. The incidence of CHI is estimated to be approximately 1 in 28,000 to 1 in 50,000 newborns in non-consanguineous populations.[6,10]000 live births, but it may be as high as 1/2, 500 in countries with substantial consanguinity. Recurrent episodes of hyperinsulinemic hypoglycemia may expose to high risk of brain damage. Hypoglycemias are diagnosed because of seizures, a faint, or any other neurological symptom, in the neonatal period or later, usually within the first two years of life. After the neonatal period, the patient can present the typical clinical features of a hypoglycemia: pallor, sweat and tachycardia. HI is a heterogeneous disorder with two main clinically indistinguishable histopathological lesions: diffuse and focal. Atypical lesions are under characterization. Recessive ABCC8 mutations (encoding SUR1, subunit of a potassium channel Mutations in 36 different genes have been reported, which can follow recessive, dominant, X-linked, or sporadic inheritance.[9]

HI/HA syndrome is the second most common form of congenital hyperinsulinism and is the only condition with both hypoglycemia and hyperammonemia. This syndrome results from a mutation of the *GLUD1* gene, which encodes for the mitochondrial enzyme glutamate dehydrogenase (GDH). GDH activities in pancreatic islet, liver, kidney, and brain.[2] It catalyzes the reversible oxidative deamination of glutamate to α-ketoglutarate, ammonia, and NADH or NADPH.[5,11] GDH is activated by Leucin and adenosine diphosphate (ADP) and is inhibited by guanosine triphosphate (GTP).[3] α-ketoglutarate metabolized within the Krebs cycle generates cellular ATP, leading to the closure of ATP-sensitive potassium channels, which activates calcium channels and triggers insulin release, resulting in severe hypoglycemia due to unregulated insulin secretion. The *GLUD1* gene mutation leads to decreased inhibition by GTP and increased activation by Leucine on GDH, resulting in increased ammonia production.[4]

The main symptoms of this syndrome are recurrent hypoglycemia together with asymptomatic hyperammonemia. However, this patient's hypoglycemia was masked by vomiting and poor appetite, resulting in the need for fluid infusion. As such hypoglycemia was not initially detected. On the other hand, the patient required a high glucose infusion rate due to hyperammonemia and suspected metabolic disease. When the patient was able to take milk orally, the fluid infusion was discontinued and hypoglycemia was detected. Combined with genetic analysis, the patient was diagnosed with HI/HA syndrome and started using diazoxide to control her blood glucose.

The patient still experiences episodes of cyanosis, unrelated to hypoglycemia. She needs to undergo an EEG to evaluate for seizures as there is an increased risk of seizures in patients with HI/HA syndrome.[4] Undiagnosed seizure disorder can lead to developmental delays and, if it remains undiagnosed, can lead to permanent

neurologic damage. This risk is based on the hypothesis is an alternation of center nervous system glutamate concentrations due to GDH overactivity.[7] However, as of now, there is no evidence of the correlation between serum concentration of ammonia and the risk for epilepsy and/or intellectual impairment in patients with HI/HA syndrome.[8]

V. CONCLUSION

HI/HA syndrome is a rare disease in which hypoglycemia, hyperammonemia, and neurological symptoms may be present in children. The approach to patients with nonspecific neurological symptoms should consider the evaluation for hyperammonemia; one should always take note to the patient's hypoglycemia status, especially during fluid infusion.

Informed Consent: The patient's parents provided informed consent to publish this case report.

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