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Case Report

A Very Rare Case of Diabetes Mellitus Occurring in a Patient With Hyperinsulinism Hyperammonemia Syndrome

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ABSTRACT

Background/Objective: To illustrate an unusual case of type 2 diabetes mellitus (T2DM) developing many years after the diagnosis of hyperinsulinism hyperammonemia (HI/HA) syndrome.
Case Report: This article reports about a 36-year-old female with a history of congenital hyperinsulinism due to HI/HA syndrome, which was diagnosed in infancy. The patient presented with hypoglycemia and seizures as an infant and was treated with diazoxide and a low-protein diet for many years with reduction in her hypoglycemic events. She subsequently developed T2DM >30 years later. Genetic analysis was positive for a glutamate dehydrogenase 1 gene (*GLUD1*) alteration. She was treated with metformin and a glucagon-like peptide 1 agonist, with significant improvement in her blood glucose control and weight loss.
Discussion: HI/HA syndrome is a rare genetic syndrome that manifests in childhood with signs and symptoms of hypoglycemia and neurologic symptoms. This is the first case reported in the literature of a patient with HI/HA syndrome due to a *GLUD1* alteration who developed T2DM much later in life. Patients with this disorder usually have recurrent hypoglycemia and require long-term medical therapy or very occasionally may have a resolution. She had class 3 obesity and evidence of insulin resistance, which likely contributed to her risk of diabetes.
Conclusion: This is a rare case of T2DM presenting in a patient with HI/HA syndrome. This should be considered a possible outcome in patients with this disorder, especially in the presence of obesity.

Introduction

Hyperinsulinism hyperammonemia syndrome is caused by a heterozygous missense amino acid substitution on the glutamate dehydrogenase 1 (*GLUD1*) gene. Patients usually present with hypoglycemia (both fasting and protein sensitive) that causes an increased risk of generalized epilepsy, mental retardation, and behavioral disorders. Our patient initially presented with hypoglycemia but later developed type 2 diabetes mellitus (T2DM) as an adult, which is unusual in the presence of *GLUD1* alteration and is the first case reported in the literature so far.

Case Report

A 36-year-old female with a history of hyperinsulinism hyperammonemia (HI/HA) syndrome was referred to our endocrine outpatient clinic to establish care. She was diagnosed with HI/HA at the age of 6 weeks after she experienced frequent seizures that were believed to be related to hypoglycemia. She was subsequently started on diazoxide and a low-protein diet. She had no recent episodes of hypoglycemia and had been seizure-free for >10 years. She was taking diazoxide 5 mL every 12 hours. She had a strong family history of T2DM, both her parents and a couple of her aunts and uncles. Her 9-year-old son was also diagnosed with HI/HA syndrome as an infant. On physical examination, vitals were normal, and the body mass index was 45.9 kg/m^2. She notably had acanthosis nigricans on the back of her neck. The rest of her physical examination was unremarkable. Her initial laboratory testing, including a comprehensive metabolic panel, was also unremarkable except for a mild elevation in her serum ammonia level. We continued her on diazoxide at the current dosing. She was then lost to follow-up for approximately 1 year.

At her next clinic visit, she reported that her blood glucose levels had gone up to the 120 to 130 mg/dL range with no hypoglycemia. She notably had some weight gain as well. She reported eating a lot of carbohydrates as meals and snacks. Her hemoglobin A1c (HbA1c) level was 7.2% (56 mmol/mol), and her dose of diazoxide was then

Abbreviations: GLUD1, glutamate dehydrogenase 1; HI/HA, hyperinsulinism hyperammonemia; T2DM, type 2 diabetes mellitus.

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reduced to 2 mL every 12 hours from 5 mL every 12 hours. She was also counseled to reduce her carbohydrate intake. She then missed follow-up appointments and came back again approximately 8 months after her last visit. No hypoglycemia was reported during this time frame. Her basic metabolic panel was notable for a random glucose level of 238 mg/dL, and her HbA1c level was 10% (86 mmol/mol). She was diagnosed with T2DM, diazoxide was discontinued, and she was started on metformin 500 mg twice a day. Further workup was significant for glutamic acid decarboxylase antibodies (<5), a C-peptide level of 6.5 ng/mL (range, 1.1-4.4 ng/mL), negative antipancreatic islet-cell antibodies, and an insulin level of 69 μU/ml (range, 2.6-24.9). Given her history of HI/HA syndrome, we ordered a genetic analysis, which came positive for a heterozygous pathogenic variant in the *GLUD1* gene exon 12/13 on nucleotide position c1519C>T and amino acid position His507Tyr in an autosomal dominant pattern. Her HbA1c went down to 7.3% (56 mmol/mol) on metformin, but due to poor compliance (admitted by the patient) with her treatment and diet, it went back up to 9.5% (80 mmol/mol). Semaglutide was then added to her therapy with a decrease in her HbA1c to 8.2% (66 mmol/mol) and subsequent weight loss of approximately 10 lbs.

Highlights

- HI/HA syndrome is the second most common cause of congenital hyperinsulinism
- *GLUD1* alterations are responsible for hyperinsulinism hyperammonemia syndrome
- Patients usually require long-term medical therapy for hypoglycemia
- Diabetes mellitus is a very uncommon consequence in these patients
- Obesity can contribute to the progression to diabetes in these patients

Clinical Relevance

This describes a very rare case of congenital hyperinsulinism due to hyperinsulinism hyperammonemia syndrome that progressed to diabetes mellitus many years later. Obesity with insulin resistance very likely put the patient at risk of this progression. It is important for clinicians to be aware because prevention of obesity could reduce the risk of this progression.

Discussion

The most common cause of recurrent hypoglycemia in infancy is congenital hyperinsulinism. There is inappropriate insulin secretion in the presence of hypoglycemia. Alterations in different genes that are key in regulating insulin secretion have been described, including *GCK*, *ABCC8*, and *GLUD1*, among others.[1] HI/HA syndrome is the second most common cause of congenital hyperinsulinism, and it is uniquely associated with hyperammonemia.[2,3] It was first described in 1996 by Zammarchi et al.[4] Gain-of-function alterations in the mitochondrial enzyme glutamate dehydrogenase encoded by *GLUD1* are responsible for HI/HA syndrome. It increases the enzyme activity by reducing its sensitivity to allosteric inhibition by guanosine triphophate, which leads to excessive secretion of insulin by the pancreatic beta cells and impaired ammonia metabolism in both the liver and the kidney.[2,5] Ammonia levels are typically elevated 3 to 5 times the normal range, but these individuals do not exhibit the classical symptoms associated with hyperammonia due to other causes.[6]

The major clinical features of children with the HI/HA syndrome are recurrent episodes of symptomatic hypoglycemia in combination with a persistent mild hyperammonemia. Patients with HI/HA have fasting and protein-induced hypoglycemia. This is due to the loss of inhibitory control of glutamate dehydrogenase by alteration in *GLUD1*, leading to excessive insulin release under both basal and protein-stimulated conditions.[5] Episodes of hypoglycemia may occur with fasting, as in other forms of hyperinsulinism, but a distinctive feature of HI/HA is that hypoglycemia also occurs in response to protein feeding and may present as postprandial hypoglycemia.[5]

Epilepsy has been frequently associated with HI/HA syndrome.[7] This can lead to developmental delays and, if it remains undiagnosed, can lead to permanent neurologic damage.[7,8] Patients with HI/HA syndrome are usually responsive to diazoxide, which is an ATP-sensitive potassium (KATP) channel agonist.[1,5,9,10] There has been a report of variable phenotypes of this condition ranging from delayed presentation to spontaneous resolution of hypoglycemia but no report of T2DM developing in a patient with *GLUD1* alteration.[11] There have been a few reports of patients with congenital hyperinsulinism who developed diabetes later in life, but this was due to an alteration in sulfonylurea receptor 1.[12-14]

We believe that her risk for T2DM was very likely due to obesity causing insulin resistance coupled with her high intake of carbohydrates leading to burnout of her pancreatic beta cells.[12] Another risk factor was a strong family history of T2DM. Our patient initially responded well to metformin, but due to poor compliance with her diet and therapy, she experienced deterioration in her glucose control. Semaglutide was then added to her therapy with improvement in her blood glucose and weight loss.

In conclusion, HI/HA syndrome is a rare genetic disorder that presents with hypoglycemia and neurologic symptoms in childhood. Very rarely, patients with this disorder can develop T2DM later in life due to obesity and insulin resistance, and thus, there needs to be an increased awareness of this possibility. Genetic testing should be performed to confirm the diagnosis and help direct further management.

Disclosure

The authors have no multiplicity of interest to disclose.

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