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CASE REPORT

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Congenital hyperinsulinism—A case of mild hypoglycemia in an adult, detected by family testing

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Abstract

Symptoms of mild hypoglycemia are easily overlooked especially when there are no complaints from the patients, but it could be a warning sign of an underlying genetic disease. Genetic testing for the entire family is a key step in neonatal hypoglycemia workup.

KEYWORDS

diabetes, genetic hyperinsulinism, hypoglycemia

1 | INTRODUCTION

Hypoglycemia is a clinical syndrome, defined by a low blood glucose level associated with clinical symptoms such as autonomic symptoms (catecholamine-mediated, adrenergic tremor, palpitations, anxiety and sweating, hunger), paresthesias (acetylcholine-mediated, cholinergic) and neuroglycopenic symptoms (dizziness, weakness, drowsiness, and confusion or altered mental status). Low blood glucose can be mild, classified as level 1 hypoglycemia (<70 mg/dl [3.9 mmoL/L] but equal to 54 mg/dl [3 mmoL/L] or higher), moderate or level 2 hypoglycemia (<54 mg/dl [3 mmoL/L]), or severe/level 3 hypoglycemia (a person is unable to function because of mental or physical changes due to low blood glucose; they need help from another person).[1]

The most common etiologies of hypoglycemia may be related to the treatment of diabetes, but also drugs, alcohol, critical illness, cortisol insufficiency including hypopituitarism, insulinoma, bariatric or gastric surgery, pancreas transplantation or glucagon deficiency, or it may be surreptitious. Some hypoglycemic episodes remain unexplained, therefore genetic, paraneoplastic, or immune causes should be considered. Genetic causes may be related to endogenous hyperinsulinism and inborn errors of metabolism.

2 | CASE PRESENTATION

A 36-year-old Caucasian male was referred in November 2021 to our clinic, for further investigations regarding his recent genetic diagnosis of congenital hyperinsulinism. He was not on any medication and had no history of chronic treatment. No significant past or familial history to report and no important complaint was registered.

The diagnosis was revealed after genetic testing, required by recurrent hypoglycemia present in the couple's second offspring.

The newborn female was diagnosed in July 2021 with fetal macrosomia (birth weight [BW] 4.3 kg at 38 weeks), requiring follow-up and further examinations.

A massive parallel sequencing on a panel of 4867 genes using the Roche platform, performed on the entire family, revealed the presence, in the heterozygous state, of the c.4432G>A, p.Gly1478Arg variant in the ABCC8 gene (ATP-binding cassette transporter sub-family C member 8), in the newborn, her father and the couple's firstborn. The first child, born in 2018 (BW 3.6 kg at 36 weeks), inherited the variant but had no suspicious hypoglycemia event.

The baseline non-fasting venous blood analysis, performed on our patient in November 2021, showed an inappropriate normal value of C-Peptide (0.954 nmoL/L; normal values: 0.37–1.47) and insulin (92.9 pmoL/L; normal values: 17.8–173) for a sugar level of 62 mg/dL (3.4 mmoL/L; normal values: 70–100 mg/dl), well tolerated by the patient. The glycated hemoglobin was at 26 mmol/mol (normal value < 42).

Two months later, a 7-day continuous glucose monitoring (CGM) with a Dexcom G5® Mobile CGM System, highlighted several hypoglycemic events, confirmed by fingerstick measurement, reaching as low as 45 mg/dl (2.5 mmoL/L), linked mostly to meals (within 4 h after meals), occasional alcohol consumption or after a 5-h fasting period. Thinking back, considering this new medical information, the patient could relate to his condition several unexplained symptoms that he presented over time (since childhood), such as mild headaches and extreme hunger.

Regarding the treatment, the simplest strategy is to eat several small low-carbohydrate meals daily. If not sufficient, further treatment is based on Diazoxide, a potassium channel agonist which inhibits insulin secretion in some forms of congenital hyperinsulinism by stimulating the opening of KATP channels leading to hyperpolarization of the β cell membrane and inhibiting insulin secretion, or on Octreotide, a somatostatin analog acting to suppress insulin release downstream of the KATP channel.[2]

The patient was placed on a low-carb meal regimen, that successfully prevented further hypoglycemic events, assessed by CGM.

Glucose monitoring was advised to monitor a potential worsening of hypoglycemic events or a possible transition to hyperglycemia.

3 | DISCUSSION

Herein, we present the case of a patient with a heterozygous ABCC8 mutation. The condition is transmitted in the autosomal dominant mode.

Children of carrier individuals have a 50% risk of inheriting the anomaly. However, the expressivity is variable and the penetrance incomplete, therefore, the severity of the phenotype cannot be predicted.

Subtle symptoms of hyperinsulinaemic hypoglycemia followed by diabetes later in life, have been reported in patients with dominant mutations in *ABCC8* genes in a limited number of cases.[3]

The underlying mechanism in cases with dominant ABCC8 mutations, which develop hyperglycemia later in life, is unclear. Possible explanations include dysregulated insulin secretion by progressive failure in beta cell function due to 'exhaustion', beta cell apoptosis caused by raised intracellular calcium concentration, or the influence of other genetic or environmental factors.[3,4]

4 | CONCLUSION

To understand the genetic basis of familial hyperinsulinism, one should bear in mind that certain patients with hypoglycemia might present genetic forms with late onset (or late diagnosis), such as congenital hyperinsulinism or diabetes.

Mild hypoglycemia in adults can be easily missed, but the underlying cause can be rare, with important further implications for the patient and his offspring.

AUTHOR CONTRIBUTION

All authors had a role in writing the manuscript.

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None.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

None.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the "journal's patient consent policy".

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