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CASE REPORT

Glucokinase mutation–a rare cause of recurrent hypoglycemia in adults: a case report and literature review

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Background: Hypoglycemia occurs frequently in patients both in the inpatient and outpatient settings. While most hypoglycemia unrelated to diabetes treatment results from excessive endogenous insulin action, rare cases involve functional and congenital mutations in glycolytic enzymes of insulin regulation.
Case: A 21-year-old obese woman presented to the emergency department with complaints of repeated episodes of lethargy, syncope, dizziness, and sweating. She was referred from an outside facility on suspicion of insulinoma, with severe hypoglycemia unresponsive to repeated dextrose infusions. Her plasma glucose was 20 mg/dl at presentation, 44 mg/dl on arrival at our facility, and remained low in spite of multiple dextrose infusions. The patient had been treated for persistent hyperinsulinemic hypoglycemia of infancy at our neonatal facility and 4 years ago was diagnosed as having an activating glucokinase (GCK) mutation. She was then treated with octreotide and diazoxide with improvement in symptoms and blood glucose levels.
Conclusion: Improved diagnostication and management of uncommon genetic mutations as typified in this patient with an activating mutation of the GCK gene has expanded the spectrum of disease in adult medicine. This calls for improved patient information dissemination across different levels and aspects of the health care delivery system to ensure cost-effective and timely health care.

Keywords: *glucose*; *low plasma glucose*; *hypoglycemia*; *genetic*; *mutation*; *congenital hyperinsulinism*; *congenital*; *adult*; *care transition*; *care coordination*

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Hypoglycemia occurs frequently in patients presenting both in the inpatient and outpatient settings. Most hypoglycemia occurs via mismatched nutrient absorption and insulin availability. Rarely, hypoglycemia results from genetic causes and requires more extensive evaluation (1, 2). Of these, congenital hyperinsulinism (CHI) is the most common cause of recurrent hypoglycemia that can persist into adulthood. Of the nine known genes currently implicated in the pathogenesis of this condition, activating mutations of the glucokinase (GCK) gene lower the glucose set point. They have variable responses to diazoxide (3) and octreotide, both of which inhibit insulin release.

We present a 21-year-old woman referred to our facility for severe hypoglycemia that was poorly responsive to boluses and continuous infusions of dextrose. Early knowledge of a childhood diagnosis of a rare, activating mutation of the GCK gene, in conjunction with coordinated care involving her pediatrician, led to effective treatment with diazoxide and octreotide.

Case presentation

A 21-year-old Caucasian woman presented to an outside facility with altered mental status after being found lethargic by family. On arrival to the emergency department, plasma glucose was 20 mg/dl. The patient was hospitalized and started on dextrose infusion, including 10% dextrose in water but remained hypoglycemic with capillary glucose ranging between 50 and 60 mg/dl. She was transferred to our facility on suspicion of an insulinoma as the patient was unable to recall her prior diagnosis.

Medical records from our hospital revealed treatment for hypoglycemia as a neonate. The patient reported repeated episodes of seizures, syncope, dizziness, headaches, palpitations, and sweating around age 12; however, symptoms were never formally investigated as she did not seek expert care. These symptoms were also reported to have been present since birth but had been intermittent and of varying severity. She remained seizure-free and without syncopal episodes until 17 when she experienced another

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syncopal episode. At that time, she underwent extensive inpatient hypoglycemia evaluation with the following results: blood glucose of 47 mg/dl after 2 h of fasting, proinsulin levels varying from 10.4 to 84.1 pmol/l (normal range 0–10 pmol/l), C-peptide level 3.1 ng/ml (normal range 1.1–4.4 ng/ml), negative insulin antibodies and sulfonylurea screen. Magnetic resonance imaging of the abdomen showed no insulinoma, but genetic studies revealed Val452 Leu activating mutation of the GCK gene. She was successfully treated with diazoxide and discharged home on oral diazoxide 250 mg daily, which she discontinued due to side effects of hirsutism and fluid retention.

On current admission, the patient was treated with dextrose boluses initially. Her blood glucose level remained low in spite of a continuous infusion of 5% dextrose necessitating transfer to an intensive care unit. Both fasting and postprandial blood glucose levels were low. As review of her medication list did not show any implicating drugs, no additional work-up was pursued. She was then placed on octreotide 200 μg subcutaneously twice daily and diazoxide suspension 100 mg three times a day on consultation with the pediatric endocrinologist. Neuroglycopenic symptoms of hypoglycemia improved. The patient's hypoglycemia improved with capillary glucose of 55–110 mg/dl by the time of discharge. Importance of compliance with the treatment and follow-up with an endocrinologist was emphasized.

Discussion

Hypoglycemia is commonly seen in clinical practice. When encountered in the inpatient setting, it is easily recognized as patients already have risk factors such as diabetes mellitus (DM) on treatment, sepsis, and end-organ failure. However, for patients presenting emergently with hypoglycemia alone, appropriate investigations are warranted to treat and prevent recurrence.

Diagnostic work up of hypoglycemia

After establishing a diagnosis of hypoglycemia by Whipple's triad (low plasma glucose, hypoglycemic symptoms, and resolution of adrenergic/neuroglycopenic symptoms with correction of the blood sugar), interim treatment and search for risk/causative factors should ensue (Table 1). Ideally, treatment is only given after obtaining a plasma sample to ensure accuracy of diagnosis. Medical history of ethanol use, surreptitious insulin ingestion, medication use and interaction, autoimmune disease, gastric bypass (4), and subtle risk factors such as undiagnosed psychiatric disorder and polypharmacy should be excluded (5). In seemingly well patients, the timing of hypoglycemic spells (fasting/postabsorptive or postprandial/reactive) is required to determine diagnostic studies. A mixed meal tolerance test under supervision is done for postprandial hypoglycemia while a 72-h fast should be done for fasting hypoglycemia. Hepatic or renal disease, endocrine disorders of growth hormone, cortisol, adrenal insufficiency, and hypopituitarism should be excluded. Drug screens can rule out surreptitious use of hypoglycemic agents and ethanol. Plasma insulin, proinsulin, C-peptide, and beta-hydroxybutyrate levels should be assessed to exclude surreptitious use of insulin or insulin receptor antibodies. Intravenous glucagon can be given to distinguish disorders of gluconeogenesis from glycogenolysis (5). A 48-h supervised fast should be done to exclude insulinoma, with plasma insulin and proinsulin levels. Pro-IGF II to IGF II ratio can be measured to look for non-beta-cell tumors (5). Negative

Table 1. Causes of hypoglycemia in adults

Insulin induced/ alcohol induced	Beta-blockers, reactive, oral hypoglycemic agents, factitious hypoglycemia, insulinomas, insulin receptor antibodies, anti-insulin antibodies, functional B-cell disorders, idiopathic post prandial syndrome, alcoholic ketoacidosis	GI	Acute liver failure, acute fatty liver of pregnancy, cirrhosis/liver cancer, diabetic gastroparesis, dumping syndrome, idiopathic postprandial syndrome, malabsorption syndromes
Other endocrine causes	Adrenal insufficiency, Addison's disease, prediabetes, glucagon deficiency, MEN, myxedema coma, hypopituitarism, Timme syndrome	Oncologic	Adrenal cancer, IGF producing tumors, functional pancreatic endocrine tumors, mesothelioma, liver cancer
Genetic/ metabolic	Enzymes involved in glycolysis, Krebs cycle, fatty acid oxidation, glycogenolysis and urea cycle	Infectious	Sepsis, acute meningitis, malaria, visceral leishmaniasis
Renal	Benign glucosuria, renal failure, uremia	Drugs	Gatifloxacin, quinine, beta-blockers, chlorpromazine, ritonavir, pentamidine, indomethacin, trimethoprim, artemisin/ artesunate
Iatrogenic	Gastrojejunostomy, postgastrectomy syndrome, gastric bypass, pyloroplasty, Reye syndrome	Miscellaneous	Alcoholism, binge drinking, cachexia, burns, hypothermia, heavy exercise

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findings suggest non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS), which encompasses CHI (4, 6). A selective pancreatic arterial calcium stimulation test (SPACI) done at this time can detect hyperfunctioning of B-cells and confirm the diagnosis of NIPHS.

Pathophysiology of glucokinase mutations

CHI is uncommon in the pediatric population with an estimated incidence of 1 in 40,000 to 50,000 live births annually in Europe (7). Its prevalence in the adult population is yet to be described. GCK mutations account for 7% of all causes of CHI (8, 9); GCK facilitates phosphorylation of glucose to glucose-6-phosphate and is the main glucose sensor of the pancreatic beta cell and hepatocytes-controlling glucose-stimulated insulin secretion and glycogenesis (10). Activating mutations of the GCK gene are typically inherited in an autosomal dominant pattern, showing variable phenotypic penetrance and expressivity ranging from asymptomatic to marked hypoglycemia (11, 12). Inactivating forms of the mutation cause varying severity of persistent hyperglycemia depending on zygosity (13). De novo GCK mutations are very rare and exhibit marked variation in phenotypic expression (14). Over 600 heterozygous inactivating mutations have been reported, causing mild persistent hyperglycemia known as maturity onset diabetes of the young (MODY) as opposed to only 13 known activating mutations of the gene (15, 16). Activating mutations are usually clustered around the allosteric activator site of the enzyme and led to hyperinsulinemic hypoglycemia by lowering the glucose set point and threshold for glucose stimulated insulin release. This results in postprandial hypoglycemia. The sheer numbers of existing mutations of the GCK gene show it to be a highly mutable gene with varied disease outcomes depending on the type of activation.

Therapeutic utility

It is key to blood glucose homeostasis and has been identified as a potential target for anti-diabetic therapy. Trials manipulating GCK regulatory protein an allosteric switch for GCK, which indirectly restores GCK activity, are currently underway to evaluate its effect on blood glucose in patients with type 2 DM (17, 18).

Treatment of underlying cause

Treatment of NIPHS involves lifelong dietary modification consisting of frequent, low carbohydrate meals (5), which prevent surges in plasma glucose level, insulin level, and the consequent hypoglycemic spells. Medications such as diazoxide, octreotide, glucagon, verapamil, and somatostatin, whose actions all involve inhibition of calcium channels, have been employed with varying degrees of success (7).

Diazoxide binds to and activates the sulfonylurea receptor 1 subunit of the potassium adenosine triphosphate [K(ATP)] channel, causing calcium channel closure. This prevents beta-cell depolarization and inhibits glucose-stimulated secretion of insulin. Response to diazoxide therefore varies with genetic mutations [ineffective in mutations of the K(ATP) channel genes] (8) and with pattern of inheritance (7). Hypertrichosis and water retention have been reported with its use. Octreotide, a somatostatin analogue (secretin and insulin inhibitor), has been used in diazoxide unresponsive CHI with improved blood glucose in these patients; however, side effects such as gastrointestinal symptoms, dilated gallbladder, necrotizing enterocolitis, and QT prolongation sometimes limit its use (7). Long-term use of glucagon is effective in diazoxide-unresponsive cases or severe/diffuse CHI but gastrointestinal side effects and crystallization in infusion tubing have been reported (19). Glucagon-like protein 1 receptor agonists such as exendin-4 are newer drugs that improve hypoglycemia in diazoxide-unresponsive patients by inhibiting insulin release (7). Partial pancreatectomy is indicated for medical treatment failure [suggesting a K(ATP) defect] and is only curative for focal lesions while extensive resection is reserved for diffuse CHI to limit pancreatic burden (7, 8, 11, 20).

Clinical implication

Affected patients can present in adulthood; de novo mutations should be considered given the following:

- Positive family history of unremitting hypoglycemia
- Lifelong symptoms of low plasma glucose, even after eating
- Increased BMI
- Negative sulfonylurea and autoimmune work up
- Positive glycemic response to octreotide

To our knowledge, only three families with affected adults have been reported. Our case is unique because it expounds on genetic causes of hypoglycemia in adults. In addition, this case highlights the pediatric-to-adulthood transition for rare diseases and the key role that coordination and transition of care plays in timely management.

Conclusion

Despite the congenital nature of GCK mutations, some patients can go undiagnosed till early adulthood. Future research into a cost-effective and prompt scheme of patient information dissemination is warranted for uncommon diseases.

Conflict of interest and funding

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