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Cornstarch Protocol for Nocturnal Hypoglycemia in Adult Patient with Mitochondrial Disorder

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Abstract

Mitochondrial Disorders (MTDs) are a group of rare, highly heterogeneous disorders most commonly involving genetic defects in the oxidation-phosphorylation pathway. Multiple organ systems can be affected, though endocrine related conditions are particularly common. Non-diabetic patients with MTD have been found to have significantly increased rates of hypoglycemic episodes compared to the general population. Here we present a case of recurrent nocturnal hypoglycemic episodes in a 29-year-old male with unspecified mitochondrial myopathy who underwent extensive hypoglycemia testing which came back negative. The patient was ultimately started on a cornstarch therapy adapted from the treatment protocol for glycogen storage disease type Ia, leading to a resolution of his nocturnal hypoglycemia. The stabilization of blood glucose levels in this case suggests that the cornstarch protocol of 1.6 g/kg body weight before bedtime may be a viable treatment option for non-diabetic hypoglycemia in MTDs.

Keywords: Mitochondrial disorder; Hypoglycaemia; Cornstarch

Abbreviations

AUTS2: Activator of Transcription and Developmental Regulator; CGM: Continuous Glucose Monitor; D10: Dextrose 10%; DNA: Deoxyribonucleic Acid; FSBG: Finger Stick Blood Glucose; IGF: Insulin-like Growth Factor; KMT2C: Type 2 Lysine Methyltransferase; MTD: Mitochondrial Disorder; mtDNA: Mitochondrial Deoxyribonucleic Acid

Introduction

Mitochondrial Disorders (MTDs) are a group of rare, highly heterogeneous disorders most commonly involving genetic defects in the oxidation-phosphorylation pathway, which produces adenosine triphosphate [1]. As a group, they are among the most common forms of inborn errors of metabolism and inherited neurological disorders [2]. Presentation often includes multi-system characteristics and vary widely based on the hundreds of possible genetic mutations in mitochondrial or nuclear DNA as well as the varying tissue distribution of affected mitochondria. Tissues with high energy requirements, such as the brain, retina, kidney, liver and skeletal or cardiac muscle are most commonly impacted [2]. Therefore, MTDs can be classified as metabolic myopathies.

The endocrine system is commonly affected, predominantly manifesting as diabetes mellitus as well as hypogonadism, hypoadrenalism and hypoparathyroidism [3]. A 2019 study found that on chart review, non-diabetic patients with MTD had significantly increased rates of hypoglycemic episodes compared to the general population, although this complication is not well studied [4]. A 2021 review of endocrine manifestations of MTDs describes hypoglycemia as a consequence of hepatocerebral syndrome secondary to mtDNA depletion. This condition frequently presents with deranged liver function tests, coagulopathy, and lactic acidosis along with hypoglycemia in early childhood, typically during infancy. Patients typically require liver transplantation and frequently have progressive neurological involvement such as generalized hypotonia, neurodevelopmental delay and muscle weakness and sometimes neuropathy and intractable epilepsy [3].

The classification of metabolic myopathies also includes genetic defects in glycogenolysis, glycolysis, lipid metabolism and purine metabolism [5]. In addition to oxidative-phosphorylation, mitochondria are involved with many metabolic processes such as gluconeogenesis, ketogenesis, tricarboxylic acid cycle, urea cycle, amino acid metabolism and lipid metabolism [2]. Although hypoglycemia in mitochondrial disorders is not well studied, glycogen storage disorders commonly present with hypoglycemia. They can also share phenotypic characteristics with MTDs, such as lactic acidosis and exercise intolerance with muscle cramps or weakness [5].

Uncooked cornstarch has been used for many years to prevent hypoglycemia during periods of fasting in patients with glycogen storage disorders. Our institution has observed hypoglycemia to be more common in patients with MTDs but

there has been little to no reports of using cornstarch to treat severe recurrent hypoglycemia in patients with MTDs [4]. Here we present a case of severe nocturnal hypoglycemia in a patient with MTD who was successfully treated with cornstarch.

Literature Review

Here we present a 29-year-old male with a past medical history of unspecified mitochondrial myopathy and childhood seizures who presented for evaluation of new onset recurrent symptomatic hypoglycemia. The patient was born at term following an uncomplicated pregnancy. He was otherwise healthy until 3 months of age when he began to have seizures and eventually underwent muscle biopsy revealing mitochondrial myopathy. He was started on anti-epileptic drugs which were weaned off at 3 years of age. His condition led to global developmental delay, including being non-verbal, incapable of carrying out activities of daily living and unable to walk until 10 years old.

From 3 to 28 years of age, he did not experience any major medical problems or hospitalizations. But during the age of 28, over a 3-month period, he was hospitalized 3 separate times for symptomatic hypoglycemia without changes to his diet. During the first admission at an outside hospital 3 months prior to this current admission, he was brought in for symptoms of severe lethargy, unresponsiveness and profound hypoglycemia with a finger stick blood glucose Finger Stick Blood Glucose (FSBG) of 18 mg/dL. He had extensive hypoglycemia workup during that admission, which was negative.

2 months later, he presented to our hospital with symptomatic hypoglycemia. During that admission, extensive hypoglycemia testing was performed. Lab work included an A1c of 5.7%, liver function tests (normal), thyroid stimulating hormone 5.29 uIU/mL (high), T4 0.9 ng/dL (normal), creatine kinase 115 unit/L (normal), morning cortisol 10.3 mcg/dL (normal) negative insulin antibodies and negative sulfonylurea screen. Fasting hypoglycemia labs drawn when FSBG was 48mg/dL and BG 57 mg/dL, showed proinsulin of <4 pMol/L, insulin <1 uIU/mL, C-peptide of 1.47 ng/mL and serum ketones of 0.10 mmol/L. He was discharged with hypoglycemia precautions, instructed to use a continuous blood glucose monitor Continuous Glucose Monitor (CGM) and sent to outpatient endocrinology.

One month after discharge, he again presented to our hospital after his mother noticed that the patient was very lethargic and less responsive than usual upon awakening. His blood glucose *via* CGM was 29 mg/dL with his last meal being 4-5 hours prior to the episode. He received 150 mL of 10% dextrose (D10) en-route to the emergency department. On initial evaluation, the patient was afebrile and hemodynamically stable on room air. His FSBG on arrival was 124 mg/dL, which then dropped to 59 mg/dL two hours later, requiring a D10 continuous infusion. Additional lab testing during his admission included a nadir hemoglobin 9 g/dL, white blood cell 3.5 K/cmm, fluctuating lactic acid ranging from 2.3-3.6 mMol/L elevated aspartate and alanine transaminases of 162 units/L and 81 units/L respectively. Creatine kinase, urinalysis, acute viral hepatitis panel, SARS-CoV-2 and human immunodeficiency virus screening were all normal.

Hospital course was complicated by several episodes of nocturnal hypoglycemia <60 mg/dL requiring dextrose injections, as well as hypophosphatemia. Endocrinology was again consulted to evaluate for recurrent hypoglycemia but considering an extensive hypoglycemia workup had already been completed they did not have additional recommendations during this admission. Due to his known history of mitochondrial myopathy, we consulted nutrition and explored cornstarch therapy as a potential treatment modality as it has been shown to be successful with patients with glycogen storage disorders. Cornstarch mixed with water was attempted in an effort to improve nocturnal and fasting hypoglycemia. On the first night of cornstarch use, 2 tablespoons of store-bought cornstarch (approximately 1 g/kg body weight) was mixed with 8 oz of water and consumed just before bedtime (around 10:00 PM) which proved effective for the majority of the night. On the second night, the patient was given 3 tablespoons (approximately 1.6 g/kg body weight) which resulted in sustained normoglycemia the entire night. This approach was successfully used for the remainder of his hospitalization. His liver enzymes also improved over the course of his stay. The patient was discharged to home with outpatient follow-up with endocrinology and a mitochondrial disease specialist for further evaluation of his new onset hypoglycemia. Initial outpatient genetic testing revealed variants in the KMT2C and AUTS2 genes. At further outpatient appointments, the patient's mother reported successful treatment of hypoglycemia with the night time cornstarch.

Discussion

Mitochondrial disorders are a highly heterogeneous group of disorders characterized by mutations in mitochondrial or nuclear genes involved in the oxidative-phosphorylation pathway. Phenotypic characteristics may include lactic acidemia, skeletal myopathy, sensorineural hearing loss, vision loss and exercise intolerance with fatigue, peripheral neuropathy, intestinal dysmotility and a variety of central nervous system complications ranging from subacute neurodegeneration to migraine headaches. One study found that patients are more likely to experience episodes of hypoglycemia than the general population, particularly in the neonatal period [4].

The use of cornstarch supplementation has been used for 40 years as an alternative to continuous glucose infusions to prevent hypoglycemia in patients with glycogen storage diseases, especially type Ia [6]. Cornstarch is a glucose polymer that is broken down relatively slowly, providing a stable source of glucose during periods of fasting. Patients with glycogen storage disease often supplement with cornstarch every 4-6 hours during the day to maintain euglycemia with higher doses needed before bedtime. The dose for older children, adolescents and adults is 1.7-2.5 g/kg body weight every 4-6 hours, while young children typically require 1.6 g/kg every 3-4 hours, although dosing is adjusted for individual patients [7].

Literature review did not reveal reports of cornstarch being used for nocturnal hypoglycemia in MTDs. According to a 2016 review of nutritional interventions in MTD, there is wide variation in nutritional supplementation for MTDs based on patient characteristics and provider preferences [1]. Much of this supplementation focuses on vitamins and other compounds that serve as precursors for cofactors involved in the oxidative-phosphorylation pathway. Consensus from mitochondrial specialists includes recommending coenzyme Q10, alpha-lipoic acid and riboflavin supplementation for most patients, in addition to correcting any nutrient deficiencies [2]. These interventions do not focus on the treatment of hypoglycemia, likely because this complication has not been well described.

The approach to non-diabetic hypoglycemia in MTDs should initially focus on ruling out alternative causes, such as infections, autoimmune hypoglycemia, medication side effects or insulinomas. MTDs have been associated with adrenal insufficiency which should also be considered in the evaluation [2]. Certain mtDNA depletion syndromes may present with hepatocerebral syndrome causing hypoglycemia with hepatic and neurologic abnormalities, reflected by abnormal liver transaminases and coagulation studies [3]. Growth hormone deficiencies have mostly been reported as a factor in the development of short stature in patients with MTDs, as seen in our patient [8]. Growth hormone contributes to blood glucose levels by stimulating gluconeogenesis and glycogenolysis and deficiencies could contribute to hypoglycemia in patients with MTDs.

The stabilization of blood glucose levels in our patient's case suggests that the cornstarch protocol commonly used for glycogen storage disorders may be a viable treatment option for hypoglycemia in MTDs not attributable to other causes. A cornstarch dosing of approximately 1.6 g/kg bodyweight was chosen based on the established protocol for glycogen storage disorders. As a treatment option, cornstarch offered this patient an easy and inexpensive way to manage recurrent hypoglycemia at home without need for recurrent hospitalization and continuous dextrose infusions. Adequate prevention of hypoglycemic episodes may prevent seizures and neurologic injury in susceptible patients, especially during critical developmental periods [4-9].

Further studies are warranted to better establish a protocol tailored to hypoglycemia in MTDs. Due to the heterogeneity of MTDs, dosage may need to be titrated on an individual basis. A recent study investigating cornstarch protocol for adults with glycogen storage disease type Ia suggests that doses should be based on carbohydrate requirement and central nervous system demands of each patient, rather than by weight and that carbohydrate requirements decrease with age [6]. Dosage for patients with MTDs would likely need to be re-evaluated over time to prevent adverse effects from over-treatment, such as relative hyperinsulinism, rebound hypoglycemia and possible alterations in cholesterol and triglycerides [6]. Patients may also experience diarrhea, increased flatulence or excessive weight gain from cornstarch supplementation [9]. Patients should have close follow-up with mitochondrial, endocrinology and nutrition specialists.

Conclusion

In conclusion, mitochondrial disorders are characterized by defects in the oxidative-phosphorylation pathway and cause a wide variety of clinical presentations affecting many organ systems, including endocrine disorders. Minimal studies have reported hypoglycemia in these patients. We present a patient successfully treated with 1.6 g/kg body weight of cornstarch before bedtime for prevention of nocturnal hypoglycemia. Practitioners should be aware of hypoglycemia as a complication of MTDs and should consider cornstarch as a simple and inexpensive treatment option after ruling out other secondary causes. Further studies are warranted on this topic to better establish a protocol tailored to this population.

Declarations

Ethics approval and consent to participate

The need for ethics approval was not applicable to this case report. Informed consent was obtained by the patient's mother who is the patient's primary caretaker and decision-maker.

Availability of data and materials

Not applicable. All pertinent lab results were listed in the text.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

L.W., A.T., and M.H. wrote the main manuscript text.

J.C. was responsible for the general direction and integrity of the manuscript.

All authors reviewed the manuscript.

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