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Case Report

A Case of Congenital Disorder of Glycosylation Type 1b Presenting as Hyperinsulinemic Hypoglycemia and Failure to Thrive

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Abstract

We describe initial manifestations, approach to diagnosis, and treatment of a patient with congenital disorder of glycosylation type 1b (CDG 1b), previously managed as acetylcarnitine deficiency. A 9-year-old girl initially diagnosed with and treated for acetylcarnitine deficiency at an outside hospital presented with recurrent hypoglycemia, failure to thrive, poor weight gain, and short stature. She had discontinued levocarnitine therapy because of lack of response, and testing with us demonstrated a normal carnitine and acyl carnitine panel and hyperinsulinemic hypoglycemia during a diagnostic fast. Oral diazoxide and hydrochlorothiazide were initiated with resolution of hypoglycemia. She had iron deficiency anemia, but an upper gastrointestinal evaluation was normal. Genetic testing confirmed a diagnosis of CDG 1b caused by deficiency of mannose phosphate isomerase. Oral mannose was started with gradual reduction in and eventual discontinuation of the diazoxide dose. Hypoglycemia in the pediatric age group needs a systematic approach. It is important to raise awareness of CDG 1b, which can present as persistent hyperinsulinemic hypoglycemia. Mannose supplementation can ameliorate clinical symptoms and biochemical abnormalities.

Key Words: hypoglycemia, hyperinsulinism, glycosylation, mannose, diazoxide

Abbreviations: C2, acetylcarnitine; CDG 1b, congenital disorder of glycosylation 1b; GSD, glycogen storage disorder; MPI, mannose phosphate isomerase; MPI-CDG, mannose phosphate isomerase-congenital disorder of glycosylation; SD, SD score; SUR1, sulfonylurea receptor 1.

Introduction

Although hypoglycemic disorders are rare, their consequences can be severe [1]. A thorough history and physical examination are important. Age and symptoms at presentation, triggers for hypoglycemia, and duration of fasting precipitating hypoglycemia provide clues to the diagnosis. Newborn screening should be reviewed with history of birth weight, hypoglycemic episodes after birth, and prolonged jaundice. Hypoglycemia following a short duration of fasting is concerning for hyperinsulinism and glycogen storage disorders (GSD) I or II. Hypoglycemia after a longer duration of fasting suggests GSD types 0, VI, and IX; disorders of gluconeogenesis; and GH and/or cortisol deficiency [1]. Early presentation is more consistent with inborn errors of metabolism, whereas ketotic hypoglycemia typically presents in early childhood. Hormone deficiencies can occur at any age, but the combination of GH and cortisol deficiency in infants can cause severe hypoglycemia [2]. Dietary history is significant because particular foods might promote hypoglycemia in metabolic disorders such as fructose intolerance. Concurrent illness should be ruled out. A thorough physical examination includes assessment for midline defects suggestive of hypopituitarism, hepatomegaly, and hyperpigmentation (concerning for primary adrenal insufficiency). Syndromic features may suggest Beckwith-Wiedemann or Kabuki syndrome.

Threshold blood glucose for the diagnostic critical sample is <50 mg/dL, confirmed by a laboratory quality assay [1, 2]. This sample should be tested for plasma glucose, beta-hydroxybutyrate, a comprehensive metabolic panel, insulin, c-peptide, free fatty acids, lactate, ammonia, cortisol, GH, and acylcarnitine profile. Urine should be checked for organic acids and serum for amino acids. If critical sampling is not possible during a hypoglycemic episode, a diagnostic fast is necessary. The differential diagnosis is categorized by metabolic and hormonal profiles in response to fasting, including presence or absence of ketones and acidemia. Hypoketotic conditions include hyperinsulinemia, fatty acid oxidation defects, and sometimes hypopituitarism. Acidemia with ketosis suggests GSD (types 0, III, VI, or IX), GH or cortisol deficiency, or an idiopathic cause. Acidemia with lactic acidosis suggests a disorder of gluconeogenesis such as GSD type 1, fructose-1,6 bisphosphatase deficiency or pyruvate carboxylase deficiency. A glycemic response of >30 mg/dL following glucagon administration at the end of the diagnostic fast indicates excessive glycogen reserves (indirect evidence of insulin excess).

Here, we describe a 9-year-old child who presented with ongoing hypoglycemia and a diagnosis of acetylcarnitine (C2) deficiency from an outside hospital, but her diagnostic evaluation revealed hypoketotic hypoglycemia with hyperinsulinism and a normal acyl carnitine panel. She was eventually

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diagnosed with congenital disorder of glycosylation (CDG) type 1b, caused by mutations in the *MPI* gene encoding the cytosolic mannose phosphate isomerase (MPI) enzyme.

Case Presentation

A 9-year-old girl with a reported diagnosis of C2 deficiency transferred care to our pediatric endocrine clinic. She first presented with hypoglycemic seizures following breakfast at 1 year of age at an outside hospital; diagnostic evaluation performed at that time is not available. Subsequently, between 1 and 5 years of age, she had multiple hypoglycemic episodes with lethargy followed by seizures or syncope requiring admission to the emergency department. She did have a diagnostic evaluation at approximately 3 years of age at the outside hospital, which included measurable insulin, "normal" beta hydroxybutyrate, and normal pyruvate, lactate, ammonia, and serum amino acid concentrations. We were unable to trace the blood glucose concentration at the time of assessment. Around this time, she was given a diagnosis of C2 deficiency; however, we were unable to obtain documentation of biochemical or genetic diagnosis of this condition, and a previous C2 panel had been reported normal. She was started on levocarnitine therapy (10 mg 3 times per day) and uncooked cornstarch at night and continued this until a few months before presenting to our clinic. Despite levocarnitine therapy and frequent feeds, the patient continued to have intermittent hypoglycemic episodes with poor response to sugary drinks and snacks, and levocarnitine was discontinued. The patient also had a history of nausea and vomiting, but no history of bowel disturbances.

Birth history was unremarkable. Parents were not aware of hypoglycemia in the neonatal period and the patient did not have prolonged jaundice. The parents denied developmental delays, though there was no documentation of a formal evaluation for delays or learning difficulties. Family history was significant for hypoglycemic episodes in 2 maternal aunts diagnosed in adulthood. No details were available regarding their diagnostic evaluation.

Diagnostic Assessment

When the patient was seen first at our institution, her weight was 21.8 kg (1.1 percentile; −2.29 SD score [SDS]), height was 120.9 cm (0.65th percentile; −2.48 SDS), and body mass index was 14.91 kg/m^2 (17th percentile; −0.94 SDS). The growth chart indicated poor weight and height gain over time. Her weight and height had decreased from the 14th and 3rd percentiles, respectively, at 3 years of age to the current measurements. Physical examination was unremarkable with no dysmorphisms or midline defects; she did have congenital scoliosis.

The first diagnostic step was to repeat the carnitine and the acyl carnitine panel, which returned normal. A continuous glucose sensor documented frequent and repeated hypoglycemia for prolonged periods. She was admitted for a diagnostic fast, and results from the critical blood sample at the time of documented and confirmed hypoglycemia (fingerstick glucose, 2.1 mmol/L [38 mg/dL]; venous blood glucose 2.7 mmol/L [49 mg/dL]) included: insulin 96 pmol/L (16.0 µIU/mL), C-peptide 0.83 nmol/L (2.5 ng/mL), beta hydroxybutyrate 0.4 mmol/L (<0.4), free fatty acid 0.74 mmol/L (<2.0) cortisol 140.7 nmol/L (5.1 mcg/dL), GH 1.0 mcg/L (1.0 ng/mL), lactate 0.7 mmol/L (0.5-2.0), bicarbonate 23 mmol/L (23-32), and ammonia 32 micromoles/L (12-48). Given her low blood glucose concentration at the time, her insulin and C-peptide levels were high (expected to be unmeasurable), and she had low concentrations of free fatty acid and ketones (indicative of suppressed lipolysis and ketogenesis), all consistent with hyperinsulinism. Also consistent was a robust response to glucagon with an increase in blood glucose concentration from 1.94 mmol/L (35 mg/dL) to 12.4 mmol/L (223 mg/dL). Urine organic acids and serum amino acids were normal. She had low IGF-1 concentrations (−2.7 SDS), but a previous GH stimulation test with arginine and clonidine at the outside hospital had documented a normal peak GH response of 11.5 mcg/L (11.5 ng/mL). She had a normal peak cortisol response to an ACTH stimulation test.

Treatment

The patient was started on diazoxide (10 mg/k/day in divided doses) and hydrochlorothiazide (0.6 mg/kg/day) while waiting on genetic testing results, with normalization of blood glucose concentrations. The diazoxide dose was gradually reduced to 5 mg/kg/day and hydrochlorothiazide discontinued. Magnetic resonance imaging scans of the pancreas did not show an insulinoma. Genetic testing later revealed 2 heterozygous mutations (1 pathogenic—c1193T > C [p.Lle398Thr] and the other likely pathogenic [c.16 + 1G > A; splice donor]) in the gene coding for the MPI enzyme, necessary for the N-glycosylation of proteins. She was thus diagnosed with CDG 1b, a known but rare cause of hyperinsulinism, and started on oral mannose therapy at a low initial dose of 250 mg twice daily (later increased to 500 mg 4 times daily), with a plan to adjust the dose based on response and tolerance. Her diazoxide dose was further reduced and eventually discontinued, with persistence of normoglycemia.

Additional testing revealed normal thyroid and liver function, lipid profile, and coagulation studies (assessed because CDG 1b increases the risk for hypercoagulation). She had microcytic and hypochromic iron deficiency anemia and was started on iron supplements. Given these results, history of nausea, vomiting, poor feeding, and the association of CDG 1b with gastrointestinal pathology, she was referred to pediatric gastroenterology for further evaluation. Upper gastrointestinal endoscopy and small bowel endoscopic biopsy were normal, including normal villous architecture. She will continue to be monitored by pediatric hematology and gastroenterology over time.

Outcome and Follow-up

Her feeding problems improved with optimization of mannose therapy and diazoxide dose reduction and discontinuation. The pretreatment carbohydrate deficient transferrin analysis that had revealed elevated mono/dioligosacharrides and aoligo/dioligosaccharides consistent with CDG 1b, normalized within a month of starting mannose therapy.

Discussion

We describe a rare cause of hyperinsulinism, namely CDG 1b, presenting as intermittent episodes of ongoing hypoglycemia despite frequent feeds and failure to thrive. The prevalence

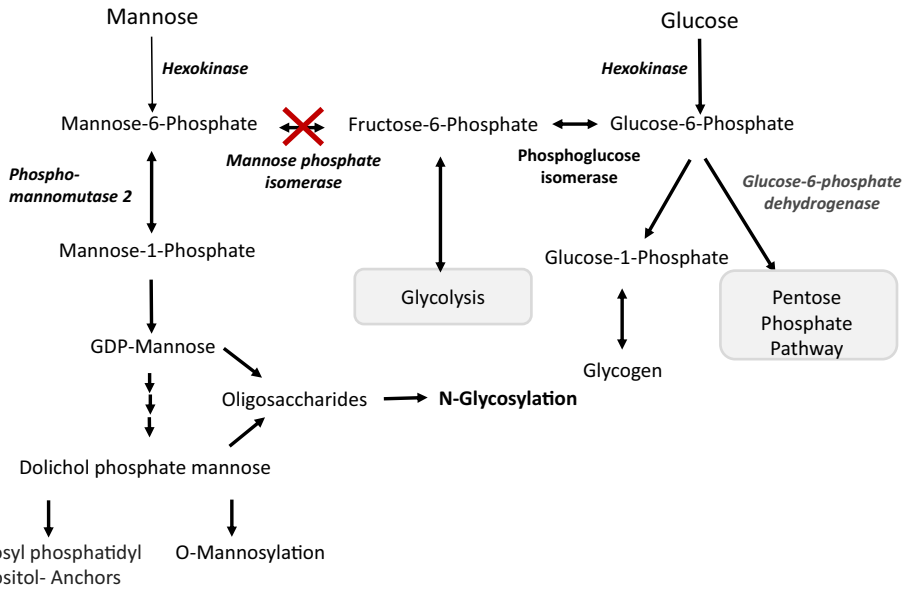

Figure 1. Mannose phosphate isomerase (MPI) and interrelated pathways. Mannose phosphate isomerase, the enzyme affected in CDG1b, catalyzes the interconversion of fructose-6-phosphate and mannose-6-phosphate, the latter being essential for synthesis of several glycosylation intermediates including GDP-mannose and dolichol phosphate mannose. Decreased activity of MPI results in decreased endogenous synthesis of mannose-1-phosphate. Hexokinase provides an alternative pathway for mannose-6-phosphate synthesis from exogenous mannose; however, normal dietary intake of mannose is low and results in impaired N-glycosylation. Oral mannose supplementation (by promoting this alternative pathway) can restore normal glycosylation. On the other hand, excessive exogenous mannose in individuals with MPI can be deleterious: the excessive mannose-6-phosphate can inhibit activities of glucose-6-phosphate dehydrogenase, hexokinase, and phosphoglucose isomerase and consequent depletion of ATP (energy) by their effects on glycolysis and the pentose phosphate shunt.

of this disorder is <1 in 1 000 000, and fewer than 50 cases of CDG 1b have been reported thus far.

CDG-Ib, now classified as MPI-CDG, is an autosomal recessive disorder caused by variants in the *MPI* gene. Mannose phosphate isomerase (Fig. 1), the enzyme affected in CDG1b, catalyzes the interconversion of fructose-6-phosphate and mannose-6-phosphate, the latter being essential for synthesis of several glycosylation intermediates including GDP-mannose and dolichol phosphate mannose. The decreased availability of mannose-6-phosphate synthesized from fructose-6-phosphate in the disorder results in impaired N-glycosylation.

The clinical spectrum includes gastrointestinal, hepatic, endocrine, and hematological symptoms. Cyclic vomiting and failure to thrive are leading symptoms; other features include chronic secretory diarrhea with protein-losing enteropathy, hypoalbuminemia, enterocolitis cystica superficialis, intestinal lymphangiectasia, partial villous atrophy, elevated aminotransferases, hepatomegaly, portal hypertension, hepatic fibrosis, hyperinsulinemic hypoglycemia, hypothyroidism, low antithrombin III activity, protein C, protein S or Factor IX deficiency, and thrombotic events as well as gastrointestinal bleeding [3–6]. CDG 1b is clinically distinct from other CDGs in that there is no significant central nervous system involvement, although secondary seizures may occur from hypoglycemia, and it can be treated with oral mannose supplementation [3, 7]. Untreated cases can be fatal.

Although mannose phosphate isomerase is deficient in CDG 1b, hexokinase provides an alternative pathway for mannose-6-phosphate synthesis from mannose [8]. Typical dietary intake of mannose is low and likely insufficient for normal glycosylation. However, oral mannose supplementation (by promoting this alternative pathway) has been successful in managing patients with CDG Ib. Response to oral mannose dosed at 1 g/kg body weight per day in 4 to 6 doses, has been reported in patients with CDG Ib with severe clinical presentations; hypoglycemia and vomiting resolved within weeks and other clinical manifestations improved within the first year, with a slower improvement in glycosylation of glycoproteins [3, 6]. Protein-wasting enteropathy is especially responsive to mannose treatment, though liver disease may progress [9]. Oral mannose supplementation is typically well tolerated, though single mannose doses of >200 mg/kg may induce osmotic diarrhea. Our patient has done well on a relatively low mannose dose. Patients have a reasonably normal life while undergoing lifelong treatment with mannose; thus, timely diagnosis is important.

Both deficiency and an excess of mannose-6-phosphate can be deleterious to health; thus, our patient's biochemical and clinical parameters will need close monitoring as we adjust her mannose supplementation. Although much higher doses of mannose can be tolerated, limiting supplementation to that required to normalize the glycosylation pattern rather than a weight-dependent dosing may prevent the progression of liver disease noted in previously reported cases.

Although the cause of hyperinsulinemia is not well understood, a proposed mechanism is hypoglycosylation of the sulfonylurea receptor 1 (SUR1) [10], a key component of the K_{ATP} channel, the closure of which results in membrane depolarization, opening of the voltage-gated calcium channels, and insulin secretion. SUR1 glycosylation is necessary for expression of the K_{ATP} channel at the β-cell surface. The excellent response to diazoxide (which acts on SUR1 to open the K_{ATP} channel and reduce insulin secretion) does suggest functional impairment of the K_{ATP} channels in CDG1b. Another proposed mechanism is hypoglycosylation of the insulin

receptor (both subunits are typically glycosylated) or at the postreceptor level, impacting insulin action [10].

This case expands our knowledge of unusual causes of hyperinsulinemic hypoglycemia, and specifically of CDG 1b.

Learning Points

- Congenital disorder of glycosylation type 1b (CDG 1b) can present as hyperinsulinemic hypoglycemia
- The condition is typically treatable with mannose supplementation
- Gastrointestinal, hepatic, and hematological complications can occur and should be monitored in children with CDG 1b

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Contributors

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Restrictions apply to the availability of some data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will, on request, detail the restrictions and any conditions under which access to some data may be provided.

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