Mannose: an unlikely cure

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The case

A 2-year-old male with protein losing enteropathy (PLE) of unknown etiology, chronic diarrhea, and hypoalbuminemia, is admitted for asymptomatic hypoglycemia (36 mg/dL) detected on outpatient labs drawn as part of his PLE surveillance. For the past year, he has been managed by pediatric gastroenterology for anasarca, hypoalbuminemia, and chronic diarrhea. His work up included a course of valganciclovir for presumed Menetrier disease, given positive urine and serum cytomegalovirus (CMV) polymerase chain reaction (PCR) studies in the setting of anasarca. He underwent an esophagogastroduodenoscopy (EGD) and colonoscopy which showed gastritis, but no evidence of colonic inflammation, and intestinal biopsy was negative for CMV. Despite antiviral treatment and multiple albumin infusions, he continued to have significant edema, hypoalbuminemia, and 4 to 8 loose nonbloody stools per day. The persistence of his symptoms prompted repeat labs which revealed his hypoglycemia. At the time of the lab draw, the patient was asymptomatic, well appearing, and walking around the office.

On history, parents deny any seizures, decreased energy, or emesis. They describe that he wakes up sweaty sometimes in the morning, and does not like sweet foods. His most prominent symptom is periorbital swelling that has been present for the past year and improves throughout the day. There is no family history of autoimmune disease, hypoglycemia, or enteropathy. He has a healthy older sister. He is developing normally without any neurological concerns. Notably, a blood glucose of 40 mg/dL was recorded prior to EGD however, this level was attributed to nothing by mouth status. He was referred to the emergency department, where he was treated for hypoglycemia and admitted to the pediatric ward for further work up.

Physical examination

The physical exam revealed a nondysmorphic toddler who was alert and well appearing with significant periorbital edema. He had moist mucous membranes and was breathing comfortably in room air. He was warm and well perfused with 2+ distal pulses, non-displaced point of maximal impulse (PMI), and no murmurs on exam. His abdomen was distended with hyperactive bowel sounds and hepatomegaly. His neurological exam was overall reassuring and he was developmentally appropriate for age. His genitourinary exam revealed scrotal edema.

Laboratory studies

On presentation to the hospital, point-of-care blood glucose was 37 mg/dL and baseline labs were notable for mildly elevated aspartate aminotransferase level (67 U/L, range < 47 U/L), hypoalbuminemia (1.7 g/dL, range 3.5-4.7 g/dL), normal international normalized ratio (INR) (0.9, range 0.9-1.1), and low antithrombin (0.36 U/ml, range 0.86-1.18 U/mL) and Factor XI levels (41 %, range 65-150%). Critical sample was obtained and significant for hyperinsulinism picture given inappropriately elevated insulin level and low free fatty acids and beta hydroxybutyrate levels in response to hypoglycemia (**Table 1**). Additionally, counterregulatory hormone levels were appropriately elevated arguing against panhypopituitarism or growth hormone deficiency. Urine organic acids labs were also obtained and were unrevealing which was reassuring against a fatty acid oxidation disorder. Given high suspicion for hyperinsulinemic hypoglycemia, a glucagon stimulation test was performed and showed plasma glucose increase from 46 mg/dL to 146 mg/dL in 30 minutes which was consistent with increased insulin action.

Hospital course part 1

Shortly after admission, a hyperinsulinism gene panel was sent and the patient was started on diazoxide 5 mg/kg/day for treatment of increased insulin secretion and chlorothiazide for risk of further fluid retention with diazoxide. Despite initiation of diazoxide, our patient continued to have persistent hypoglycemia that was confounded by increased emesis and refusal to eat. He was initiated on intravenous (IV) dextrose containing fluids at day 20, however due to tenuous IV access, he required multiple glucagon administrations for blood glucose readings as low as 17 mg/dL. His diazoxide dose was ultimately titrated up to 10 mg/kg/day however, efficacy was difficult to ascertain given he was unable to tolerate this medication which is only available in oral formulation. Due to persistent hypoglycemia, a decision was ultimately made to place a peripherally inserted central catheter (PICC) line to ensure delivery of continuous dextrose infusion.

Within 12 hours of PICC line placement, a line-associated deep venous thrombosis (DVT) developed in his L subclavian and axillary veins confirmed by ultrasound. He was started on intramuscular Lovenox and the PICC line was maintained given risk of further complications with removal. Due to concerns for malnutrition and inability to tolerate oral diazoxide, nasograstic (NG) tube was placed to deliver diazoxide and provide adequate enteral nutrition. Liver enzymes were trended, and aspartate aminotransferase and alanine aminotransferase were stably increasing to 173 U/L and 116 U/L respectively. INR and bilirubin levels remained within normal limits. The patient had decreased energy levels and concerns were shared amongst the team that he did not seem to be improving on his current regimen of diazoxide, NG feeds, and dextrose fluids.

Differential diagnosis

Given the constellation of symptoms including hepatopathy, hyperinsulinemic hypoglycemia, PLE, and coagulopathy, a unifying genetic diagnosis was favored. In consultation with the genetics team and through researching case reports of patients with a similar presentation, Mannose Phosphoisomerase Deficiency - Congenital disorder of Glycosylation 1b (MPI-CDG 1b) was highly considered. MPI-CDG 1b is an exceedingly rare autosomal recessive disorder of glycosylation that is characterized by profound hypoglycemia, gastrointestinal complications including PLE, and thrombotic events. Based on the similarity between our patient's clinical presentation and cases reported in the literature, MPI-CDG 1b was the leading diagnosis. Hereditary fructose intolerance (HFI), a disorder caused by defects in the enzyme fructose-1-phosphate aldolase leading to fructose toxicity, was also high on the differential given diarrhea, vomiting, hypoglycemia, history of patient self-restricting high sugar foods, and liver abnormalities on labs. Interestingly, HFI can present as a secondary congenital disorder of glycosylation syndrome due to inhibition of N-glycosylation of proteins secondary to build up of fructose-1-phosphate. However, reports that our patient consumed fructose high foods at home with normal transaminases prior to admission was less consistent with this diagnosis. Additional diagnoses were considered including ketotic hypoglycemia which was felt to be unlikely given no elevation in plasma ketones with critical sample, and pan hypopituitarism which was very unlikely given normal counterregulatory hormone response to low plasma glucose.

Hospital course part 2

Based on high suspicion for MPI-CDG 1b and reports that mannose, a sugar monomer that is purchased over-the-counter can reverse laboratory and clinical abnormalities in MPI-CDG 1b patients, oral mannose treatment was initiated. He was initially started on a dose of 80 mg/kg/day and titrated up to 150 mg/kg/day divided 4 times daily. Because mannose was not available on the pharmacy formulary, it was purchased over-the-counter and then weighed on a hospital scale for accurate dosing. He was closely monitored for changes in his stool and further abdominal distention to determine if mannose could be tolerated.

Within 2 weeks of initiating oral mannose, our patient showed marked improvement in his clinical symptoms and biochemical markers. His hypoglycemia completely resolved, and he was able to tolerate a 12 hour fast with blood glucose levels > 80 mg/dL. His edema decreased, albumin level normalized (3.9 g/dL), liver enzymes trended towards normal, and coagulation factors improved (**Table 2**). His energy level returned to baseline and his appetite returned. He was discharged home with close multidisciplinary follow up on diazoxide, NG feeds, and oral mannose.

Diagnosis

Mannose phosphoisomerase (MPI) gene panel and carbohydrate transferrin glycosylation studies were obtained and sent for analysis. Studies were not finalized until after the patient was safely discharged home. The MPI gene panel confirmed the diagnosis of MPI CDG 1b with 2 variants in the MPI gene including pathogenic variant c.656G>A (p.Arg219Gln) and likely pathogenic variant c.602T>C (p.Leu201Pro). Additionally, transferrin glycosylation studies showed evidence of impaired N-glycosylation further supporting this diagnosis (Table 2).

Discussion

Congenital disorders of glycosylation are a rare group of heterogenous multisystem disorders that result due to various defects in the glycosylation pathway of lipids and proteins.[2] Due to the ubiquitous presence of glycosylation pathways within the body, any organ system can be involved.[2] MPI-CDG 1b is a congenital disorder of protein glycosylation that occurs due to a deficiency in the enzyme mannose phosphate isomerase which converts fructose 6 phosphate to mannose 6 phosphate[1] (**Figure**). Due to pathogenic variants in the MPI gene, patients with MPI CDG 1b do not produce endogenous mannose which is a critical substrate in the protein N-glycosylation cascade.[1] This deficiency results in truncated or missing carbohydrate side chains of glycoproteins that play a role in normal cellular function. However, because fructose 6- phosphate does not accumulate intracellularly due to metabolism in the glycolytic pathway, MPI-CDG 1b does not cause significant neurological involvement seen in other disorders of glycosylation. Similar to our patient, most cases of MPI-CDG 1b describe hepatic and gastrointestinal involvement in addition to hyperinsulinemic hypoglycemia and coagulation disorders with thrombosis or bleeding tendencies. Specifically, Factor XI, Factor IX, Factor V, anti-thrombin, Protein C, and Protein S deficiencies have been observed.[1] With only 35 cases reported in the literature as of 2020, a high index of suspicion and familiarity with reported manifestations aids in time to diagnosis which is important as this condition can be life threatening if left untreated.[1]

In the case of our patient, the combination of symptoms coupled with an increased suspicion for a genetic syndrome led to the identification of his rare disorder. His development of a PICC line associated DVT may have been prevented had the diagnosis been established and increased risk of thrombosis understood. Whether due to glycosylation defects or loss of proteins secondary to enteropathy, coagulopathy is a serious side effect seen in patients with MPI-CDG 1b that can lead to stroke or hemorrhage if not properly managed. Hepatomegaly in the setting of elevated transaminases, as seen in our patient, is another common presenting symptom in patients with MPI-CDG 1b. Due to increased risk of liver fibrosis and steatosis, patients are monitored closely for evidence of liver changes due to increased risk of portal hypertension into adulthood.

Treatment and patient outcome

MPI-CDG 1b is the only treatable congenital disorder of glycosylation. Oral mannose supplementation has been shown to reverse both laboratory abnormalities and clinical symptoms in MPI-CDG 1b by overcoming the metabolic block in the glycosylation cascade. Within 1 week of treatment, most patients will see an improvement in clinical symptoms, with up to 1 month for biochemical markers to stabilize.[1] However, despite correction of most laboratory abnormalities, some patients will continue to display persistent liver involvement despite initiation of treatment. Osmotic diarrhea is the major limiting factor for increasing mannose, most often seen with a single dose of 200 mg/kg[3]. Therefore, the recommended dose is 150-170 mg/kg/day divided 4 times daily to normalize glucose levels.[1] Our patient was initially started on a dose of 80 mg/kg/day and titrated up to 150 mg/kg/day divided 4 times with the goal of balancing resolution of symptoms and side effect profile.

Within 2 months after discharge, our patient's diarrhea had resolved; he was titrated off of NG feeds; and diazoxide was discontinued. Additionally, repeat CDG transferrin studies showed significant improvement in glycosylation defects and he remained euglycemic. Within 3 months, he had complete resolution of his thrombosis on Lovenox therapy. Due to thrombotic and hemorrhagic tendencies with dehydration and illness, a plan was developed and updated in his chart to inform providers of his increased risk for coagulopathy. He is currently maintained on 150 mg/kg/day of oral mannose without significant side effects, including diarrhea. He continues to follow up with multidisciplinary teams including gastroenterology for his increased risk of hepatic fibrosis. At this time, there is no clinical indication of liver involvement. He is developing appropriately and his family is actively involved in advocating for children with MPI-CDG 1b. His case demonstrates the importance of considering MPI-CDG 1b on the differential when a patient presents with characteristic myriad of clinical symptoms without a clear diagnosis.

Tables/Figures:

Table 1.

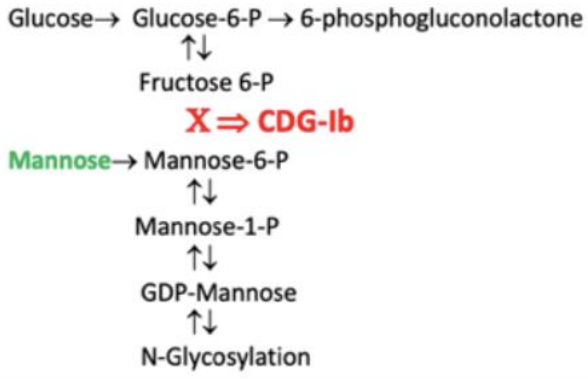
Critical Sample Results

Test	Value	Test Interpretation
Plasma Glucose	50 mg/dL	Appropriate value for sample
Insulin Level	2 uIU/mL	**Inappropriately elevated**
Cortisol level	3.1 ug/dL	Normal value
Beta Hydroxybutyrate	1.2 mg/dL	**Inappropriately low**
Growth Hormone	5.39 ng/mL	Normal value
Free Fatty Acid level	0.28	**Inappropriately low**
Ammonia	32 umol/L	Normal value

Table 2.

Lab	Pre Mannose	2 weeks s/p Mannose	Normal Range
Glucose	49	91	70-99 mg/dL
AST	173	29	< 47 U/L
ALT	116	30	< 60 U/L
Alk Phos	137	114	85-270 U/L
Albumin	1.7	3.9	3.5-4.7 g/dL
INR	0.9	0.84	0.9-1.1
ATIII	0.36	1.39	0.86-1.18 U/mL
Factor XI	41	139	65-150%
Carbohydrate Deficient Transferrin levels			
MO-OLI/DI-OLIGOSACCHARIDE-CDG	1.63	0.09	<=0.06
A-OLI/DO-OLIGOSACCHARIDE-CDG	0.862	0.008	<=0.011
TRI-SIALO/DI-OLIGOSACCHARIDE-CDG	0.06	0.03	<=0.05
APO CIII-1/APO CIII-2-CDG	1.48	1.72	<=2.91
APO CIII-0/APO CIII-2-CDG	0.16	0.28	<=0.48

Figure



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