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Glycogen Storage Disease Type Ia, Different Clinical Manifestations and Outcome: A Case Series

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Received: 18 September 2022 **Revised:** 14 November 2022 **Accepted:** 07 December 2022

ARTICLE INFO

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Keywords:
Glycogen storage disease type I;
Glucose-6-phosphatase;
Hypoglycemia;
Clinical manifestations;
Outcome

ABSTRACT

Background: Conversion of glucose-6-phosphate to glucose is the final step in both glycogenolysis and gluconeogenesis. In glycogen storage disease type Ia (GSD type Ia), decreased activity of the enzyme glucose-6-phosphatase leads to an increased concentration of glucose-6-phosphate within the hepatocytes and shunting into alternative pathway with the following consequences: hyperlactatemia, hyperuricemia and hypertriglyceridemia. Patients develop hypoglycemia within 3 to 4 hours after a meal.

Case Report: We reported four patients with GSD type Ia with different clinical manifestations such as hypoglycemia, hepatomegaly, lactic acidosis, hyperchylomicronemia, and hyperuricemia and also described their prognosis.

Conclusion: Previously, many children with GSD Ia died in infancy or early childhood. Recurrent severe hypoglycemia can cause brain damage, but the prognosis has improved dramatically with early diagnosis and long term maintenance of optimal metabolic control.

Introduction

Glycogen storage disease type I (GSD I) is an autosomal recessive disorder due to the absence or deficiency of glucose-6-phosphatase activity in the liver, kidney and intestinal mucosa. It has two subtypes: type Ia, in which glucose-6-phosphatase is the defective enzyme and type Ib, in which the defective enzyme is a translocase that transports glucose-6-phosphate across the microsomal membrane. Deficiency of the enzymes in both type Ia and Ib cause inadequate hepatic conversion of glucose-6-phosphate to glucose through

normal glycogenolysis and gluconeogenesis, leading to fasting hypoglycemia.[1,2]

The genes for glucose-6-phosphatase and translocase are located on chromosomes 17q21 and 11q23, respectively. Common pathogenic variants have been identified.

Clinical manifestation: Patients with GSD type Ia may present in the neonatal period with hypoglycemia and lactic acidosis but more often present at 3-4 months of age with hepatomegaly, hypoglycemic seizures, or both.[1] Affected children often have a doll-like face with fat cheeks, relatively thin extremities, short stature and a protuberant abdomen, which could be a consequence of massive hepatomegaly.[1] The kidneys are also enlarged, whereas the spleen and heart are not involved.[1]

Hypoglycemia and lactic acidosis, hyperuricemia and hyperlipidemia are the biochemical characteristics of GSD type Ia. Hypoglycemia and lactic acidosis can develop after a short fast. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. Easy bruising and epistaxis are common and are associated with a prolonged bleeding time as a result of impaired platelet aggregation and adhesion. The plasma may be milky in appearance due to strikingly elevated triglyceride levels. Cholesterol and phospholipids are also elevated, but are less prominent.

There is an increased risk of pancreatitis secondary to the lipid abnormalities. In the 2nd or 3rd decade of life, some patients with GSD type Ia develop hepatic adenomas that can hemorrhage and turn malignant in some cases.

Renal diseases are another late complication and most patients with GSD type Ia > 20 yr of age have proteinuria. Many also have hypertension, renal stones, nephrocalcinosis and altered creatinine clearance.

Diagnosis: The clinical presentation and laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia and hyperlipidemia lead to a suspected diagnosis of GSD type Ia. Gene-based variant analysis by single gene sequencing or gene panels provides a non-invasive way to diagnose most patients with GSD types Ia and Ib.[3]

Treatment: Treatment focuses on maintaining normal blood glucose levels and is achieved by continuous nasogastric (NG) infusion of glucose or oral administration of uncooked cornstarch.

Medium-chain triglyceride (MCT) supplementation improves metabolic control, leading to improved growth in children. Since fructose and galactose cannot be converted directly to glucose in GSD type Ia, these sugars should be restricted in the diet.[4]

Dietary therapy improves hyperuricemia, hyperlipidemia and renal function. The control of hyperuricemia can be further augmented by the use of allopurinol. Hyperlipidemia can be reduced with lipid-lowering drugs such as HMG-CoA reductase inhibitors and fibrate. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and the development of urinary calculi.

Prognosis: Previously, GSD type Ia was associated with high mortality at a young age, and even for those who survived, the prognosis was guarded. Inadequate metabolic control during childhood can lead to long-term complications during adulthood. Clinical outcomes have improved dramatically with early diagnosis and effective treatment. However, serious complications such as renal disease and the formation of hepatic adenomas with a potential risk for malignant transformation persist.[5]

Case report

Case 1: A 3.5-month-old infant boy was admitted to our center due to poor feeding, lethargy, frequent vomiting, respiratory distress and generalized tonic-clonic seizure following a respiratory infection. The patient had a history of hospitalization on the first day of birth due to apnea, cyanosis and hypoglycemia (BS = 10mg/dl) for six days.

The patient's parents were consanguineous. There was a history of GSD type Ia in the patient's paternal family (case 2). He had hepatomegaly in the examination (Table 1).

Table 1. Case 1: Laboratory Test Results

pH = 7.32	HCO3 = 4.2 mg/dl	Pco2 = 8
Lactate > 100 mg/dl	BS = 12 mg/dl	TG = 541 mg/dl
Cholesterol = 178 mg/dl	Uric acid = 7.3 mg/dl	SGPT = 103 mg/dl
SGOT = 321 mg/dl	AlKP = 1544 mg/dl	Urine ketone +

The patient was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. Phenobarbital was prescribed to the patient under the supervision of a neurologist. After correcting the acidosis, the patient was treated with frequent lactose-free formula feeds every 1.5-3h and MCT.oil. OMEGA-3 was also prescribed due to hyperlipidemia. The patient was also treated with oral bicarbonate after discharge. The diagnosis of GSD type Ia was confirmed in the genetic study. In the follow-up, the patient had a history of repeated hospitalizations with the same symptoms as above, which decreased after starting raw corn starch from six months, and now at the age of 4.5 years, he is metabolically controlled with the above treatments and is doing very well.

Case 2: A 9-year-old boy was admitted to our center due to lethargy, vomiting and respiratory distress. The patient had a history of frequent hypoglycemia and metabolic acidosis following fasting since birth. She was fed via gastrostomy feeding tube insertion. Huge hepatomegaly was observed in the examination. The patient had a liver biopsy and the result was reported to be macrovesicular steatosis. His parents were consanguineous (Table 2).

The patient was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. After correcting the acidosis, according to the nutritionist's opinion, the patient was given a limited galactose, fructose and sorbitol diet that was included raw corn starch and MCT.oil. Allopurinol was prescribed due to high uric acid. Genetic study of this patient confirmed GSD type Ia. In follow-up, the patient had frequent epistaxis and hematuria due to kidney stones, which were broken down by ultrasonic lithotripsy. The patient also had short stature and delayed puberty. At the age of 15, he is now relatively controlled metabolically with the above treatments.

Case 3: A 4.5-month-old infant boy who was hospitalized since two months due to abdominal distension. He had a medical history of being hospitalized in two days due to hypoglycemia and 3.5 months due to COVID-19. He had huge hepatomegaly in the examination. He was born to consanguineous parents (Table 3).

The patient had melena during hospitalization. He was treated with omega-3, MCT.oil and lactose-free formula every 1.5-3 hours. In the follow-up, the patient's triglyceride remained around 1300 mg/dl. GSD type Ia was confirmed in the genetic study and raw corn starch was started after 6 months of age. At the age of 2 years, the patient was admitted in our center with lethargy and respiratory distress due to a respiratory viral infection, the results of the tests are in Table 4.

He was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. He is now relatively metabolically controlled, but the patient's TG is still above 1000.

Table 2. Case 2: Laboratory Test Results

pH = 7.21	HCO3 = 6.4 mg/dl	Pco2 = 16
BS = 25 mg/dl	Uric acid = 10.9 mg/dl	Lactate = 59 mg/dl
TG = 200 mg/dl	Cholesterol = 140 mg/dl	SGOT = 24 mg/dl
SGPT = 18 mg/dl	AlKP = 391 mg/dl	Urine ketone +2

Table 3. Case 3: Laboratory Test Results (The Blood Sample Was Milky)

pH = 7.39	HCO3 = 19.4 mg/dl	Pco2 = 32
TG = 15130 mg/dl	Cholesterol = 966 mg/dl	BS = 55 mg/dl

Table 4. Case 3: Results of Laboratory Test at the Age of 2 Years

pH =7.03	HCO3 = 6.3 mg/dl	Pco2 = 24
BS = 32 mg/dl	TG = 1814 mg/dl	Cholesterol = 235 mg/dl
Uric acid = 11 mg/dl	SGOT = 264 mg/dl	SGPT = 311 mg/dl

Case 4: A 12-year-7-month-old girl was admitted to our center due to hypoglycemia and respiratory distress following a respiratory viral infection. The patient had a history of frequent hypoglycemia and metabolic acidosis since the age of 4 months and was treated with raw corn starch after being diagnosed with GSD type Ia. (Genetic testing has not been done for the patient). In the examination, the patient had huge hepatomegaly, thin limbs and delayed puberty. Her laboratory data is presented in Table 5.

She was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. After correcting the acidosis, according to the nutritionist's opinion, the patient was given a limited galactose, fructose and sorbitol diet which was contained raw corn starch, MCT.oil, oMega-3 and oral bicarbonate.

Discussion

GSD type Ia is caused by glucose 6-phosphatase deficiency. The incidence of GSD type Ia is approximately 1 in 100,000 births.[6,7] Patients have impaired production of glucose from both glycogenolysis and gluconeogenesis which leads to develop hypoglycemia within 3 to 4 hours after a meal. Lactic acid, uric acid, cholesterol and triglycerides are characteristically elevated. GSD type Ia is occasionally diagnosed when hepatomegaly and a protuberant abdomen are discovered during a routine physical examination. Symptomatic hypoglycemia develops when the interval between feedings increases or when illness disrupts normal feeding. Hypoglycemia is not often recognized. The disorder is discovered when the child presents with tachypnea (from lactic acidosis), seizures, lethargy, developmental delay, or failure to thrive.[8]

Conclusion

Intensive dietary treatment with improved metabolic control has led to reduced morbidity and mortality and improved quality of life. Long-term cerebral function is normal if hypoglycemic damage is prevented. Most patients can lead fairly normal lives, but patients may develop complications of different organ systems.[4,7]

Conflict of Interest

The authors have no conflict of interest.

Acknowledgments

The authors would like to thank the patient's family for their cooperation in this study.

The present study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC.1401.071).

How to Cite: Mirhosseini NA, Mirhosseini S, Aflatoonian M, Saeida-Ardekani M. Glycogen Storage Disease Type Ia, Different Clinical Manifestations and Outcome: A Case Series. World J Peri & Neonatol 2022; 5(2): 102-6. DOI: 10.18502/wjpn.v5i2.11998

Table 5. Case 4: Laboratory Test Results

pH = 7.19	HCO3 = 6.9 mg/dl	Pco2 = 18
BS = 22 mg/dl	Uric acid = 6.7 mg/dl	Lactate = 122 mg/dl
TG = 703 mg/dl	Cholesterol = 229 mg/dl	SGOT = 313 mg/dl
SGPT = 178 mg/dl	Urine ketone +	

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