

Glycogen Storage Disease IXa in a 9-year-old Filipino Boy with Short Stature: A Case Report

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ABSTRACT

Glycogen storage disease (GSD) type IXa, due to a deficiency of hepatic phosphorylase b kinase, results in liver enlargement, growth retardation and fasting ketosis. Many are asymptomatic and do not require treatment. This is the first documented GSD IXa in a Filipino boy evaluated for short stature.

Key Words: Glycogen storage disease IXa, hepatomegaly, poor growth, uncooked cornstarch

INTRODUCTION

Glycogen storage diseases (GSD) result from deficiencies of enzymes involved in the synthesis or breakdown of glycogen. They are classified based on the enzyme deficiency and according to the primary organ system affected: “liver” or “muscle” glycogenosis. GSD IX is caused by defects in the activity of the phosphorylase kinase complex (PHK) which plays a role in regulating glucose release from glycogen. Further, GSD IX is said to be the most frequently occurring of the GSDs, accounting for about 25% of all GSDs^{1,2} and has an estimated worldwide incidence of 1:100,000 births.¹

GSDs are not frequently encountered, hence are not immediately included among the differential diagnosis of hepatomegaly; but are usually considered when hypoglycemia becomes a prominent manifestation. The most common reported manifestations of GSD IXa are hepatomegaly and short stature. This patient is the first reported case of a Filipino diagnosed with GSD IXa. His case highlights the importance of including GSDs in the differential diagnosis of hepatomegaly with elevated liver transaminases, even in the absence of overt hypoglycemia.

CASE REPORT

MT is a 9-year-old boy who was referred for sub-optimal growth. He was born at term, the second child of healthy non-consanguineous parents. The pregnancy, birth and perinatal events were unremarkable. His weight (2.52 kg) and length (51 cm) at birth were within normal for gestational age. He was mixed fed with breast milk and lactose containing formula which he tolerated well. His mother was always concerned that he had a “distended” abdomen, which was considered normal by his pediatrician since the liver and spleen were not palpable. No diagnostics were performed because he was a healthy boy with normal

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developmental milestones, who went for clinic visits only for routine immunizations. He attended regular school and had good academic performance. Although described as a picky eater, preferring to eat only pasta and fish, his energy level is good. He plays baseball and is able to keep up with his teammates. His height plotted on the 10th centile while his weight was on the 25th centile of the WHO growth charts. His midparental height (MPH) is above the 25th centile. The discrepancy between the patient's height centile and MPH centile initiated the evaluation for short stature.

The liver ultrasound findings of hepatomegaly and fatty infiltration associated with elevated blood liver transaminases prompted further work-up. Diagnostic evaluations for viral hepatitis, autoimmune hepatitis, Wilson's disease, hypothyroidism, iron overload, celiac disease, alpha 1-antitrypsin deficiency, and acid lipase deficiency yielded normal results. Lipid profile showed elevated levels of total cholesterol, LDL, VLDL and triglycerides. Uric acid was normal. Liver fibroscan documented moderate steatosis with a CAP (controlled attenuation parameter) of 287 dB/m (ref < 238) but no fibrosis. Despite the liver abnormalities, the patient did not manifest with complications of liver disease such as pruritus, jaundice, ascites nor splenomegaly. Liver biopsy revealed diffuse micro vesicular steatosis, non-alcoholic fatty liver and fibrosis stage I. Electron microscopic findings showed ballooned hepatocytes with increased cytosolic glycogen and rare lipid droplets. Whole exome sequencing of the PHKA2 gene documented a previously reported hemizygous variant c.3614 C>T (p.P1205L).

Dietary management commenced with complex carbohydrates, high protein and restriction of simple sugars. Uncooked cornstarch was incorporated into the diet regimen which MT tolerated well. In order to optimize intake of cornstarch, blood glucose and ketone monitoring were done upon waking up in the morning (after 8-9 hour fast); before and after his baseball training in the afternoon and at bedtime. With cornstarch given three times a day, MT made significant gains in height: 3.0 cm over 5 months. The ketone levels diminished and are negligible in the mornings. Table 1 summarizes the clinical and biochemical parameters at baseline and after 5 months of cornstarch treatment. His cornstarch intake at bedtime is titrated to target a fasting blood glucose of 4.14- 5.47 mmol/l. MT reports feeling more energetic during his baseball games compared to when he was not on cornstarch therapy. His mother reports better stamina, increased attention at school and better academic performance. MT no longer reports being sleepy during class.

DISCUSSION

Glycogen storage disease (GSD) IX is caused by a deficiency in the enzyme phosphorylase b kinase, a regulatory enzyme in the glycogenolytic pathway.³ It has four subunits: alpha (α), beta (β), gamma (γ), and delta (δ). Mutations in the genes coding for each subunit results in subtypes of the

Table 1. Clinical and laboratory data

Parameter	Baseline	On cornstarch diet (5 th month)
Weight, kg	25.9	27.7
Height, cm	123.0	126.0
Liver Span, cm (by ultrasound)	15.3	14.0
Steatosis (CAP **, dBm)	287 (moderate)	250 (mild)
Fibrosis (ref < 5.8 kPa)	2.7	2.6
SGPT (ALT) (ref 10-50 U/L)	429.2	78.6
SGOT (AST) (ref 10-50 U/L)	247.9	51.3
Total Cholesterol (ref < 4.40 mmol/L)	5.24	2.89
LDL (ref < 2.59 mmol/L)	3.12	1.58
Triglycerides (ref < 1.69 mmol/L)	1.99	0.90
HbA1c (%)	4.8	5.1

** CAP, Controlled Attenuation Parameter: < 238, No steatosis (S0); 238-259 = mild (S1); 260-291 = moderate (S2); > 291 = severe (S3).

phosphorylase b kinase deficiency. The α unit is coded for by 2 genes on the X chromosome: PHKA1 and PHKA2. Only the latter is expressed in the liver. It is an X-linked disorder and accounts for 75-80% of GSD IX.^{2,4,5} PHKB codes for the β unit and its deficiency causes GSD IXb, an autosomal recessive disorder. PHKG1 and PHKG2 code for the γ subunit, and PHKG2 causes severe liver glycogenosis and early fibrosis. The δ unit has not been reported to cause any GSD. GSD IXa is the most common subtype caused by mutations in PHKA2.

GSD IXa is primarily a liver glycogenosis. While hypoglycemia is expected, this is not always evident, as was seen in our patient. Normoglycemia with ketosis has been reported in patients.^{4,5} The more common manifestations in children include hepatomegaly, short stature, ketosis, elevated liver transaminases, hypercholesterolemia and hypertriglyceridemia.^{2,3} These symptoms improve with age. Cirrhosis and cardiomyopathy have been reported.^{2,4} The diagnosis is usually suspected clinically in any patient presenting with hepatomegaly. Although phosphorylase b kinase activity may be assayed from erythrocytes, liver and muscle tissue, it has been replaced by DNA molecular testing. To date, 114 mutations in the PHKA2 gene have been reported.⁶ Mutations in this gene is responsible for 80% of GSD IX among males with the disease. However, because GSD IX presents primarily with hepatomegaly, many cases are still diagnosed by liver biopsy.²

In general, GSDs are managed with strict dietary prescription consisting of complex carbohydrates, high protein, and the restriction of simple sugars. The goal is maintenance of euglycemia and prevention of ketosis.^{2,7} Uncooked cornstarch, a complex carbohydrate, has been the cornerstone of treatment to ensure adequate source of glucose that is metabolized in a manner that sustains glucose levels over longer periods. In GSD IXa, since hypoglycemia is not always evident, the monitoring of blood ketones especially after an overnight fast may help detect the need for supplemental complex carbohydrates as was the case

in MT. Protein intake of 2-3 g/kg/day ensures adequate glucose through gluconeogenesis.²

Liver ultrasound is not part of the routine diagnostic evaluation of short stature. For MT, because of the significantly elevated liver enzymes, an ultrasound was requested revealing hepatomegaly. This patient demonstrates that GSD IX can easily be missed because of its subtle manifestations. In the absence of hypoglycemia in a boy who belongs to a race with an average adult male height of 157.5 cm (5 feet 2 inches),⁸ GSD is not a common differential diagnosis.

Hypoglycemia is a feature of the liver glycogenesis, most prominently in GSD I where a 4-hour fast results in low blood glucose. On the other hand, hypoglycemia in GSD III, VI, and IX may occur after a more prolonged fast of 12 hours.⁴ Prior to diagnosis, our patient had no documented hypoglycemia, but had symptoms suggestive of suboptimal glucose levels: he was always tired at the end of the day and after baseball practice, had poor appetite, and was often sleepy in class. With confirmed GSD IXa, home blood glucose monitoring commenced and low pre-breakfast capillary blood glucose (CBG) of 3.3-3.5 mmol/L was documented although MT remained asymptomatic. Supplementation with uncooked cornstarch at bedtime resulted in normal pre-breakfast glucose, as well as better overall energy and stamina.

The patient's energy and growth response to uncooked cornstarch is similar to the reported response of patients with hepatic GSD. The resolution of hypercholesterolemia and dyslipidemia; improvement in liver function and steatosis index support the recommendation for supplementation of cornstarch in patients with GSD IX even in the absence of overt hypoglycemia. Tsilianidis reports 2 children with GSD IXa who both had fibrosis responding with marked improvements after structured intake of uncooked cornstarch and a high protein diet.⁵

No correlation has been observed between genotype and the clinical severity. There is wide spectrum of phenotypes associated with GSD IXa due to various mutations in the PHKA2 gene. Even patients with the same pathogenic mutation can have different clinical symptoms.³ Steatosis, elevated liver transaminases, hepatomegaly and ketosis are consistently reported. Severe fibrosis is not a common finding in PKHA 2 but is associated with the PHKG 2 gene. However, of late, fibrosis is now reported as one of the manifestations of GSD IX.^{2,5} MT's liver biopsy documented fibrosis stage I (however, his fibroscan index was normal). This changes the view that GSD IXa is benign. With severe fibrosis at the onset, patients need more aggressive therapy to prevent further liver damage. Early supplementation with uncooked cornstarch and a high protein diet offers GSD IXa patients a chance to reverse liver fibrosis.⁵

Management and monitoring guidelines for GSD IX still need to be published. Only GSD I and GSD III have published diagnostic and management guidelines.⁷ Different institutions draw from these recommendations. Our patient, like many patients with GSD IXa has regular clinical

evaluations, biochemical monitoring and liver imaging as well as home blood glucose and ketone monitoring.

The prognosis for patients with GSD IXa is good because their glucose levels stabilize in adulthood. However, cardiomyopathy and liver cirrhosis have been reported.⁴ With these reported long-term consequences, regular monitoring of patient's clinical and biochemical status is recommended as well as imaging of the liver and heart, if warranted.^{2,4} In MT's case, since fibrosis was present at the diagnosis, closer monitoring is recommended. The repeat liver fibroscan showed improvement in the steatosis index after 5 months of cornstarch supplementation (Table 1).

CONCLUSION

GSD IXa must be included in the differential diagnosis of boys who are short for their genetic potential and manifest with hepatomegaly with or without hypoglycemia. While DNA mutation for GSDs has become the standard diagnostic procedure, liver biopsy continues to be useful in the Philippines because it is more readily accessible. The finding of steatosis and/or fibrosis should alert the physician to consider GSD. Uncooked cornstarch and high protein intake ensure general well-being, euglycemia and may reverse early liver damage in GSD IXa.

Statement of Authorship

The author approved the final version submitted.

Author Disclosure

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