Structured Dietary Management Dramatically Improves Marked Transaminitis, Metabolic and Clinical Profiles in Glycogen Storage Disease Type IXa

Indrajit S. Karande, DCH, FRACP1, Emily Boulter, FRACP1, Leah Queit, APD2, and Shanti Balasubramaniam, FRACP1,3,4,5

Abstract
Glycogen storage disease type IXa (GSD IXa) presents in childhood with hepatomegaly, poor growth, and ketotic hypoglycemia. Clinical course is usually mild, often not requiring treatment with attenuation of symptoms with increasing age. The phenotypic spectrum has recently expanded to include more severe involvement with hepatic fibrosis or cirrhosis warranting dietary therapy. We report a 2-year-old boy with a severe phenotype of GSD IXa presenting with a massive hepatomegaly, significant transaminitis, recurrent ketotic hypoglycemia, and short stature. Aggressive dietary management with regular feeds, frequent uncooked cornstarch doses, and protein supplementation resulted in clinical improvements including enhanced growth velocity, energy levels, overall well-being, and reduction in hepatomegaly with restitutions in biochemical parameters. We concur with a recent report which proposed that GSD IXa is not always a mild condition but instead part of an expanding phenotypic spectrum warranting intensive dietary management to optimize metabolic control and quality of life.

Keywords
GSD IXa, severe phenotype, aggressive dietary management, restitution of clinical and biochemical profiles

Introduction
Glycogen storage disease type IXa (GSD IXa), also known as X-linked liver glycogenosis (XLG), is one of the most common forms of GSD, accounting for approximately 75% of liver phosphorylase-b kinase (PhK) deficiency. It is caused by a mutation in the phosphorylase kinase liver alpha-subunit 2 (PHKA2) gene encoding the liver isoform of the α-subunit located on Xp22.2-p22.1. The enzyme PhK has a key regulatory role in the breakdown of glycogen and is one of the most common forms of GSD. It accounts for about 25% of all GSDs and has an estimated frequency of 1 in 100 000.1 The disorder may however be underdiagnosed as a result of the variable presentation and challenges with diagnostic confirmation.2 Phosphorylase-b kinase is a large hexadecameric complex that is composed of 4 copies each of 4 subunits (α, β, γ, and δ/calmodulin). The γ-subunit contains the catalytic site, which is regulated by the phosphorylation state of the α- and β-subunits, as well as by calmodulin via calcium levels.3 The complexity of the enzyme structure is further increased by tissue-specific isoforms and alternative splicing of different subunit genes leading to heterogeneity in the clinical phenotypes and patterns.

1 Metabolic Unit, Department of Rheumatology and Metabolic Medicine, Princess Margaret Hospital, Perth, Western Australia, Australia
2 Department of Nutrition and Dietetics, Princess Margaret Hospital, Perth, Western Australia, Australia
3 School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia
4 Western Sydney Genetics Program, Children’s Hospital at Westmead, Westmead, New South Wales, Australia
5 Discipline of Genetic Medicine & Paediatrics and Child Health, University of Sydney, New South Wales, Australia

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Corresponding Author:
Shanti Balasubramaniam, Western Sydney Genetics Program, Children’s Hospital at Westmead, Westmead, New South Wales 2145, Australia.
Email: shanti.balasubramaniam@health.nsw.gov.au
of inheritance. Clinically, PhK deficiencies can be categorized based on the principally affected tissues into either liver or muscle phenotypes. Liver PhK deficiency is characterized by early childhood onset of hepatomegaly and growth retardation, and often, but not always, fasting ketosis and hypoglycemia. Muscle PhK deficiency, which is considerably rarer, may be characterized by exercise intolerance, myalgia, muscle cramps, myoglobinuria, and progressive muscle weakness.

The liver isoforms of α-, β-, and γ- subunits are encoded by PHKA2 (type IXα liver specific, OMIM# 300798; Xp22.2-p22.1), phosphorylase kinase beta subunit (PHKB) (type IXα liver and muscle deficiency, OMIM# 172490; 16q12-q13), and phosphorylase kinase, testis/liver gamma-2 (PHKG2) genes (type IXc, liver type, OMIM# 172471; 16p12.1-p11.2), respectively. PHKA2-related PhK deficiency, also known as XLG, is the most common cause of liver PhK deficiency, accounting for about 75% of all GSD IX. Patients with XLG can be divided into 2 biochemical subtypes depending on the enzyme activity in various tissues: XLG type 1 (XLG1 or GSD-IXα1), with reduced activities of PhK in blood cells and liver, and XLG type 2 (XLG2 or GSD-IXα2), with normal PhK activity in blood cells and variable activity in liver. X-linked liver glycogenosis is characterized by hypoglycemia, hepatomegaly, chronic liver disease, growth retardation and delayed motor development, hypercholesterolemia, hypertriglyceridemia, and hyperketosis following fasting. These symptoms ameliorate during puberty. Mutations in PHKB result in PhK deficiency both in liver and muscle; however, the symptoms from muscle involvement can be mild or absent, thus making it clinically indistinguishable from the liver PhK deficiencies caused by mutations in PHKA2 and PHKG2. Patients with mutations in γ-subunits (PHKG2) are at risk of a more severe phenotype that can present with cirrhosis in childhood.

Although XLG subtype of GSD IX due to mutations in PHKA2 has largely been presumed as a benign condition, which improve with age and not warranting treatment, a broad phenotypic spectrum has however recently expanded to include chronic liver disease with fibrosis and cirrhosis. We present a 2-year 6-month-old boy with novel α-subunit (PHKA2) gene mutation presenting with severe GSD IXα phenotype in the form of massive hepatomegaly with fibrosis at the time of diagnosis, in addition to growth retardation, recurrent hypoglycemia, ketosis, and significant transaminitis. Structured therapy with regular feeds, uncooked cornstarch (UCCS), and protein supplementation led to dramatic clinical improvements and amelioration of biochemical abnormalities.

Case Report

The patient, a 2-year 6-month-old boy, was born at term to nonconsanguineous, healthy parents following an uneventful pregnancy. He had normal growth parameters at birth and an unremarkable perinatal period. Retrospectively, his parents noted abdominal distension from 3 to 4 months of age. He was described to be an often irritable, hungry infant who usually settled easily with a feed. At 2 years of age, he was presented to a general pediatrician with a protuberant abdomen, faltered growth velocity, delay in gross motor milestones, and recurrent infections with intermittent vomiting, diarrhea, and pneumonia. Massive hepatomegaly was detected on clinical examination and he was subsequently referred to a tertiary center. Initial clinical evaluation at 2 years 6 months revealed a fretful, sweaty, pale toddler with doll-like features. His weight, height, and head circumference were 10th to 25th, <1st, and 25th percentiles, respectively. The liver measured 13 cm below the right costal margin at the midclavicular line and was soft and not tender. The spleen was not palpable and there was no ascites. His respiratory and cardiovascular systems were normal; however, muscle tone and power were mildly decreased, with normal deep tendon reflexes. The patient’s mother reported having mild abdominal distension as a child, which had resolved by late adolescence. She was never investigated for it and did not recall having symptoms of hypoglycemia. She has a sister who is healthy and did not share similar features.

Further evaluation revealed marked hepatic transaminase elevations, ketosis, hypercholesterolemia, hypertriglyceridemia, mild hyperuricemia, and lactic academia (Table 1). Random blood sugar was 2.3 mmol/L (reference range 3.0-5.4 mmol/L). α-1 antitrypsin deficiency was excluded by an appropriate test. Serological tests showed no evidence of infection with hepatitis virus A, B, or C. Urine organic acid profile showed a mild increase in 3-methylglutaconate but was otherwise unremarkable. Urinary tetrasccharide excretion was markedly increased at 645 standardized ratios to internal standard (reference range <25). Abdominal ultrasound confirmed profound hepatomegaly with a homogeneous echo texture and no evidence of cirrhosis, portal hypertension, or focal hepatic lesion. A liver biopsy showed stage 3 perportal and portal-central vein fibrosis with mild steatosis. The hepatocytes were diffusely enlarged exhibiting cytoplasmic accumulation of periodic acid–Schiff-positive, diastase-sensitive glycogen. Scattered fat droplets were observed within the hepatocytes. There was no evidence of lobular inflammation. Electron microscopy revealed abundant hepatocellular glycogen with cytoplasmic lipid. Both monogranular and rosetted glycogen granules were present, but fibrillar forms were not seen and only occasional lysosomes contained these glycogen granules. The morphological features were reported to be suggestive of either GSD type I or type III, with the presence of lipid globules favoring type I. Normal glucose-6-phosphatase levels, sequencing of the SLC37A4 gene, and peripheral leucocytes debrancher assay excluded GSD types Ia, Ib, and III, respectively. Liver tissue assayed for the phosphorylase system (Table 2) showed low normal PhK activity with an abnormal ratio of phosphorylase-a to total phosphorylase, indicating a degree of functional abnormality in the phosphorylase-activating system. Subsequent mutation analysis revealed a novel splice site hemizygous mutation in the PHKA2 gene, c.1325-2 A>G that is predicted to be pathogenic by disrupting the consensus splice acceptor site at the junctions of exons 13 and 14, resulting in abnormal gene splicing (www.fruitfly.org/cgi-bin/seq tools/splice.pl). This mutation was also detected in his mother.
Aggressive dietary therapy was initiated with a regime consisting of 3 main meals and 3 snacks fed at approximately 3 hourly intervals. Low glycemic index foods were used and initial total protein intake was 2.8 g/kg/d. Uncooked cornstarch at 1.0 g/kg/d per dosage was given post main meals 3 times per day. Nocturnal continuous nasogastric tube feeds using Abbott PediaSure (Zwolle, Netherlands) vanilla providing 6.1 mg/kg/day. Nocturnal continuous nasogastric tube feeds using Abbott PediaSure (Zwolle, Netherlands) vanilla providing 6.1 mg/kg/ min of carbohydrates were commenced instead of glucose polymers, as we had initial difficulties in encouraging oral solid intake during the day. Dramatic improvements in energy levels occurred with resolution of his vomiting, irritability, improvements in liver function, and maintenance of euglycemia. Once sustained improvements were observed within 6 weeks, the continuous overnight feeds were ceased and replaced with a fourth feed of UCCS given at 6 hourly intervals. Low glycemic index foods were used and initial total protein intake was 2.8 g/kg/d. Uncooked cornstarch at 1.0 g/kg/d per dosage was given post main meals 3 times per day. Nocturnal continuous nasogastric tube feeds using Abbott PediaSure (Zwolle, Netherlands) vanilla providing 6.1 mg/kg/ min of carbohydrates were commenced instead of glucose polymers, as we had initial difficulties in encouraging oral solid intake during the day. Dramatic improvements in energy levels occurred with resolution of his vomiting, irritability, improvements in liver function, and maintenance of euglycemia. Once sustained improvements were observed within 6 weeks, the continuous overnight feeds were ceased and replaced with a fourth feed of UCCS given at 6 hourly intervals. Daytime doses of UCCS remained at 1.0 g/kg/dose and the nocturnal feed was increased to 1.5 g/kg/d. Supplementary protein powder (Ascend Sport WPI, Cobram, Victoria, Australia) at 1.0 g/kg/dose was added to all UCCS feeds as his oral intake of proteins was unsatisfactory. Frequent liver function profiles, home blood glucose and ketone monitoring, and semi-quantitative estimation of liver size were used to assess clinical improvement.

With the initiation of formal, structured therapy, a dramatic increase in growth occurred, with amelioration of metabolic derangements (Table 1). Suboptimal growth, which was a presenting concern, resolved with treatment, and a height increase of 6 cm was observed in 2-month duration. Home monitoring prior to treatment revealed intermittent day and night ketosis with occasional hypoglycemia, which in addition to other laboratory studies including hepatic transaminases, triglycerides, blood glucose, ketones, and lactate were markedly improved following initiation of a structured treatment regimen. The clinically palpable liver measuring 13 cm below the right costal margin at presentation at 2 years decreased in size to 9 cm over the initial course of 6 months and has remained stable thereafter. Serial abdominal 6 monthly ultrasonography demonstrated stable hepatomegaly with no evidence of cirrhosis, portal hypertension, or focal hepatic lesion.

**Table 1. Liver Biochemistry on Presentation, 3, 6, 12, 24, and 36 Months After Instituting Dietary Therapy.**

| Age (Months) | At Presentation (24 Months of Age) | 3 Months After Dietary Therapy | 6 Months After Dietary Therapy | 12 Months After Dietary Therapy | 2 Years After Dietary Therapy | 3 Years After Dietary Therapy |
|--------------|-----------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Alanine transaminase (U/L) | 4540 | 146 | 216 | 185 | 185 | 241 |
| Aspartate transaminase (U/L) | 4540 | 146 | 216 | 185 | 185 | 241 |
| Alkaline phosphatase (U/L) | 374 | 37 | 34 | 34 | 34 | 34 |
| γ-glutamyl transferase (U/L) | 294 | 37 | 34 | 34 | 34 | 34 |
| Glucose (mmol/L) | 2.3 | 5.1 | 5.3 | 5.0 | 5.1 | 5.1 |
| Cholesterol (mmol/L) | 16.3 | – | – | 3.9 | – | 3.9 |
| Triglyceride (mmol/L) | 3.6 | – | – | 1.9 | – | 1.9 |
| Lactate (mmol/L) | 3.3 | 12 | 12 | 1.4 | – | 3.2 |
| Uric acid (mmol/L) | 0.49 | 0.26 | 0.26 | 0.24 | 0.20 | 0.18 |

**Table 2. Growth Percentiles on Presentation, 3, 6, 12, 24, and 36 Months After Instituting Dietary Therapy.**

| On Referral | At Presentation | 3 Months After Dietary Therapy | 6 Months After Dietary Therapy | 12 Months After Dietary Therapy | 2 Years After Dietary Therapy | 3 Years After Dietary Therapy |
|-------------|-----------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Weight (kg) | 13.7 | 13.5 | 15.6 | 17.4 | 17.7 | 18.4 | 22.7 |
| Weight (percentile) | 85th | Just >50th | Just >85th | 85th-97th | 85th-97th | 85th | 85th-97th |
| Height (cm) | 78 | 86 | 86 | 89 | 90.5 | 97.5 | 105.6 |
| Height (percentile) | <1st | <1st | 3rd | 3rd-15th | 3rd-15th | 3rd-15th | >15th |

**Discussion**

The first case of GSD IXa was described in 1966. The last 5 decades has seen an evolution in our understanding of the expanding spectrum of clinical presentation and management strategies for this condition.

Glycogen storage disease type IXa has previously been considered to be a benign condition that often does not warrant treatment. Typically, an affected child presents in first years of life with hepatomegaly and growth retardation. Hyperketotic hypoglycemia, if present, is usually mild but can be severe and recurrent. However, there is a wide spectrum of severity of clinical presentations, including ketotic hypoglycemia, hepatomegaly, growth retardation, delayed motor development, and as more recently reported, chronic liver disease with cirrhosis. The first known case of GSD IXa due to \( \text{PHKA2} \) mutation with liver cirrhosis was reported in 2011. More recently, the phenotypic spectrum of GSD IX secondary to \( \text{PHKA2} \) gene defects has been described to potentially include a more severe presentation almost mimicking GSD I. We have described a boy with GSD IXa due to a hemizygous novel mutation that is predicted to be pathogenic in the \( \text{PHKA2} \) gene at the splicing site c.1325-2 A > G.

Traditionally, it is widely believed that individuals with GSD IXa often do not require treatment as the childhood symptoms frequently improve with age. However, increasing
evidence of long-term complications particularly attributed to chronic ketosis, which may occur even in the setting of relative normoglycemia, suggests that optimization of metabolic control is imperative in minimizing these risks, which include morning nausea, vomiting, school absence, and subsequent academic difficulties; psychological distress associated with poor growth and pubertal delay, irrespective of catch growth; and increased fracture risk due to lower peak bone mineral accretions in adults with a history of delayed puberty. Normalization of ketone concentrations and other laboratory abnormalities through treatment with cornstarch and protein substantiates the importance of dietary interventions in improving metabolic control.

We concur with the recent report which proposed that GSD IXa is not always a mild condition but instead part of an expanding phenotypic spectrum. Considerable biochemical and clinical improvements including reduction in hepatomegaly, enhanced growth velocity, improved energy levels, and overall well-being were demonstrated in our patient with the initiation of aggressive dietary therapy. The minimal improvement in his height was in keeping with the characteristic growth pattern seen in patients with GSD IXa. Our patient’s improvement on dietary intervention reemphasizes that even in the absence of cirrhosis, aggressive therapy is warranted to improve not only the quality of life but also the clinical and biochemical profile of patients with GSD IXa.

Authors’ Note
S.B. was the physician in charge of the family. L.Q. helped with dietary management. S.B., I.S.K., and E.B. drafted the original manuscript. All authors have read/critically revised the manuscript.

Declaration of Conflicting Interests
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