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Hepatic glycogen storage disease: Deciphering the genotype-phenotype conundrum

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Abstract

Glycogen storage diseases (GSDs) are a group of inherited disorders caused by genetic defects in various enzymes involved in glycogen production or breakdown. Hepatic GSDs often have overlapping clinical features, making subtyping or prognostication difficult. With the availability and advancement of next-generation sequencing, definitive molecular diagnosis is now available for most patients, with newer variants being increasingly identified. Molecular diagnosis could help in systematic follow-up, anticipating complications and prognostications. However, the mutations reported in the published literature display wide variations across racial and geographical groups. Hence, natural history, long-term outcome, and genotype-phenotypic correlation studies in patients with various hepatic GSDs are needed for a deeper understanding. Considering the emerging evidence of genetic profiling of patients with hepatic GSDs, including the recent study by Vanduangden *et al*, this editorial aims to review the various clinical subtypes, the spectrum of genetic mutations, and genotype-phenotype correlations for various hepatic GSDs.

Key Words: Hepatic glycogen storage disease; Genotype-phenotype correlation; Children; Next-generation sequencing; Metabolic control

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Core Tip: Glycogen storage diseases (GSDs) are a group of clinically and genetically heterogeneous diseases. The various subtypes of hepatic GSDs are often clinically overlapping, especially in hepatic GSDs. Early diagnosis and proper dietary therapy are paramount for optimal clinical outcomes. Certain clinical features and laboratory derangements such as hypoglycemia, elevated liver enzymes and abnormal lipid profile are helpful in diagnosis. Liver biopsy is an invasive diagnostic test, which has recently been replaced by genetic testing. Next-generation sequencing is now being used more frequently for definitive diagnosis of GSD.

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INTRODUCTION

Glycogen storage diseases (GSDs) are inherited disorders of glycogen metabolism, causing abnormal glycogen storage or degradation[1]. The incidence of GSDs is estimated to be 1 per 10000 live births[2]. The majority of GSDs have an autosomal recessive (AR) inheritance, except for X-linked inheritance in GSD IX[3]. There are over 20 subtypes of GSD[1]. The different subtypes of GSDs are classified based on the deficient enzymes of glycogen metabolism and the primarily affected tissues. GSDs affect the liver and/or muscle, as maximal glycogen levels are found in these two tissues. Depending on the affected enzyme and its expression in various tissues, there can be cardiac, renal or neurological involvement. In this editorial, we discuss the different clinical phenotypes, genotypical variations, and genotype-phenotype correlations.

HISTORICAL PERSPECTIVE

GSD was first described by von Gierke in 1929, who observed excessive glycogen accumulation in the liver and kidneys of children during autopsies, later identified as GSD type I (Von Gierke disease)[4]. Later in 1952, Cori *et al.* further elucidated the underlying cause by linking GSD type I to a deficiency of the glucose-6-phosphatase (G6Pase) enzyme, establishing the first known metabolic disorder with a specific enzyme defect[5]. The following decades saw further in-depth genetic analysis, which led to the identification of the genes responsible for different GSD types, allowing for more precise diagnosis and understanding of the disease at the genetic level[6,7].

CLINICAL SPECTRUM OF HEPATIC GSDS

Although various hepatic GSDs share certain clinical features, there is a wide spectrum of clinical phenotypes. GSD I [online mendelian inheritance in man (OMIM), No. 240600], III (OMIM, No. 232400), IV (OMIM, No. 232500), VI (OMIM, No. 232700), IXa (OMIM, No. 306000), IXb (OMIM, No. 261750), IXc (OMIM, No. 613027) and XI (OMIM, No. 227810) are known to have hepatic involvement[8]. Hypoglycemia is the hallmark of hepatic GSDs. Hepatomegaly is seen in all subtypes of hepatic GSDs except for GSD type 0.

GSD I

GSD I is caused by a deficiency in either G6Pase enzyme or G6Pase transporter (G6PT). Two major subtypes of GSD-I, GSD Ia and Ib, are defined based on the defective component of this enzyme complex. GSD Ia results from the deficiency of the catalytic subunit of G6Pase enzyme complex, while GSD Ib occurs when there is deficiency of G6PT activity. GSD Ia is the most common subtype (80%), followed by GSD Ib (20%)[8]. Data regarding further subtypes (GSD Ic and GSD Id) are scant and controversial. GSD I is clinically characterized by profound hypoglycemia and neuroglycopenic episodes in early infancy due to the involvement of both glycogenolysis and gluconeogenesis pathways. Increased bleeding due to impaired platelet function has been reported. Decreased glucose uptake into platelets due to long-standing hypoglycemia and intracellular adenosine triphosphate deficiency are potential causes of platelet dysfunction in GSD Ia[9]. The concentration of von Willebrand factor was reported to be low for patients with GSD Ia[10]. Hyperlipidemia may cause xanthomas, pancreatitis, and cholelithiasis[3,9].

GSD Ib is characterized by recurrent infections, cyclic neutropenia, neutrophil dysfunction, and inflammatory bowel disease (IBD) in addition to the clinical features of GSD Ia. Patients with GSD Ia or GSD Ib may experience intermittent episodes of diarrhea, which can worsen with age [11]. Diarrhea occurs in up to 35% of GSD Ia and 55% of GSD Ib patients [12]. However, the mechanism underlying diarrhea occurrence is not completely understood. Intolerance to uncooked corn starch (UCCS) and IBD are possible causes of diarrhea[8,11]. IBD is one of the cardinal features of GSD Ib, along with neutropenia and impaired neutrophil function, which is thought to be the causative factor for developing intestinal inflammation[13].

GSD III

GSD III is caused by mutations in the *amylo-alpha-1,6-glucosidase and 4-alpha-glucanotransferase (AGL)* gene, which encodes debranching enzyme. It is characterized by liver and muscle involvement, leading to variable clinical phenotypes. GSD IIIa, which affects the liver and skeletal and cardiac muscle, is the most common subtype, accounting for 80%-85% of GSD III cases[8-10]. GSD IIIb solely affects the liver and accounts for 15% of cases[14,15]. Hepatomegaly, hypoglycemia, dyslipidemia and failure to thrive are the common clinical features in infants and young children. As the gluconeogenesis pathway is intact in GSD III, fasting hypoglycemia is milder and later in onset compared to GSD I. Serum transaminases are significantly elevated, while serum uric acid and lactate levels are relatively normal, which is contrary to the biochemical derangements in GSD I[16]. Signs and symptoms of hepatic involvement often improve with age and disappear after puberty[17,18]. In some patients, liver involvement can be progressive, leading to fibrosis and cirrhosis[18,19]. Muscle symptoms can manifest concurrently with the onset of hepatic symptoms or even after the hepatic symptoms resolve. Increased creatine kinase (CK) levels are seen in a large proportion (81%-94%) of patients[20]. The median age of onset of CK elevation was 10 years[21]. Although myopathy becomes more pronounced in adulthood, muscular weakness on physical examination, motor delay, exercise intolerance, and hypotonia are present in most patients[20-22]. Muscular weakness slowly progresses and becomes crippling by the 3rd or 4th decade of life[18]. Cardiac involvement in GSD III is variable, ranging from ventricular hypertrophy detected on electrocardiography to clinically apparent cardiomegaly[23]. According to an international study on GSD data, 58% of patients had cardiac hypertrophy, detected by electrocardiography and/or echocardiograph[21]. A small proportion of patients (15%) developed hypertrophic cardiomyopathy. Mogahed *et al*[22] demonstrated that cardiac involvement is less common and mostly subclinical in children. However, a recent study found that 91% of patients had some form of cardiac involvement, even at a median age of 2.6 years[24].

GSD IV

GSD IV exhibits significant clinical heterogeneity. The liver is the primary affected organ, with rapid progression to cirrhosis and liver failure in early life, culminating in death before 5 years of age[25]. Patients with the non-progressive hepatic form may have hepatosplenomegaly and elevated liver enzymes, but experience normal growth and native liver survival into adulthood.

GSD VI

GSD VI is an AR disorder caused by *glycogen phosphorylase liver form (PYGL)* gene mutations, leading to hepatic glycogen phosphorylase deficiency. Three human glycogen phosphorylase isoforms exist- muscle, liver, and brain[26]. GSD VI has a wide variation in clinical features[27]. Infants with liver involvement mainly present with hepatomegaly, failure to thrive and mild hypoglycemia, which tend to improve with age. Some may present with only gross hepatomegaly without hypoglycemia, while some patients may experience severe and potentially life-threatening hypoglycemia. A small proportion of patients may show hypotonia, muscle weakness, or developmental delay[27]. In contrast to GSD I, serum lactate and uric acid are normal in GSD VI[8,10]. Interestingly, in a recent study of 56 patients with GSD VI, hyperuricemia was reported in adults, which indicates the need for its monitoring in older patients[28]. GSD VI has a benign course in most patients. However, case reports of focal nodular hyperplasia, cirrhosis and hepatocellular carcinoma do exist [29,30].

GSD IX

The clinical picture of GSD VI often overlaps with patients with GSD IX, caused by phosphorylase kinase (PHK) deficiency. The α subunit of PHK has two isoforms, muscle and liver, encoded by two genes [*PHK regulatory subunit alpha 1* and *PHK regulatory subunit alpha 2 (PHKA2)*, respectively][31,32]. The γ subunit also has muscle and liver isoforms, encoded by *PHK catalytic subunit gamma 1* and *PHK catalytic subunit gamma 2 (PHKG2)* genes, respectively. Only one gene, *glycogen PHK beta-subunit (PHKB)*, encodes the β -subunit[33,34].

GSD IXa has an X-linked inheritance pattern while GSD IXb and GSD IXc are inherited in an AR manner. *PHKA2* gene mutation causes GSD IXa, while GSD IXb and GSD IXc are caused by mutations in *PHKB* and *PHKG2* genes, respectively.

GSD IXa is the most common subtype of GSD IX, accounting for 75% of all GSD IX cases[8-10]. Hepatomegaly, failure to thrive, delayed motor milestones, hypotonia, elevated serum transaminase levels, hyperlipidemia, and fasting hypoglycemia are the cardinal features[35,36]. Both clinical symptoms and laboratory abnormalities show gradual normalization with age. Emerging evidence suggest that GSD IXa may not be a benign entity, and hepatic fibrosis might even be present at the time of diagnosis[37].

GSD IXb is characterized by marked hepatomegaly, increased hepatic and muscle glycogen accumulation, and neuroglycopenic symptoms after physical exercise or prolonged fasting[38]. Hepatic fibrosis, cardiomyopathy, and interventricular septal hypertrophy are commonly found[38].

GSD IXc can lead to early cirrhosis in early childhood, much like GSD IV. Portal hypertension-related complications (esophageal varices, splenomegaly), hepatic adenomas, and renal tubulopathy were other reported clinical associations [39]. There is a wide spectrum of clinical manifestations ranging from fasting hypoglycemia, elevated transaminases, hepatic fibrosis, cirrhosis, myopathy, delayed motor milestones and growth retardation[39].

FANCONI BICKEL SYNDROME

Fanconi Bickel syndrome (FBS) (formerly GSD XI) is caused by solute carrier family (SLC) 2A2 mutations that cause a deficiency in glucose transporter 2 (GLUT2), which is responsible for glucose and galactose transport across the membranes in hepatocytes, enterocytes, and renal tubular cells. Hepatorenal glycogen accumulation and proximal renal tubular dysfunction are the hallmarks of FBS[40,41]. Patients with FBS typically present with fasting hypoglycemia with postprandial hyperglycemia, elevated galactose levels, proximal renal tubular acidosis, hypophosphatemic rickets and marked growth retardation. Nephrocalcinosis is found in one-third of the patients[42], while cataracts are found in a small proportion of patients[43,44]. The exact pathogenesis underlying dysglycemia in FBS is not well studied. Sharari *et al*[45] suggested that *SLC2A2* mutations cause different glucose patterns by two possible mechanisms-1: (1) By impaired GLUT2 expression; and (2) By the dysregulated expression of microRNAs involved in glucose metabolism. After meals, the liver may not effectively store excess glucose due to the GLUT2 deficiency, causing postprandial hyperglycemia. Newborn screening for galactosemia can sometimes identify patients with FBS, as elevated galactose levels are found in FBS[46]. Nutrition support and preventing hypoglycemia and hypokalemia are the primary treatment goals for patients with FBS.

DIFFERENTIAL DIAGNOSIS OF HEPATIC GSDs

When considering a differential diagnosis for hepatic GSDs, the important disorders to include are other metabolic disorders like hereditary fructose intolerance, fatty acid oxidation disorders, and disorders of fructose metabolism, all of which can present with similar symptoms like hepatomegaly, hypoglycemia, and hyperlipidemia. A thorough evaluation with genetic testing is often required for a definitive diagnosis.

MANAGEMENT

Management of hepatic GSD primarily focuses on dietary modifications, such as raw UCCS at timely intervals to prevent hypoglycemia, along with managing secondary metabolic derangements[3]. Many children may require continuous nocturnal gastric drip feeding in severe cases. Multi-disciplinary management involving dietitians, clinical nutritionists, pharmacists, and patient educators is necessary to provide holistic care and ensure proper adherence for better clinical outcomes.

PROGNOSIS AND FOLLOW-UP PLANS

Regular follow-up is of utmost importance to achieve good metabolic and glycemic control and monitor the possible long-term complications. Nutritional evaluations and assessment of laboratory parameters (liver function test, renal function test, lipid profile, calcium, vitamin D, blood gas analysis, and urinalysis) should be performed every 3-6 months. Continuous glucose monitoring is a useful tool to detect the glycemic fluctuations and episodes of asymptomatic hypoglycemia. Serum alpha-fetoprotein levels, along with an abdominal ultrasound should be used to screen for hepatic adenoma and hepatocellular carcinoma[3].

GENOTIC MUTATIONS OF HEPATIC GSD AND THEIR VARIATIONS

GSDs are a group of clinically and genetically heterogeneous diseases. With the advent of and advances in genetic technology, next-generation sequencing (NGS) has replaced invasive diagnostic tests, such as liver biopsy. The geographical distribution of GSD subtypes and genotype differ across countries (Table 1)[47-51]. In a cohort of Iranian patients, GSD III and GSD IX were the major subtypes of GSD (Table 1)[50]. In a Turkish cohort, the highest proportion of GSDs was type III (15, 39.5%), followed by type I (14, 36.8%)[52]. The study by Vanduangden *et al*[51], published in the current issue demonstrated that GSD III and IX were the most common subtypes of hepatic GSD among Thai children, which is consistent with published literature.

GSD I

The underlying pathogenesis appears to be different among patients with GSD Ia and GSD Ib. A multicenter study of 202 patients with GSD-I (Ia 163, Ib 39) found that anemia is marked in GSD Ib compared to GSD Ia (71.8% *vs* 41.7%, respectively)[53]. Development of severe anemia during the follow-up may indicate the possibility of hepatic adenoma and IBD in GSD Ia and GSD Ib, respectively and thus warrant further work-up.

GSD Ib: Dysfunction of G6PT due to G6PT mutation disrupts cellular functions by inducing apoptosis, leading to dysfunction of neutrophils in GSD Ib[54]. A small subset of patients do not develop neutropenia, potentially due to residual transporter activity associated with certain G6PT mutations[55]. However, extensive pathophysiological studies, including genetic and functional analysis, delving into the exact cause of neutropenia and its variations, need to be

Table 1 Summary of various studies showing genetic mutations in patients with hepatic glycogen storage disease

Ref.	Kumar <i>et al</i> [47]	Liang <i>et al</i> [48]	Ahmed <i>et al</i> [49]	Beyzaei <i>et al</i> [50]	Vanduangden <i>et al</i> [51]
Country	India	China	Pakistan	Iran	Thailand
Genetic analysis done	<i>n</i> = 57	<i>n</i> = 49	<i>n</i> = 33	<i>n</i> = 13	<i>n</i> = 8
Genetic subtypes	Ia = 6, Ib = 4, III = 28, VI = 8, Ixa = 2, Ixb = 3, Ixc = 6	Ia = 24, IIIa = 11, Ixa = 8, VI = 3, Ib = 3	Ia = 3, Ib = 7, III = 9, VI = 4, Ixa = 1, Ixb = 2, Ixc = 6, XI = 3	I = 1, III = 4, IV = 1, VI = 2, IX = 3, X = 1, glycogen storage disease II = 1	Ia = 1, III = 3, VI = 3, IX = 1
Variants	<i>n</i> = 49 [G6PC (<i>n</i> = 6), glucose-6-phosphatase transporter/SLC37A4 (<i>n</i> = 4), AGL (<i>n</i> = 28), PYGL (<i>n</i> = 8), PHKA2 (<i>n</i> = 2), PHKB (<i>n</i> = 3), PHKG2 (<i>n</i> = 6)]	<i>n</i> = 45 [G6PC (<i>n</i> = 11), AGL (<i>n</i> = 15), PHKA2 (<i>n</i> = 8), PYGL (<i>n</i> = 6), SLC37A4 (<i>n</i> = 3)]	<i>n</i> = 19 (in 8 genes)	<i>n</i> = 15 [SLC37A4 (<i>n</i> = 2), AGL (<i>n</i> = 4), GBE1 (<i>n</i> = 1), PYGL (<i>n</i> = 2), PHKG2 (<i>n</i> = 1), PHKB (<i>n</i> = 3), PGAM2 (<i>n</i> = 1), PRKAG2 (<i>n</i> = 1)]	<i>n</i> = 11 [G6PC (<i>n</i> = 1), AGL (<i>n</i> = 4), PYGL (<i>n</i> = 5), PHKA2 (<i>n</i> = 1)]
Novel variants	<i>n</i> = 27 [G6PC1 (<i>n</i> = 6), SLC37A4 (<i>n</i> = 5), AGL (<i>n</i> = 24), PYGL (<i>n</i> = 5), PHKA2 (<i>n</i> = 2), PHKB (<i>n</i> = 3) and PHKG2 (<i>n</i> = 4)]	<i>n</i> = 22 [G6PC (<i>n</i> = 3), AGL (<i>n</i> = 7), PHKA2 (<i>n</i> = 5), PYGL (<i>n</i> = 6), SLC37A4 (<i>n</i> = 1)]	<i>n</i> = 5 [SLC37A4 (<i>n</i> = 2), AGL (<i>n</i> = 1), PYGL (<i>n</i> = 2)]	<i>n</i> = 10 [AGL (<i>n</i> = 1), SLC37A4 (<i>n</i> = 2), PHKB (<i>n</i> = 3), PGAM2 (<i>n</i> = 1), PYGL (<i>n</i> = 1), PRKAG2 (<i>n</i> = 1), GBE (<i>n</i> = 1)]	<i>n</i> = 2 [AGL (<i>n</i> = 2)]

AGL: amylo-alpha-1,6-glucosidase and 4-alpha-glucanotransferase; GBE: Glycogen branching enzyme; G6PC: Glucose-6-phosphatase- α ; PGAM2: Phosphoglycerate mutase 2; PHKA2: Phosphorylase kinase regulatory subunit alpha 2; PHKB: Glycogen phosphorylase kinase beta-subunit; PHKG2: Phosphorylase kinase catalytic subunit gamma 2; PRKAG2: Protein kinase AMP-activated non-catalytic subunit gamma 2; PYGL: Glycogen phosphorylase liver form; SLC37A4: Solute carrier family 37 member 4.

undertaken.

GSD III, VI, and IX α share similar clinical features, thus making it almost impossible to distinguish them clinically. Nonetheless, some subtypes have been found to have characteristic phenotypic features: (1) Failure to thrive is more common in GSD IX than GSD VI; and (2) Hypoglycemia is marked in GSD III [39,56,57]. However, there is a paucity of large-scale genetic studies involving these GSDs to point out any genotype-phenotype correlations.

GSD VI is relatively rare compared to other types of GSD, with an incidence of 1/60000 to 1/85000 [58]. Around 80 subtypes of mutations in the *PYGL* gene have been reported in the human gene mutation database [10,58]. To date, 17 Chinese patients with GSD VI have been reported [58-60]. However, no *PYGL* mutation has been documented [58-60]. Around 166 *PHKA2* variants have been reported worldwide, with missense mutations being most commonly detected, followed by deletions. Among 11 Thai children with hepatic GSDs, the study by Vanduangden *et al* [51] reported two novel variants in *AGL* and *PYGL* genes.

FBS (GSD XI)

So far, over 100 cases of FBS with various *SLC2A2* mutations have been reported worldwide [45]. Patients with FBS can have fasting hypoglycemia, hyperglycemia post-meal, transient neonatal diabetes and gestational diabetes mellitus [4]. The exact pathogenesis underlying dysglycemia in FBS is still unclear. Impaired glucose reabsorption in the kidney, as well as hepatic glucose accumulation, results in fasting hypoglycemia [45]. Postprandial hyperglycemia occurs due to decreased uptake into hepatocytes and blunted insulin response [44]. There is an unmet need of in-depth analysis of the possible correlation between variable dysglycemia and variations in genetic mutations.

CLINICAL IMPLICATIONS OF GENETIC CONFIRMATION OF HEPATIC GSD

Still, a significant subset of children with GSDs are diagnosed based on clinical features, suggestive laboratory parameters, and histopathology. Despite clear recommendation by the American College of Medical Genetics for genetic testing for all hepatic GSDs, genetic confirmation of clinically suspected cases is still lagging in most parts of the world [39]. Molecular diagnosis plays a pivotal role in determining the GSD subtype and deciding further treatment modalities and follow-up. Treatment of hepatic GSDs includes frequent, timely feeding and using raw and uncooked cornstarch to minimize hypoglycemic events. Dietary therapy aims to maintain normoglycemia, prevent secondary metabolic dysfunction and monitor for complications such as adenomas, hepatocellular carcinoma, myopathy, renal dysfunction and osteoporosis [3,8,10]. In GSD I, the restriction of sucrose, fructose, and galactose is routinely advocated, while in patients with GSDs III and IX, sucrose intake is restricted and a high-protein diet is recommended [6]. With strict adherence to dietary therapy, liver glycogen storage and other secondary metabolic derangements improve over time. Currently, the patients' overall "metabolic control" is assessed by clinical (anthropometry, liver size) and biochemical (blood glucose level, lactate, triglycerides, cholesterol, uric acid) parameters. The study by Vanduangden *et al* [51],

published in the latest issue, has convincingly shown that personalized treatment plans used in eight Thai children with hepatic GSDs (GSD Ia-1, GSD IX-1, GSD III-3, GSD VI-3) after genetic subtyping, helped in their long-term clinical outcomes. All eight children had improvement in their growth parameters, with only 25% having stunting and none having wasting during a median follow-up period of 9.59 years (1.20–10.56 years). Liver function test, dyslipidemia, and hypoglycemic episodes improved, with 37.5% patients showing normalization of liver enzymes. The authors also reported that a child with GSD VI was successfully weaned off corn starch before bedtime without any hypoglycemia. This study highlights the importance of the genetic subtyping of hepatic GSDs.

For a progressive disease like GSD, it is important to monitor patients after treatment initiation to continually evaluate treatment response. Various GSDs can give rise to a wide range of long-term complications[10]. While some complications are common for all subtypes of hepatic GSDs, such as growth retardation and anemia, others are unique to certain genotypes. Hepatic adenomas and, rarely hepatocellular carcinoma, are seen in patients with GSD I and III. Patients with GSD Ia are at risk of developing renal dysfunction, urolithiasis, pulmonary hypertension, osteoporosis, polycystic ovary syndrome, and increased bleeding tendency. Patients with GSD Ib are prone to develop neutropenia and IBD-type intestinal inflammation. Patients with GSD III are prone to develop cardiac involvement and even sudden death. Hence, they need close monitoring. Patients with GSD III, IV, and IXb can develop hepatic fibrosis and cirrhosis. Fibroscan might be a useful non-invasive monitoring tool for the progression/resolution of hepatic steatosis and fibrosis.

FUTURE DIRECTIONS

The available literature has limited evidence that suggests a correlation between disease severity and pathogenic mutation variants. As more patients undergo genetic testing by NGS, newer genetic variants will be identified and added to the existing genetic database. Formation of national and international registries is the way forward for large-scale data generation, which will augment the process of genotype-phenotype correlation of hepatic GSDs.

New biomarkers are emerging, such as urinary glucose tetrasaccharide (Glc4)[61–64]. Glc4 is a glycogen limit dextrin produced by circulatory amylases and α 1-4-glycosidases[62]. It is detected at low levels in healthy patients, but it can be elevated in pregnancy and disorders of increased glycogen accumulation or increased release of glycogen from damaged tissues[62]. The use of urinary Glc4 as a non-invasive biomarker is well established in patients with Pompe disease, correlating with muscle glycogen storage and disease status among them[63,64]. Urinary Glc4 is measured in randomly collected urine samples. With better glycemic control, urine Glc4 concentration should go down. Further prospective studies on the utility of urine Glc4 as a non-invasive biomarker of hepatic glycogen storage and overall metabolic control are required.

CONCLUSION

Hepatic GSDs exhibit a phenotypic continuum. Early genetic confirmation of diagnosis of hepatic GSD is an important step in formulating a personalized treatment plan for optimal treatment outcome. More large-scale studies with genetic testing in patients with hepatic GSDs will help identify novel mutations and better genotype-phenotype correlation.

FOOTNOTES

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