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Glycogen storage diseases: An update

Gumus E *et al*. Liver and muscle glycogenoses

Abstract

Glycogen storage diseases (GSDs), also referred to as glycogenoses, are inherited metabolic disorders of glycogen metabolism caused by deficiency of enzymes or transporters involved in the synthesis or degradation of glycogen leading to aberrant storage and/or utilization. The overall estimated GSD incidence is 1 case per 20000-43000 live births. There are over 20 types of GSD including the subtypes. This heterogeneous group of rare diseases represents inborn errors of carbohydrate metabolism and are classified based on the deficient enzyme and affected tissues. GSDs primarily affect liver or muscle or both as glycogen is particularly abundant in these tissues. However, besides liver and skeletal muscle, depending on the affected enzyme and its expression in various tissues, multiorgan involvement including heart, kidney and/or brain may be seen. Although GSDs share similar clinical features to some extent, there is wide spectrum of clinical phenotypes. Currently, the goal of treatment is to maintain glucose homeostasis by dietary management and use of uncooked cornstarch. In addition to nutritional interventions, pharmacological treatment, physical and supportive therapies, enzyme replacement therapy (ERT) and organ transplantation are other treatment approaches for both disease manifestations and long-term complications. The lack of a specific therapy for GSDs has prompted efforts to develop new treatment strategies like gene therapy. Since early diagnosis and aggressive treatment are related with better prognosis, physicians should be aware of these conditions and include GSDs in differential diagnosis of patients with relevant manifestations including fasting hypoglycemia, hepatomegaly, hypertransaminasemia, hyperlipidemia, exercise intolerance, muscle cramps/pain, rhabdomyolysis, and muscle weakness. Here, we aim to provide a comprehensive review of GSDs. This review provides general characteristics of all types of GSDs with a focus on those with liver involvement.

Key Words: Glycogen storage disease; Liver; Muscle; Hypoglycemia

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Core Tip: Glycogen storage diseases are multisystemic diseases that can present at any age. Primarily affected organs are the liver and skeletal muscle, but heart, central nervous system, kidneys, intestines, and other organs may also be affected. Since the initial presenting symptoms can occur in adulthood, it is a group of rare diseases that should be recognized and managed by not only pediatricians but also physicians taking care of adults.

INTRODUCTION

Glycogen storage diseases (GSDs), also referred to as glycogenoses, are inherited metabolic disorders of glycogen metabolism caused by deficiency of enzymes or transporters involved in the synthesis or degradation of glycogen[1]. Disturbances in glycogen metabolism result in aberrant storage and/or utilization of glycogen. Both glycogen formation and breakdown involve several enzymatic reactions and are strictly dependent on hormone regulation (Figure 1)[2]. After a meal, insulin stimulates glycogen storage in muscle and liver by simultaneously promoting glycogen synthesis and inhibiting glycogen breakdown. During exercise or between meals, glucagon and cathecolamines inhibit glycogen synthesis while promoting glycogen breakdown[3]. Hepatic glycogen serves as a depot source of glucose to maintain euglycemia during fasting periods while glycogen in muscle provides glucose to produce necessary energy during high-intensity exertion.

GSDs are multisystemic diseases that can present at any age from neonatal period to adulthood. The overall GSD incidence is approximately 1 case per 20000-43000 live births and 80% of hepatic GSDs are caused by types I, III, and IX[4,5]. This heterogeneous group of rare diseases represents inborn errors of carbohydrate metabolism and are classified based on the deficient enzyme and affected tissues (Table 1). GSDs primarily affect liver or muscle or both as glycogen is particularly abundant in these tissues.

However, besides liver and skeletal muscle, depending on the affected enzyme and its expression in various tissues, multiorgan involvement including heart, kidney and/or brain may be seen[6]. Although GSDs share similar clinical features to some extent, there is a wide spectrum of clinical phenotypes. Hypoglycemia is the hallmark of hepatic GSDs. Hepatomegaly is also a cardinal manifestation of GSDs with liver involvement except for GSD-0. Muscle GSDs, on the other hand, may present with exercise intolerance, muscle cramps/pain, rhabdomyolysis, and muscle weakness and in case of cardiac involvement cardiomyopathy[7]. Since the initial presenting symptoms can occur in adulthood, it is a group of rare diseases that should be recognized and managed by not only pediatricians but also physicians taking care of adults. Being multisystemic diseases, GSDs are best managed by a cross-disciplinary approach to achieve good metabolic control, improve the quality of life of patients, and reduce morbidity and mortality[7]. It is recommended that a medical professional with expertise in treating such conditions (*e.g.,* a metabolic disorders specialist, a biochemical geneticist, an endocrinologist, or a hepatologist) should lead and coordinate the patient's care together with a metabolic dietician. Nephrologists, hematologists, genetic counselors, cardiologists, gastroenterologists, neurologists, physical therapists, social workers, and transplant specialists may also be required in the management of a GSD depending on the specific manifestations, complications, and type of the disease. In this article, we aimed to update the review published in 2007[1] based on new data and provide a comprehensive review of GSDs. This review provides general characteristics of all types of GSDs with a focus on those with liver involvement.

GSDS INVOLVING LIVER

GSD type 0 (GSD-0; glycogen synthase deficiency)

There are two types of glycogen synthase (GYS) encoded at different genetic loci; muscle GYS (*GYS1*; 19q13.33) and liver GYS (*GYS2*; 12p12.1)[8]. In 1963, GSD-0 was initially reported as glycogen synthetase deficiency in the liver[9]. GSD-0 is distinct from other hepatic GSDs due to the marked decrease in liver glycogen content, thereby

making its classification questionable as a genuine GSD. However, since the disease exhibits a phenotype like that of the classic glycogenoses due to unavailability of glycogen during periods of fasting, it is classified as a GSD. GSD-0 is inherited autosomal recessively[10]. The disease is caused by homozygous or compound heterozygous mutations in the *GYS2* gene which was mapped to 12p12.2 in 1994[11]. Liver GYS, the hepatic isoform, is responsible for catalyzing the rate-limiting step in hepatic glycogen synthesis. GYS deficiency in liver leads to a marked reduction in hepatic glycogen stores. Inability to synthase glycogen inevitably leads to conversion of dietary carbohydrate to lactate rather than being stored as glycogen in the liver. Postprandial hyperglycemia, glycosuria, and hyperlactic acidemia are replaced by ketotic hypoglycemia during fasting[12]. There is often ketosis after a routine overnight fast.

There are wide phenotypical variations[13]. Fasting hypoglycemia usually manifests in late infancy when overnight feedings are discontinued. Hypoglycemia typically occurs early in the morning prior to having breakfast. Hypoglycemia is responsible for the symptoms observed in GSD-0, which encompasses lethargy, pallor, nausea, vomiting, and, in some cases, seizures. Although some children may display developmental delay, most are neurologically normal. Some patients may remain asymptomatic or experience only mild symptoms[14]. Notably, liver enlargement is not a feature of GSD-0. GSD-0 is the only hepatic GSD that is not typically associated with hepatomegaly[15]. Short stature and osteopenia are frequently observed in GSD-0, but other long-term complications commonly seen in other GSDs have not been documented[16]. Hyperglycemia and glycosuria are rare presentations in GSD-0 but may pose diagnostic difficulties when observed[17]. Postprandial hyperglycemia and glycosuria when taken together with a normal sized liver may mistakenly indicate early stages of diabetes. GSD-0 is underdiagnosed due to the lack of physical findings and milder phenotype[16,18].

Symptoms in GSD-0 are rapidly alleviated by frequent intake of protein-rich meals and bedtime consumption of uncooked cornstarch (UCCS), a slow-release glucose

source. The preservation of gluconeogenesis and fatty acid oxidation pathways explains the less severe clinical course of GSD-0 compared to other types of hepatic GSDs. Increased protein intake during meals provides necessary substrates for gluconeogenesis and shows a protective effect against overweight/obesity and insulin resistance[19]. Extended periods of fasting can result in severe hyperketonemia and elevated plasma free fatty acid levels, which in turn leads to the inhibition of alanine release from skeletal muscle causing a reduction in the availability of gluconeogenic substrates, thereby exacerbating hypoglycemia[16]. While fasting is associated with hypoglycemia, hyperketonemia, and low alanine concentrations, feeding causes hyperglycemia and hyperlactatemia. Simple carbohydrates should be limited, and low-glycemic-index complex carbohydrates should be included in the diet to minimize postprandial hyperglycemia and hyperlactatemia. Patients are generally fed more frequently during the daytime to prevent hypoglycemia.

The administration of glucose or galactose to patients with GSD-0 results in elevated levels of serum lactate and lipids and can be used as a diagnostic test[2,17]. Traditional methods of diagnosis, such as liver biopsy to confirm extremely low hepatic glycogen levels and low to absent GYS activity, have been replaced by non-invasive mutation analysis of the *GYS2* gene.

Browner *et al*[20] discovered that muscle GYS, which is distinct form liver GYS, is expressed in both muscle and heart. The defect may be inherited or acquired. Enzyme activity is decreased in patients with type 2 diabetes. Muscle GYS deficiency causes cardiomyopathy and exercise intolerance in affected patients[8]. Histologic examination of muscle shows lack of glycogen and mitochondrial proliferation.

GSD-I, von Gierke disease, hepatorenal glycogenosis

The disease was first described by Gierke[21] in 1929 based on autopsy results showing excessive glycogen storage in livers and kidneys of two patients. In 1952, Cori and Cori[22] discovered the deficiency of glucose-6-phosphatase (G6Pase) as the causative defect in patients with similar disease phenotype. After more than two decades, in 1978,

Narisawa *et al*[23] described the deficiency of glucose-6-phosphate translocase (G6PT), the transporter protein of G6Pase complex (G6PC).

The deficiency of either G6Pase or G6PT activity causes GSD type I (GSD-I). The G6PT/G6PC functions as a multicomponent system and is responsible for glucose production by catalyzing the terminal step of both the glycogenolysis and gluconeogenesis pathways[24]. G6PT translocates G6P into the endoplasmic reticulum, wherein G6Pase converts G6P into free glucose and inorganic phosphate[25]. Two major subtypes of GSD-I are defined according to which part of the complex is defective. Deficiency of catalytic subunit of G6Pase causes GSD-Ia while deficiency of G6PT activity results in GSD-Ib. Approximately 80% of cases with GSD-I are type Ia while the remaining 20% are type Ib. The presence of further subtypes (GSD-Ic and GSD-Id) is controversial. The majority, if not all, of typical cases of GSD-I are attributed to mutations in the genes encoding G6Pase and G6PT. Additionally, it has been noted that only two subtypes of GSD-I (namely, GSD-Ia and GSD-Ib) have been confirmed in clinical practice, and the existence of other forms of GSD-I requires further substantiation. Because both glycogenolysis and gluconeogenesis are affected due to inability in converting G6P to free glucose the main metabolic derangement of both subtypes is fasting hypoglycemia.

GSD-I is inherited in an autosomal recessive manner. The overall incidence of the disease is approximately 1:100000[26]. The estimated carrier rate in the general population is 1:150. The disease may be more prevalent in people of Ashkenazi Jewish (c.247C>T), Mexican-Hispanic (c.379_380dupTA) and Japanese heritage (c.648G>T) due to the increased frequency of mentioned pathogenic variants. The carrier frequency for the c.247C>T variant among Ashkenazi Jews has been reported to be as high as 1:63[27].

GSD-Ia; G6Pase deficiency

In 1952, Cori and Cori[22] identified the first specific enzyme deficiency associated with an inherited disorder through demonstration of G6Pase deficiency. Subsequently, in 1995, the gene that encodes the catalytic subunit of the G6PC was identified on

chromosome 17q21[28]. Later, its molecular and biochemical characteristics were described in detail[29].

While some neonates may exhibit severe hypoglycemia and lactic acidosis, infants who do not receive any treatment typically present between 3-6 mo of age (at a median age of 6 mo) coinciding with prolonged feeding intervals, increased sleeping time through the night or onset of an intercurrent illness disrupting normal patterns of feeding[30]. The onset of symptoms can be soon after birth, and episodes typically remain unresponsive to glucagon therapy. Symptoms mainly include difficulties with feeding, tremors, pallor, excessive sweating, hyperventilation, cyanosis, apnea, irritability, seizures, somnolence, and cerebral edema/dysfunction, with exacerbations typically occurring in the morning or prior to feedings. Severe episodes of ketotic hypoglycemia, if untreated, may eventually lead to coma and sudden infant death[31]. Older infants may exhibit certain physical characteristics, such as doll-like facies with full cheeks and relatively thin extremities along with frequent lethargy, difficulty in waking from sleep, tremors, an insatiable appetite, growth retardation, and a prominent abdomen resulting from pronounced enlargement of the liver and kidneys. In some cases, xanthomas may appear on extensor surfaces, such as the elbows, knees, or buttocks. During an infection, symptoms of severe hypoglycemia are more prevalent owing to diminished appetite and/or gastrointestinal symptoms (*e.g.,* vomiting and diarrhea) both preventing adequate oral intake. Delayed motor development can be seen but cognitive development is generally normal unless there is cerebral damage due to prolonged or recurrent neuroglycopenia[1,32].

Impaired platelet function, especially in individuals with inadequate metabolic control predispose patients to nose bleeding[33]. Diminished glucose uptake into platelets due to chronic hypoglycemia and subsequent intracellular ATP deficiency have been proposed as potential causes of platelet dysfunction in GSD-Ia[34]. Additionally, decreased plasma concentration of von Willebrand factor antigen indicating an acquired von Willebrand disease was reported for patients with GSD-

Ia[35]. Besides epistaxis, easy bruising, menorrhagia, intrahepatic adenoma hemorrhage, and excessive bleeding during surgical procedures can also occur[36,37].

Patients with GSD-I have hypovitaminosis D despite adequate supplementation[38]. Low bone mineral density is a long-term complication of GSD-I particularly in those with poor metabolic control[39,40]. Osteoporosis may arise as a consequence of poor nutrition, chronic lactic acidosis and hypogonadism[41]. Anemia is a common complication in both subtypes of GSD-I with a reported prevalence ranging from 17% to 60% across different age groups[30]. The etiology of anemia in GSD-I is complex and involves various factors, including the restrictive nature of the diet, altered iron absorption due to excessive intake of UCCS, chronic lactic acidosis, chronic kidney disease, bleeding diathesis, chronic illness, suboptimal metabolic control, hepatic adenomas, and inflammatory bowel disease. The prevalence and pathophysiology appear to differ in individuals with GSD-Ia and those with GSD-Ib. A multicenter study involving 202 subjects with GSD-I (Ia/Ib: 163/39 subjects) showed that anemia is more common in patients with GSD-Ib compared to GSD-Ia (71.8% *vs* 41.7%, respectively). In addition, prevalence of severe anemia is also increased in GSD-Ib in comparison to patients with GSD-Ia (41% *vs* 4.9%, respectively)[42]. Severe anemia in GSD-Ia appears to be related with large hepatic adenomas, while in GSD-Ib it is often associated with enterocolitis[42]. Development of severe anemia during the course of the disease warrants further evaluation for hepatic adenomas and inflammatory bowel disease in GSD-Ia and GSD-Ib, respectively.

Patients diagnosed with GSD-Ia or GSD-Ib may experience intermittent diarrhea which seems to deteriorate with age[43]. Diarrhea was reported in 35% of the GSD-Ia and in 55% of the GSD-Ib patients[30]. However, the cause of diarrhea remains unknown. Intolerance to UCCS and inflammatory bowel disease are possible causes of diarrhea in this population. Inflammatory bowel disease is a well characterized feature in individuals with GSD-Ib. Neutropenia and impaired neutrophil function are the underlying causes for inflammatory bowel disease in GSD-Ib[44]. However, it is recently that inflammatory bowel disease was also reported in adult patients with GSD-Ia as a

new, long-term complication of the disease[45]. The prevalence of symptomatic inflammatory bowel disease in adults with GSD-Ia also seems to be higher than the general population[45]. The authors speculated that inflammatory bowel disease in GSD-Ia may be caused by chronic UCCS therapy, which could be altering the microbiota of the gastrointestinal tract leading to inflammation. More recently, very early onset inflammatory bowel disease was reported in a child with GSD-Ia at the age of 42 mo[46].

A notable finding among the majority of patients with this condition during childhood is growth retardation, while short stature is commonly observed in affected adults[5,47,48]. In the absence of effective treatment, a range of long-term complications may arise in individuals with GSD-I, including delayed puberty, liver adenomas, hepatocellular carcinoma, renal dysfunction, chronic kidney disease, chronic renal failure, urolithiasis, arterial and pulmonary hypertension, osteopenia/osteoporosis, polycystic ovary syndrome, gout and cognitive delays and epilepsy due to repeated or severe hypoglycemic events may occur[31]. Hyperlipidemia may cause xanthomas, pancreatitis, and cholelithiasis[30,49]. Acute pancreatitis may develop secondary to very high serum triglycerides in GSD-I and necessitate plasmapheresis[50].

Systemic metabolic perturbations and glycogen deposition in the kidneys result in glomerular and proximal and distal renal tubular injury. Renal manifestations may occur in childhood but often are not noticed without proper diagnostic work-up. The prevalence of renal involvement tends to rise as patients age[51]. Glomerular hyperfiltration, whose underlying mechanism is not yet fully understood, is typically the initial manifestation of renal involvement. Possible etiologies that have been suggested include activation of the renin-angiotensin system, persistent oxidative stress, profibrotic cytokines such as transforming growth factor-β, and changes in energy reserves of renal tubular epithelial cells[52-54]. Glomerular hyperfiltration then progresses to microalbuminuria, proteinuria, glomerular scarring and interstitial fibrosis, and end-stage renal disease in adult patients[48,55]. Hypercalciuria and hypocitraturia due to proximal and distal tubular dysfunction cause nephrocalcinosis and/or urolithiasis[56,57]. This may increase the risk of urinary tract infections causing further renal parenchymal

damage. Hypertension and hematuria are other findings[55,56]. Systemic hypertension may develop early in childhood but is seen more often in adults with GSD-I[58]. Renal cysts have also been described in individuals with GSD-I[59]. Gout can develop due to persistent hyperuricemia as gouty attacks, gouty tophi, and kidney stones.

In GSD-Ia patients, various types of liver lesions, including hepatic adenoma, hepatocellular carcinoma, hepatoblastoma, focal fatty infiltration, focal fatty sparing, peliosis hepatis, and focal nodular hyperplasia have been reported, with hepatic adenomas being the most prevalent among them[37]. The prevalence of hepatic adenomas was reported to vary between 22% to 75%, and they usually manifest during or after puberty, particularly in the second or third decade of life. The median age of adenoma presentation is 15 years[30]. Although the prevalence of hepatic adenomas increases with age in GSD-I, they may be seen in younger children[60]. Progression in size and/or number of hepatic adenomas occurs in half of the patients[30]. Inadequate metabolic control appears to play a central role in hepatic adenoma formation. The degree of hyperlipidemia is associated with development of hepatic adenomas[61]. However, the pathophysiological mechanisms are yet to be fully understood and factors other than metabolic control may also be responsible for adenoma formation. In a recent study by Cho *et al*[62], in addition to mitochondrial dysfunction and metabolic alterations caused by G6Pase deficiency, persistent autophagy impairment and activation of multiple tumor-promoting pathways were reported as contributing factors to hepatic adenoma/hepatocellular carcinoma development in GSD-I. Chromosomal and genetic alterations may also play a role in hepatocellular carcinoma associated with GSD-I[63]. Hepatic adenomas have the potential to transform into hepatocellular carcinoma over an extended period, with reports of malignant transformation occurring as long as 28 years after initial diagnosis[64,65]. A rapid increase in size or number of adenomas is associated with increased risk for adenoma to hepatocellular carcinoma transformation and should be evaluated carefully.

The link between GSD-I and risk for cardiovascular disease is controversial. Although GSD-Ia patients have elevated levels of triglycerides, very low density lipoprotein and

low density lipoprotein, the occurrence of endothelial vascular dysfunction and atherosclerosis is uncommon. It has been suggested that the increased serum levels of apoE may offset the elevated risk of atherosclerosis associated with dyslipidemia[66]. Moreover, the reduced von Willebrand factor antigen and density of individual oligomers found in 60% of GSD-Ia patients may also contribute to protection against vascular complications[35]. In addition, an increase in serum levels of antioxidative factors may contribute as a protective mechanism[67,68]. There are conflicting data regarding if patients with GSD-I are at increased risk for atherosclerosis[69,70]. Pulmonary hypertension is a rare long-term complication of GSD-I with a few numbers of cases reported. Patients with a concomitant predisposing condition for pulmonary arterial hypertension are at increased risk[37].

The main neurological impact of GSD is related to hypoglycemia. Patients with GSD-I may suffer from brain damage, which may be caused by recurrent severe hypoglycemia[71]. Studies have found a significant correlation between the frequency of hospital admissions for hypoglycemia and abnormalities in both performance ability tests and brainstem auditory evoked potentials. In addition, electroencephalography abnormalities were found to be correlated with dietary compliance. The magnetic resonance imaging abnormalities observed in GSD-I patients were the dilatation of occipital horns and/or hyperintensity of subcortical white matter in the occipital lobes[71]. Brain imaging abnormalities were more frequent among GSD-I patients with early symptom onset, frequent and longer hospital admissions, and poor metabolic control including elevated levels of uric acid, lactate, and triglyceride[32,72].

Some females may have polycystic ovaries and irregular menstrual cycles with normal fertility[73]. Women with GSD-Ia may have pregnancies and deliveries without complication[74]. In consideration of the risk of development of hepatic adenomas in GSD-I patients, estrogen-containing contraceptives should be avoided whenever possible[75]. In addition to hypoglycemia, the most prominent laboratory abnormalities observed in patients with GSD-I include lactic acidosis, hyperlipidemia (especially hypertriglyceridemia but also hypercholesterolemia), and hyperuricemia (Figure 1).

Mild elevation in transaminase levels is usually detected[30]. Ultrasonographic examination may reveal enlarged kidneys in affected patients of all ages. Serum biotinidase activity is increased in GSD-Ia patients[76-79]. Biotinidase activity was reported to be correlated positively with hypertriglyceridemia in subjects with GSD-I while severe fibrosis and cirrhosis were related with reduced enzyme activity[80]. There may be hypercalciuria[5]. There is little or no increase in blood glucose concentration in response to administration of glucagon and this may even lead to worsening of the metabolic acidosis. The histopathological examination of the liver in patients with GSD-Ia typically reveals a mosaic pattern with pale-staining and swollen hepatocytes. Other observed features include steatosis and nuclear hyperglycogenation. Periodic acid-Schiff (PAS)-positive and diastase sensitive glycogen is evenly dispersed throughout the cytoplasm. Glycogen accumulation may be within the normal range or exhibit only a mild increase. While fibrosis is not as prominent in GSD-I as in GSD types III, IV, and VI, it may still be present in some affected individuals[5,81-83]. GSD-Ia is usually suspected based on a set of clinical (*e.g.,* hepatomegaly) and biochemical features (*e.g.,* hypoglycemia, lactic acidosis, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia). The definitive diagnosis is confirmed by a mutation analysis or a liver biopsy and an enzyme assay. If a liver biopsy is performed, diagnosis can be confirmed by measuring G6Pase enzyme activity on a liver biopsy specimen; however, it should be kept in mind that measurement of G6Pase enzyme activity will not detect GSD-Ib. When the specific mutation in the index case is known, prenatal diagnosis *via* chorionic villus sampling can be performed for GSD-I[84].

The mainstay of the treatment is to prevent hypoglycemia by avoiding prolonged fasting[85]. Continuously providing a dietary supply of glucose during day and night by frequent feedings, frequent ingestion of UCCS or nocturnal enteral tube feeding are possible feeding strategies. Infants and children should be fed frequently, not allowing fasting periods longer than 3-4 h. In adolescents and adults, fasting more than 5-6 h should be avoided. Small, frequent meals with balanced macronutrient content and use of UCCS are recommended. Continuous intragastric feeding through a nasogastric or

gastrostomy tube can be used overnight allowing the patients to sleep through the night[37]. To ensure adequate glucose supply, a glucose infusion rate of 8-10 mg/kg/min should be maintained for infants, while a rate of 4-8 mg/kg/min is recommended for older children. UCSS can be introduced as early as 6-12 mo of age. For the administration of UCSS in GSD-I patients, the recommended dosing is 1-1.5 g of UCCS per kilogram of ideal body weight every 3-4 h for young children and 1.5-2 g of UCCS per kilogram of body weight every 4-5 h for older children, adolescents, and adults[85]. Digestion of UCCS is slow, enabling a sustained release of glucose, thereby achieving a more stable glycemic profile over an extended duration, in contrast to other carbohydrate sources. An administration of UCCS has been shown to achieve adequate glycemia for a median duration of 4.25 h (ranging between 2.5-6 h)[86]. Glycosade®, a modified, waxy maize extended-release cornstarch, is available as a single-dose overnight treatment[87].

In GSD-1, intake of fructose and galactose, which cannot be metabolized to G6P, further contributes to the metabolic derangement. Lactose (galactose and glucose), fructose and sucrose (fructose and glucose) should be restricted in all age groups. Restricting intake of fruits, vegetables, juices, and dairy products renders the diet inadequate. Micronutrients, vitamins, and minerals should be supplemented to avoid nutritional deficiencies. A recommended dietary plan is to provide 60%-70% of calories from complex carbohydrates, such as whole-grain breads, pastas, legumes, and rice, with a portion of the carbohydrates coming from cornstarch. Additionally, 10%-15% of calories should come from protein and 25%-30% from fat. Effective dietary management is essential to minimize the metabolic derangement associated with GSD-I and to reduce the development of long-term complications[37,85]. However, caution must be exercised to avoid overtreatment. Overtreatment with UCCS has many consequences including obesity, increased glycogen storage in the liver, worsening lactic acidosis, increased gastrointestinal disturbances, hyperinsulinemia, and insulin resistance[88].

If there is anemia, the causes must be evaluated (*e.g.*, nutritional deficiencies, liver adenomas, enterocolitis, menorrhagia in females, and occult blood loss from

gastrointestinal tract) and appropriate treatment should be started. In case of severe anemia, hepatic adenomas in GSD-Ia and enterocolitis in GSD-Ib should be investigated[42]. To prevent gout in the presence of hyperuricemia, allopurinol is typically administered at a dosage of 10 mg/kg/d, divided into three doses. If acidosis is present, indicated by a blood base excess of less than -5 mmol/L or a blood bicarbonate level below 20 mmol/L, bicarbonate or potassium citrate should be prescribed, with a recommended dose of 1 to 2 mmol/kg/d divided into four doses and 5 to 10 mEq every 8-12 h, respectively[85]. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers should be used to delay the progression of renal damage[53,89-91]. Evidence of hyperfiltration (sustained estimated glomerular filtration rate > 140 mL/min/1.73 m^2), persistent microalbuminuria and frank proteinuria should prompt initiation of angiotensin converting enzyme inhibitors or angiotensin receptor blockers[37]. If serum triglyceride levels remain high despite optimizing dietary treatment, the administration of lipid-lowering drugs, such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and fibrates, may be necessary to decrease the risk of atherosclerosis, cholelithiasis, and pancreatitis. For adults with persistently elevated cholesterol levels, statins may be considered as a treatment option[85]. The positive effect of medium-chain triglycerides on lowering serum cholesterol and triglyceride levels has been reported[92,93].

Recommendations regarding perioperative management of patients with GSD-I are available[37,94]. Close monitoring of blood glucose, electrolytes, and lactate levels is crucial during the peri-operative period. The patient should be admitted to the hospital 24 h before the surgery, continuous intravenous supply with 10% dextrose should be provided and continued until oral feeding is re-established. The administration of Ringer lactate solution should be avoided in GSD-1 patients, as it may exacerbate lactic acidosis and worsen metabolic decompensation[37]. Bleeding time must be normalized before elective surgical interventions by 24-h continuous gastric drip feeding for one week or by intravenous glucose infusion over 24 to 48 h[85].

GSD-Ib; G6PT deficiency

In 1968, after realizing that *in vitro* G6 glomerular filtration rate e activity was normal despite glucose not being released from G6P *in vivo*, a second subtype of GSD-I was identified[95]. In 1975, it was elucidated that a transport system specific to G6P exists and is responsible for transporting G6P from the cytoplasm to the endoplasmic reticulum[96]. The responsible gene, *SLC37A4* (the solute carrier family 37 member 4), has been cloned and located on chromosome 11q23[97,98].

GSD-Ib is characterized by distinctive features such as recurrent infections, neutropenia, and neutrophil dysfunction, in addition to the clinical symptoms and findings observed in GSD-Ia. While not all GSD-Ib patients have neutropenia and neutrophil dysfunction, these conditions are common and predispose patients to severe infections and inflammatory bowel disease[44]. Patients with GSD-Ib may have normal neutrophil counts in the first year of life. *G6PT* gene, unlike *G6Pase*, is also expressed in hematopoietic progenitor cells, which may be responsible for neutropenia and recurrent infections in GSD-Ib[99]. The neutrophil dysfunction in GSD-Ib includes both impaired motility and respiratory burst[100,101]. Impaired glucose transport across the cell membrane of polymorphonuclear leukocytes may be responsible for neutrophil dysfunction in GSD-Ib. Microsomal transport of G6P has a potential role in the antioxidant protection of neutrophils. Dysfunction of this transporter due to genetic defects in *G6PT* may impair cellular functions and induce apoptosis, contributing to the neutrophil dysfunction seen in GSD-Ib[102]. Some individuals with GSD-Ib do not develop neutropenia. It has been suggested that this could be due to residual transporter activity of some *G6PT* mutations[103]. GSD-Ib patients with neutropenia and neutrophil/monocyte dysfunction are at an increased risk for severe infectious complications due to impaired immune function. Young children with GSD-Ib may experience frequent otitis, gingivitis, periodontal disease, dental caries, and skin abscesses. Oral and genital ulcerations and intestinal mucosal ulcers may occur[43,104]. Individuals with GSD-Ib may experience recurrent episodes of diarrhea. The underlying cause of this symptom appears to be inflammation of the intestinal mucosa,

as evidenced by elevated fecal α1-antitrypsin excretion and colonic inflammation in colonoscopic biopsies[44]. There is no established association between the specific genetic mutations causing GSD-Ib and the occurrence of neutropenia, bacterial infections, and other systemic complications in affected individuals[105]. Patients with GSD-Ib may require liver transplantation. Although hypoglycemia, lactic acidosis and dyslipidemia improve after liver transplantation, neutropenia generally continues to be present as it is primarily attributable to an intrinsic defect in the neutrophils[106-108].

Another characteristic clinical finding of GSD-Ib is the occurrence of Crohn disease-like colitis[109,110]. The enterocolitis observed in GSD-Ib patients has been found to have histological features similar to those seen in inflammatory bowel disease/Crohn disease, characterized by transmural inflammatory changes and formation of granulomas[111]. Accompanying findings and symptoms include fever, diarrhea, and perioral and anal ulcers. Interestingly, the severity of the primary disorder does not appear to be correlated with the occurrence or severity of intestinal symptoms[109,110]. Manifestations of inflammatory bowel disease may improve with granulocyte colony-stimulating factor (G-CSF) treatment[112]. Enteral nutrition with a polymeric formula enriched in the anti-inflammatory cytokine transforming growth factor-β is recommended as a first line treatment of digestive complications in GSD-Ib[113]. Inflammatory bowel disease may require treatment with anti-inflammatory and immunosuppressive medications[113]. Successful treatment of inflammatory bowel disease with biologics including infliximab and adalimumab in GSD-Ib patients refractory to conventional treatment has been reported[114,115].

GSD-Ib is characterized by an increased risk for developing autoimmune disorders like thyroid autoimmunity and myasthenia gravis[116]. GSD-Ib patients have a higher likelihood of developing thyroid autoimmunity and hypothyroidism, while GSD-Ia patients show little indication of thyroid pathologies[117,118]. Based on the slightly elevated levels of thyrotropin, even in patients with overt hypothyroidism, it could be postulated that there is concomitant damage occurring at the hypothalamus or pituitary gland[118]. Recently, predisposition to autoimmunity in GSD-Ib patients was linked with

a profound defect in conventional T cells and regulatory T cells caused by defective engagement of glycolysis in T cells due to G6PT deficiency[119]. Although a rare outcome of GSD-Ib, patients may develop terminal kidney disease, which may necessitate kidney transplantation[106].

Nutritional management of GSD-Ib is similar with GSD-Ia. Neutropenic patients with GSD-Ib should be treated with G-CSF. G-CSF therapy may normalize the number of neutrophils and restore myeloid functions[120-122]. The implementation of a combined therapeutic approach including both dietary management and G-CSF treatment improves the prognosis of patients by significantly mitigating metabolic and myeloid abnormalities. G-CSF administration is associated with not only elevation of peripheral neutrophil counts, but also reduction in the incidence of febrile episodes and infections, as well as improvement in enterocolitis in patients with GSD-Ib[123]. In conjunction with other therapies (aminosalicylates, mesalamine, and corticosteroids), G-CSF ameliorates inflammatory bowel symptoms[124]. To prevent complications such as splenomegaly, hypersplenism, hepatomegaly, and bone pain, it is recommended to use the lowest effective dose of G-CSF. Caution must be exercised regarding development of splenomegaly and myeloid malignancy[124,125]. Vitamin E has been reported to be effective in reducing the frequency of infections and improving neutropenia[126].

Liver transplantation is the ultimate therapy for hepatic metabolic disease related with GSD-I. There is no possibility of recurrence of GSD-I within the allograft. Liver transplantation is warranted in various situations, such as hepatic adenomas with a high risk of malignant transformation, rapid progression in size and/or number of hepatic adenomas, development of hepatocellular carcinoma, poor metabolic control despite medical therapy, and growth failure[127]. Liver transplantation corrects all liver related biochemical abnormalities including hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia, but its potential to reverse and/or prevent renal disease remains uncertain[107,128-130]. Recently, an unusual finding of two post-transplant siblings with persistent hyperuricemia requiring allopurinol treatment has been reported[131]. Moreover, chronic renal failure is a well-known complication that may

arise as a consequence of liver transplantation in individuals with GSD-Ia, and progression to renal failure within a few years of transplantation was reported[128]. It is uncertain whether post-transplantation renal failure is related with disease progression, toxicity from immunosuppressants used after liver transplantation, a secondary reaction to poor metabolic control, or a combination of these factors. Renal transplantation in GSD-I, on the other hand, corrects only renal abnormalities[132]. Conflicting results have been reported in different studies regarding whether catch-up growth is achieved or not following liver transplantation in children with GSD-I[133,134].

Despite improved survival and growth, long-term complications of GSD-I like progressive renal failure and development of hepatic adenomas do not respond completely to dietary treatment. Although liver transplantation corrects metabolic derangement and improves the quality of life of these patients, it is not without complications[128]. These findings suggest that novel therapeutic approaches with higher success and lower complication rates are warranted. A recent advance in the treatment of neutropenia and neutrophil dysfunction in individuals with GSD-Ib is repurposing empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor that is approved to treat type 2 diabetes in adults, to improve neutrophil number and function. A study conducted by Veiga-Da-Cunha *et al*[135] revealed the crucial function of glucose-6-phosphate transporter in neutrophils, which clarifies the pathophysiology of neutropenia in GSD-Ib patients. In addition to G6P, G6PT transports G6P's structural analog 1,5-anhydroglucitol-6-phosphate (1,5AG6P). Neutrophils lacking G6PT activity cannot transport 1,5AG6P from the cytosol into the endoplasmic reticulum, where it is normally dephosphorylated by G6PC3, a phosphatase in the membrane of the endoplasmic reticulum. Cytosolic accumulation of 1,5AG6P inhibits glucose phosphorylation by hexokinases that catalyzes the first step of glycolysis. As glycolysis is the sole energy source for mature neutrophils, depletion of intracellular G6P leads to a deficit in energy production which in turn results in neutrophil dysfunction and subsequent apoptosis. Empagliflozin inhibits renal SGLT2 leading to increased urinary excretion of 1,5AG. This leads to a reduction in the concentration of 1,5AG in the blood,

thereby decreasing the cellular accumulation of toxic 1,5-AG6P in neutrophils[136]. Following the first report of successful repurposing empagliflozin to treat neutropenia and neutrophil dysfunction in 4 patients with GSD-Ib, several case reports and case series have shown beneficial effects of this treatment approach on neutrophil number and function, inflammatory bowel disease, recurrent infections[137-139], oral and urogenital mucosal lesions, skin abscesses, anemia, wound healing, and dose reduction or even cessation of G-CSF therapy in GSD-Ib patients[140-144]. A recent international multicenter study examining the clinical experience of 112 patients with GSD-Ib treated with empagliflozin reported improvements in neutrophil counts in the majority of patients, leading to the cessation of regular G-CSF injections in 55% of the participants[145]. Despite a favorable safety profile in patients with GSD-Ib, there is a risk of hypoglycemia with SGLT2 inhibitors. A low dose at treatment initiation with careful titration to optimal dosing is recommended[141]. Growing evidence suggests that empagliflozin is a candidate for first-line treatment of neutropenia and neutrophil dysfunction related symptoms in GSD-Ib patients.

Another promising novel therapeutic strategy is gene therapy by using recombinant adeno-associated virus vectors. The use of a viral vector to administer G6Pase and hepatocyte transplantation are being investigated as potential treatments for GSD-I. Various animal models have shown an increase in hepatic G6Pase and G6PT activity, as well as improvements in metabolic parameters[146-150]. Multiple approaches have been explored for the integration of the G6Pase transgene into the host genome[151,152]. The successful correction of metabolic imbalances in animal models through gene therapy shows promising potential for future applications of gene therapy in humans. A phase I/II clinical trial using a recombinant adeno-associated virus vector expressing a codon-optimized human G6Pase-α or G6PC for treatment of human GSD-Ia (NCT 03517085) has just been completed and the results are pending.

GSD-III; Cori disease; Forbes disease; limit dextrinosis; amylo-1,6-glucosidase deficiency; glycogen debrancher deficiency

Glycogen debrancher enzyme has two independent catalytic activities; alpha-glucanotransferase and amylo-1,6-glucosidase, with the two catalytic sites being separated on the same polypeptide. Both catalytic activities are required for complete debranching enzyme activity[153]. Deficient activity of these catalytic sites results in accumulation of glycogen with short outer chains, previously defined as limit-dextrins. Deficiency in glycogen debranching enzyme due to biallelic pathogenic variants in the *AGL* gene results in the harmful accumulation of abnormal glycogen in hepatocytes. The *AGL* gene was mapped to the chromosomal locus 1p21, and its nucleotide sequence was determined, revealing the existence of multiple tissue-specific isoforms[154,155]. GSD-III is inherited in an autosomal recessive manner.

GSD-III makes up about 24% of all GSDs, and its estimated incidence is approximately 1 case per 83000 live births in Europe, and 1 in 100000 live births in North America[156]. Certain populations have an increased prevalence due to a founder effect. The highest known GSD-III prevalence occurs in Inuit population in Nunavik (about 1:2500, c.4456delT variant), the Faroese population of the Faroe Islands (about 1:3600, c.1222C>T variant) and North African Jews from Israel (about 1:5400, c.4456delT variant)[156-158]. There is currently limited evidence supporting a correlation between disease severity and pathogenic variants in the *AGL* gene, except for specific exon 3 variants (c.18_19delGA and c.16C>T) which have been found to be associated with GSD-IIIb (liver involvement only). It was suggested that in muscle isoforms of the *AGL* gene, alternative exon or translation initiation may not require exon 3, thereby resulting in normal enzyme activity in the muscle tissues of patients with GSD-IIIb who harbor an exon 3 deletion[159,160]. Recent evidence suggests that the presence of frameshift, nonsense, and splice site variants may lead to severe phenotypes. Differences in tissue expression of the deficient enzyme is responsible for the phenotypic variability observed in GSD-III patients[153].

GSD-III is characterized by heterogeneous involvement of the liver, skeletal muscle, and cardiac muscle, leading to variable clinical presentations. Various subtypes are defined by the extent of the tissue involvement. Two major subtypes of GSD-III have

been identified. GSD-IIIa affects both the liver and the muscle (skeletal and cardiac) and is the most prevalent subtype accounting for approximately 85% of cases. Meanwhile, GSD-IIIb primarily affects only the liver and comprises approximately 15% of all GSD-III cases[48,159]. In a limited number of cases, it has been demonstrated that there is a selective loss of either glucosidase activity (resulting in muscle involvement, referred to as GSD-IIIc) or transferase activity (resulting in both muscle and liver involvement, referred to as GSD-IIId)[161,162].

Hepatomegaly, ketotic hypoglycemia, growth retardation and dyslipidemia (hypertriglyceridemia) are the dominant features of hepatic involvement in infancy and childhood. Because gluconeogenesis is intact in GSD-III, fasting hypoglycemia tends to be milder than what is seen in GSD-I. During infancy, serum hepatic transaminases are markedly elevated. Uric acid and lactate concentrations are relatively normal[163]. Symptoms and laboratory findings related with liver involvement often improve with age and usually disappear after puberty[164,165]. However, liver disease can also be progressive resulting in liver fibrosis, cirrhosis, hepatic failure, and end-stage liver disease[107,165]. Hepatic fibrosis may occur as early as 1 year of age[166]. Overt liver cirrhosis is not common and occurs rarely[153,165]. Hepatocellular carcinoma can develop as a long-term complication of liver cirrhosis, rather than transformation of an adenoma to carcinoma, as seen in GSD-I[167,168]. The prevalence of hepatic adenomas has been reported to be ranging from 4% to as high as 25%[169]. A recent descriptive, retrospective, international, multi-center cohort study revealed that the overall prevalence of severe hepatic complications (hepatic cirrhosis, hepatic adenomas and/or hepatocellular carcinoma) was 11%[170]. Liver transplantation for cirrhosis and/or hepatocellular carcinoma have been reported[107,168]. Children with failure to thrive often catch-up in height in adulthood with optimized, individualized dietary management.

Muscle symptoms associated with GSD-III can manifest concurrently with liver disease or long after hepatic disorders or even after the resolution of hepatic symptoms during childhood. An elevation in creatine kinase (CK) level is observed in 81% to 94% of cases with muscle involvement, serving as a useful indicator of muscle pathology[171].

Nonetheless, a normal CK level does not entirely exclude the possibility of an underlying muscular disease[172,173]. The median age of onset of CK elevation was reported to be 10 years[170]. Although muscle involvement becomes clinically more obvious later in life, mild muscle weakness on physical examination, motor developmental delay (delayed sitting, delayed standing upright, delayed onset of walking), exercise intolerance, and hypotonia were reported in the majority of pediatric patients with GSD-III[174-176]. Muscle weakness and wasting may slowly progress and become severe by the third or fourth decade of life[165,173].

In a subset of adult patients with GSD-III, muscle symptoms can present in the absence of any clinical or previous history evidence of liver dysfunction[165,177]. Muscle weakness, although minimal during childhood, is slowly progressive in nature and may become the predominant feature with significant permanent muscle weakness in adults with type IIIa disease[171]. Although myopathy is generally slowly progressing and not severely debilitating, some patients may have severe muscle involvement leading to loss of ambulation[170]. Myopathy can be proximal, distal, or more generalized. Exercise intolerance with muscle fatigue, cramps and pain are evident in more than half of the patients[170,174,175]. Bulbar or respiratory dysfunctions are rarely seen in GSD-III patients while no clinical involvement of facial or ocular muscles has been described in the literature[178].

Cardiac involvement in GSD-III is variable. Cardiac involvement is present in most patients, with varying degrees of severity ranging from ventricular hypertrophy detected on electrocardiography to clinically apparent cardiomegaly[179]. Left ventricular hypertrophy, right ventricular hypertrophy, interventricular septal hypertrophy, QT prolongation, sinus tachycardia, and pulmonary hypertension were among electrocardiographic and/or echocardiographic findings of cardiac involvement[170,180]. According to International Study on Glycogen Storage Disease data presented by Sentner *et al*[170], 58% of patients with GSD-IIIa showed cardiac hypertrophy mostly presented by electrocardiographic and/or echocardiographic signs of left ventricular hypertrophy. In the same cohort, only 15% of all patients developed

hypertrophic cardiomyopathy. Mogahed *et al*[175] reported that cardiac muscle involvement is less common and mostly subclinical in pediatric age group. However, a more recent study reported that 91% of patients showed cardiac involvement at a median age of 2.6 years, 86% of cases being under 2 years of age[181]. Moreover, 56% of the patients presented with a symptomatic cardiomyopathy at some point during the follow-up indicating a more severe cardiac phenotype especially in those on a diet with insufficient caloric and protein intake and suboptimal UCSS treatment[181]. Cardiomyopathy usually presents with asymptomatic left ventricular hypertrophy but can progress to hypertrophic cardiomyopathy with decreased left ventricular function and/or arrhythmias, severe cardiac dysfunction, congestive heart failure[181,182]. Sudden death has occasionally been reported[183].

Patients with GSD-III may exhibit facial abnormalities such as indistinct philtral pillars, bow-shaped lips with a thin vermillion border, a depressed nasal bridge and a broad upturned nasal tip, and deep-set eyes, particularly in younger patients[184]. Some individuals with GSD-III may have an increased risk of developing osteoporosis with reduced bone mineral density which, in part, may be due to suboptimal nutrition, the effects of metabolic abnormalities and muscle weakness[41,185,186]. Bone fractures due to osteopenia and osteoporosis were reported in patients with GSD-III[170]. Polycystic ovary disease has been reported in women with GSD-III with no significant effect on fertility[187]. Type 2 diabetes may occur during the course of the disease in adulthood[188]. Michon *et al*[189] reported global cognitive impairment in adult GSD-III patients as an underlying cause of psychological and attention deficits seen in this patient group.

Liver histology shows uniform distension of hepatocytes secondary to glycogen accumulation. There is often septal formation, periportal and reticular fibrosis, fine microsteatosis, and less frequently, micronodular cirrhosis without inflammation or interface hepatitis. Skeletal muscle shows subsarcolemmal glycogen accumulation[12]. The diagnosis of GSD-III is made by identification of biallelic *AGL* pathogenic variants on molecular genetic testing. In case the diagnosis cannot be established by genetic

analysis, demonstrating enzyme deficiency in peripheral leukocytes or erythrocytes, cultured skin fibroblasts or in the liver or muscle tissue samples is necessary.

A practice guideline was published by American College of Medical Genetics and Genomics in 2010 providing recommendations on the diagnosis and management of the complications of GSD-III[176]. The mainstay of GSD-III treatment is dietary intervention, which aims to maintain normal blood glucose levels while balancing macronutrient and total caloric intake. This is achieved by avoidance of fasting, frequent meals enriched in complex carbohydrates and use of UCSS. Continuous enteral feeding may be needed in some cases. Sucrose, fructose, and lactose are not contraindicated unlike GSD-I. UCSS can be used as early as the first year of life to prevent hypoglycemia. As an alternative, Glycosade®, an extended-release cornstarch, can also be used[87]. Caution must be exercised to avoid overtreating with cornstarch or carbohydrates, which may lead to excessive storage of glycogen in liver and weight gain. In patients with myopathy, along with managing hypoglycemia, a high-protein diet is recommended as it prevents muscle protein breakdown during glucose deprivation, thereby preserving skeletal and cardiac muscle[176]. A ketogenic diet (alone or in combination with high protein and ketone bodies) was also shown to ameliorate cardiomyopathy[190,191]. It has been shown that high-fat, low-calorie and high-protein diet can reduce cardiomyopathy in individuals with GSD-III[192,193]. The beneficial effects on cardiac or skeletal muscle function of these ketogenic or high-fat diets are possibly related to the increased ketone bodies or fats as fuel sources, or reduced glycogen accumulation through decreased carbohydrate intake. Whether long-term muscular, cardiac, or even liver complications can be prevented by these dietary approaches warrants further studies[194].

Liver transplantation corrects all liver related biochemical abnormalities but does not correct myopathy or cardiomyopathy[107,133,195]. Cirrhosis, liver dysfunction, and/or hepatocellular carcinoma are the main indications for liver transplantation. Detailed information about surveillance recommendations on hepatic, metabolic, musculoskeletal, cardiac, nutritional, and endocrine aspects of the disease can be found

elsewhere[176]. Gene therapy and gene-based therapeutic approaches are in development.

GSD-IV; Andersen disease; brancher deficiency; amylopectinosis; glycogen branching enzyme deficiency

The disease was described by Andersen[196] in 1956 as "familial cirrhosis of the liver with storage of abnormal glycogen" and, in 1966, amylo-1,4 to 1,6-transglucosidase [glycogen branching enzyme (GBE)] deficiency was reported[197]. Branching of the chains is essential to pack a very large number of glycosyl units into a relatively soluble spherical molecule. Without GBE, an abnormal glycogen with fewer branching points and longer outer chains resembling an amylopectin-like structure (polyglucosan) accumulates in various tissues including hepatocytes and myocytes[198]. The mapping of the *GBE1* gene to chromosome 3p12.2 was first accomplished in 1993[199]. Notably, mutations in the same gene are also responsible for adult polyglucosan body disease. GSD-IV accounts for only 0.3% of all GSDs and follows an autosomal recessive inheritance pattern[200]. This rare disorder has a prevalence of 1:600000 to 1:800000[201].

GSD-IV exhibits significant clinical heterogeneity and phenotypic variability, partly due to variations in tissue involvement, which may be influenced by the presence of tissue-specific isozymes[198,200]. The liver is the primary organ affected, with the classical hepatic form appearing normal at birth but progressing rapidly to cirrhosis in early life, leading to liver failure and death between 3 to 5 years of age[196]. Children with GSD-IV experience growth failure, hepatomegaly and/or splenomegaly, and cirrhosis within the first 18 mo of life. Besides the complications of progressive cirrhosis including portal hypertension, ascites and esophageal varices, development of hepatocellular carcinoma was also reported[202]. In rare cases, the hepatic disease in GSD-IV may not progress or progress slowly[203]. Patients with non-progressive hepatic form may present with hepatosplenomegaly and mildly elevated liver transaminases, experience normal growth. Liver size and transaminase levels may return to normal[203]. Patients with non-progressive hepatic form usually survive into adulthood.

GSD-IV can present with multiple system involvement, with the enzyme deficiency in both liver and muscle[204]. This form of the disease can manifest as peripheral myopathy with or without cardiomyopathy, neuropathy, and liver cirrhosis. The onset of the disease can be from the neonatal period to adulthood[205]. The neuromuscular presentation can be divided into four groups based on age at onset[206]. In the perinatal (fetal) form, which can lead to hydrops fetalis and polyhydramnios, arthrogryposis develops due to akinesia[207]. Detection of cervical cystic hygroma during pregnancy may indicate the disease[200]. Prenatal diagnosis can be performed by determining enzyme activity in cultured amniocytes or chorionic villi samples. Genetic studies can complement uncertain enzyme activity studies, such as equivocal results in prenatal fetal samples s and in patients with higher levels of residual enzyme activity that overlap heterozygote levels[208]. Mortality is unavoidable in the neonatal period. Liver cirrhosis or liver failure has not been reported. Severe hypotonia, hyporeflexia, cardiomyopathy, depressed respiration, and neuronal involvement are the features of the congenital form of the disease[198,209-211]. Liver disease is not severe, and the child dies in early infancy due to other reasons. Childhood neuromuscular form may start at any age with either myopathy or cardiomyopathy[206,212]. Presenting symptoms mainly include exercise intolerance, exertional dyspnea, and congestive heart failure in advanced stages. The disease can be confined to muscular tissue and serum CK level could be within the normal range. In adult form, there is isolated myopathy or a multisystemic disease called adult polyglucosan body disease. Onset of symptoms can occur at any age during adulthood, usually after the age of 50, and may exhibit resemblance to muscular dystrophies. Symptomatology includes progressive gait difficulty and proximal muscle weakness, which is more pronounced in the arms as compared to the legs. Both upper and lower motor neurons are affected in the disorder. The disease may manifest as pyramidal tetraparesis, peripheral neuropathy, early onset of neurogenic bladder, extrapyramidal symptoms, seizures, and cognitive dysfunction leading to dementia[210]. The diagnosis can be established by enzyme activity assay in erythrocytes[213]. Amylopectin-like inclusions are detected through ultrastructural

examination of the central nervous system and skeletal muscle. These inclusions are intensely PAS-positive and diastase-resistant, both in neurons and muscular fibers[214]. Magnetic resonance imaging shows white matter abnormalities[215].

Liver biopsy can be diagnostic in patients with hepatic involvement[216]. The histopathological evaluation of the liver reveals abnormal hepatocellular glycogen deposits in the form of periodic-acid Schiff positive, diastase-resistant inclusions. Ultrastructural examination with electron microscopy reveals accumulation of fibrillar aggregations that are typical of amylopectin. Typically, enzyme deficiency can be documented through diagnostic assays performed on hepatocytes, leukocytes, erythrocytes, and fibroblasts. However, patients with cardioskeletal myopathy may exhibit normal leukocyte enzyme activity[198]. The diagnosis of GSD-IV can be confirmed through histopathological examination, detection of enzyme deficiency, and mutation analysis of the *GBE1* gene. Genetic confirmation is recommended whenever possible in patients with suspected GSD-IV to provide more data for genotype-phenotype correlations in this extremely rare disease. The genotype-phenotype correlation remains unclear for GSD-IV and the same genetic defect may cause different clinical presentations in unrelated patients[217]. Mutation analysis can also provide crucial diagnostic information in cases with equivocal results of biochemical analyses[218]. Mutations with significant preservation of enzyme activity may be related with milder (*e.g.,* non-progressive hepatic form) and late-onset (*e.g.,* adult polyglucosan body disease) phenotypes of the disease.

Hypoglycemia has traditionally been considered as a late manifestation and generally develops due to hepatocellular dysfunction caused by progressive cirrhosis. At this stage of the disease, the biochemical profile of the patients is representative of what is observed in other causes of liver cirrhosis. However, a recent study has reported that fasting intolerance, as indicated by a through medical history, along with the presence of hypoglycemia and/or ketosis, can be observed in patients even in the absence of detectable liver injury or dysfunction based on biochemical or radiological assessment[201].

No specific dietary and pharmacological treatment are available for GSD-IV. There is a lack of established guidelines based on either evidence or expert consensus for the dietary management of GSD-IV. Improvement in clinical, anthropometric, and laboratory parameters was reported with a high-protein and low-carbohydrate diet[219,220]. Derks *et al*[201] recently reported improved clinical and biochemical outcomes after dietary interventions including a late evening meal, continuous nocturnal intragastric drip feeding, restriction of mono- and disaccharides, addition of UCCS, and protein enrichment in patients with GSD-IV. Individual dietary plans should also aim to avoid hyperglycemia to minimize glycogen accumulation in the liver.

At present, there is no effective therapeutic approach other than liver transplantation for GSD-IV patients who are affected by progressive liver disease. However, anecdotal reports indicate that liver transplantation may not alter the extrahepatic progression of GSD-IV[217]. The presence of extrahepatic involvement, especially amylopectin storage in the myocardium, may lead to fatal complications following liver transplantation[221-223]. Careful assessment of cardiac function even in the absence of clinical decompensation or consideration of combined liver-heart transplantation is warranted for patients with GSD-IV[224]. Liver transplantation may provide beneficial effects not only for patients with liver disease but also for those affected by muscular involvement in GSD-IV[107,225,226]. This may be explained by systemic microchimerism (donor cells presenting in various tissues of the liver recipient) after liver allotransplantation and amelioration of pancellular enzyme deficiencies resulting in a decrease in amylopectin in other organ systems[12]. It has been suggested that the donor cells can transfer enzyme to the native enzyme-deficient cells[226].

In recent years, animal studies have been conducted to prevent glycogen and polyglucosan body accumulation in GSD-IV patients, and GYS inhibitor guaiacol and 144DG11 are promising in this regard[227,228]. The molecular target of 144DG11 is the lysosomal membrane protein lysosome-associated membrane protein 1 (LAMP1), which enhances autolysosomal degradation of glycogen and lysosomal acidification. In

adult polyglucosan body disease mouse model, 144DG11 reduced polyglucosan and glycogen in brain, liver, heart, and peripheral nerve[228].

GSD-VI; Hers disease; liver glycogen phosphorylase deficiency

GSD-VI was first reported by Hers[229] in three patients with hepatomegaly, mild hypoglycemia, an increased glycogen content and deficient activity of glycogen phosphorylase in the liver in 1959. GSD-VI is a rare autosomal recessive genetic disease caused by deficiency of hepatic glycogen phosphorylase. At least three human glycogen phosphorylases exist including muscle, liver, and brain isoforms[230]. In response to hypoglycemia liver glycogen phosphorylase catalyzes the cleavage of glucosyl units from glycogen which results in the release of glucose-1-phosphate. The glucose-1-phosphate is subsequently converted to glucose-6-phosphate. The *PYGL* gene is currently the only known genetic locus associated with the development of GSD-VI and was mapped to chromosome 14q21-q22 in 1987[231]. The incidence of the disease is estimated to be 1:100000 and believed to be underestimated because of nonspecific and variable phenotypes, and paucity of cases confirmed by genetic testing[232]. GSD-VI is more prevalent among the Mennonite community, with a prevalence of 1 in 1000, representing the only known population at higher risk for the disease[232].

GSD-VI is a disorder with broad clinical heterogeneity[232]. Infants with liver phosphorylase deficiency mainly present with hepatomegaly and growth retardation. The condition typically has a benign course, and symptoms tend to improve as the child grows[229]. Hepatomegaly usually normalizes by the second decade of life[233]. The child shows mild to moderate ketotic hypoglycemia related with prolonged fasting, illness, or stressful conditions[232]. Because gluconeogenesis is intact in GSD-VI, hypoglycemia is usually mild. Despite gross hepatomegaly, the patient may be largely asymptomatic without hypoglycemia. However, there is a range of clinical severity in GSD-VI, with some patients experiencing severe and potentially life-threatening hypoglycemia. There is generally mild ketosis, growth retardation, abdominal distension due to marked hepatomegaly and mildly elevated levels of serum transaminases, triglycerides, and

cholesterol. However, in patients with high residual enzyme activity, biochemical investigations may be normal[234,235]. Hypertriglyceridemia may persist despite treatment[108]. A few patients showing mild muscular hypotonia, muscle weakness or developmental impairment were observed, but otherwise, no neurological symptoms were reported in the literature[232]. Sleep difficulties and overnight irritability are common[236]. In contrast to GSD-I, serum levels of lactic acid and uric acid are generally within the normal range[15]. However, in a recent clinical study including 56 GSD-VI patients, hyperuricemia was reported as a complication in adolescent and adult patients with GSD-VI, which indicates the need for long-term monitoring of uric acid in older GSD-VI patients[237]. CK concentration is usually normal. In some patients, severe and recurrent hypoglycemia, pronounced hepatomegaly, and postprandial lactic acidosis have been reported[238]. Recently, children with GSD-VI have been reported to present with only ketotic hypoglycemia as the sole manifestation of the disease, without the characteristic hepatomegaly[239]. Mild cardiopathy has also been described for GSD-VI[233].

The clinical picture of GSD-VI virtually overlaps with phosphorylase kinase (PHK) deficiency (GSD-IX) and differential diagnosis includes other forms of GSDs associated with hepatomegaly and hypoglycemia, especially GSD-I and GSD-III[236]. It is not possible to distinguish between GSD-VI and GSD-IX based on clinical or laboratory findings alone[232].

Mutation analysis is the suggested method for the diagnosis of GSD-VI. A liver biopsy is not recommended to establish the diagnosis to avoid an invasive procedure. Excessive glycogen accumulation with structurally normal glycogen in the liver biopsy is consistent with GSD-VI. Fibrosis, mild steatosis, lobular inflammatory activity and periportal copper binding protein staining have also been reported in GSD-VI patients. Although it is possible to document glycogen phosphorylase deficiency in frozen liver biopsy tissue or blood cells including leukocytes and erythrocytes, normal *in vitro* residual enzyme activity may be seen and prevent to establish a definitive diagnosis by an enzyme assay alone in some patients[234,235].

In GSD-VI, nutrition therapy aims to improve metabolic control and prevent primary manifestations such as hypoglycemia, ketosis, and hepatomegaly, as well as secondary complications including delayed puberty, short stature, and cirrhosis. Frequent meals, a high-protein diet providing 2-3 g protein/kg body weight/day, limitation but not prohibition of simple sugars like sucrose, fructose, lactose, a late evening meal and use of UCCS are the main recommendations in GSD-VI patients[236]. The aim of the therapeutic approach is to achieve euglycemia and normoketosis through the administration of the appropriate doses of cornstarch. The target level for blood glucose should be within 70-100 mg/dL, while the optimal range for blood ketones is 0.0-0.2 mmol/L[236]. An extended-release corn starch derived from waxy maize, marketed as Glycosade®, has been found to have a positive impact in delaying overnight hypoglycemia in children over 5 years of age and adults[87]. Some individuals with GSD-VI may not require any treatment.

GSD-VI usually has a benign disease course. However, focal nodular hyperplasia, fibrosis, cirrhosis, and a degeneration to hepatocellular carcinoma have been reported in some patients[240-242]. Cirrhosis has been reported in patients as young as preschool age, even within the second year of life[242]. Based on these findings, aggressive treatment of GSD-VI is recently suggested to maintain optimal metabolic control and prevent long-term complications[243]. Long-term monitoring of hepatic function is also recommended[236].

GSD-IX; PHK deficiency

Glucagon and epinephrin play a critical role in the regulation of glycogenolysis by activation of adenylate cyclase which leads to an increase in the cytosolic concentration of cyclic adenosine monophosphate (cAMP). The increased level of cAMP activates cAMP-dependent protein kinase which activates PHK. In the next step PHK, a serine/threonine-specific protein kinase, functionally activates glycogen phosphorylase in liver. PHK is a heterotetramer composed of 4 different subunits (α, β, γ, and δ). Each subunit is encoded by different genes that are located on different chromosomes and

differentially expressed in a variety of tissues[244]. α and β subunits have regulatory functions, γ subunit contains the catalytic site, and δ is a calmodulin protein[245]. PHK has a wide tissue distribution with multiple tissue-specific isoforms.

The α subunit has two isoforms, a muscle isoform, and a liver isoform, which are encoded by two different genes (*PHKA1* and *PHKA2*, respectively) on X chromosome[244]. The genetic loci of other subunits are mapped to autosomal chromosomes. The γ subunit also has muscle and liver isoforms, each of which is encoded by a distinct gene (*PHKG1* and *PHKG2*, respectively). There is only one gene encoding the β-subunit (*PHKB*). However, *PHKB* is expressed in both muscle and liver[246,247].

Liver PHK deficiency (liver GSD-IX) can be classified according to the involved gene, the X-linked form (GSD-IXa, X-linked glycogenosis) and autosomal recessive forms (GSD-IXb and GSD-IXc). GSD-IXa (*PHKA2*-related GSD-IX) is caused by pathogenic variants in *PHKA2* gene on X chromosome. GSD-IXb (*PHKB*-related GSD-IX) and GSD-IXc (*PHKG2*-related GSD-IX) are inherited autosomal recessively and caused by mutations in *PHKB* and *PHKG2* genes, respectively (Table 1). GSD-IXa is further classified into subtypes XLG-I (formerly GSD-VIII) with no enzyme activity in liver or erythrocytes, and XLG-II with no enzyme activity in liver, but normal activity in erythrocytes[248,249].

GSD-IX is one of the most common forms of GSDs. Roughly 25% of all GSDs can be attributed to PHK deficiency[249]. The frequency of liver PHK deficiency was estimated to be 1:100000[15]. GSD-IXa, the most common subtype of liver PHK deficiency, accounts for 75% of all GSD-IX cases. On the X chromosome, there are two enzyme loci; one for the alpha subunit of muscle PHK, and one for the alpha subunit of liver PHK. In 1992, the liver PHK gene was located to Xp22.2-p22.1[244]. GSD-IXa is more common in males due to X-linked inheritance pattern. Female carriers may become symptomatic due to X chromosome inactivation[250].

Hepatomegaly, growth retardation, delayed motor development, mild hypotonia, significantly elevated serum transaminase levels, hyperlipidemia, fasting hyperketosis,

and hypoglycemia are the main symptoms and findings[251-254]. Rarely described clinical features include splenomegaly, liver cirrhosis, doll-like facies, osteoporosis, neurologic involvement, high serum lactate levels, metabolic acidosis, and renal tubular acidosis[233]. With increasing age, there is a gradual resolution of both clinical symptoms and laboratory abnormalities. Although puberty may be delayed, eventual attainment of normal height and complete sexual development is still possible[253]. Most adult patients are asymptomatic[252]. Unusual presentations including asymptomatic hepatomegaly and isolated ketotic hypoglycemia without hepatomegaly have been reported in affected male children underscoring the importance of screening for GSD-IXa in male patients who are suspected of having GSD with atypical features[239,255]. More severe phenotypes including severe recurrent hypoglycemia and liver cirrhosis have also been reported[243,256,257]. Recent findings suggest that GSD-IXa is not a benign condition as is often reported in the literature and patients may have fibrosis even at the time of diagnosis[258].

GSD-IXc is caused by autosomal recessive mutations in *PHKG2* gene. There are two isoforms, encoded by different genes, for the gamma subunit: The muscle form (*PHKG1* gene) and the testis/liver form (*PHKG2* gene)[259]. The genetic locus of the liver form was located to 16p12.1-p11.2. The presence of *PHKG2* mutations has been linked to more severe clinical and biochemical abnormalities, such as an elevated risk for liver fibrosis and cirrhosis[260-262]. Liver cirrhosis can develop in infancy[263]. Cirrhosis related esophageal varices and splenomegaly, liver adenomas, renal tubulopathy and significant hypocalcemia were other reported clinical findings[236]. Patients with this condition commonly present with severe hypoglycemia requiring overnight feeding, show very low PHK activity in the liver, and exhibit highly elevated serum transaminase levels. A wide range of clinical symptoms can be observed, including hypoglycemia during fasting, hepatomegaly, elevated levels of transaminases, hepatic fibrosis, cirrhosis, muscle weakness, hypotonia, delayed motor development, growth retardation, and fatigue[264].

The genetic cause of GSD-IXb is attributed to mutations in the *PHKB* gene, which is located on 16q12-q13 and encodes the beta subunit of PHK[265]. The main features of the disease include a marked hepatomegaly, increased glycogen content in both liver and muscle, and development of hypoglycemic symptoms after physical activity or several hours of fasting[265]. Patients with liver fibrosis, adenoma-like mass, mild cardiopathy and interventricular septal hypertrophy were reported[233]. The muscle symptoms are generally mild or absent, affecting virtually only the liver. Distinction between GSD-IXb and individuals with pathogenic variants in *PHKA2* or *PHKG2* cannot be done based on clinical findings alone.

Genetic analysis is the preferred first line diagnostic test in suspected patients. An approach using next-generation sequencing panels is advised due to the involvement of multiple genes. Liver biopsy can be a valuable diagnostic tool for confirming the diagnosis in cases where there are variants of unknown significance. Histopathological assessment of the liver involvement is superior to biochemical parameters[266]. It is important to keep in mind that PHK enzyme activity can be normal in blood cells and even in liver tissue of affected patients. On the other hand, a reduction in PHK enzyme activity can also occur secondary to other metabolic defects such as pathogenic variants in *GLUT2* in Fanconi-Bickel syndrome (FBS), PRKAG2 cardiomyopathy syndrome, or mitochondrial complex 1 deficiency[236].

In patients with GSD-IX, close monitoring of long-term liver and cardiac complications is recommended[233]. Aggressive structured dietary treatment with UCSS and relatively high protein intake was associated with considerable improvement in growth velocity, energy, biochemical abnormalities, hepatomegaly, and overall well-being of patients with GSD-IX. Radiographic features of fibrosis were also reported to be improved with early and aggressive dietary management[243]. General nutritional recommendations for GSD-IX are similar to those for GSD-VI and has recently been published[236].

FBS (formerly GSD-XI)

The primary defect is deficiency of glucose transporter 2 (GLUT2), a monosaccharide carrier that is responsible for the transport of both glucose and galactose across the membranes in hepatocytes, pancreatic β-cells, enterocytes, and renal tubular cells. Utilization of both glucose and galactose is impaired in FBS[267]. Hepatorenal glycogen accumulation and proximal renal tubular dysfunction are the characteristic features of this rare disease[268,269]. FBS follows an autosomal recessive inheritance pattern. The responsible gene, *GLUT2* gene (solute carrier family 2 member 2, *SLC2A2*), was localized to 3q26.1-q26.3 in 1988[270,271]. Since the first patient reported by Fanconi and Bickel in 1949, over 100 cases of FBS with various *SLC2A2* mutations including missense, nonsense, frameshift/insertion-deletion, intronic, and compound heterozygous mutations have been reported[272].

Infants with FBS typically present between the ages of 3 to 10 mo. In addition to hepatorenal glycogen accumulation and proximal renal tubular dysfunction, FBS is characterized by fasting hypoglycemia, postprandial hyperglycemia and hypergalactosemia, rickets and marked growth retardation. Patients have entirely normal mental development. In older patients, dwarfism is the most notable finding. Puberty is significantly delayed, with other remarkable observations including a distended abdomen caused by hepatomegaly, deposition of fat on the abdomen and shoulders, and a moon-shaped face[273]. Some patients may not exhibit hepatomegaly during the early stages of the disease[269,274]. Hyperlipidemia and hypercholesterolemia are prominent and may cause acute pancreatitis. The development of generalized osteopenia occurs early and may result in fractures. Hypophosphatemic rickets and osteoporosis are characteristics of the disease that emerge later in life[275]. Tubular nephropathy is characterized by excessive glucosuria, moderate hyperphosphaturia along with persistenthypophosphatemia, hyperuricemia, hyperaminoaciduria, and intermittent albuminuria, collectively referred to as renal Fanconi syndrome[267,268]. Hypercalciuria is also evident. Due to increased renal losses, there is a frequent tendency towards hyponatremia and hypokalemia. Polyuria may develop due to high urinary osmotic load[276]. Progression to renal failure is not the case. Nephrocalcinosis

was also reported in one third of the patients in a recent retrospective study[277]. There may be mild metabolic hyperchloremic acidosis with normal anion gap due to renal loss of bicarbonate[267]. Cataracts, a frequently documented consequence of hypergalactosemia, are only present in a small number of patients[278].

Laboratory findings include fasting hypoglycemia and ketonuria, hyperglycemia and hypergalactosemia in the postabsorptive state, hypercholesterolemia, hyperlipidemia, moderately elevated alkaline phosphatase, mildly elevated transaminases, normal hepatic synthetic function, hypophosphatemia, hyperaminoaciduria, glucosuria, galactosuria, proteinuria, normal activity of enzymes involved in galactose and glycogen metabolism, normal fructose metabolism, and normal endocrinologic results[267]. FBS patients develop different patterns of dysglycemia, ranging from fasting hypoglycemia, postprandial hyperglycemia, glucose intolerance, to transient neonatal diabetes to gestational diabetes and frank diabetes mellitus[279]. The exact molecular mechanisms underlying the occurrence of dysglycemia in individuals with FBS are not yet fully understood. Sharari *et al*[272] recently suggested that *SLC2A2* mutations cause dysglycemia either by a direct effect on *GLUT2* expression and/or activity or, indirectly, by the dysregulated expression of microRNAs implicated in glucose homeostasis. Impaired renal glucose reabsorption, as well as the accumulation of glucose within the hepatocytes, which stimulates glycogen synthesis and inhibits gluconeogenesis and glycogenolysis, result in fasting ketotic hypoglycemia and hepatic glycogen deposition. Postprandial findings of hyperglycemia and hypergalactosemia are caused by impaired hepatic uptake and diminished insulin response[279]. Glycated hemoglobin A1c is usually within normal range due to recurrent hypoglycemia episodes[280]. Accumulation of glycogen and free glucose in renal tubular cells lead to general impairment in proximal renal tubular function. Histological evaluation of liver biopsy indicates an excessive buildup of glycogen along with steatosis. Due to the presence of galactose intolerance, newborn screening for galactosemia can sometimes identify patients with FBS[281]. The diagnosis is ultimately confirmed by the genetic analysis of *SLC2A2* gene.

The management of symptoms involves measures to stabilize glucose homeostasis and compensate for the renal loss of water and various solutes. Patients typically require replacement of water, electrolytes, and vitamin D, while also restricting galactose intake and adhering to a diabetes mellitus-like diet. Frequent small meals with adequate caloric intake and administration of UCCS are important components of symptomatic treatment. In cases of renal tubular acidosis, it may be required to administer alkali to maintain acid-base balance. Catch-up growth was reported to be induced by UCCS[282]. Continuous nocturnal gastric drip feeding during the night may be indicated in some cases with growth failure[283]. With these measures, the prognosis is good. However, a recent retrospective study reported poor outcome despite adequate metabolic management emphasizing the importance of early genetic diagnosis and facilitating prompt nutritional interventions[277].

GSDS INVOLVING MUSCLE

GSD-II; Pompe disease; acid alpha-glucosidase deficiency; acid maltase deficiency; alpha-1,4-glucosidase deficiency

Pompe disease is a typical example of a lysosomal storage disease. The clinical manifestations of Pompe disease are variable, predominantly due to the varying amounts of residual acid alpha-glucosidase (GAA) activity linked with distinct mutations in the causative gene (*GAA*). *GAA* gene is mapped to chromosome 17q25.2-q25.3[284]. Enzyme deficiency results in intra-lysosomal storage of glycogen especially in skeletal and cardiac muscles. There is no genotype-phenotype correlation, but DD genotype in the angiotensin converting enzyme gene and XX genotype in the alpha actinin 3 gene are significantly associated with an earlier age of onset of the disease[285].

There are mainly two types of GSD-II according to age of onset: Infantile-onset and late-onset Pompe disease. Patients with disease onset before the age of 12 mo without cardiomyopathy and all patients with disease onset after 12 mo of age are included in late-onset form[286]. The combined frequency of infantile onset and late onset GSD-II varies between 1:14000 and 1:100000 depending on ethnicity and geographic region. In

the infantile-onset form, cardiomyopathy and muscular hypotonia are the cardinal features and patients die around 1 year of age. The enzyme activity is less than 1% of normal controls, and the enzyme is deficient in all tissues. Patients also have feeding difficulties, macroglossia, failure to thrive, hearing impairment and respiratory distress due to muscle weakness. The liver is rarely enlarged unless there is heart failure. Hypoglycemia and acidosis do not occur[286]. In the late-onset form, involvement of skeletal muscles dominates the clinical picture, and cardiac involvement is generally clinically insignificant depending on the age of onset. Enzyme activity is partially deficient (2% to 40% of normal controls)[286]. Glycogen accumulation in vascular smooth muscle may cause the formation and subsequent rupture of an aneurysm[287]. Both severe infantile and asymptomatic adult forms of the disease were observed in two generations of the same family[288]. Although women with GSD-II do not have an increased risk of pregnancy or delivery complications, pregnancy may worsen muscle weakness and respiratory complications[289]. As a rule, there is an inverse correlation between the age at disease onset and the severity of clinical manifestations with the level of residual enzyme activity[286].

Laboratory testing reveals nonspecific elevations in CK, aldolase, aminotransferases, and lactate dehydrogenase. Elevated urinary tetrasaccharide is highly sensitive but not specific. To establish the final diagnosis, the measurement of enzyme activity in skin fibroblasts or muscle tissue or the demonstration of the responsible mutation is required[286].

Although it is not curative, ERT has changed the course of Pompe disease since its first use in 2001[290]. Alglucosidase alfa, a lysosomal glycogen-specific recombinant enzyme, was approved by the European Medicines Agency (EMA) in 2006 in the European Union and by Food and Drug Administration (FDA) in 2010 in the United States. The indication criteria were to be ≥ 8 years and absence of cardiac hypertrophy (https://www.accessdata.fda.gov/drugsatfda_docs/Label/2010/125291 Lbl.pdf; accessed on November 5, 2022). Based on data from later studies, treatment initiation was shifted to the neonatal period. The recommended dosage is 20 mg/kg body weight

every two weeks as an intravenous administration. A new formulation of GAA enzyme, avalglucosidase alfa, improves the delivery of the enzyme to target cells and has a 15 times higher cellular uptake when compared with alglucosidase alfa. FDA and EMA approved avalglucosidase in 2021 and in 2022, respectively, for the treatment of patients who are one year of age and older with late-onset Pompe disease[291]. Ongoing studies show that avalglucosidase is generally well tolerated in patients with infantile-onset Pompe disease[291]. The recommended dose is 5 to 20 mg/kg every 2 wk[291]. Criteria for starting and stopping ERT in adult patients with GSD-II are similar in different countries. While a confirmed diagnosis and being symptomatic are general criteria for starting ERT, patient wish, severe infusion associated reactions, noncompliance to treatment, and lack of effect are criteria for stopping ERT[292]. Another way to increase the effectiveness of ERT is to use antibodies as an intracellular delivery vehicle. The 3E10 anti-nuclear antibody, that penetrates cells and localizes to cell nucleus, has been used for this purpose. VAL-1221 is a fusion protein consisting of 3E10 antibody and GAA complex. The presence of 3E10 increases the delivery of GAA to both lysosomal and extra-lysosomal storage of glycogen within cells[293]. The earlier ERT is started, the better is its effectiveness. Therefore, it is recommended to start ERT before irreversible clinical symptoms begin. This concept has led to the development of screening programs for Pompe disease[294]. Recently, it has been shown that in utero alglucosidase alfa treatment, which was started at 24 wk 5 d of gestation and given 6 times at 2-wk intervals through the umbilical vein, was successful[295].

Although antibodies against the enzyme may develop, a recent study showed that the development of antibodies did not affect the clinical course[296]. Whether additional treatments such as oral supplementation of L-alanine is beneficial is being investigated[297]. As an alternative to ERT, studies on gene therapy have also commenced[298].

Danon disease

Although Danon disease was previously classified as a variant of GSD-II with normal alpha-glucosidase activity, it is still controversial whether it is a real GSD. A lysosomal structural protein, LAMP2, is deficient in Danon disease. LAMP2 is involved in autophagosome maturation. Disruption of autophagy leads to accumulation of glycogen granules and autophagic vacuoles[299]. It is an X-linked (Xq24) dominant hereditary disease affecting both skeletal and cardiac muscles, and characterized by skeletal and cardiac myopathy, proximal muscle weakness and intellectual disability. Female patients have a milder disease predominantly involving cardiac muscle[300]. There is currently no treatment for Danon disease. There are ongoing studies evaluating the efficacy and safety of gene therapy[300].

AMP-activated protein kinase deficiency

Another glycogen storage cardiomyopathy results from *PRKAG2* (the gene encoding gamma-2 non-catalytic subunit of adenosine monophosphate-activated protein kinase) mutations on chromosome 7q36.1. The disease is characterized by left ventricular hypertrophy due to altered glycogen metabolism and glycogen storage in cardiac muscle, similar to Danon disease[301-303]. It is inherited in an autosomal dominant pattern. *PRKAG2* gene variants cause a syndrome characterized by cardiomyopathy, conduction disease, and ventricular pre-excitation[302]. It may cause atrial fibrillation/flutter or conduction abnormalities that may cause sudden cardiac death and severe heart failure typically in the third and fourth decade[301,302]. Mutations in gamma-2 non-catalytic subunit of AMP-activated protein kinase may cause lethal congenital storage disease of the heart, and death in the first year of life[303]. It is important to differentiate clinical picture related with *PRKAG2* mutations from Danon disease, as management and prognosis are different.

GSD-V; McArdle disease; myophospharylase deficiency; muscle glycogen phosphorylase deficiency

GSD-V is caused by mutations in *PYGM* gene which is the gene encoding muscle isoform of glycogen phosphorylase. *PYGM* gene is located on 11q13.1[304]. In a recently published European registry for patients with muscle glycogenosis, 95% of all patients had GSD-V[305]. The clinical manifestations generally occur during early adulthood with physical activity intolerance and muscle cramps characterized by muscle fatigue and pain, contracture, tachypnea, tachycardia, ptosis, and retinal dystrophy. Most of the patients are symptomatic at pediatric age (< 18 years)[306]. An improvement of exercise induced symptoms, named as "second wind phenomenon", characterized by the improvement of exercise tolerance after 8 to 10 min of aerobic exercise, is observed[306,307]. Exercise induced rhabdomyolysis can cause transient myoglobinuria, leading to acute renal failure. Hyperuricemia, gout development and thyroid dysfunction are not uncommon[306]. Many patients are diagnosed with an incidental finding of abnormal serum CK levels[307].

Echaniz-Laguna *et al*[308] studied a family with 13 affected members with adult-onset muscle weakness, and reported a phenotype caused by a dominant myophosphorylase gene mutation (p.Asp639His). The first signs of the disease occurred after 40 years of age with proximal leg weakness, followed by proximal arm weakness. In contrast to McArdle disease, the patients did not have exercise intolerance, second wind phenomenon, markedly increased CK levels, or rhabdomyolysis. The authors concluded that specific *PYGM* mutations can cause either dominant or recessive GSDs[308].

GSD-VII; Tarui disease; muscle phosphofructokinase deficiency; GSD of muscle

The responsible gene is located on chromosome 12q13.3[309]. Exercise induced muscle cramps and myoglobinuria are the main characteristics of GSD-VII. Neurological examination does not reveal any abnormalities during rest. Muscle weakness and stiffness invariably occur in muscle groups that are subjected to intense or prolonged exertion. The ischemic exercise test is characterized by the absence of an increase in venous lactate level. Myoglobinuria may develop following exercise. Nausea and

vomiting, icterus, elevated CK, hyperuricemia and reticulosis may also be observed[307]. In contrast to GSD-V, glucose intake prior to exercise worsens exercise capacity due to blocked use of both muscle glycogen and blood glucose[307].

GSD-IXd; X-linked muscle PHK alpha-1 subunit deficiency

The gene is located on chromosome Xq13.1, and the disease is inherited recessively[310]. In most patients, clinical findings appear in adulthood and are characterized by muscle weakness and muscle cramps during exercise. Elevated serum CK level and myopathic findings in electromyography may guide the diagnosis[311].

GSD-X; muscle phosphoglycerate mutase deficiency

The last steps of glycogenolysis are abnormal. The disease is inherited in an autosomal recessive manner and characterized by exercise induced muscle cramps, myalgia, rhabdomyolysis and myoglobinuria. Serum CK level is increased between episodes[312].

GSD-XI; lactate dehydrogenase a deficiency

It was first described by Kanno *et al*[313] in 1980 and characterized by easy fatigue, increase in serum CK, myoglobin, lactate, and pyruvate levels immediately after ischemic work. The gene locus is on chromosome 11p15.1[314].

GSD-XII; aldolase deficiency

GSD-XII is a very rare disease resulting from aldolase A deficiency and characterized by muscle glycogen accumulation, crisis of rhabdomyolysis induced by fever and/or exercise and hemolytic anemia with or without myopathy or cognitive dysfunction[315]. It is an autosomal recessive disorder, and the gene is located on chromosome 16p11.2[316].

GSD-XIII; muscle enolase 3 deficiency

It was first described by Comi *et al*[317] in 2001 in a 47-year-old man with severe deficiency of muscle enolase activity. The patient had recurrent exercise induced myalgias without cramps. Serum CK concentration was elevated while serum lactate level was normal with the ischemic forearm exercise. The related gene is located on chromosome 17p13.2[317].

GSD-XV; glycogenin deficiency

Similar to Danon disease and *PRKAG2* variants, glycogenin deficiency may cause a left ventricular arrhythmogenic cardiomyopathy. Patients present with chest pain, progressive weakness, and vague presyncope spells[318].

CONCLUSION

There have been significant changes and improvements in the classification, diagnosis, and treatment of GSDs in recent years. We are now more aware of that many GSDs, which were previously identified as childhood diseases, may present first in adulthood. Diagnosis can be challenging, especially for GSDs with milder phenotypes and those with only skeletal and/or cardiac muscle involvement. Since early diagnosis and aggressive treatment is related with better prognosis, physicians should be aware of these conditions and include GSDs in differential diagnosis of pediatric and adult patients with not only liver related manifestations but also skeletal and/or cardiac muscle, central nervous system, and multisystemic involvement.

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