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Speckle Tracking Echocardiography for Early Detection of Myocardial Damage in Children with Glycogen Storage Diseases

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Background
Hereditary glycogen storage disorders (GSDs) manifest as abnormalities in glycogen types or deposits in tissues and are caused by a deficiency in one or more enzymes involved in glycogen production or breakdown. Hereditary glycogen storage disorders (GSDs) manifest as abnormalities in glycogen types or deposits in tissues and are caused by a deficiency in one or more enzymes involved in glycogen production or breakdown. These illnesses are considered uncommon due to their very low prevalence. An estimated 1 case per 2,000–43,000 live births is the total incidence of GSDs. Twelve different kinds of GLDs, all of which are inherited in an autosomal recessive fashion, have been recognized as a result of human enzyme deficiencies. The hereditary unusual enzyme shortage may impact several organs and tissues, including the brain, skeletal muscles, heart, kidneys, and liver. Our research will use speckle tracking echocardiography to determine how GSDs influence the anatomy and function of the heart. To identify early myocardial involvement in young patients with GSDs, longitudinal myocardial left ventricular strain evaluated with speckle tracking is a promising method. This data has significant therapeutic value since it enables early diagnosis and therapy of myocardial dysfunction.

Keywords: Speckle, Myocardial, Glycogen.

Incidence
These illnesses are considered uncommon due to their very low prevalence. An estimated 1 case per 2,000–43,000 live births is the total incidence of GSDs. Twelve different kinds of GLDs, all of which are inherited in an autosomal recessive fashion, have been recognized as a result of human enzyme deficiencies. (1).

Physiology
Not only does the liver have glycogen, but so do the kidneys, skeletal muscles, and enterocytes. Glycogen is a complex/polymeric physiological glucose carbohydrate. In order to keep blood sugar levels stable, it stores glucose for use as an internal energy source in the three to four hours after a meal, after the body has finished digesting the food via the glycolysis process. In the initial, early stages of myocyte development, skeletal muscles utilize glycogen as a source of glucose; alternatively, hepatocytes may produce glycogen after brief fasting (2).

To avoid postprandial hyperglycemia, the liver stores carbs as glycogen, an essential step in the metabolic pathway under normal physiological circumstances. When glucose monomers are combined with glycogen protein and α1,4- or α1,6-glycosidic linkages, glycogen is synthesized. When cellular energy demands increase and blood glucose levels decrease, this process may be swiftly undone (3).

Medical epidemiology and pathogenesis

Enzymes involved in glycogen production (glycogenesis) or glycogen breakdown (glycogenolysis) may become genetically locked, leading to glycogen storage disorder (GSD). Glycogenosis comes in several forms, each of which is characterized by a different kind of aberrant buildup of this branching polysaccharide (4).

Additionally, GSD can also mean a deficiency in glycogen synthase, which results in tissues not storing glycogen because the enzyme that normally catalyzes the glycogen synthesis reaction is absent (type 0 GSD) (5). This is despite the fact that the name is not semantically correct.

- **Inheritance**

Autosomal recessive (AR) inheritance is the norm for metabolic illnesses, including glycogen storage diseases. These are the genetic abnormalities that impact the body's ability to process carbohydrates; they may manifest in the liver, the muscles, or a combination of the two (the so-called mixed cases) (6).

The AR inherited disorders in a particular location or community are determined by the degree of consanguinity. In areas with significant mutation rates, de novo mutations are still possible. Only the IX-alpha glycogenosis form of GSD is recessive and X-linked (7).

- **Typology of GSDs**

It remains an unresolved issue. Various assessment criteria, such as author, enzyme, occupied tissues, or mutation site, are used to classify the results. It is commonly acknowledged and used that GSDs are categorized according to the order in which they were discovered or described by the authors. Names for glycogen storage disorders have been derived from the original research, treatment, or diagnosis of these conditions, going back to when they were not yet considered a distinct medical

entity. Additionally, this subfield is prevalent in a wide variety of general medical biochemistry, genetics, pediatrics, and neonatology studies (8).

The Shin research is another effort to characterize GSDs; it yields 12 GSDs when classified according to the enzymatic substrate of glycogen metabolism and the subtypes linked with certain organs (9).

GSDs, mostly using existing case reports, in light of current understanding of the field, their enzyme deficiencies, or the tissues involved. There has been a rise in the amount of research examining GSDs, as shown by case studies and data collected during patient health monitoring (10).

More and more, people are becoming aware of and learning about these complicated metabolic diseases. The aforementioned diseases were classified by the author into three types: hepatic, mixed, and muscle GSDs (11).

The glucose transporter

Glycogen molecule breakdown is regulated by activating the appropriate chemicals and enzymes, and it is directly tied to energy generation. When glycogen synthase and phosphorylase activities are in harmony, glycogen metabolism functions well in the organism. Multiple sites of reversible phosphorylation by distinct kinases are possible for both enzymes (12).

A three-step process is involved in glycogenolysis, also known as branched glucose polymer phosphorolysis:

1. The phosphorylase function of glucose-1-phosphate-kinase (PhK) is activated.
2. Glucomutase involved in the transformation of glucose-1-phosphate into glucose-6-phosphate.

G6PC, an enzyme involved in glucose-6-phosphate metabolism, is the third compound on the list.

To make up for a drop in blood glucose levels or a shortage of cellular molecular energy carriers—ATP—glycogenolysis occurs in the liver when we're hungry or in the muscles when we're exercising vigorously. The liberated glucose is already phosphorylated and capable of undergoing further modification in the first stage of glycogenolysis. Because it is unable to exit the cell easily in this condition, the working muscle experiences a very energy-beneficial response. Having said that, glycogen metabolism isn't always enough (13).

- **GSD type IX**

About a quarter of all cases of glycogenosis are of GSD type IX, which is characterized by an absence of the glycogen breakdown enzyme phosphorylase kinase (PhK). Since the enzyme is present in a wide variety of tissues, its subunits may also take on different shapes. Research on PhK's function has focused on several tissues and organs, including the heart, muscles, kidneys, testes, liver, and erythrocytes, leukocytes, and nerve cells (14).

The following genes encode the 4-subunit PhK enzyme: • PHKA1 and PHKA2 (α1 and α2 subunits) expressed in the liver. • PHKB (subunit β), PHKG1 and PHKG2 (subunit γ) expressed in the liver. • CALM1, CALM2, and CALM3 (subunit δ).

The α and β subunits govern phosphorylation and account for four-fifths of the holoenzyme's total weight. In the α and β subunits, the phosphorylation of the Ser residues is controlled by the cAMP-dependent protein kinase. Calmodulin is bound by the calcium-binding subunit δ, and there is a catalytic site in the γ subunit (15).

Type IX is unique among GSDs in that it is recessively transmitted via the X-chromosome, with the α1 subunit being X-linked and the other subunit units being AR inherited. For GSD IX, the most prevalent genetic mutation is a PHKA2 gene mutation (16).

- **GSD type III and VI**

A loss of activity in a glycogenolysis-critical enzyme called amylo-1,6 glucosidase + transferase (GDE) results in type III GSD. There are two subtypes of GSD III, namely hepatic-muscle type (subtype a) and hepatic type (subtype b), which are distinguished by the extra involvement of the heart and skeletal muscles. The AGL gene, which is situated on chromosome 1p21 (17), is mutated, and the condition is transmitted in an autosomal recessive manner, much like all other GSDs except type IX-α.

While hypoglycemia (neurohyglycemia) is uncommon, the disease's first symptoms—an enlarged liver and stunted physical development—appear in early infancy. Reversal of hepatomegaly and delayed progression of subtype IIIa muscular weakening occur with advancing age. Cardiomyopathy and muscular hypotension are further hallmarks of this GSD subtype. With the exception of very rare instances involving cirrhosis of the liver or myopathy, symptoms often improve throughout adolescence (18).

A minor variant of GSD is Type VI. Decreased activity of the glycogenolysis-involved liver enzyme phosphorylase makes up the enzyme block. Mutations in the PYGL gene on chromosome 14q21-q22 cause the autosomal recessive inheritance of the illness. The symptoms are identical to those of type III. Rarely do patients with this form of GSD get liver adenomas, and neither the heart nor the skeletal muscles are ever affected. Organ failure is not a concern associated with the condition (19).

- **GSD type IV**

Type IV glycogenosis is very uncommon and severe, making up just around 3% of cases. Autosomal recessive inheritance, a mutation in the GBE1 gene on chromosome 3p12, and decreased glycogen brancher enzyme (GBE) activity make up the enzyme deficiency. The buildup of aberrant glycogen structures resembling amylopectin (polyglucosan body) is the consequence of GBE

deficiency. A second term for it is adult polyglucosan body disease (APBD) (20).

Liver and neuromuscular system symptoms are among the many different types. Hepatomegaly, hypotonia, and delayed psycho-motor development manifest in infants as early as the first few months of life, despite the fact that most children are born healthy. The illness is moving at a breakneck pace. It causes portal hypertension and liver fibrosis, the latter of which causes ascites and, ultimately, mortality. But there are a number of reports in the literature with hepatic GSD IV that is not accessible (21).

- **GSD type I**

Livers, in contrast to muscles, have the membrane enzyme glucose-6-phosphatase, which controls the concentration of glucose in the blood by removing the phosphate residue before it enters the circulation (22).

As a last stage in glycogenolysis and gluconeogenesis, the hydrolysis of glucose-6-phosphate to glucose is catalyzed by the glucose-6-phosphatase 1 (G6PC) enzyme (23).

There is an inherited pattern of mutations affecting the G6PC enzyme, which is encoded by the G6pc gene and expressed in the pancreas, kidneys, and liver (24). The enzyme can't accomplish its job until it crosses the endoplasmic reticulum membrane. Along with this mechanism, the SLC37A4 gene encodes another enzyme called G6PC translocase. This gene may be altered (AR inheritance) to decrease neutrophil function, as shown in GSD type Ib (25). The level of glucose in the blood increases after a meal. The concentrations of the hormone's glucagon and insulin, which control these metabolic pathways, are inversely proportional (26). In such case, glycogen is not broken down. Inactive phosphorylase (b) cannot undergo phosphorylation and so cannot become active phosphorylase (a). Conversely, the process of phosphorylation from active (a) to inactive (b) synthase is initiated. Glucagon, an adrenaline-like hormone, has an increasing tendency just before meals, when insulin levels decrease and blood glucose levels decline. The process of glycogen breakdown in response to glucose has begun. A functional glycogen phosphorylase (a) and a dormant glycogen synthase (b) were isolated (27).

- **Clinical symptoms**

Hypoglycemia and hepatomegaly are the hallmark clinical signs shared by all forms of hepatic GSD. muscular GSDs are characterized by a steady deterioration of muscular function, which might manifest as weakness during physical activity. Metabolic acidosis is detected in blood biochemistry as hyperlipidemia and hypercholesterolemia (28).

Hypertransaminasemia, or an increase in the activity of certain liver enzymes called aminotransferases, is a feature of both forms of GSDs. Common clinical manifestations include a lag in physical development, most often shown as a lack of height or delayed motor skills. The clinical manifestations of GSDs vary greatly from one type to another since these disorders are a collection of diverse hereditary conditions (29).

- **Diagnosis**

Clinical symptoms and indicators associated with hypoglycemia and hepatomegaly are used to diagnose GSD. Hypertransaminasemia, an elevated blood cholesterol and triglyceride level, an elevated lactate level (in GSD type I), and other laboratory indicators aid in the development of a diagnosis (30). Classifying GSD into type I and so-called ketotic types (III/VI/IX) is crucial. Most cases of GSD I manifest in the early months of infancy, and the symptoms include acute hypoglycemia within three to four hours after eating. Patients with GSD III/VI/IX often have milder hypoglycemia because their gluconeogenesis mechanism is intact (31).

In GSD I, blood lactate levels rise quickly when blood glucose (BG) concentrations fall below the levels that ordinarily cause a counter-regulatory response, which is about 70 mg/dl or 4 mmol/l. When BG levels drop below 40-50 mg/dl or 2.2-2.8 mmol/l, there is a significant increase in blood lactate levels. Unlike GSD 0, III, VI, and IX, which are characterized by severe hyperketonemia with fasting hypoglycemia (32, 33), GSD I only shows a small rise in blood β-hydroxybutyrate levels.

Increased uric acid and lactate levels in GSD I, in contrast to normally occurring levels in ketotic GSDs, are further biochemical features that aid in differentiating these illnesses (34).

Always, molecular testing establishes or confirm the final diagnosis. Genetic testing, which does not involve intrusive procedures and provides a definitive diagnosis, has surpassed liver biopsy as the preferred method of evaluating hepatocyte enzymatic activity. Still expensive, inconvenient, and taking a long time to get findings are some of the drawbacks of molecular testing (35).

complications

Various difficulties may arise from GSDs, depending on:

• On the off chance that your diagnosis is postponed.

• If it isn't maintained consistently well.

As an example, potential outcomes of untreated GSD type 1 comprise: Decreased bone mass, bone fractures, and osteoporosis.

Postponed adolescence.

Painful arthritis.

Kidney illness.

High blood pressure in the lungs.

Hepatic adenomas are tumors of the liver that are not malignant.

"PCOS" stands for polycystic ovarian syndrome.

Gut inflammation.

Recurring bouts of low blood sugar cause changes in brain function.

The danger of hepatocellular cancer, heart problems, hepatic adenomas, renal failure, and nephrolithiasis are all long-term consequences that may still occur.

Dietary management

To prevent hypoglycemia, nutritional therapy is the goal. Patients must eat raw cornstarch (RS) with each meal during the day (every 3 to 4 hours) and take an extra serving of RS in the middle of the night to keep the night break at bay (36).

A polysaccharide, starch prolongs the time it takes for the body to release pure glucose into the circulation, much like glycogen. This limits its storage in tissues and involves glycogen, since substrates are always accessible to the metabolic activities of energy production pathways (37).

A snack before bedtime provides enough energy and glucose for individuals with GSD type III, VI, or IX, according to studies. To avoid morning hypoglycemia, however, patients with ketosis or an unstable glucose level should prepare 2 grams of unprocessed RS per kilogram of body weight. Patients with type I GSD have a different story; they have the worst cases of hypoglycemia and the most unpredictable glucose levels; they also have defective glycogenolysis and gluconeogenesis, as well as inadequate ketogenesis and the possibility of neuroglycopenia. (38) Hence, type I starch is more of a medicine than a nutritional supplement in GSD; it has to be taken at regular intervals throughout the day, every three to four hours, with a night gap of no more than seven or eight hours. In order to prevent the potentially fatal consequences of hypoglycemia, patients with decompensated glycemia should take an additional starch dosage at night and have a steady supply of carbs in liquid form on hand, particularly while they sleep (39).

A nasogastric tube or percutaneous endoscopic gastrostomy (PEG) may be necessary to sustain the enteral supply for more than 6-8 weeks in cases when RS is either intoleranced or reluctantly administered (40). Starch is indigestible, which is a drawback; supplementing with starch might aggravate gastrointestinal infections un infants with glycogenosis (41). Blood glucose measurement with a glucometer is an essential part in treating hypoglycemia and RS, as is monitoring the kid. In the case of GSD III/VI/IX, it is also necessary to quantify ketones in the urine (42). A modified, artificially made starch called "Glycosade" may be given to these kinds and type Ia. Its delayed release ensures that normoglycemia can be maintained over an 8-hour nightly rest. Patients with type Ib should not take it because they often have inflammatory bowel illness, which further hinders its absorption (43). Anyone above the age of five may utilize the formula. Glycosade is now undergoing daytime administration studies in the US. Adults may benefit from the extended-release formulation during the day as well as at night since their metabolism is slower than children's. The current US dietary recommendations state that all GSDs should limit their sugar intake to less than 5-10 g per meal, with type I GSDs being the most severely restricted. Type I GSDs should take RS supplements every three to four hours, with an additional dose given at night, and other types should take only one night dose (44).

Following the so-called high-protein diet is advised for Type III, Type VI, and Type IX (GSD type III: 3-4 g/kg BW, VI and IX: 2-3 g protein per kilogram BW daily). It is also advised to take multivitamins and vitamin D3 supplements due to the higher risk of micronutrient deficiencies, such as osteopenia, calcium-phosphate abnormalities, and vitamin D3 deficiency. Therefore, a diet high in complex carbs should have simple sugars limited as a therapy strategy. A metabolic dietician, the patient, his family, and the patient's current biochemical results (metabolic equilibrium) and anthropometric measurements are all used to create a personalized meal plan for each patient (45).

- **Gene therapy**

Following the success of early-stage clinical trials of gene therapy in hemophilia, the development of adeno-associated virus (AAV) vector-mediated gene therapy for GSD type I is now underway in the USA. So far, animal models of GSD Ia have shown efficacy for AAV vectors harboring a human G6Pase regulatory cassette/promoter. These vectors include sequence components that correctly control G6Pase expression (46).

Conclusion

Patients with glycogen storage disorders are now able to enjoy longer and better quality of life because to advances in treatment and a deeper knowledge of the biochemical abnormalities that cause these conditions.

These metabolic abnormalities are particularly difficult to treat, but gene therapy might soon be an option thanks to recent breakthroughs in molecular biology.

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