Glycogen Storage Disease: A Guide for Families

What are glycogen storage diseases?

Glycogen storage diseases (or GSDs), as the name suggests, are a group of conditions caused by an inability to store or release glycogen in the liver or muscle. Glycogen is made from joining multiple glucose (or sugar) molecules together. In order to save extra glucose eaten during a meal, liver and muscle make and store glycogen to be used later. During fasting, glycogen in the liver can be broken down to glucose and released into the blood. Breakdown of glycogen in the liver is important to prevent blood glucose levels from becoming too low (called hypoglycemia) during times of fasting in between meals or overnight. Glycogen stored in the muscle can be broken down to glucose but can only be used by muscle for energy and is not released into the blood.

What causes glycogen storage diseases?

Glycogen storage diseases are inherited conditions. Usually neither parent has the disease but can pass it on to their children. In the liver and muscle cells there is machinery, called enzymes, which help the cell make and release glycogen. GSDs are caused by differences, or mutations in the genes that make the enzymes involved in glycogen production and breakdown. These mutations make the enzymes work less well and, as a result, the liver and/or the muscle cannot properly store or break down glycogen. Mutations can have different severities: mild mutations result in milder enzyme problems and milder disease while more severe mutations result in more severe enzyme problems and disease.

What are the symptoms of glycogen storage diseases?

Though they are all grouped together as GSDs, liver GSDs and muscle GSDs have very different problems and symptoms. Some of the enzymes involved in glycogen production and breakdown are the same in liver and muscle and some are different. If the problem or mutation is in an enzyme present in both the liver and the muscle, then the individuals may have symptoms of both liver and muscle GSD.

If the mutation is in a liver enzyme, then the individual may have hypoglycemia (low blood sugar) between meals or when fasting overnight. Symptoms of hypoglycemia include feeling irritable, tired, shaky, nauseated, hungry, or sweaty. Because the liver cannot release glucose during fasting, these individuals will break down fat into a fuel source called ketones more quickly than other people. Ketones can be used by some tissues in the body for energy, but high levels of ketones can cause acid buildup in the blood, causing nausea and fatigue. If a child with GSD has frequent episodes of hypoglycemia and high ketone levels, he or she will not gain weight or grow well. If the problem involves breakdown of liver glycogen, the individual will have an enlarged liver, called hepatomegaly, due to excess glycogen stores that cannot be broken down.

If the mutation is in a muscle enzyme, then the individual may have muscle weakness or difficulty exercising. In addition, they can have cardiac problems as heart muscle stores and breaks down glycogen to use for energy.

What are the different types of glycogen storage diseases?

There are 5 different types of liver GSDs that result in hypoglycemia and are treated by pediatric endocrinologists.

- **Type I**: is also called von Gierke disease. This is the most common GSD and results from mutations in an enzyme called glucose-6-phosphatase, which helps breakdown glycogen in the liver. Individuals with GSD type I can have hypoglycemia and high ketone levels after several hours of fasting. Their liver can partially break down glycogen but cannot release glucose into the blood. The trapped glucose gets converted into lactate, which can be released into the blood and cause lactic acidosis, causing the individual to become ill. The fasting hypoglycemia caused by GSD type I is usually more severe than that of other GSDs. These individuals have very large livers because the glycogen is stored but cannot be broken down. As children, they can have poor growth or developmental delays as a consequence of the frequent hypoglycemia, high ketone levels and lactic acidosis. Children with Type 1b can be at higher risk for infections and colitis (inflammation in the intestines).

- **Type 0a**: is caused by mutations in an enzyme called glycogen synthase 2, which helps produce glycogen in the liver. These individuals have fasting hypoglycemia, poor growth and developmental delays, but do not have large livers as they cannot produce glycogen. Some individuals can have a mild form of this disease.

- **Type III**: is also called Cori's disease. This is caused by mutations in an enzyme called glycogen debrancher, which helps break down glycogen in the liver. These individuals have fasting hypoglycemia, an enlarged liver, poor growth and developmental delays. This enzyme also helps break down glycogen in the muscle, so some

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individuals may also have muscle weakness, difficulty exercising or heart problems. The treatment for GSD III is a little different than for GSD 1 as these children need to eat a lot of protein in addition to carbohydrates

- **Type VI**: is also called Hers disease. This is caused by mutations in an enzyme called glycogen phosphorylase, which helps breakdown glycogen in the liver. These individuals have fasting hypoglycemia, an enlarged liver and poor growth, though this tends to be milder than GSD Type I or III. Some children with type VI will not have large livers and may be incorrectly diagnosed with ketotic hypoglycemia

- **Type IX**: is caused by mutations in an enzyme called glycogen phosphorylase kinase, which helps breakdown glycogen in the liver. This condition is very similar to GSD Type VI and usually causes mild fasting hypoglycemia, an enlarged liver and poor growth. Like type VI they may also be diagnosed as having ketotic hypoglycemia as they too may not have enlarged livers. This condition is more common in boys as it is passed from mothers to their sons because the gene is on the X chromosome

There are several types of muscle GSDs, each of which is very rare.

- **Type IV**: is also called Andersen disease. This is caused by mutations in an enzyme called glycogen branching enzyme, which helps produce glycogen in muscle and liver. Individuals can have a wide range of severity of symptoms, largely nerve and muscle problems, an enlarged liver, liver failure and poor growth.

- **Type V**: is also called McArdle disease. This is caused by mutations in an enzyme called muscle phosphorylase, which helps break down glycogen in muscle. Individuals have muscle weakness, especially with exercise.

- **Type VII**: is also called Tauri disease. This is caused by mutations in an enzyme called phosphofructokinase, which helps produce glycogen in muscle. Individuals have muscle weakness, especially with exercise.

- **Type II**: is also called Pompe disease. This was originally included as a glycogen storage disease, but has since been classified as another type of disorder called a lysosomal storage disease. It is caused by mutations in an enzyme called lysosomal acid maltase and results in heart dysfunction, muscle weakness and difficulty exercising.

How are glycogen storage diseases diagnosed?

Liver GSDs are most commonly diagnosed when a child is growing poorly or not gaining weight and has an enlarged liver. In addition, they can be diagnosed if a child has an episode of hypoglycemia and elevated ketone levels. Muscle GSDs are usually diagnosed when a child is discovered to have heart problems, muscle weakness or difficulty exercising.

While GSDs used to be diagnosed by taking a small sample of the individual's liver or muscle (called a biopsy), they are now diagnosed by genetic testing. Using a blood sample, the genes that make the enzymes responsible for GSDs can be tested for mutations.

How are glycogen storage diseases treated?

For those children with liver GSDs with hypoglycemia, the most important goal of treatment is to prevent hypoglycemia and elevated ketone levels. Infants and younger children require frequent feedings, and some may require continuous feeds or glucose-containing fluids through a feeding tube. Uncooked cornstarch is a long-acting source of carbohydrates which can be given several times a day and overnight when children get older and go longer between feeds. Other medicines may be used to treat liver problems. When children with liver GSDs get sick, they are at increased risk of hypoglycemia, elevated ketones and lactic acidosis (if they have GSD Type I), and may have to be admitted to the hospital for intravenous (IV) glucose-containing fluids. While there is no specific treatment for many muscle GSDs, avoiding intense exercise to prevent muscle fatigue may be necessary.

How can I learn more about glycogen storage diseases?

There are multiple excellent patient and parent advocacy groups for patients with glycogen storage disease, including The Association for Glycogen Storage Disease (www.agsdus.org) and The Children's Fund for Glycogen Storage Disease Research (www.curegsd.org).

PES Pediatric Endocrine Society