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Glycogen Storage Disease type 1

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Glycogen storage disease type 1(GSD1) is a rare autosomal recessive disease that affects the bodies natural way to break down stored glycogen in the body. This can cause great concern since the body relies on the breakdown of glycogen for stabilizing blood glucose levels. There are many issues that can arise when looking the body can not utilize stored glycogen such as, hypoglycemia, seizures, kidney and liver issues, bio markers such as lipid levels.

Glycogen storage disease can be broken down into many different forms, however the focus is glycogen storage disease type 1. As previously mentioned, GSD is an extremely rare disease, only occurring in about 1/100,000 people. (Parikh, Ahlawat, 2023). There are 2 distinct types of GSD1, type 1a, and type 1b, we will discuss the variation between the two later on, but we do know that 80% of people who are diagnosed with GSD1 are type 1a and the other 20% is type 1b (Parikh, Ahlawat, 2023). The Ashkenazi Jewish people do have a 5-time greater prevalence compared to the rest of the population. (Parikh, Ahlawat, 2023). The Ashkenazi Jewish people have an historic region of living in the Rhineland valley which is a region near France.

Depending on what type you have is what enzyme you are deficient in. GSD1a when the body lacks the ability to produce glucose-6-phosphatase (G6pase) (Parikh, Ahlawat, 2023). G6pase has an extremely important role within the body, it is mostly found within the liver and kidneys. (Van Schaftingen, Gerin, 2002). The major role that this enzyme provides is when a fasting or starvation stage occurs the enzymes breaks down the stored glycogen within the liver to be released into the blood stream to maintain equilibrium for the body. There are two main system in which G6pase plays a

role in, gluconeogenesis, (Van Schaftingen, Gerin, 2002) this is a process that allows the body to produce glucose from other sources when glycogen levels are low, such as glycerol, lactate, pyruvate, and glycogenic amino acids. In the final step of gluconeogenesis g6pase attacks glucose-6-phosphate which releases the phosphate group and allows the glucose to reach out of the cells. The other main system that g6pase plays a role in is Glycogenolysis. If someone experiences GSD1b then there is a different enzyme that their body is deficient in. GSD1b individuals lack the ability to produce glucose-6-phosphate translocase (G6PT). The primary function of G6PT is to transport glucose-6-phosphate from the cytoplasm of the cell and send it to lumen of the endoplasmic reticulum (ER). Once glucose-6-phosphate reaches the Er it undergoes hydrolysis and becomes glucose then is able to reach into circulation. Either diagnosis someone gets, wether it is type 1a or type 1b, the body lacks a specific enzyme that makes it impossible for the body to breakdown glycogen to glucose for the body.

With an understanding the importance of the the enzymes we addressed is to the role of creating and maintaining glucose, we need to address the underlying reason why the body can't produce the enzymes that are needed. GSD 1a results from a mutation in the G6PC gene on chromosomes 17q21, this encodes for the catalytic subunit to produce the enzyme. (Parikh, Ahlawat, 2023). For GSD1b we see that the mutation occurs on the gene SLC37A4 which is on the chromosome 11q23. (Parikh,Ahlawat, 2023). To determine which diagnosis is appropriate for the individual a liver biopsy would be an option, however, theres a number of reasons why that would not be the first options, some of those reasons include, they are invasive, expensive, as well as the

majority of individuals diagnosed are between the ages of 3-6 months of age. (Parikh, Ahlawat, 2023). Genetic testing is what is used to ensure the correct diagnosis is made.

Glycogen storage disease has many different types of conditions with other enzymes that are deficient within the body. There are at least 19 different types of variations that are known to medicine. (Cleveland Clinic n.d). With so many variations of this disease with all of them being considered rare makes it difficult to address the treatment of this disease. While other variations do have options like enzyme replacement therapy like glycogen storage disease type 2. However, GSD1 does not have any pharmaceutical treatments that present to aid individuals with this disease. Someone who is diagnosed GSD1 it is importantly to properly focus on nutrition for their treatment. However, the pharmaceutical company Moderna is running a phase 1 clinical trial specifically for individuals with GSD1a. Moderna is using new technology called mRNA-3745. Messenger ribonucleic acid is a molecule that acts as an instruction guide, it helps sends information to the cells. The goal for the research is to see if mRNA-3745 has ability to reverse the bodies' ability to produce the enzyme needed to breakdown glycogen (Moderna n.d). There are currently 45 individuals enrolled and the trial has been running since June 2022 and is expected to continue until December 2028. So not much has come out of the research as of now but positive future may be on the way for individuals with this disorder.

As of now, nutrition is the only current course of an action a person can take when treating GSD1. It is extremely crucial that the parent is educated on proper nutrition care for their child. Nutritional concerns for someone with GSD1 are present that needed to be addressed. People with this condition strongly need to avoid sucrose,

fructose, and galactose, as it has been shown to elevated lactate concentration and acidosis. (Ross et al., 2020). Typically, your kidney and liver clear excess lactate in the body, but the fructose, sucrose, and galactose cause the kidney and liver to not be able to keep up with the demand. This can suppress your cardiac output and cause organ failure, so it is extremely important to be aware of the food the patient needs to avoid. So, avoiding the carbohydrate fructose will probably be the easiest for anyone to point out, you have to eliminate majority if not all fruit from the diet. Fructose is extremely prevalent within fruit. Some other sources to avoid would be honey and sugar cane. Galactose is also an easy source to identify, all dairy products must be avoided as well with fruit. It is best to avoid products with added sugars as well. It is worth pointing out the patient or parent that vegetable is a viable option that should not be a concern since they are relatively low in carbohydrates and high in fiber, it is crucial they understand common foods like tomatoes, peppers, and avacados are actually not vegetables and are fruits. Overall people with GSD1 best source of carbohydrates need to come from complex carbohydrate sources. (Ross et al, 2020). Complex carbohydrates would come from whole grain products like brown rice, wheat bread, potatoes, whole grain pasta etc…

With understanding what foods are acceptable and needed to be avoided then can be addressed the nutritional concerns that will come with that. The first concern, is the quality of life, this condition requires the patient, if old enough, or the parents to be extremely mindful of what is being consumed. On top of that it is extremely restrictive diet which can be mentally taxing for some individuals. Another concern comes from this diet is the lack of calcium since dairy must be avoided, as well as a good source of

protein for younger people who tend to be pickier when comes to eating new foods. Avoiding food like fruit is extremely unfortunate for any person at any stage of life, fruits of extremely high in vitamins, minerals, fiber, and antioxidants, as well as providing unique nutrients called polyphenols. Eating a diet with a variety of vegetables, legumes, nuts, and whole grains can help make up for missing out on fruits and dairy, however, it can not fully replace those food groups. As of now, the best recommendation is to supplement these losses, more specifically, supplementing with a multivitamin that is 100% sugar free, a calcium supplement paired with vitamin d. Some doctors may want to add more supplements to the routine but that what is recommended to start. And to assure the supplement is high quality and not tainted with any substance that may be harmful to an individual's health, make sure the supplement is 3rd party test. Supplement that has been 3rd party tested will usually have a stamp on their bottle such as, NSF, USP, these are well trusted companies, and it is illegal for a company to falsely put those stamps on their product.

It is crucial to understand what to look out for some of the signs of symptoms of GSD1 and why it is important to follow this diet so closely. The main goal that diet therapy is treating the prevention of hypoglycemia that is what is most important, hypoglycemia can be seen shortly after birth, the symptoms of this are tremors, convulsions paleness, sweating, and death. (Ozen, 2007). Another common sign is that the infant will experience failure to thrive and want to feed as frequent, they will experience illness and that is when usually the diagnosis is discovered when the child is taking into the healthcare setting. Older infant may expeirence lethargic behavior, slow growth, and extreme hunger. (Ozen 2007). In middle childhood there is a chance that a

child can experience rickets. Rickets is a disease that is preventable and reversible but can have lastly damage, it is when a child does not have enough intake of vitamin d, low calcium levels and increase the affects of low vitamin d. Rickets causes the bones to become soft, which can cause them to bend, if not treated they can become permanently morphed. GSD1a and GSD1b share very similar signs and symptoms but there is one major difference that affects GSD1b only, as of right now, the research is unsure of why, however, individuals with GSD1b experience neutropenia. (Ozen, 2007). Neutropenia is a condition where the body has a low number of neutrophils which are the most abundant form of white blood cells, this means that people who are GSD1b have higher risk of infections which plays a role when considering inserting a feeding device.

When following this diet and lifestyle changes, we tend to focus on the blood glucose level to avoid hypoglycemia and prevent brain damage, coma, or even death. (Ozen, 2007). However, there are risk that needed to be kept in check. One of these labs values that needs to be checked is hyperuricemia, this is when blood serum levels of Uris acid levels are high. Hyperuricemia can cause to joint pain, specifically in your ankles and big toe, better known as gout. Another concern is kidney stones, there are many ways to treat this through diet and medication, typically GSD1 individuals will be prescribed medication to treat the condition, example would be Allopurinol (Ozen, 2007)

The first time GSD was “discovered” in the scientific world was 1939 when a case study looked at a child that was experiencing from low blood glucose and was administered IV galactose and did not respond. The next time a progression for GSD was made in 1956 when an individual ingested fructose and their lactate levels

increased. This is when practitioners began to make the connection that these sugars required effort from the levels to digest. (Ross el al, 2020). Since then, there has been some discovers and standards set, however, since it is such a rare disease there still needs to be more information updated, however, we do have enough information to make suggestion and help patients with GSD1. To start, calories, there is no specific recommendation as far as formula, however, it is critically that we do the best to protect the liver, it is important that individuals with GSD1 do not eat more calories than needed, to prevent weight gain, metabolic stress, increase lipid levels, and Increased glycogen levels. Excess energy will be converted to fat and glycogen. (Ross el al, 2020). The gold standard within the hospital setting for calorie measurement is indirect calorimetry. If that is not an option, it would be best to do Mifflin St Jeor equation. The Academy of Dietetics and Nutriton recommend protein be 10%-15% of your total calories. (Goldberg, Slonim, 1993). Lipids should be typically around 20%-25% of total calories. Typically, carbohydrates will be 65% of total calories. (Goldberg, Slonim, 1993). When treating an individual in the hospital they should have a medical alert bracelet, as well as monitoring their blood glucose. Hypoglycemia should be treated right away with a fast-acting glucose source.

One of the main standards that has been set for the treatment of GSD1 has been the introduction of corn starch. In 1970 there was a need for a carbohydrate source that was slow release that helped maintain the glucose concentration for more than 3 hours. (Ross el al, 2020). Researchers tested many of the starches and carbohydrates sources that they could think of and none of them achieved the goal of maintaining blood glucose for more than 3 hours. Out of all the starches were tested they found that corn

starch not only did the best at maintaining blood glucose for 3 hours but also came with other unique benefits. Corn starch achieved the best insulin response out of all the starches tested, this means that less was needed to achieve a balance glucose level compared to the other sources. (Ross el al, 2020). Cornstarch also has a unique benefit in that it acts a neuroprotective agent.

The current recommendation for administration of corn starch is ever 3 to 4 hours, young children need about 1.6 grams per kilogram of body weight. Older children, young adults, and adults, need about 1.7-2.5 grams of cornstarch per kilogram of body weight. (Parikh, Ahlawat, 2023). It was previously mentioned how it is typical for young infants to get diagnosed and one of the symptoms was, low feed, and lack of sleep. When infants are finally diagnosed the first step in treatment is to introduce the infant to a soy based, sugar free formula and this should be administered ever 2 to 3 hours. (Parikh, Ahlawat, 2023). Doing this will allow the infant to begin experiencing better sleeping habits, however, the infant can not sleep through out the night and not experience hypoglycemia. This is where the physician will educate parents on the options of doing a nasogastric tube or surgically inserting a G-tube. This prevents the child from being woken up from its sleep and allows parents to feed the child if they are not hunger or not feeling well. (Parikh, Ahlawat, 2023).

GSD1 Laboratory values that should be monitored within a hospital setting are, Urine Lactate/ Creatinine ratio less than 0.06 mmol/mmol, Serum Uric acid concentration, serum triglyceride concentration less than 6 mmol/L, BMI within a normal range (Parikh, Ahlawat, 2023). When the patient goes for a routine check up the blood pressure should be checked often since GSD1 paitents are known for high blood

pressure and high lipid levels. Serum Creatinine levels will be checked every 3-6 months to monitor kidney functions. If kidney function continues to be worsened indicated by microalbuminuria levels then the patient should treated with angiotensin-converting enzyme inhibitor. (Parikh, Ahlawat, 2023.)

The understanding of GSD1 is still developing and new ideas will come and improvements will be made. A person who is able to be following the recommendation that have been placed forward have an opportunity to live well into adult hood. This once fatal rare disease would be deadly for many people without the proper knowledge, who would think that eating fruit could kill you. The data is still unsure wether not an individual can live a long healthy life; however, we do have strong data that supports that infants under the proper care can confidently make into adulthood. The issue that GSD1 has is that it not just managing the blood sugar levels. All the other issues that threaten the liver, kidney, heart, brain, etc.. all become more taxing on the body as an individual ages. But as far as the main treatment goes for GSD1 which is blood sugar control the best method we have is the consumption of complex carbohydrates and dosing corn starch every 3-4 hours at 1.6 grams per kilogram of body weight if it is a child to 1.7-2.5 grams if it is an adult.

While there may not be a cure just yet to the problem individuals have with GSD1 we have strong data that can help people reach well into adult hood. However, there are some major restrictions that need to monitored like the restriction of consumption of fructose and galactose. Those two sources of do not get utilized by the kidney and just get stored in the liver, that does not do any good for a person with GSD1, matter of fact it can only do harm. So, understanding which foods are high in fructose and galactose

are extremely important. An individual who is trying to manage their blood glucose should be consuming 60-70% of their total calories from complex carbohydrates, this includes, brown rice, whole grain bread, pasta, and oats. To compensate for the lack of fruit and dairy in one's diet, it is recommended to consume a non sugary multivitamin, while also taking a calcium vitamin d supplement.

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