Glycogen Storage Diseases

The Patient-Parent Handbook
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Chapter 1
The Biochemistry of Glycogen Storage Disease

The underlying problem in all of the glycogen storage diseases is the use and storage of glycogen. Glycogen is a complex material composed of glucose molecules linked together.

HOW THE BODY STORES GLUCOSE AS GLYCOGEN

Glucose is a basic sugar (see Figure 1). It is an important source of energy for the body and is the main transport form of energy in the blood stream. The body usually keeps the level of glucose in the blood within a narrow range of concentrations: 60-100 units (mg per deciliters). To regulate the level of glucose so tightly, the body must be able to perform some rather complex biochemical reactions. This is because we consume food periodically, the type of food we eat varies, and we use energy in an equally irregular manner.

Figure 1

After we eat, the glucose in our food that is not needed immediately by the body is stored in the liver and muscle as glycogen. Glycogen is simply a large molecule made of many glucose molecules linked together in a chain-like fashion with many branches off the long chains (see Figure 2). Think of glycogen as a tree. The branches are very important because they make the glycogen much more soluble in the body. (Plants store glucose as starch; starch is very much like glycogen except it lacks the branch points; most of you know how difficult it is to get starch into solution!).
The glycogen thus stored serves as a reservoir for glucose when the body’s blood sugar drops below normal, or when the muscle exercises vigorously and needs more instantaneous energy. The body sends signals (hormones in the blood) to tell the liver that the stored glycogen is needed for glucose (see Figure 3). When the glycogen is broken down, it is released as glucose into the blood. In some of the glycogen storage diseases (but not all) maintaining the blood glucose levels is a very central and major problem.

Let’s look at how blood glucose levels are kept constant. We get glucose in our diet in many ways; common table sugar, sucrose (a disaccharide, two sugar molecules hooked together), is broken down in the intestine to one molecule of glucose and one of fructose (a similar sugar). Starches in our diet are broken down by enzymes to glucose; these sugars are taken into the body by the intestine and then carried by the portal vein to the liver where the sugars are largely
handled. They are either sent to the body tissues (if needed) or stored, depending on the body's needs.

After we eat a meal, a hormone called insulin is released from the pancreas (an organ near the stomach). Insulin enters the blood stream and exerts its effects by reducing high blood glucose levels. Insulin causes glucose to be taken up by tissues and glycogen to be stored in the liver (in normal persons, insulin cannot cause the accumulation of 'excessive' amounts of glycogen as the body's regulatory systems see to that). The accumulation by the liver consists of the actual combining of glycogen molecules. Figure 4 illustrates the key chemical reactions in the formation of glycogen from dietary glucose.

Figure 4

Glucose is first changed to glucose-6-phosphate (G6P); the 6 refers to the position on the glucose molecule to which the phosphorus (P) is attached. The next step in the sequence is the movement of the phosphorus to the 1 position. Although they sound similar, there is a world of difference to the body between the 1 and 6 position in glucose. Uridine diphosphoglucose (UDP glucose) is produced from G1P by the addition of a uridine diphosphate molecule. Once a molecule of glucose is converted to UDP it can begin the intricate process of building the glycogen molecule.

Each of the reactions glucose → G6P → G1P → UDPG requires a different enzyme. Enzymes are protein molecules which help chemical reactions to occur in the body without changing themselves. They usually are written above a chemical reaction like this:

enzyme
A →B →C →D

The enzyme itself is unchanged by the reaction.
Back to Figure 4; once UDP glucose is formed the glucose molecules are linked together in a chain-like fashion with the help of the enzyme glycogen synthetase. As the chains become longer, an important enzyme enters the picture. About every 8 to 10 links, the brancher enzyme produces a branch point. This branch point is between the 1-6 linkages of glucose molecules.

HOW THE BODY BREAKS DOWN GLYCOGEN INTO GLUCOSE

When a person is fasting and the blood glucose levels start to fall, glycogen is broken down or modified to release glucose into the blood. Various enzyme are involved in this process. The long straight portions of glycogen (the 1,4 linkages) are broken by the enzyme, phosphorylase, in its active form to release glucose-1-phosphate (G1P). G1P can then be converted to glucose by the action of other enzymes including glucose-6-phosphatase. When phosphorylase breaks down glycogen and nears a branch point (a 1,6 linkage), a special enzyme called debranching enzyme is needed to break this branch. Debranching enzyme releases free glucose. After the debrancher has worked, phosphorylase (active) can again break down the linear (straight or non-branched) portions of glycogen. If there is no debrancher enzyme, the glycogen molecule is trimmed off so it has short outer branches called limit dextrin (like a tree with its branches clipped short).

If any of the enzymes or transport proteins involved in the storage or breakdown of glycogen does not work correctly, too much glycogen, or abnormal forms of glycogen, can accumulate in the tissues of the body and cause damage. As liver and muscle are the main stores of glycogen in the body, these conditions most often affect liver, muscle or both. Low blood sugar levels (hypoglycemia) can also occur, particularly when the liver is affected. This is the basis of GSD.

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Chapter 2
Important Terms

It is well known that medicine has a language of its own. To understand much of what is written and discussed about your child or yourself, you will need to know a few basic terms.

A very important concept is heredity. All of the glycogen storage diseases are inherited, that is, they are genetically determined. They do not result from any action of the parents, but they are encoded in the parents’ genes. They are passed on to children as a part of their makeup.

Every human being has 46 chromosomes, consisting of 23 pairs. They reside in the center (the nucleus) of the cell. Half of these chromosomes come from the mother and half from the father. The germ cells, that is the sperm cell and the egg, have only ½ of each person’s chromosomes, one member of each of the 23 pairs. The chromosomes are rather “big,” in that they can be seen under the light microscope with special stains.

Located on the chromosomes are the genes (see Figure 5). The genes are very small and cannot be seen with the microscope. Humans have about 100,000 genes arranged on these 23 chromosomes. The gene is the basic biological information unit in which characteristics are passed on to a child, such as hair color, eye color, ultimate height potential. Genes code for all the enzyme proteins in the body, including those involved in glycogen synthesis and degradation. One of the 23 pairs of chromosomes is a special pair, the sex chromosomes. These 2 chromosomes (one pair) carry the important genes which determine whether the child is male or female.

Figure 5

As mentioned, the germ cells each have one member of each chromosome pair. The distribution of the chromosomes, when chromosomes divide, is random. This segregation is necessary to form the germ cells. When the sperm and the egg unite at conception, the maternal chromosomes join with the paternal chromosomes and a typical human cell with 23 pairs or 46 chromosomes is formed (see Figure 6).
A remarkable feature of human biology is that each enzyme, except those that are located on the sex chromosomes, which are not “matched,” are duplicated; that is, there is a spare copy for every enzyme protein. If there is a defective gene on one chromosome, the partner on the other chromosome makes the protein. Although the protein may be in reduced amounts, it is usually more than adequate. In this situation, each parent is a carrier and their genetic make-up for GSD is called heterozygous. Each of us is a carrier or heterozygote for at least 6 or 7 serious defects, but we usually never know this unless we by unlikely chance mate with someone who is deficient in exactly the same gene. In this situation an off-spring can be produced who is deficient in both genes on both chromosomes and can make no active enzyme.

All but one of the glycogen storage diseases are transmitted from generation to generation in an autosomal recessive fashion. Autosomal is the name given to all the chromosomes except the sex chromosomes. Recessive means that both members of a chromosomal pair must carry the gene for the disease to be manifested, as in the manner which was discussed above.

Figure 7 diagrams such an autosomal recessive pattern of heredity. The mother in this case has one gene that is defective (this is indicated by the half black circle). The gene on the paired chromosome is functional so the mother doesn’t show the disease. The father also has a chromosomal pair, one with a GSD (glycogen storage disease) gene and the other with a normal gene. When this couple conceives, random chance will allow germ cells bearing the defective gene laden chromosome to unite with a similar germ cell one fourth of the time.
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When both the mother’s and the father’s germ cells donate the defective gene, both members of the off-spring’s chromosomal pair have the GSD genes and thus the child manifests the disease. This genetic make-up is termed homozygous.

Figure 7

There is no field of medicine that is moving as rapidly as molecular genetics. Although genes are very small, and cannot be seen, the Human Genome Project characterized all of the approximately 20,000-25,000 human genes. As a result the genes from an individual patient can be tested to diagnose a genetic disease.

Prenatal diagnosis is available in most cases of Glycogen Storage Disease either by amniocentesis or chorionic villus sampling or CVS. Amniocentesis is the penetration of the pregnant female womb, via the abdomen by a needle, to draw out fluid (amniotic fluid) in which the fetus is suspended. This fluid contains cells (mostly skin and bladder cells) from the fetus. These cells can be grown in the laboratory and examined to detect disease states in the unborn.

Amniocentesis is usually performed between the 14th and 16th weeks of pregnancy. It takes several weeks to a month for the laboratory to complete the tests. The danger to the fetus is very low, and the accuracy of the test approaches 100% but of course is not perfect.

Your physician can advise you on the safety of the procedure, and whether amniocentesis can and should be performed, in your particular case. Amniocentesis can be performed on an outpatient basis.

Another method of prenatal diagnosis is chorionic villus sampling. This is a technique where a small amount of the chorionic villi (tissues surrounding the fetus) are biopsied. The
advantage over amniocentesis is that the test can be done earlier, and the results are ordinarily available sooner. The same glycogen storage diseases can be diagnosed by both techniques.

The last topic of general interest is the term biopsy. A biopsy is the removal of a small piece of body tissue for laboratory examination. A punch biopsy can be done (needle sized) from both liver and muscle, and is adequate if one is reasonably sure of the diagnosis.

Open biopsies of both liver and muscle can provide for extensive testing to be done. The pathologist can interpret light and electron microscopic studies of the biopsy, and specialized laboratories perform biochemical studies. The risk associated with surgical liver and/or muscle biopsies under normal circumstances is very modest. The removal of the tissue (commonly done in a surgical suite for sterility) does not harm the patient, as only a small amount of tissue is taken. The tissue is taken or sent out for special studies. The biopsy should always have light and electron microscopy. Only a few laboratories in the United States are equipped for the comprehensive study of such biopsies. These few laboratories receive biopsies from all over the world.

It is now possible to screen DNA specimens obtained from affected individuals and potential carriers (as explained in the Chapters on Type I and IV). Because a specific protocol must be followed, have your physician contact the laboratories that perform this service.

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Chapter 3
Glycogen Storage Diseases

Glycogen storage diseases (GSDs), also referred to as glycogenosis, is a term used to describe a number of different diseases, all of which are caused by inherited abnormalities of enzymes that are involved in the formation or breakdown of glycogen (a storage form of glucose). These enzyme defects lead to abnormal tissue concentrations of glycogen or structurally abnormal forms of glycogen. The liver normally stores glucose as glycogen (up to about 6 grams of glycogen per 100 grams of liver tissue). The feature that all GSD's have in common is that they all result in the body not being able to produce sufficient glucose into the bloodstream or utilize glucose (sugar) as a source of energy.

When glucose from the bloodstream enters the liver cell, it is converted first to glucose-6-phosphate (G6P) before it can enter one of several metabolic pathways. G6P can be converted to glucose by glucose-6-phosphatase (G6Pase) enzyme. Glycogen formation and breakdown in the liver follows distinct pathways that begin and end with glucose-1-phosphate (Figure 8). Glycogen synthase enzyme helps the formation of α-1,4-linkages in glycogen; a branching enzyme forms α-1,6-linkages and makes glycogen a branched polymer. The breakdown of glycogen (glycogenolysis) involves a series of enzymatic reactions that lead to the activation of hepatic glycogen phosphorylase, which breaks off glucose from the outer branches of glycogen, producing glucose-1-phosphate (Figure 8).

Figure 8

This figure shows glycogen formation and breakdown in the liver. The heavy line at the perimeter of the figure represents the liver cell membrane. Glut2 is the glucose transporter that brings glucose into and out of the liver cell. The oval figure represents the endoplasmic reticulum that sits within the cytoplasm of the liver cell. The key to the figure: 1 glucokinase; 2 phosphoglucomutase; 3 glycogen synthase; 4 branching enzyme; 5 glycogen phosphorylase; 6 debranching enzyme; 7 glucose-6-phosphatase system; 8 glycolysis; 9 pentose phosphate pathway. Interrupted lines indicate multiple biochemical steps (not shown) leading to the product.
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Chapter 4

Type I Glycogen Storage Disease

Synonyms: GSD I; Type I Glycogenosis; von Gierke Disease; Glucose-6-Phosphatase Deficiency Glycogen Storage Disease; Hepatorenal Glycogenosis

The Nature of the Defect

-von Gierke first described this disease in 1929. The enzyme defect, deficiency of glucose-6-phosphatase (G6Pase) activity, which causes the disease, was discovered in 1952 by the Drs. Cori, a husband and wife research team. Their discovery was the first demonstration that a metabolic disorder was caused by an enzyme deficiency.

GSD I accounts for about 25% of all cases of GSD diagnosed in the USA and in Europe and has an estimated incidence of about 1 in 100,000 live births.

Deficiency of G6Pase activity results in the inability of the liver to convert glucose-6-phosphate to free glucose. Glucose from the blood stream readily enters the liver and can be stored as glycogen, but cannot be normally released back into the bloodstream. As a result, blood glucose falls to low levels (hypoglycemia) within a few hours after eating. Patients with GSD I may experience episodes of severe hypoglycemia, especially during infancy and early childhood or when illness prevents normal feeding or causes vomiting and diarrhea.

Normally, when the blood glucose level falls, liver glycogen is rapidly broken down (glycogenolysis) to glucose, which leaves the liver cell and enters the blood. This process is a critically important way in which the body normally keeps the blood glucose level within the normal range (approximately 70-110mg/dL) in the interval between meals and during the period of overnight fasting or sleep.

Because patients with GSD I can store glucose as glycogen but cannot release it normally, stored glycogen accumulates in the liver. The liver may contain up to 10-12 grams of glycogen per 100 grams of liver tissue in GSD I. In response to falling levels of blood glucose, the levels of hormones (chemical messengers), particularly glucagon and epinephrine, increase in the blood giving the signal to the liver to release glucose in a futile attempt to bring the blood glucose level up to normal. The deficiency of G6Pase prevents the liver from responding normally to the hormonal signals. Instead of raising the blood glucose level, the signal from these hormones results in increased levels of lactic acid, fats (especially triglycerides) and uric acid in the blood. (see Figure 8, Chapter III). Fat released from the body’s fat stores accumulates in the liver, and together with excess glycogen, causes considerable liver enlargement. The liver performs its many other functions normally and patients with GSD I do not develop liver failure, as in some other inborn metabolic liver diseases.
The G6Pase enzyme system is made up of several components (subunits) required for its proper function. The catalytic subunit (located in a special compartment of the cell called the endoplasmic reticulum) catalyzes the final reaction of glycogen breakdown; the conversion of glucose-6-phosphate to glucose (Figure 9). Deficiency of the catalytic subunit of the G6Pase enzyme system is responsible for Type Ia glycogen storage disease. A glucose-6-phosphate transporter (G6PT) carries glucose-6-phosphate across the liver endoplasmic reticulum membrane (Figure 8). Defects in G6PT prevent glucose-6-phosphate from being broken down to glucose and phosphate. In 1968, Senior and Loridan recognized that there were patients with typical clinical features of Type Ia GSD whose G6Pase activity was found not to be deficient in liver biopsy specimens. These individuals were referred to as having Type Ib GSD. It is now known that Type Ib is caused by deficiency of G6PT. Type Ib accounts for about 20% of patients with Type I GSD. There is an important difference between Type Ia and Ib GSD. Patients with Type Ib get recurrent bacterial infections because they have reduced quantities of neutrophils and the function of their neutrophils is abnormal. Neutrophils are white blood cells that normally kill bacteria.

Figure 9

This figure shows the endoplasmic reticulum within the liver cell and the G6Pase enzyme system. G6Pase is found in the endoplasmic reticulum membrane. Glucose-6-phosphate transporter (G6PT) carries glucose-6-phosphate across the endoplasmic reticulum membrane. G6Pase is deficient in GSD Ia, and G6PT is deficient in GSD Ib.

Clinical Manifestations

The presenting clinical symptoms vary according to the patient’s age, largely because of the differences in the content and frequency of feedings between newborn infants and older infants.
and children. Infants occasionally show symptoms of low blood sugar (hypoglycemia) soon after birth. Most do not have symptoms as long as they receive frequent feedings (e.g. every 2-4 hours) that contain sufficient glucose to prevent hypoglycemia.

For this reason, the condition may not be diagnosed until the child is several months old, when an enlarged liver and swollen abdomen are noted during a routine physical examination by their doctor. Rapid deep breathing and a low-grade fever may be present without any signs of infection. The rapid breathing is caused by lactic acidosis (from excessive production of lactic acid by the liver) resulting from hypoglycemia. Symptoms of hypoglycemia typically only begin to appear when the interval between feedings gradually increases and the infant starts to sleep through the night or when an illness disrupts normal patterns of feeding.

Later in infancy, untreated patients tend to have characteristic physical features due to a progressive decrease in growth, muscle wasting, delayed motor development, and build-up of body fat. Infants with GSD often have a doll-like face with excess fat in their cheeks. Social and cognitive development are not affected unless the infant has suffered brain damage from repeated severe hypoglycemic seizures. If glucose is not administered continuously in amounts necessary to prevent fasting hypoglycemia (see Treatment), severe biochemical abnormalities persist and growth and physical development are markedly delayed (this is referred to as “failure to thrive”). Nose bleeds or oozing after dental or other surgery can result due to impaired function of the platelets (the components of blood involved in stopping bleeding) in untreated individuals. The platelet dysfunction is secondary to the metabolic abnormalities and corrects with improvement of the metabolic state during glucose therapy.

In untreated patients, the blood levels of free fatty acids and triglycerides are markedly increased. Phospholipid and cholesterol levels are moderately elevated. Severe hyperlipidemia (extremely high levels of triglycerides) can lead to the appearance of yellowish plaques (eruptive xanthomata) on the eyelids, elbows, knees, and on the buttocks. Severe hypertriglyceridemia can also cause acute pancreatitis (inflammation of the pancreas), a medical emergency characterized by severe abdominal pain and vomiting.

Although hypoglycemia tends to become less severe with increasing age, inadequate therapy causes severe retardation of physical growth and delay in the onset of puberty. Fasting blood glucose levels improve as the child gets older.

Professor von Gierke described enlargement of the kidneys in his original pathologic description of the disease. Glucose-6-phosphatase is deficient in the kidneys. The kidney enlargement is easily demonstrated by ultrasonography of the abdomen. Despite their large size, kidney function in childhood usually is not significantly impaired provided the child receives proper treatment. However, in the untreated state (under conditions that should no longer occur), a form of kidney dysfunction involving the tubules can occur in which there is considerable leakage of phosphate, potassium, and amino acids into the urine. This is referred to as proximal tubular dysfunction. This abnormality of kidney tubular function is reversed by appropriate treatment that corrects the severe metabolic abnormalities described above. Treated children usually show no significant abnormality of kidney function except increased rates of glomerular filtration. Increased urinary excretion of albumin may be observed in
adolescents. More severe kidney injury may occur with large amounts of protein in the urine, high blood pressure, and decreased ability of the kidneys to filter waste products due to damage to the filtering units of the kidney (glomeruli). This is caused by the development of focal segmental glomerulosclerosis and interstitial fibrosis, a condition that can ultimately progress to kidney failure in young adults.

For unknown reasons, patients may develop benign tumors in the liver (hepatic adenomas). Adenomas are usually first noted between the ages of 10 and 30 years. They typically do not cause symptoms and are identified by a routine ultrasound examination of the liver. It has been suggested (this is not proven) that they might disappear or become smaller with effective treatment.

Adenomas may become malignant (i.e. liver cancer) or bleed. Magnetic resonance imaging (MRI) of the abdomen is an effective method to monitor hepatic adenomas and to follow their progress over time.

In the past, osteoporosis was demonstrated in radiographic studies of patients with GSD I and it has been reported that the bone mineral (calcium and phosphorus) content is decreased compared to normal children of the same age. Dietary therapy of GSD may slow or prevent osteoporosis.

Type IB GSD

In addition to the clinical disturbances described above, patients with Type Ib GSD have either intermittent or constant low neutrophil counts (neutropenia), which is associated with recurrent bacterial and fungal infections. Neutropenia is the result of a defect in the maturation of neutrophils in the bone marrow. It is accompanied by defects in the function of circulating neutrophils. In addition to the problem of repeated infections, some patients develop an inflammatory bowel disease characterized by loss of appetite, abdominal pain, diarrhea, and weight loss. Fortunately, the neutropenia and inflammatory bowel disease respond to treatment with granulocyte colony stimulating factor (GCSF).

Laboratory Investigation

During infancy, the blood glucose concentration may fall to less than 40 g/dL within 3-4 hours of a feed. If the interval between feeds is more than four hours, the blood glucose level may decrease to less than 20 mg/dL. The hypoglycemia is accompanied by a marked increase in the blood level of lactic acid and acidosis (an acid state of the blood). The blood plasma is often cloudy or milky with very high triglyceride and moderately increased levels of cholesterol. Serum uric acid is increased. The liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are usually moderately increased.
Historically, an assay of G6Pase activity on a liver biopsy specimen confirmed the enzyme deficiency in patients with GSD Ia. G6Pase activity is very low or non-detectable in the liver biopsy sample of the patient with GSD Ia. Differentiation between GSD Ia and Ib required analysis of G6Pase activity in both intact and fully disrupted liver cells. G6Pase hydrolytic activity in GSD Ib patients was totally or partially inactive in fresh liver biopsy samples, but normal when the assay is performed on previously frozen tissue that disrupts microsomes.

Currently GSD Ia and Ib can be diagnosed by a genetic test that analyses the genes for G6Pase and G6PT. The gene for Type Ia maps to chromosome 17q12 and the Ib gene to 11q23. Numerous mutations have been found that cause either GSD Ia or Ib. Prior to the isolation of these genes, a definitive diagnosis of GSD I required a liver biopsy to demonstrate a deficiency. Gene-based mutation analysis now provides a non-invasive way for diagnosis for the majority of Type Ia and Ib patients, making liver biopsy for enzyme analysis unnecessary in the majority of cases.

**Treatment**

In the early 1970’s, a critically important observation was made that changed the treatment of GSD I. It was shown that continuous glucose infusion during the night benefited patients with Type I GSD. It is now known that the metabolic and hormonal abnormalities in Type I GSD result from hypoglycemia, which becomes evident a few hours after feeding and is much worse with fasting. If the blood glucose level is maintained at or above 70mg/dL throughout the day and night, considerable clinical improvement occurs. The goal was to ensure that the blood glucose level is maintained within the normal range, and the goal of current diet therapy remains the same today.

In 1984, Drs. Chen and Sidbury reported that intermittent administration of a suspension of uncooked (raw) cornstarch in water during the day and night could maintain normal blood glucose levels in Type I GSD, thereby eliminating the need for nasogastric or gastrostomy feedings. Uncooked cornstarch appears to act as an intestinal reservoir of glucose that is slowly absorbed into the circulation.

The fundamental principle of treatment is to provide a continuous dietary source of glucose to prevent blood glucose levels from falling below 70 mg/dL. This is the threshold below which an increase in the blood levels of the hormones that raise blood glucose levels is triggered. When hypoglycemia is prevented by providing an adequate amount of glucose throughout the day and night, the size of the liver decreases, the biochemical abnormalities improve to nearly normal, the bleeding tendency disappears, and growth and development progress normally.

In many centers, uncooked cornstarch has replaced frequent daytime feedings of glucose or glucose polymers and continuous intragastric infusion of glucose overnight. It has been used successfully in infants as young as eight months of age. The un-cooked cornstarch is given in a slurry of water or artificially sweetened fluid without citric acid (e.g. Kool-Aid®), or in formula for infants (Prosobee or Lactofree). The usual frequency of feeds is 3-5 hour intervals during the
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day and 4-6 hour intervals overnight. Infants should receive 2-3 hourly feedings of formula (either Prosobee or Lactofree, neither of which contains lactose or sucrose) containing an amount of glucose approximately equal to the calculated glucose production rate (6mg/kg/minute) during the day and 3 hourly feedings at night. If nighttime feedings are problematic, continuous overnight feedings using the same formula can be given controlled by an infusion pump via a nasogastric tube or via a gastrostomy tube if the nasogastric tube is not well tolerated.

More recently, modified cornstarch (Glycosade®) has been developed as an alternative to uncooked cornstarch. Glycosade® has been approved for nighttime feedings for treating GSD I, because it prevents hypoglycemia for longer times than uncooked cornstarch.

When adequate glucose is provided, significant hyperuricemia and hyperlipidemia are usually restored to near normal. If severe hyperuricemia persists, allopurinol, a xanthine oxidase inhibitor, effectively lowers serum uric acid to normal levels. Lipid-lowering agents (niacin and/or gemfibrozil) are seldom required, but are indicated when persistent severe hyperlipidemia (despite optimal glucose therapy) poses a significant risk of acute pancreatitis.

The Dietitian

A registered dietitian must be involved in management. Review of the diet and dietary counseling at regular intervals is essential to ensure that the diet is meeting the goals of therapy and contains the recommended dietary allowances (RDA’s) of nutrients, vitamins, and minerals for normal physical growth, development, and maintenance of good health.

In general, the diet contains 60–70% calories from carbohydrates, 10–15% calories from protein (to provide the daily recommended intake), and the remaining calories from fat (<30% for children older than 2 years). It is important to insure that the diet contains an adequate amount of protein, fat, minerals, and vitamins to support optimal growth. Protein should comprise 10-15% of calories, and the remaining calories should be from fat (<30% of total calories from fat in children >2 years old). When adequate glucose is prescribed to maintain normal blood glucose levels, milk products and fruit, despite their content of galactose and fructose, respectively, may be consumed in limited amounts to supply essential nutrients, minerals, and vitamins. Individuals should consult with their physician regarding specific dietary guidelines. A careful balance between regular healthy food and glucose polymer and uncooked cornstarch is needed.

Exercise

Patients should be encouraged to be physically active within the limits of their tolerance. Participation in contact sports (e.g. football, basketball) is discouraged because of the possibility that a direct blow to the liver or kidney could be harmful. Because the rate of glucose utilization increases considerably during vigorous physical activity, additional carbohydrate (either snacks
containing complex carbohydrates or uncooked cornstarch) must be consumed before strenuous exercise and at 1-2 hour intervals if exercise is continued for many hours.

Liver Transplantation

Liver transplants have been performed and may be indicated in rare circumstances. All the biochemical abnormalities of GSD are completely reversed following successful liver transplantation. In the future, this option may be more acceptable if the procedure becomes safer and the risk associated with long-term immunosuppression is reduced. However, neutropenia is not corrected and still requires treatment following liver transplantation in GSD Ib.

Surgery

If possible, surgery should be performed in GSD patients only after the metabolic state has been corrected by optimal dietary therapy which restores the platelet abnormality to normal and corrects the prolonged bleeding time. The prolonged bleeding time can be reversed by intravenous 10% glucose solution at the normal rate of glucose production for 24-48 hours. The patient should never fast before surgery without receiving intravenous glucose. During surgery and the post-operative period until the patient is eating and drinking normally, the blood glucose concentration should be maintained in the normal range by intravenous administration of 10% glucose solution. Care should be taken to provide intravenous glucose until after the patient resumes their regular diet, to avoid hypoglycemia during postop care.

Genetics

GSD I is inherited as an autosomal recessive condition and affects the sexes equally. This means that parents each carry one abnormal gene and are unaffected carriers of the disease (heterozygotes). Carriers are clinically normal and show none of the biochemical abnormalities. An affected child has two copies of the abnormal gene (homozygous) – one copy inherited from each parent. With each pregnancy, the same parents have a 1 in 4 chance of having another affected child. They have a 2 in 4 chance of having an unaffected carrier child (with one abnormal gene), and a 1 in 4 chance of having an unaffected child who has no abnormal copies of the gene and, therefore, is not a carrier.

A person with Type I glycogen storage disease will not have affected children unless he/she were to marry another carrier or another person affected by Type I glycogen storage disease. The likelihood of such an event occurring is very rare unless one married a relative (e.g. a cousin).

Prenatal Diagnosis and Testing Carriers of GSD I by Direct DNA Mutational Analysis

With the cloning of the G6Pase and G6PT genes, gene-based diagnostic testing for this disorder became possible and is available at specialized genetics laboratories. Mutations can
now be diagnosed accurately and rapidly next generation sequencing of the genes. The types of mutations appear to cluster according to the ethnic background of patients.

The mutation database provides a foundation for gene-based diagnosis of carriers in at-risk families and for prenatal screening. It is now possible to screen DNA specimens obtained both from affected individuals and potential carriers in their families. Mutational analysis can be performed on the proband (the known affected person in a family) and on both parents. Then, prenatal mutational analysis is performed directly on cells obtained by chorionic villus sampling to determine the status of the fetus. With this knowledge, parents are able to choose whether or not to continue a pregnancy and how to plan for birth of the child.

With DNA based diagnosis, carrier testing is also possible. Parents of the affected person are definite carriers. Other family members who are at high risk for being carriers are the siblings (brothers and sisters) of the affected person and the siblings of the parents of the affected individual. DNA testing for GSD I requires a small blood specimen (5 mL or about one teaspoon of blood).

Prognosis

In the past, many patients with GSD I did not survive infancy and childhood. Today, maintenance of normal or near normal blood glucose levels with effective therapy improves the metabolic abnormalities and reverses the severe growth failure characteristic of the untreated state. It is still unclear whether long-term complications can be prevented by dietary therapy.

The Future

Although it is nearly 50 years since the Coris’ showed that GSD I is caused by a specific enzyme defect, progress towards a cure has been slow. At the present time, a normally active enzyme cannot be inserted into liver cells. Gene therapy to replace the gene that is defective has been successful in mice with GSD Ia and Ib, and in dogs with GSD Ia. However, gene therapy for GSD Ib has not effectively treated the neutropenia from that condition. It is realistic, therefore, to imagine that further development of gene therapy will provide a new treatment for this disease.

Reference:


Revised May 1, 2016. Authors: Dwight D. Koeberl, MD,PhD; Professor, Department of Pediatrics/Division of Medical Genetics; Duke University, and Stephanie Austin, MS, MA; CGC Genetic Counselor/Research Project Manager; Department of Pediatrics/Division of Medical Genetics; Duke University.
Chapter 5
Type II Glycogen Storage Disease (abbreviated GSD II)

Synonyms: Pompe Disease, Acid Maltase Deficiency

Clinical Manifestations

Pompe disease is a muscle disease that progressively affects skeletal and cardiac muscle. The type of Pompe disease that affects infants and involves the heart is called the infantile type. In infants, the heart muscle is also affected and without treatment, the heart muscle thickens and progressively fails to pump blood. Limb girdle muscles and muscles involved in breathing such as the diaphragm are affected. Without treatment, the condition worsens and the children usually die before the end of the first year of life due to combined heart failure and respiratory weakness. In patients who do not have the infantile type, the disease presents as a spectrum of severity primarily affecting the limb girdle and respiratory muscles. The involvement of respiratory muscles results in difficulty breathing, especially when lying down. This can lead to pronounced fatigue during the day, changed behavior and mood, and morning headaches. The nighttime breathing of these patients must be systematically reviewed. Many patients require nighttime ventilatory assistance using a breathing machine. The involvement of skeletal muscles leads to difficulty with walking, climbing stairs, and tasks of daily living. The involvement of the muscles progresses slowly over the years and patients may require wheelchair and ventilator support. Survival varies from several years to several decades. The age at which problems become apparent varies; the earliest being the first year of life to as late as the 6th decade of life. Usually a distinction is made between those patients who develop symptoms as children (juvenile type) and those who develop symptoms as adults (adult type). An enlarged heart is usually not a feature in older patients; the latter may be noted, but is not as severe or significant as in the infantile form. Other cardiac symptoms such as arrhythmia and enlarged heart vessels are often noted.

The Nature of the Defect

Pompe disease is a genetic inborn disorder of metabolism that belongs to the group of lysosomal disorders. Every cell in our body contains vesicles (lysosomes) that are involved in the digestion of various compounds. Every cell renews itself continuously by digesting old material and making new material. Old material that has to be discarded enters into the lysosomes in the cell. Lysosomes contain all the processes to completely digest all this material into small units that can be recycled. The tools needed to break down the waste products are called lysosomal enzymes. GSD II is caused by lack of function of the enzyme acid alpha-glucosidase (or acid maltase), which is present in lysosomes.
All cells contain glycogen. During the renewal of the cell, some of this glycogen enters into the lysosomes, and must be broken down. In patients with Pompe disease, there is a problem in the way the enzyme acid alpha-glucosidase is produced. Because there is insufficient activity of the enzyme lysosomal acid alpha-glucosidase, the glycogen that is in the lysosomes is no longer broken down and continuously accumulates.

Over time, the lysosomes are filled with glycogen, become larger and larger, and disrupt the normal functions of the cell. In particular, in muscle cells these enlarged lysosomes cause problems. Eventually the muscle cells become dysfunctional and die. When muscle cells are injured, the contents, such as the enzyme creatine kinase (CK), spill into the blood.

Genetics

In Pompe disease, there is a fault in the genetic instruction for how the cell should make the enzyme acid alpha-glucosidase. In the infantile form, there is little to no enzyme activity, and in the rest of the disease spectrum, these patients have more residual function of the enzyme acid alpha-glucosidase.

The gene for Pompe disease is known, and genetic mutations can be identified through a blood test. A large number of patients with infantile Pompe have a unique or private change in this gene. Most errors in the gene lead either to absence of the enzyme, an unstable enzyme, or to an enzyme that does not reach the place where the enzyme functions, the lysosome.

In patients with the adult form of Pompe disease in the United States, one of the two copies of the gene in most patients is a mutation that is common to most adults with Pompe disease. This error involves the assembly of the genetic instruction (splicing defect). This error does not lead to the complete loss of production of the enzyme, which explains the later presentation and form of the disease.

Pompe disease is inherited in an autosomal recessive manner through the process of both parents passing on the GAA gene mutation or defect, causing a malfunction in the GAA enzyme. If parents are carriers of the GAA gene defect, with each pregnancy, a child has a 25% chance of inheriting the disease, 50% of being a carrier, and a 25% chance of neither having Pompe disease nor being a carrier.

Laboratory Investigation

Pompe disease is diagnosed by measuring the activity of the enzyme alpha-glucosidase. This can be performed on a blood sample, muscle biopsy or on cultured cells (fibroblasts) from a skin biopsy. Prenatal diagnosis is possible during pregnancy via a chorionic villus biopsy or amniocentesis. The use of family history and genetic testing can further clarify the genetic status of Pompe disease for family members. Molecular genetic testing requires prior identification of the GAA pathogenic variants in the family.
If both genes in the pair have a mutation, the individual has Pompe disease. If only one gene has the mutation, the person is considered a carrier. Through genotyping, we can identify carriers who “carry” the gene defect and may pass it on to their children. Thus, it is of particular interest to identify carriers within families with a history of Pompe disease.

Treatment

While there is no cure for Pompe disease, there are several types of treatments and care that can significantly help people with Pompe disease. Since there is a wide-range of symptoms of Pompe disease, proper management requires a multidisciplinary approach, generally by a team of specialists.

Enzyme replacement therapy (ERT) is widely used today to replace the acid alpha-glucosidase (GAA) enzyme which is deficient in Pompe patients. The development of ERT has been shown to decrease heart size, maintain normal heart function, improve muscle function, and strength, and reduce lysosomal glycogen accumulation. Lumizyme, an alglucosidase alfa drug, has been approved for treating all types of Pompe disease.

In addition to ERT, it is important to have a multidisciplinary team to care for these patients. Pediatricians or internists, geneticists, neurologists, orthopedists, cardiologists, dieticians, genetic counselors, and other healthcare professionals may need to comprehensively plan the patient’s treatment.

Metabolic dietitian: By using a protein rich diet, most adult patients find improvement in their wellbeing. Adults and children with Pompe disease have an increase in the turnover of proteins. This increased turnover of proteins puts the muscles under stress. To relieve this increased protein need, a protein rich diet is used (proteins make up to 20-24% of caloric intake). The guidance of a dietician is indicated for such a diet. It is necessary to monitor kidney function closely when on a high protein diet.

Physical therapy: Patients with Pompe may also benefit from sub maximal exercise to increase muscle strength, decrease stiffness, increase energy, and improve mental health. Such exercises can also increase strength in muscles. Exercise plans should be catered towards the individual’s needs, abilities, and physical limitations.

Neurology: Motor and functional assessments are recommended to establish a baseline with repeat testing at 3–6 month intervals for children under age five years, and annually in older children and adults, except where additional testing is clinically indicated by change in function or failure to make expected progress.

Cardiology: Cardiac assessments are recommended to test for common cardiac issues occurring in Pompe disease including cardiomyopathy, heart failure, and arrhythmia. There is also a component of cardiac dysfunction which contributes to respiratory failure.
Pulmonology: Pulmonary function testing can identify respiratory compromise in patients with Pompe. This can help monitor the cardiopulmonary response to activity level, exercise, and body position.

The Future

Progress continues to be made in the development of gene therapy for Pompe disease. Gene therapy is described as giving a normal functioning copy of the genetic instruction for making the enzyme acid alpha-glucosidase. The second-generation recombinant ERTs have a better ability to target the muscles and clear the glycogen more efficiently. Additionally, chaperone therapy is a viable treatment for Pompe disease since chaperones stabilize the recombinant enzyme used for ERT. In the future, these treatments may be combined to better treat this group of patients. To learn more about this information and to get current information about these clinical research studies, visit ClinicalTrials.gov.

There are many organizations such as Association for Glycogen Storage Disease (AGSD), United Pompe Foundation (UPF), and Acid Maltase Deficiency Association (AMDA) that may be useful in finding more information including new treatments, clinical trials, genetics, and emotional counseling. Guidelines are also available which can help patients manage their Pompe disease.

Gene therapy is also a treatment on the horizon. In most cases, a genetically altered virus is used to administer the Pompe gene. Several technical problems will have to be solved before trials will become available for successful use in humans.

With the advent of ERT and a possibility of gene therapy, the pathology of Pompe disease will drastically be changed, with a number of findings being uncovered along the way.
Chapter 6

Type III Glycogen Storage Disease (abbreviated GSD III)

Synonyms: Debrancher Deficiency, Forbes Disease, Cori Disease, Limit Dextrinosis

The Nature of the Defect

Debrancher enzyme is required to break and digest the branch points of stored glycogen when glycogen is being broken down to glucose molecules that our body can use for energy and maintaining blood sugar levels. Another enzyme in our body, the branching enzyme helps create these same branch points when glycogen is being made in our body. When the debrancher enzyme (DE) is not present, the leftover glycogen that accumulates has many short branch points and therefore has an abnormal structure. The accumulation of glycogen with shorter outer branches (limit dextrin) and the failure to break down glycogen to glucose is what causes most of the symptoms that are seen in glycogen storage disease type III (GSD III).

Clinical Manifestations

Some of the symptoms of debrancher deficiency are much like those that were described for GSD type I (glucose-6-phosphatase deficiency); however, the patient with debrancher deficiency usually has a milder course due to lack of severe hypoglycemia. Patients usually have a large liver, suffer growth retardation and can have low blood sugar levels. Some patients do show some liver fibrosis on liver biopsy tissue. Muscle weakness is commonly present in childhood and can, at times, be severe (GSD IIIa). For reasons that are not clear, the liver may return to normal size at puberty, although the enzyme defect persists. By contrast with GSD I, patients with GSD III also often have muscle symptoms related to an abnormal glycogen storage and breakdown during exercise (Type IIIa). Muscle fatigability limiting sports activities is commonly present in childhood, but become in some patients an increasing problem with age with occurrence of muscle weakness at adult age (GSD type IIIa). The heart can be mildly enlarged, that is visible on echocardiography, but the function is usually normal. Scarring in the liver is unusual in GSD III, but it can be severe in some patients (liver cirrhosis). Persons with debrancher deficiency have lived well into late adulthood.

Laboratory Diagnosis

Depending on the assay used, two main subtypes of this disorder have been observed. There is considerable variation in the tissues affected by the debranching enzyme defect, (such as white blood cells, muscle, liver, heart and so forth). Most patients with debrancher deficiency are classified as Type IIIa (the disease that involves both liver and muscle). Less frequently, the disease appears to affect only the liver, and is classified as Type IIIb.
Laboratory findings in the blood usually show low blood sugar, elevated glycogen content in red blood cells, and elevated levels of fat (total cholesterol). However, uric acid and lactic acid are usually normal. Liver enzymes such as AST, ALT, serum glutamic pyruvate transaminase are elevated. Biopsy of the liver shows excessive glycogen accumulation, inflammatory changes and on rare occasions fibrosis, which progresses to severe scarring or cirrhosis. Biochemical analysis of liver biopsy shows elevations of glycogen content with short outer branches and a deficiency of the debrancher enzyme. Monitoring serum creatine kinase is important to detect muscle involvement. Since this disease cannot be easily distinguished from the other glycogen storage diseases by clinical symptoms alone, it is important that debrancher enzyme activity is tested on blood or biopsy sample for accurate diagnosis. Gene sequencing for GSD III (AGL gene) is readily available for confirmation of diagnosis.

**Treatment**

Treatment for this disease is dietary. During the early years continuous nasogastric feedings and the starch regimens outlined under glucose-6-phosphatase deficiency are useful. As patient gets older a high protein diet may be useful.

**Genetics**

The inheritance of Type III GSD is autosomal recessive, the same as for Types I and II. When a condition is inherited in an autosomal recessive manner, both copies of the gene have to be altered for a person to have the condition. Usually, both of the parents are carriers; they have one normal and one altered copy of the gene. There is a 1 in 4 (25%) chance for other children to have the same condition. Prenatal diagnosis and carrier detection is not available based on enzyme assays, but it is possible using a DNA-based method, if family mutations are known.

**The Future**

This gene and the associated AGL gene mutations causing the GSDIII disease have been very well studied and documented. This information is being used to help make the diagnosis and detect carriers, and in the long term we hope will have considerable therapeutic usefulness. Gene therapy or enzyme replacement therapy, as discussed in previous chapters, may take considerable time to develop.
AGSD’s “Glycogen Storage Diseases: A Patient-Parent Handbook”

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Chapter 7

Type IV Glycogen Storage Disease (abbreviated GSD IV)

Synonyms: Branching Enzyme Deficiency, Amylopectinosis, Andersen Disease

The Nature of the Defect

Glycogen synthesis is catalyzed by the two enzymes: glycogen synthase (GS) which elongates the glycogen chain, and glycogen branching enzyme (GBE) which produces new branches. A proper GS/GBE ratio is required to create normal glycogen molecules. Mutations in the GBE1 gene cause a complete or partial loss of the GBE activity in patients with GSD IV, resulting in production of less-branched insoluble glycogen in the body’s cells. As the accumulation of this structurally abnormal glycogen increases, it impairs the function of certain organs and tissues, especially the liver and muscles, and triggers the body’s immune system to attack these tissues. This normally results in severe cirrhosis (scarring) of the liver as well as other organs, such as muscle. GSD IV is estimated to occur in 1 in 600,000 to 800,000 individuals worldwide and accounts for approximately 3 percent of all cases of glycogen storage diseases.

Clinical Manifestations

A baby with the typical branching enzyme deficiency, originally described by Andersen in 1956, appears to be normal at birth. The first indication of a problem is “failure to thrive”. The rate of growth and mental progress of the baby stops at a certain point and does not continue normally. The abdomen expands because the liver and spleen enlarge, there is little weight gain, and muscles develop poor tone. The course of the disease is one of progressive cirrhosis of the liver and the problems associated with this. Death typically occurs by five years of age. The central problem is liver failure. Occasionally, patients with liver problems do not develop cirrhosis and have survived well into adulthood.

Recently, patients with various neuromuscular involvements have been recognized who have been very different from the typical presentation. There are patients whose problems are primarily related to muscle and nervous systems with or without liver problems. Some babies develop severe muscle wasting and poor tone and die of heart failure and breathing difficulty at birth or in early infancy. Patients with muscle and heart problems which developed in late childhood and patients with central and peripheral neuropathy noted in adulthood (adult polyglucosan body disease) have also been noted.

Treatment

Treatment of this failing liver has been symptomatic. For some individuals, maintaining normal blood sugar levels and adequate nutrient intake may improve liver function and muscle strength. Several patients with progressive liver failure have had successful liver transplants; however, after transplant, muscle and heart disease may still be a problem. There is currently no treatment for muscle and nervous system problems.

Genetics
The branching enzyme is present in cultured amniotic fluid cells, and prenatal diagnosis can, and has been, carried out. The disease is transmitted as an autosomal recessive disorder, each parent being a carrier. Carriers can be detected using white blood cells from a peripheral blood sample, as well as cultured skin fibroblasts.

The Future

The GBE1 gene that encodes the branching enzyme has been isolated and several animal models (mouse and cat) of GSD IV have been developed. As an increased ratio of GS activity and GBE activity is the cause of the formation of abnormal glycogen in GSD IV, currently treatment approaches that aim to increase GBE activity or reduce GS activity are being actively tested in animal disease models using gene-based therapy and small molecule drugs. It is hoped that these treatment will soon change the outcome of this disease.

Revised May 1, 2016. Author: Baodong Sun, PhD; Associate Professor of Pediatrics, Division of Medical Genetics; Duke University.
Chapter 8

McArdle Disease

Synonyms: Type V Glycogen Storage Disease (abbreviated GSD V), Myophosphorylase Deficiency, Muscle Phosphorylase Deficiency.

The Cause of the Condition

Glycogen is a form of stored energy. The main stores in the human body are in skeletal muscle and in the liver. People with McArdle Disease are deficient in an enzyme called myophosphorylase (muscle phosphorylase) which plays a vital role in the break-down of glycogen into glucose so that it can be utilized to power the muscles.

The use of muscle glycogen is particularly important in the early stages of activity, after the first few seconds and up to about eight or ten minutes. It is also used in all intense (anaerobic) activity. So it is in these two situations that people with McArdle’s may have great difficulty and are exposed to the risk of muscle pain, cramps and contractures (muscle that is “locked up”, swollen and extremely painful).

Clinical Presentation

The clinical presentation of myophosphorylase deficiency was first described in 1951 by Dr. Brian McArdle, whose name is now associated with the condition. The onset is almost always in childhood with repeated presentation to general practitioners around the ages of 5 to 10. Children are often dismissed as lazy, unfit or having ‘growing pains’. It is rare to be diagnosed before adulthood and many people are not diagnosed until their 30s, 40s and even older. Men and women are equally affected.

Individuals present with painful muscle cramps within a minute or two of commencing activity, which ease with rest if activity is ceased soon enough. All skeletal muscle is affected. These cramps can be associated with such routine tasks as cleaning teeth or hanging up clothes. People with McArdle Disease experience a ‘second wind’ phenomenon, whereby symptoms experienced during exercise such as walking improve slightly after about 8 to 10 minutes. This is due to other fuel sources coming into use, particularly fat metabolism and glucose released from the liver’s glycogen stores. People with McArdle Disease have great trouble lifting and carrying heavy items, squatting, climbing stairs/hills and walking or running fast. These activities can lead to a muscle contracture, a painful muscle spasm that causes muscle damage (rhabdomyolysis). These activities should be strictly limited to 6 seconds of maximal effort, or avoided altogether.

The physical exam is often normal, although older people over the age of 40 years may notice weakness of the trunk and shoulder muscles. People with McArdle’s may have muscular legs but in older people the shoulders can appear thin and wasted. They may experience dark
red or red brown urine (myoglobinuria) after there has been muscle damage (rhabdomyolysis) from cramps or contractures. The myoglobin (red muscle protein) comes from the breakdown of skeletal muscle and is excreted in the urine.

The typical clinical presentation described above is by far the most common; however, variations are well known. At one end of the spectrum, a patient with McArdle’s who has lost aerobic fitness or accumulated years of muscle damage may be a regular wheelchair user. Whereas at the other end of the spectrum a patient who has learned to manage their condition and has achieved a high level of aerobic fitness, may have no symptoms other than when something unexpected happens and they have a severe episode of muscle breakdown.

**Diagnosis**

Any person with painful cramps during exercise should be evaluated. A blood test for serum creatine kinase (CK or CKP, a muscle enzyme) will usually show an abnormally high level. A functional test, such as a 12-minute walk test or static cycle test, can demonstrate the symptoms and the ‘second wind’ phenomenon described above. These are strong clues to the diagnosis.

Some medical centers may perform a forearm exercise test for diagnosis. In this test the person is asked to squeeze a rubber ball tightly on and off for several minutes. Each minute a blood sample is taken for lactate and ammonia. In healthy people the lactate increases four-fold and the ammonia does not rise, whereas in people with McArdle Disease the lactate does not rise, and sometimes even falls, and there is a marked rise in ammonia.

Genetic testing will usually confirm the diagnosis. Caucasians from Northern America and Northern Europe have a high chance of carrying one of two very common genetic mutations (R50X and G205S). Testing for these two mutations can diagnose 80% of people in this ethnic group. For people from other ethnic backgrounds full sequencing of the gene may be required.

Ultimately, a patient may need a muscle biopsy to test for the deficiency of the enzyme myophosphorylase and for the presence of raised levels of glycogen in the muscle.

**Treatment**

Although there is no specific medical treatment for McArdle’s, regular aerobic exercise following a warm up into the ‘second wind’ has been shown to be safe and is increasingly proven to be beneficial.

It is very important to avoid maximal activity such as sprinting and isometric (static) activities such as weight lifting or squatting because they can cause muscle breakdown (acute rhabdomyolysis) resulting in dark urine (myoglobinuria). This is a potentially serious complication as it may cause temporary kidney failure. If the urine looks like coca cola patients should go to hospital. The treatment is intravenous fluids to flush out the myoglobin. Blood tests will be required to monitor kidney function. If there is evidence of compartment syndrome an urgent surgical referral may be needed.
The long-term outlook is good. The prognosis is enhanced by an early diagnosis, expert advice and good self-management by the patient. However, a small number of patients have developed significant muscle problems (myopathies) later in life, usually muscle atrophy (wasting) through avoidance of activity or accumulated muscle damage through repeated episodes of rhabdomyolysis.

Research has demonstrated an improved exercise tolerance after high carbohydrate intake (sugar equivalent to a soft drink just before exercise), or with aerobic training. The high carbohydrate intake makes sense as more energy would be available in the blood supply going to the muscle. However, some people anecdotally report doing better on high protein diet and others on high fat. Patients may usefully consult with their medical doctor to see what diet works best for them.

**The Genetics of McArdle Disease**

McArdle Disease is inherited in what is known as an autosomal recessive pattern. This means that both parents will have been carriers and their children each had a 25% chance of getting McArdle’s, a 50% chance of being a carrier and a 25% chance of being completely clear of the condition. The parents are unlikely to have been aware that they were carriers, as carriers have no symptoms.

The single gene responsible for myophosphorylase is the PYGM gene on chromosome 11. To date about 150 mutations of this gene have been identified and nearly all result in a total absence of myophosphorylase. These days DNA-based diagnosis and carrier detection is possible in most cases, without the need for a muscle biopsy.

The children of people with McArdle Disease will all be carriers as they will inherit one of the mutated copies of the gene from their affected parent. However, there is only a risk of them getting McArdle Disease, if the other parent is a carrier. It is believed that the number of carriers is around 1 in 160. If a McArdle person and a carrier have children together there is a 50% risk of their children having McArdle’s. The normal pattern is for McArdle Disease to appear in one generation, with no family history of the disease, and then disappear again for many generations.

**Further information**

There is a YouTube Channel ‘AGSDUK’ and Facebook Groups ‘McArdle’s Disease’ and ‘McArdle parents’. Advice is available in the book ‘101 Tips for a Good Life with McArdle Disease’ and information for the patient’s GP and other doctors is available in ‘McArdle Disease: medical overview’. The ‘McArdle Disease Handbook’ is useful for details of the medical and scientific research into McArdle Disease.

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Chapter 9

Type VI Glycogen Storage Disease (abbreviated GSD VI) and Type IX Glycogen Storage Disease (abbreviated GSD IX)

Synonyms:

GSD VI: Liver phosphorylase deficiency, Hers disease, GSD 6
GSD IX: phosphorylase kinase deficiency, phosphorylase b kinase deficiency, GSD 9

The Nature of the Defect

Because the clinical picture is similar in liver phosphorylase deficiency (GSD VI) and in liver phosphorylase kinase deficiency (GSD IX), they will be considered together. There are muscle specific forms of phosphorylase deficiency (GSD V; McArdle disease) and phosphorylase kinase deficiency (GSD IXd), which will be described separately.

The enzyme phosphorylase kinase (PhK) acts as a switch to turn on (activate) phosphorylase enzyme. Phosphorylase is an enzyme which helps to break down stored glycogen (the storage form of glucose) into single glucose molecule. When the body needs glucose, PhK activates phosphorylase in response to various signals from the body. A defect in either phosphorylase or PhK can cause glycogen storage disease.

The phosphorylase enzyme is a single protein molecule (polypeptide). It is encoded by a single gene called PYGL. Phosphorylase kinase is a complex enzyme composed of sixteen parts (subunits); there are four copies each of four different subunits (alpha, beta, gamma, delta or calmodulin). Each subunit is a protein molecule. These different subunits are encoded by different genes. A problem with any of the subunits can cause the PhK enzyme to not work correctly. Due to these complexities, that is why sometimes it gets very difficult to get accurate diagnosis of GSD IX in certain patients.

Clinical Manifestations

When the liver forms of phosphorylase or PhK do not work correctly, glycogen builds up in the liver, causing it to be enlarged. Sometimes, in GSD IX (PK deficiency) the extra glycogen can cause scarring (fibrosis) of the liver which in rare cases can become permanent (cirrhosis). Because glycogen in the liver cannot be efficiently broken down when the body needs glucose, people with phosphorylase deficiency (GSD VI) and PhK deficiency (GSD IX) can have low
blood glucose levels at times of fasting. Instead, fats are used for energy, resulting in higher ketone levels.

Enlargement of the liver and slow growth are often the first symptoms in children with GSD VI or GSD IX. These symptoms are seen in the first few years of life. Hypoglycemia and ketosis may be present at times of fasting, such as in the morning before breakfast, or during times of illness when a child is not eating well. Some children may have mild delays in motor development. Liver enzymes (AST, ALT), cholesterol, and triglycerides are generally elevated. The symptoms usually improve as the child gets older. Most adults are of normal height. While most children have fairly mild symptoms, there is a lot of variation. For example, some children have more severe hypoglycemia and a small number of children develop liver cirrhosis.

**Diagnosis**

GSD VI and GSD IX can be diagnosed by laboratory tests which measure how well the phosphorylase and PhK enzymes work. These enzyme assays can be done on blood cells and liver biopsy samples. However, sometimes, the results of the enzyme tests are hard to interpret or normal, even when a child has one of these conditions.

GSD VI and GSD IX can also be diagnosed by genetic testing. This involves gene sequencing to look for differences in the genes involved in these disorders i.e. the gene containing the instructions to make the phosphorylase enzyme and PhK enzyme subunits (PYGL and various PHK genes). Gene sequencing usually requires a blood sample but can also be done on cells obtained from a cheek swab.

**Treatment**

Some children with GSD VI and GSD IX take uncooked cornstarch 1-4 times a day. Uncooked cornstarch provides a source of glucose that is slowly released. Protein supplements are also helpful as they provide an alternative source of energy. A dietician can tailor these treatments to the needs of each person, depending on their age, activity level and individual risk for low blood sugar and high ketone levels. Blood glucose and ketone levels can be monitored closely over two or three days to find out at which times of days a person is more likely to have problems.

**Genetics**

The inheritance pattern of liver phosphorylase deficiency is autosomal recessive. The gene for liver phosphorylase deficiency is called PYGL. When a condition is inherited in an autosomal recessive manner, both copies of the gene have to be altered for a person to have the condition.
Usually, both of the parents are carriers; they have one normal and one altered copy of the gene. There is a 1 in 4 (25%) chance for other children to have the same condition.

The inheritance pattern of liver PhK deficiency can be autosomal recessive or X-linked, depending upon which gene is altered. The most common form is the X-linked form. It accounts for as many as 75% of all cases of GSD IX and is caused by changes in the PHKA2 gene. Males have only one X chromosome, and therefore have only one copy of the PHKA2 gene. Males who inherit an altered copy of the PHKA2 gene will have GSD IX. Females have two X chromosomes, and therefore have two copies of the PHKA2 gene. Women who have one normal and one altered copy of the PHKA2 gene (heterozygous carriers) usually have no symptoms, or very mild symptoms, such a mild liver enlargement. Rarely, female carriers have symptoms similar to males. A female carrier of a PHKA2 gene change has a 50% (1 in 2) chance to pass on the altered gene to each of her children. A male with X-linked GSD IX will pass on the altered gene to all of his daughters but none of his sons.

The other subtypes of liver GSD IX are inherited in an autosomal recessive manner and can be caused by changes in the PHKB and PHKG2 genes. In autosomal recessive inheritance both parents are carriers and have no symptoms. Each child born to carrier parents has a 1 in 4 chance to have GSD IX at birth.

Future

As with the other GSDs, animal models are available for GSD VI and IX, and research is being done to develop new therapies for these conditions.

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Chapter 10

Type VII Glycogen Storage Disease (abbreviated GSD VII)

Synonyms: Muscle Phosphofructokinase Deficiency, Tarui Disease

The Nature of the Defect

Type VII glycogen storage disease is also known as Tarui disease, in recognition of Tarui’s first clinical and enzymatic description in 1965 of a family with three affected siblings, one female and two males in their 20’s, who presented with rapid onset fatigue and exercise intolerance similar to that seen in Type V glycogen storage disease.

Clinical Manifestations

The clinical features are similar to those of Type V glycogen storage disease. Patients experience early onset of fatigue and muscle pain with exercise. Vigorous exercise causes severe muscle cramps and myoglobinuria. There are, however, some features that may differentiate Type VII from Type V. There is no second wind phenomenon and exercise intolerance worsens after a high-carbohydrate meal. In addition, these symptoms may be associated with nausea, dizziness and vomiting after exercise. Hemolytic anemia with increased bilirubin levels, and hyperuricaemia, are frequently associated with exercise intolerance. In some patients a permanent, but moderate, muscle weakness may occur at adult age.

Diagnosis

The forearm exercise test can show a blunted lactate increase during exercise, with abnormal increase in ammonia, similarly to what is observed in GSD V. The diagnosis relies on enzyme deficiency assessment on blood sample, or muscle biopsy when it has been performed. Increasingly patients will be diagnosed by genetic testing.

Treatment

There is no specific treatment for this condition and in contrast to GSD V, in PFK deficiency both sucrose and a high-carbohydrate diet should be avoided. Strenuous exercise should be avoided in order to prevent acute attacks of muscle cramps and myoglobinuria.

Genetics
AGSD’s “Glycogen Storage Diseases: A Patient-Parent Handbook”

Type VII glycogen storage disease is inherited as an autosomal recessive trait. Each parent is a carrier for GSD VII, having no symptoms and only one mutation in \textit{PFK-M} gene. An affected child has two mutations in the \textit{PFK-M} gene, one inherited from each parent.

**Future**

As with the other GSDs, animal models are available for GSD VII, and research is being done to develop new therapies for this condition.

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Chapter 11

Type 0 Glycogen Storage Disease (abbreviated GSD 0)

Synonyms: Hepatic Glycogen Synthase Deficiency

The Nature of the Defect

Type 0 Glycogen Storage Disease (GSD 0) is caused by a deficiency in the enzyme named glycogen synthase. This enzyme is needed for the body to make glycogen. When a person has glycogen synthase deficiency the amount of glycogen that the body can store in the liver is very low. Low amounts of glycogen in the liver mean that when a person is not eating (fasting) their blood sugar levels can get very low (hypoglycemia).

Clinical Manifestations

In patients with Type 0 glycogen storage disease, the symptom of fasting hypoglycemia typically develops when a baby no longer gets fed during the night (late infancy). Early in infancy, children usually have no symptoms, but weaning from overnight feeds is often difficult. Children may have early-morning (before eating breakfast) drowsiness, appearance of looking pale, vomiting and fatigue, and sometimes convulsions associated with low blood glucose. During gastrointestinal illnesses (“stomach bugs”) or periods of poor eating, children may appear to be very tired and lazy. Usually low blood sugar (hypoglycemia) is found as part of the labwork that the doctor or hospital does in order to figure out as to why a child is not acting energetic.

Children with GSD 0 may grow a bit slower than expected (have a mild growth delay). In general, people with Type 0 glycogen storage disease do not have learning problems (they are developmentally normal). When exercising, people with GSD 0 may become tired more quickly than other individuals. Furthermore a person with GSD 0 may have muscle cramps because the body is trying to make energy from accumulated lactic acid. A person with Type 0 glycogen storage disease will typically look no different from a person who does not have GSD 0. The liver will not be larger than normal.

Laboratory Diagnosis

A doctor examining the first morning urine of someone with GSD 0 may see some signs (increased ketones in urine) that might make the diagnosis of diabetes as the first thing mentioned to a family.

Any child with a history of needing frequent meals or snacks and with hypoglycemia) may have Type 0 glycogen storage disease. Detailed blood and urine tests performed by a doctor may
show patterns that are unique to GSD 0, including low blood glucose and high urine ketones. Blood glucose can be abnormally high after a meal. If a doctor obtains a liver biopsy from a person with GSD 0, the pathologist will find very little glycogen. Genetic DNA testing that is performed on a blood sample is now available.

**Treatment**

The goal of treatment for Type 0 glycogen storage disease is to prevent low blood sugar (hypoglycemia) by avoiding fasting. Frequent meals and snacks can be given every 3-4 hours during the day. Uncooked cornstarch can act as a “slow release” form of glucose for the body. Given in the proper amounts, it will prevent hypoglycemia overnight. A diet high in protein may help with the cramping, tiredness, and fatigue that many people with GSD 0 experience.

**Genetics**

GSD 0 from glycogen synthase deficiency is caused by a change in the glycogen synthase-2 (GYS2) gene. GSD 0 is inherited in an autosomal recessive manner, and it is considered very rare. However, because testing for Type 0 glycogen storage disease just recently became available, doctors think that GSD 0 is more common than previously thought. GSD Type 0 affects both males and females. People with GSD 0 have been described from Eastern Europe, Western Europe, North America, and South America.
Chapter 12

Newer Glycogen Storage Diseases

Summary

Several newer GSDs have been described in recent years. These typically involve muscle, causing cramping during exercise and weakness. Some cause anemia due to the breakdown of red blood cells (hemolytic anemia). Table 1, below, summarizes information on GSD type XI-XIV. More information will be emerging about these conditions as more patients are diagnosed and reported in the scientific literature.

Table 1: Newer GSDs

<table>
<thead>
<tr>
<th>Enzyme (glycogen storage disease type/GSD#)¹</th>
<th>Gene</th>
<th>Inheritance²</th>
<th>Clinical presentation³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoglycerate mutase (GSD X)</td>
<td>PGAM2</td>
<td>AR</td>
<td>M</td>
</tr>
<tr>
<td>Lactate dehydrogenase (GSD XI)</td>
<td>LDHA</td>
<td>AR</td>
<td>M</td>
</tr>
<tr>
<td>Aldolase (GSD XII)</td>
<td>ALDOA</td>
<td>AR</td>
<td>H,M</td>
</tr>
<tr>
<td>Enolase (GSD XIII)</td>
<td>ENO1</td>
<td>AR</td>
<td>H,M</td>
</tr>
<tr>
<td>Phosphoglucomutase 1 (GSD XIV)</td>
<td>PGM1</td>
<td>AR</td>
<td>M</td>
</tr>
</tbody>
</table>

¹Numbering system varies between authors
²AR=autosomal recessive; AD=autosomal dominant; XL=X-linked.
³H=hemolytic anemia; M=myopathic weakness

GSD X

Phosphoglycerate mutase (PGAM) deficiency (OMIM #261670/GSD X), is considered to be a relatively benign muscle GSD (NAINI et al. 2009). Patients are asymptomatic until they perform brief strenuous exercise that triggers myalgia, muscle cramps, and often muscle necrosis and myoglobinuria. CK may be elevated, and forearm ischemic exercise testing shows mildly increased venous lactate levels (OH et al. 2006). Muscle biopsy shows normal to mild glycogen accumulation. The prevalence of the disease appears to be more common in African Americans. One nonsense mutation (W78X) in exon1 of the PGAM2 gene encoding the muscle subunit has been commonly found in African American patients suggesting a founder effect (NAINI et al.). where a common ancestor carried a mutation in the PGAM2 gene and passed it on to many descendants in this population. GSD X is an autosomal recessive disorder.

GSD XI

Lactate dehydrogenase (LDH) deficiency (GSD XI/OMIM #612933) is associated with muscle symptoms. Symptoms are caused by diminished energy supply and impaired ability to sustain exercise due to muscle pain and stiffness. Patients present with variable degrees of intolerance to intense exercise, cramps, and recurrent myoglobinuria. At the time of an episode very high levels of CK contrast with low levels of serum LDH. LDH deficiency causes a poor rise of lactate during the forearm ischemia test, but an increased rise of pyruvate (in other muscle
glycogenosis pyruvate rises minimally or does not rise) (Takahashi et al. 1995). GSD XI is caused by mutations in the LDHA gene, and it is an autosomal recessive disorder.

**GSD XII**
Aldolase A Deficiency (GSD XII; OMIM #611881) causes hemolytic anemia. A predominantly muscle type with exercise-triggered symptoms has been reported in a child with suspected hemolytic anemia (Kreuder 1996). The muscle biopsy does not show gross glycogen accumulation, although an increased amount of glycogen can be detected by electron microscopy (Tsujino, Nonaka, and DiMauro 2000). Mutations in the ALDOA gene cause GSD XII, which is inherited in an autosomal recessive manner.

**GSD XIII**
Patients with muscle-specific enolase deficiency, or β-enolase deficiency (GSD XIII; OMIM #612932) present by exercise induced myalgia, and increased CK levels after intense exercise. Symptoms may be episodic for years, with no lactate rise on the ischemic forearm test. The muscle biopsy does not show gross glycogen accumulation, although an increased amount of glycogen be detected by electron microscopy (Comi et al. 2001). Autosomal recessive β-enolase deficiency is caused by mutations in ENO3, the gene encoding β-enolase.

**GSD XIV**
Phosphoglucomutase (PGM1) deficiency (GSD XIV/OMIM #612934) has been described in a patient with exercise-induced intolerance and episodes of rhabdomyolysis (Stojkovic et al. 2009). The patient had normal elevation of lactate, and hyperammonemia on a forearm-exercise test. A muscle biopsy revealed abnormal accumulations of glycogen. Analysis of the PGM1 gene revealed two new mutations (Stojkovic et al. 2009), because GSD XIV is autosomal recessive inheritance.

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**References**


Chapter 13
Parent, Family and Patient Involvement

Coping with glycogen storage disease goes beyond gaining knowledge of the biochemistry and medical results of the condition. Everyone in the family unit will need support to deal with the emotional stress of a chronic condition such as glycogen storage disease.

In this chapter, we hope to review some of the common concerns created by GSD. This brief discussion will not answer all your questions about GSD since everyone’s experience with chronic illness is different. Since GSD has many forms, ranging from a relatively mild muscle ailment to the severe and fatal forms, our discussion must be rather general.

The first phase in dealing with GSD is often denial, one of the most common defense mechanisms, where there is a strong hope that things were ‘right.’ People often times ‘shop’ for physicians, who will tell you things are okay, and that the people who made the diagnosis were in error. Very commonly, because of the rarity of these conditions and the highly technical studies required for a diagnosis, families are referred to physicians who are new to them, and in whom confidence must develop over time. The denial reaction is common, and requires emotional support from family, friends, church or other spiritual counselors, medical staff and frequent discussions with other families dealing with glycogen storage disease. Knowledge and time can help assuage the denial reaction. Part of the denial reaction may be a fear of the GSD condition. Both the fear and the denial reactions can be reduced by further understanding the situation and informing yourself about the condition. The more informed you are, the less fear you will experience.

Another emotion experienced by many parents is a feeling of guilt; most parents at some time will ask, “Am I to BLAME? Am I the one RESPONSIBLE?”. There is no way, or need to assign blame or responsibility in this situation, as there is no guilty party. These situations are natural events, and we know of no act (alcohol, drugs, etc.) that contributes to the causing the disorder in a family.

Many couples find that the strength of their marriage is placed under stress by these emotional factors as well as financial demands. Recognizing that these problems will and do occur can commonly help in dealing with them.

The major goal of the parents (and friends) of persons with glycogen storage disease is helping the patient understand the disease, and to support that person in developing a realistic self-image and positive self-esteem. The child may have a high level of self-doubt and may begin to question why they are ‘different.’ Children may wonder: “Am I weird?”. A parent should attempt to answer the child’s questions frankly and not avoid them. Your child will recognize the fact that you are reluctant to discuss his/her questions, and this can heighten anxiety. Answer the questions as clearly as possible with appropriate vocabulary and with proper concern. For example, a child with GSD might ask, “Why is my tummy so big?” or “Why can’t I eat that?”; the parents’ answer might include the idea that the child’s body is special and that it works differently from others and as a result, they must do special things to be healthy. As a child’s
AGSD’s “Glycogen Storage Diseases: A Patient-Parent Handbook”

curiosity develops, it is very important to begin to let them be a part of their own treatment; this helps to develop an understanding of the condition and some sense of independence and control. As the child grows older, more in-depth conversations will take place. A young child may begin inserting nasogastric tubes at night, and taking a major role in their care; this is to be encouraged, but not forced.

Lastly, there may be times when a parent feels defeated and ready to give up. The stress of hospitalization, finances, emotional drains, treatment demands, and various aspects of coping with a chronic illness may at times seem insurmountable. When this occurs, seek support from sources that have been mentioned. It is also recommended that you attempt to contact other parents of children with GSD. They, more than any others, will understand your situation and may have answers to many of your questions.

The only thing different about your child with glycogen storage disease is a metabolic imbalance; your child will still have the natural wants, desires and love of any child. The child must grow up learning the usual rules and demands that are made on everybody; the expectations should not be modified except in the few objective ways that are necessary due to the disease condition. It will always be important to focus on the special talents and abilities of the child and to minimize the few areas in which restrictions must take place.

Revised May 1, 2016. Author: Stephanie Austin, MS, MA; CGC Genetic Counselor/Research Project Manager; Department of Pediatrics/Division of Medical Genetics; Duke University.
Chapter 14

Questions and Answers

A small group of parents have prepared a list of questions which they felt had significant interest to them, and which they have been asked by other parents and friends of persons associated and not associated with glycogen storage disease. Hollie Swain, Judy Zimmerman, and Maggie Smith have been particularly helpful.

Many of the questions don’t have a clear, single, correct answer but the response given is based on currently available best information about the disease.

1) Does the liver release any stored glycogen as a waste into the system?

Glycogen itself is not released from the liver into the body. Glycogen is a very large molecule and cannot pass through cell walls.

2) Does glycogen store in any other organs than liver with glucose-6-phosphatase deficiency (Type I)?

Glucose-6-phosphatase deficiency is also known as hepatorenal glycogen storage disease. This comes from the fact that there is storage of glycogen within the kidney as well as the liver. This leads to enlargement of the kidneys, but usually does not directly affect renal (kidney) function. Some patients do develop high blood pressure but it is unclear what the cause of this is. Kidneys can be affected, as well as the intestines, please see Chapter 4.

3) Do many children have convulsions when their blood sugar drops?

Some children with glucose-6-phosphatase deficiency and debrancher deficiency who have serious manifestations rarely have convulsions related to low blood sugar. It appears that the metabolism of the brains of most children gradually changes in order to use other energy sources and do not have convulsions even when blood sugar is low.

4) Are there any different kinds of convulsions, seizures, or spells they can have?

Patients with glucose-6-phosphatase deficiency (Type I) and low blood sugar have a variety of different types of spells. These may be a direct loss of consciousness so that the patient lies motionless or drops motionless to the floor. At other times there are generalized jerking movements, chewing movements, and seizures not unlike those seen in epilepsy. This can happen to anyone, not just GSD patients.
5) Is a high protein diet important to these children?

There may be benefits to persons with alpha-1,4 glucosidase deficiency (Type II; Pompe disease) and debrancher deficiency (Type III) when a high protein diet is used.

In patients with glucose-6-phosphatase deficiency protein cannot be converted to glucose, due to a deficiency of this key enzyme. Patients with GSD-I typically have 60-70% of calories as carbohydrates. Relatively low fat diets appear to be good for everyone. Since blood lipid (fat) levels tend to be high in several of the liver forms of the glycogen storage diseases, most experts recommend a diet low in saturated fats and cholesterol.

6) Does it do much harm or throw their systems off if they eat candy, or foods that are restricted?

The important thing is to eat a well-balanced nutritious diet. Occasional small indiscretions are not likely to produce serious problems in patients with GSDs.

7) When children get very sick with vomiting and nothing stays down, even glucose, what is the best solution?

Children with some glycogen storage diseases have low blood sugar whenever their normal diet is interrupted. It is important for anyone with a history of low blood sugar to seek medical attention, if they have repeated vomiting. Usually repeated vomiting will require intravenous fluids containing glucose. Your doctor can best assess this need, but experienced parents are good judges. You should make plans for this in advance (have your doctor write instructions for a local 24-hour facility, either an emergency room or other emergency facility). If traveling out of your area, it is worthwhile having your physician provide written materials so this situation can be handled in a strange city.

8) What are the chances of a person with glycogen storage disease having children of their own?

Many adults with glucose-6-phosphatase deficiency, debrancher deficiency, alpha-1,4 glucosidase deficiency, phosphorylase b kinase deficiency and muscle phosphorylase deficiency have had children.
9) If two children at age 4 years had liver biopsies (one who has been on treatment and the other with no special treatment) could you see a difference in their livers?

The liver biopsy of the patient with GSD type I who had been well controlled might contain less fat. The glycogen concentration would not be significantly changed and the enzyme defect (glucose-6-phosphatase deficiency) would persist. The effect of treatment on the liver is not as well understood for GSD III or other GSDs involving the liver.

10) What is the life expectancy of a person with glycogen storage disease?

The life expectancy of persons with glucose-6-phosphatase deficiency, debrancher deficiency, and with liver phosphorylase deficiency is probably somewhat reduced although many do quite well.

The big risks are kidney disease and high blood pressure. It is uncommon, but some adults with GSD type I develop liver cancer. Patients with severe alpha-1,4 glucosidase deficiency or brancher deficiency usually die in early childhood. Patients with muscle phosphorylase deficiency (McArdle Disease) and usual forms of phosphorylase b kinase deficiency probably have an average life expectancy.

11) Will the liver ever be a normal size in proportion to the body size?

The liver in glucose-6-phosphatase deficiency will never be normal in size. However, as the person grows taller, the liver ‘fits’ better and the abdomen is considerably less prominent. The liver in debrancher deficiency does get smaller following puberty. This also appears to be true for phosphorylase-b-kinase deficiency, but not well established.

12) Will my child outgrow glycogen storage disease?

No. This is a genetic defect which is permanently encoded in the genetic makeup of the person, and will always be a medical issue, but perhaps not so much as the child gets older.

13) Is research being done for a cure?

YES. There is a great deal of work being done in the glycogen storage diseases. Enzyme replacement therapy is available for GSD II (Pompe disease). Modified cornstarch has improved the dietary therapy for GSD I. Gene therapy is under development for several GSDs. The rapid advances in genetic technology should impact the treatment of glycogen storage disease quite positively.
14) **How many patients are there?**

We do not have an accurate estimate. Pompe disease has been shown to occur in about 1 in 20,000 babies during newborn screening. Other types of GSD are estimated to occur in about one of 50,000 to 100,000 births. That means that there are several thousand such persons in the United States with one or another type of GSD. Some patients with severe infantile forms might die before a diagnosis is made, and some milder forms might go unrecognized.

15) **Is this disease restrictive to one nationality?**

No. All nationalities are affected with about the same frequency.

16) **Would a liver transplant help a child with glycogen storage disease?**

Liver transplants have been performed in the glycogen storage diseases with some very good results. Liver transplants are extremely complex and risky, and are performed only for life-threatening situations. If performed for glucose-6-phosphatase deficiency it can be expected to have good results. In brancher deficiency where liver failure is prominent, liver transplantation fixes the liver problem, but the muscle disease will continue to worsen. The same is true for the common form of debrancher deficiency. Liver transplantation would not be helpful for Pompe disease or McArdle disease.

17) **Who can we talk to that will understand and are there other parents, and patients?**

Yes. The Association for Glycogen Storage Disease is a parent/patients group. The address and telephone number is:

Association for Glycogen Storage Disease  
PO Box 896  
Durant, IA  52747  
Telephone/Fax: (563) 514-4022  
website: www.agsdus.org

Revised May 1, 2016. Author: Dr. Stephen Kahler MD, Professor; Department of Pediatrics,  
Section of Genetics & Metabolism, University of Arkansas Medical School.
Chapter 15
Where to Get More Information

The most important source of information about the patient with glycogen storage disease is the patient’s physician. As we have outlined, there are many types of glycogen storage disease and each patient is unique with respect to the situations which is presented. Each person has in the range of 20,000 genes, and the defective gene is only one of these. This defective gene functions in a unique environment of other genes, and produces a very special person.

Because of the rarity of this diagnosis, your family doctor might not be fully aware of all the current research and treatment of the glycogen storage diseases. The ideal situation is to develop a relationship with a group of specialists whom your personal physician recommends, and together they can form the team to provide the most accurate diagnosis and best treatment program. It is essential to have a physician who sees the patient on a regular basis and provides all the care needed, in addition to the special needs.

You will want to avail yourself of other sources of information. Be cautious about out-of-date medical materials. Books that are more than 5 years old are likely to be very much out-of-date. The field is moving so rapidly that a few years usually dates material. Be sure to show the material to your physician. Libraries will be of little help except those of a large college or medical school facility.

Be wary of word of mouth, old wives tales and testimonies from non-professionals involved in GSD treatment and research. This also is appropriate for the many avenues the computer has now made available. Not every address gives current and/or correct information. NEVER should the computer information be used for self-diagnosis. ALWAYS seek out confirmed GSD medical professionals for the correct procedures to determine your correct diagnosis and treatment.

The most authoritative information on the Glycogen Storage Diseases is contained in the Chapter by Drs. Chen and colleagues in “The Online Metabolic and Molecular Basis of Inherited Disease,” edited by Scriver, et al, and published by McGraw-Hill.

*The Ray,* newsletter for the Association for Glycogen Storage Disease, PO Box 896, Durant, IA 52747 is a publication that is a must for parents and persons with glycogen storage disease. The newsletter is filled with helpful, authoritative and current information. The group itself is parent-oriented and is advised by a national, experienced group of professionals who assist GSD families.
Chapter 16

Glossary of Terms Related to Glycogen Storage Disease

GLYCOGEN: A polysaccharide (this means many glucose molecules) is composed of a group of glucose molecules attached in a linear fashion, with branch points. The body stores glucose in this way, and uses glycogen breakdown to elevate blood sugar.

Types of Glycogen Storage Disease:

Type I Glycogen Storage Disease: Glucose-6-phosphatase deficiency (Ia); Glucose-6 phosphate transporter (Ib); von Gierke Disease; Hepatorenal glycogenosis. Type Ia and Ib affect the patient similarly. The main difference is the lack of neutrophils (white blood cells) in Type Ib.

Type II Glycogen Storage Disease: Alpha-1,4 glucosidase deficiency; acid maltase deficiency; Pompe Disease. There are at least three types, by age of onset and severity: infantile, juvenile, and adult.

Type III Glycogen Storage Disease: Amylo-1,6 glucosidase deficiency (liver/muscle - IIIa); Debrancher deficiency (liver-IIIb); Cori or Forbes Disease; Limit Dextrinosis.

Type IV Glycogen Storage Disease: Alpha-1,4-glucan deficiency; alpha-1,4-Glucan 6 glucosyl transferase deficiency; brancher deficiency; Andersen Disease; amylopectinosis.

Type V Glycogen Storage Disease: Muscle phosphorylase deficiency; McArdle Disease; myophosphorylase deficiency. A very similar clinical picture is seen with deficiency of muscle phosphofructokinase, known as Tarui Disease (sometimes called Type VII GSD).

Type VI Glycogen Storage Disease: Liver (hepatic) phosphorylase deficiency; Hers Disease.

Type VII Glycogen Storage Disease: Muscle phosphofructokinase deficiency, Tarui Disease.

Type VIII Glycogen Storage Disease: No associated terms.

Type IX Glycogen Storage Disease: Phosphorylase b kinase deficiency.