Chapter Amyloidosis

Amyloidosis is a condition that causes an abnormal protein called amyloid to build up in your body. Amyloid deposits can eventually damage organs and cause them to fail. This condition is rare, but it can be serious.

Organs that amyloidosis can affect include the:

- heart
- kidneys
- intestines
- joints
- liver
- nerves
- skin
- soft tissues

Sometimes, amyloid collects throughout your body. This is called systemic, or body-wide, amyloidosis.

Most forms of amyloidosis aren’t preventable. However, you can manage symptoms with treatment.

What are the symptoms?

In its early stages, amyloidosis might not cause symptoms. When it becomes more severe, which symptoms you have depend on the organ or organs that are affected.

If your heart is affected, you may experience:

- shortness of breath
- fast, slow, or irregular heart rate
- chest pain
- low blood pressure, which could cause lightheadedness

If your kidneys are affected, you may experience swelling in your legs due to fluid buildup (edema) or foamy urine from excess protein.

If your liver is affected, you may experience pain and swelling in the upper part of your abdomen.If your gastrointestinal tract is affected, you may experience:

- nausea
- diarrhea
- constipation
- appetite loss
- weight loss
- feeling of fullness right after eating

If your nerves are affected, you may experience:

- pain, numbness, and tingling in your hands, feet, and lower legs
- dizziness when standing up
- nausea
- diarrhea
- inability to feel cold or heat

Types and causes

Your bone marrow normally produces the blood cells your body uses to transport oxygen to your tissues, fight infections, and help your blood clot.

In one type of amyloidosis, infection-fighting white blood cells (plasma cells) in the bone marrow produce an abnormal protein called amyloid. This protein folds and clumps, and is harder for the body to break down.

In general, amyloidosis is caused by a buildup of amyloid in your organs. How the amyloid gets there depends on which type of the condition you have:

Light chain (AL) amyloidosis: This is the most common type. It happens when abnormal amyloid proteins called light chains build up in organs like your heart, kidneys, liver, and skin. This type used to be called primary amyloidosis.

Autoimmune (AA) amyloidosis: You can get this type after an infection like tuberculosis, or a disease that causes inflammation such as rheumatoid arthritis or inflammatory bowel disease. About half of people with AA amyloidosis have rheumatoid arthritis. AA amyloidosis mainly affects your kidneys. Sometimes it also can damage your intestines, liver, or heart. This type used to be called secondary amyloidosis.

Dialysis-related amyloidosis: This type affects people who are on dialysis for a long period of time as a result of kidney problems. The amyloid deposits in the joints and tendons, causing pain and stiffness.

Hereditary (familial) amyloidosis: This rare type is caused by a mutation in a gene that runs in families. Hereditary amyloidosis can affect the nerves, heart, liver, and kidneys.

Senile amyloidosis: This type affects the heart

- Amyloid is an abnormal insoluble extracellular protein that deposits in the different tissues and causes organic dysfunction and a wide variety of clinical syndromes.
- These abnormal amyloids are derived from misfolding and aggregation of normally soluble proteins.
- Amyloid deposition can disrupt tissue structure of involved organ and consequently leads to organ failure.

Systemic Amyloidosis

- In systemic amyloidosis, amyloid gradually accumulates and amyloid deposition is widespread in the viscera, blood vessel walls, and different connective tissues.

Primary Amyloidosis (AL)

- Primary (AL) amyloidosis) is the most common type of amyloidosis.
- It results from aggregation and deposition of monoclonal immunoglobulin (Ig) light chains that are usually produced by plasma cell clones.
- Change in the secondary structure or tertiary structure of a monoclonal light chain results in abnormal folding of the light chain that abnormally form amyloid fibrils.
- This type of amyloidosis most frequently involve the kidney (nephrotic syndrome) and the heart.
- In primary (AL) amyloidosis survival rate depends on:
  - Type of organ involvement (amyloid heart disease is the main prognostic factor)
  - The severity of different organ involvement
  - Hematological response to treatment
- The median survival of patients with AL amyloidosis is approximately 3.8 years.

Secondary Amyloidosis (AA)

- Secondary amyloidosis occurs as a reaction to an existing illness.
- Secondary amyloidosis is associated with chronic inflammation (such as tuberculosis or rheumatoid arthritis).
- Secondary or reactive amyloidosis (AA) comprises approximately 45% of the systemic amyloidoses.

- Pathogenesis of secondary amyloidosis is multifactorial, including:
  - Primary structure of the precursor protein
  - Acute phase response
  - Nonfibril proteins (amyloid P component, apo E, GAGs, proteoglycans and basement membrane proteins)
  - Receptors
  - Lipid metabolism
  - Proteases

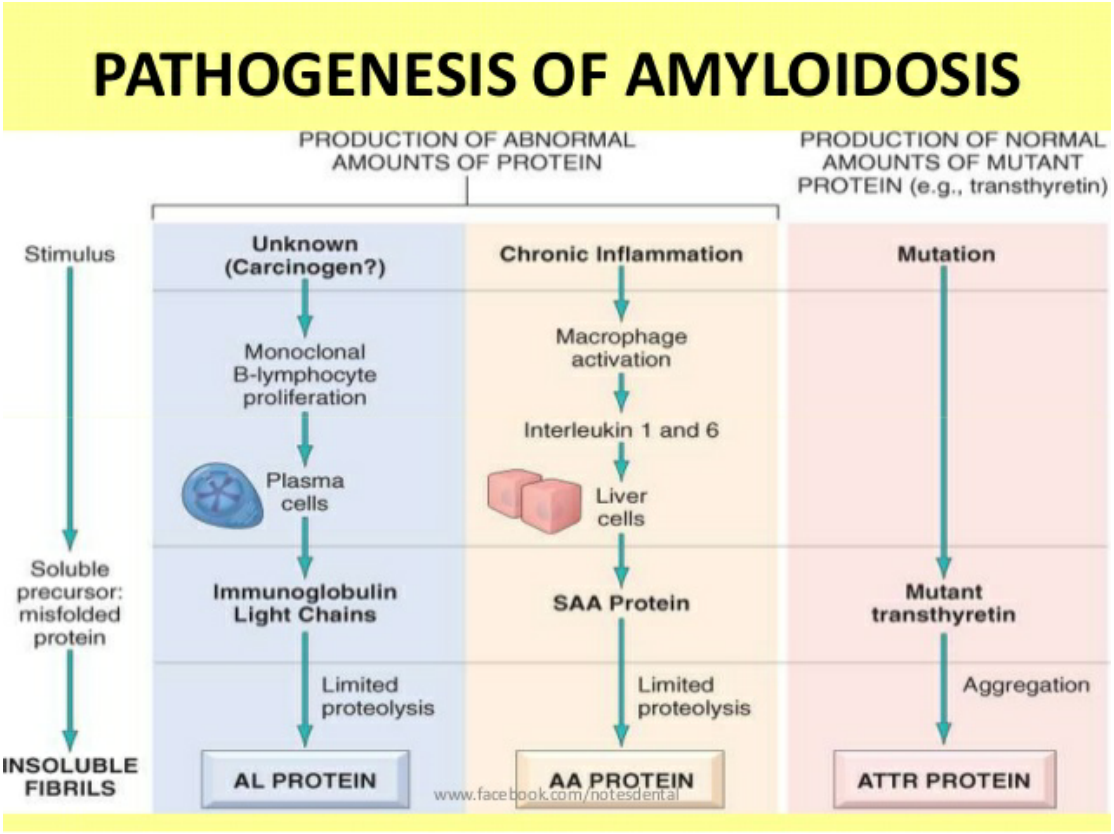
Hereditary Amyloidosis

- Hereditary amyloidosis is an autosomal dominant disorder.
- It can have a heterogeneous nature of presentation and can be complicated by significant disability and mortality.
- Inherited variant proteins cause the production and deposition of amyloid fibrils.
- Hereditary amyloidosis is due to amyloidogenic mutations and the subsequent deposition of amyloids which include:
  - Transthyretin (TTR) (most common inherited mutation)
  - Fibrinogen
  - Apolipoprotein A1
  - Apolipoprotein A2
  - Lysozyme
  - Gelsolin genes

Organ-specific Amyloidosis

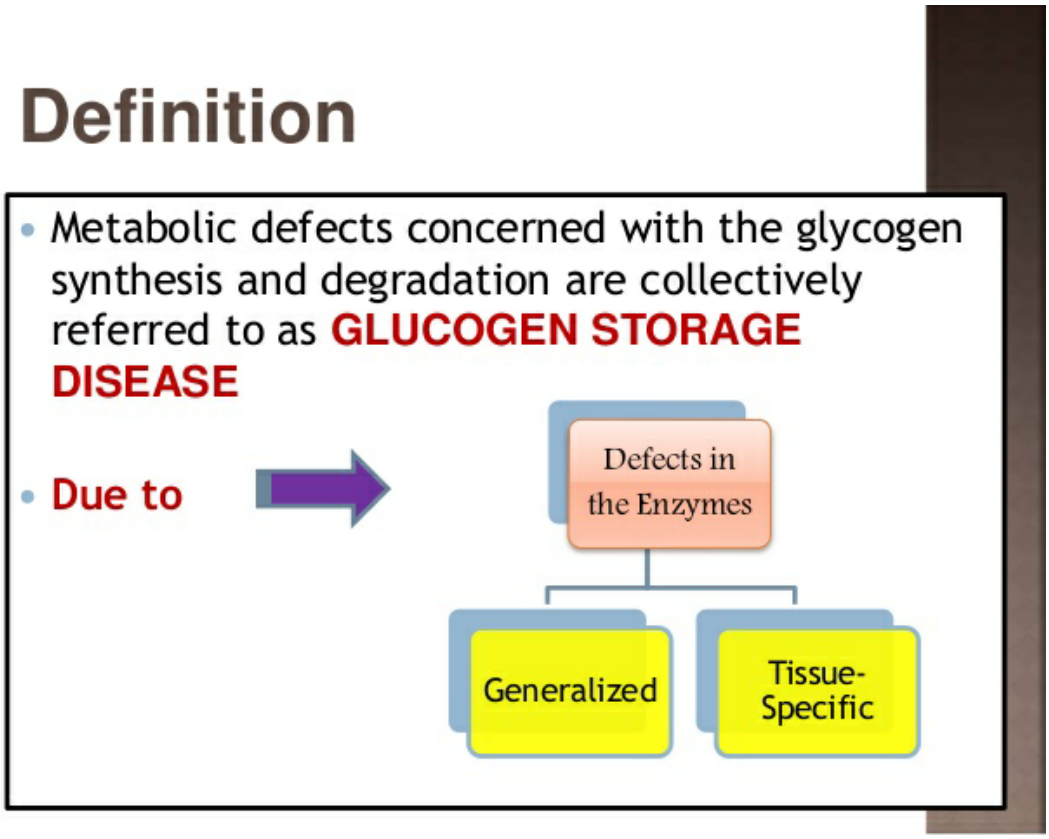
- In this type of amyloidosis, amyloid deposition occurs only in the organ of origin or tissue of precursor protein.
- Neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease, may occur in localized amyloidosis.
- Localized amyloidoses can develop due to the deposition of intracellular and/or extracellular amyloid.

- Huntington's disease: intracellular protein deposition
- Parkinson's disease: intracellular protein deposition
- Alzheimer's disease: intracellular (Tau protein fibrils) and extracellular (amyloid β fibrils) deposition



Glycogen storage diseases

What is glycogen and glycogen storage disease (GSD)?



The body's cells need a steady supply of fuel in order to function the right way. This fuel is a simple sugar called glucose. Glucose comes from breaking down the food we eat. The body uses as much glucose as it needs to function and stores the rest to use later.

Before it can be stored, the body must combine the simple glucose units into a new, complex sugar called glycogen. The glycogen is then stored in the liver and muscle cells. When the body needs extra fuel, it breaks down the glycogen stored in the liver back into the glucose units the cells can use. Special proteins called enzymes help both make and break down the glycogen in a process called glycogen metabolism.

Sometimes a person is born missing an enzyme needed for this process or it may not work right. Then the body is not able to store or break down the glycogen as it should. This can lead to very low blood glucose levels during periods of fasting. The muscles and organs need a certain level of glucose in the blood to work properly.

When the body is missing an enzyme or has a flawed enzyme and is not able to use glycogen the right way, it leads to a condition called glycogen storage disease (GSD). Many different enzymes are used by the body to process glycogen. And, as a result, there are several types of GSD.

How common are they?

A glycogen storage disorder occurs in about one in 20,000 to 25,000 babies. The most common types of GSD are types I, II, III, and IV, with type I being the most common. It is believed that nearly 90% of all patients with GSD have types I through IV. About 25% of patients with GSD are thought to have type I. However, GSD types VI and IX can have very mild symptoms and may be underdiagnosed.

Most of the severe forms of GSD are diagnosed in babies and children. Some of the milder types might not be found until the person is an adult.

What are the symptoms of glycogen storage disease (GSD)?

Symptoms vary based on the type of GSD. Some GSDs affect mostly the liver. These include Types 0, I, III, IV, VI and IX. However, they may sometimes have overlapping symptoms affecting muscle and heart. These types (except for GSD type 0) may cause the liver to become enlarged. An enlarged liver is linked to low blood glucose levels because excess glycogen is stored in the liver instead of being released as glucose in the blood stream. Symptoms of low blood glucose, or hypoglycemia, include sweating, tremor, drowsiness, confusion and sometimes seizures. Some GSDs, such as types V and VII, mostly affect the skeletal muscles. Muscle weakness and muscle cramps are the most common symptoms of these types.

Other symptoms that may occur include:

- Tiredness.
- Very slow growth.
- Obesity (being very overweight).
- Problems with bleeding and blood clotting.
- Kidney problems.
- Low resistance to infections.
- Breathing problems.
- Heart problems.
- Mouth sores.
- Gout.

What causes GSDs?

GSDs occur when there is a problem with the gene that has the instructions for making the enzyme that is missing or not working right. The gene is passed down from parents to children. In most cases, in order to have the GSD, a child must get a bad gene from both parents. Just because both parents have the gene does not always mean they will both pass it on to their children.

How are types of glycogen storage diseases (GSDs) detected?

There are four symptoms that might cause the doctor to suspect a type of GSD that affects the liver.

These include:

- A low blood glucose level.
- An enlarged liver.
- Lagging growth.
- Abnormal blood tests.

Because GSDs can run in families, a thorough medical history can also give the doctor a first clue. He or she may suggest some tests that might include:

- Blood tests – To find out your blood glucose level and to see how your liver, kidneys and muscles are working.
- Abdominal ultrasound – To see if your liver is enlarged.
- Tissue biopsy – Testing a sample of tissue from a muscle or your liver to measure the level of glycogen or enzymes present.
- Gene testing – To look for problems with the genes for different enzymes. Gene testing can confirm a GSD.

What are the types of GSD?

Each type of GSD centers on a certain enzyme or set of enzymes involved in glycogen storage or break down. There are at least 13 types of glycogen storage disease. Doctors know more about some types than others. GSD mostly affects the liver and the muscles. Some types cause problems in other areas of the body as well. Types of GSD and the parts of the body they affect the most include:

Type 0 (Lewis' disease) – **Affected tissue**; Liver

Affected enzyme; Hepatic glycogen synthase.

Clinical features

✓ Seizures can occur
✓ Fatigue and muscle cramps after exertion
✓ Mild growth retardation in some cases

Investigation

Blood test;

a. Liver function test; monitoring for hepatic failure
b. Anion gap calculation; if glucose low,this may indicate lactic acidaemia
c. Urate
d. Creatinine clearance

e. Creatinine kinase
f. Full blood count

Urine test

Mycoglobinuria after exercise found in 50% of people with McArdle's diseases

Imagining

a) Abdominal ultrasoundscan;hepatomegaly
b) Echocardiography;to look for cardiac involvement in certain types of GSD

Pre-natal diagnosis

a. Genetic counselling
b. Referral to geneticist for possible prenatal investigation(amniotic fluid analysis) and diagnosis

Type I (von Gierke's disease) Affected enzyme:glucose-6-phosphate

Affected tissue: Liver and Kidney

Clinical features;

- ✓ Large quantities of glycogen are formed and stored in hepatocytes,renal and intestinal mucosa cells. The liver and kidneys become enlarged
- ✓ Abnormalities of lipids may lead to xanthoma formation
- ✓ Uric acid is often elevated and may causes clinical gout,galactose,fructose, and glycerol are metabolised to lactate.The elevated blood lactate levels cause metabolic acidosis.

Treatment.

a. Blood loss may require oral iron
b. Raised uric acid levels may require allopurinol
c. Treatment of hyperuricaemia and pyelenephritis protect renal function
d. Diaoxide to maintain blood glucose has been disappointing
e. Liver transplantation for primary diseases or for hepatocellular carcinoma seems effective

Type II (Pompe's disease) Muscles,heart,liver,nervous system, blood vessels.

Causes

The deficiency of the lysosomal enzyme alpha-1,4-glucosidase(acid maltase) leads to the accumulation of glycogen in many tissue

Clinical features

a) The clinical spectrum is continuous and broad,with presentation in infants,children, and adults
b) In the infantile form, accumulation of glycogen in cardiac muscle leads to cardiac failure.
c) Accumulation may als occur in the liver,which results in hepatomegaly and elevation of hepatic enzymes.
d) Glycogen accumulation in muscle and peripheral nerves causes hypotonia and weakness
e) Glycogen deposition in blood vessels may result in intracranial aneurysms

Treatment

a. Enzyme replacement therapy (Alglucosidase alfa)
b. Diet therapy may provide temporary improvement but does not after the diseases course; high-protein,low-carbohydrate diet may beneficial.
c. Physiotherapy and occupational therapy may be required
d. Genetic counselling and prenatal diagnosis;chronicvillus sampling and amniocentesis can be used to determine enzyme activity in a fetus
e. Gene therapy remains a potentially effective for the future

Type III (Forbes-cori disease) – **Affected tissue;** Liver, muscles,

Affected enzymes;Glycogen debranching enzyme,deposition of abnormalglycogen structure

Clinical features

a) About 15% affected liver only, hypoglycemia, poor growth,heptatomegaly,moderate progressive myopathy.
b) Symptoms can regress with age
c) Afew cases of liver cirrhosis andhepatocellular carcinoma have been report

Treatment

As with type I, also protein supplement for muscle disorder

Type IV (Andersen's disease) –**Affected tissue**s; Liver, brain,heart, muscle,skin,nervous system

Affected enzyme; Glycogen branching enzyme ,abnormally structured glycogen forms

Clinical features

Hepatomegaly, failure to thrive, cirrhosis,splenomegaly,jaundice,hypotonia,lumbar lordosis

Treatment

Liver transplant

Type V (McArdle's disease) – **Affected tissue;** Skeletal muscles

Causes; Myphosphorlyase deficiency

Clinical features

a. Clinical findings may be absent on physical examination,muscle strengthand reflexes may be normal
b. In later adult life,persistent proximal weakness and muscle wasting may be present
c. The fatal infantile form presents with hypotonia and reduced reflexes.
d. Ischaemic forearm test;traditional test but it is painful and non-ischaemic exercise test are preferred

Treatment

a) No specific treatment exists.
b) Avoid strenuous (anaerobic or sustained) exercise, including liftinf or pushing
c) A carbohydrate rich diet did benefit patients

Type VI (Hers' diseases) – **Affected tissues**; Liver, blood cells

Affected enzyme; Liver phosphorylase

Clinical features

a. Most common variants is X-linked therefore usually affected only males
b. Hepatomegaly,hypoglycaemia,growth retardation,hyperlipidaemia

Treatment

Cardiac transplantationn fore rare cardiac form,may need frequent feeding to **avoid hypoglycemia**

Prognosis

Usally normal life span

Type VII (Tarui's disease) Affected tissue; Skeletal muscle

Causes; Phosphofructokinase(PFK)deficiency

Clinical features

Exercise intolerance,muscle cramping,exertional myopathy,compensated haemolysis and myoglobinuria.

Note symptoms can be similar to McArdle's Glycogen storage diseases but more severe

Treatment

a) No specific treatment exists
b) There is evidence that a high protein diet may improve muscle function and slow progression of the disease
c) Vigorous exercise should be avoided as it causes myoglobinuria

Type IX-Liver

a. GSD type IX is a disorder in which body cannot break down glycogen people with GSD IX are deficient in an enzyme called phosphorylase kinase (PhK).A deficiency in PhK causes glycogen to accumulate in various tissues including liver,muscle,red blood cells,and some times in heart
b. Phosphorylase kinase(Phk) specefic protein kinase which activates glycogen phosphorylase to releasglucose-1--phosphate from glycogen

Symptoms

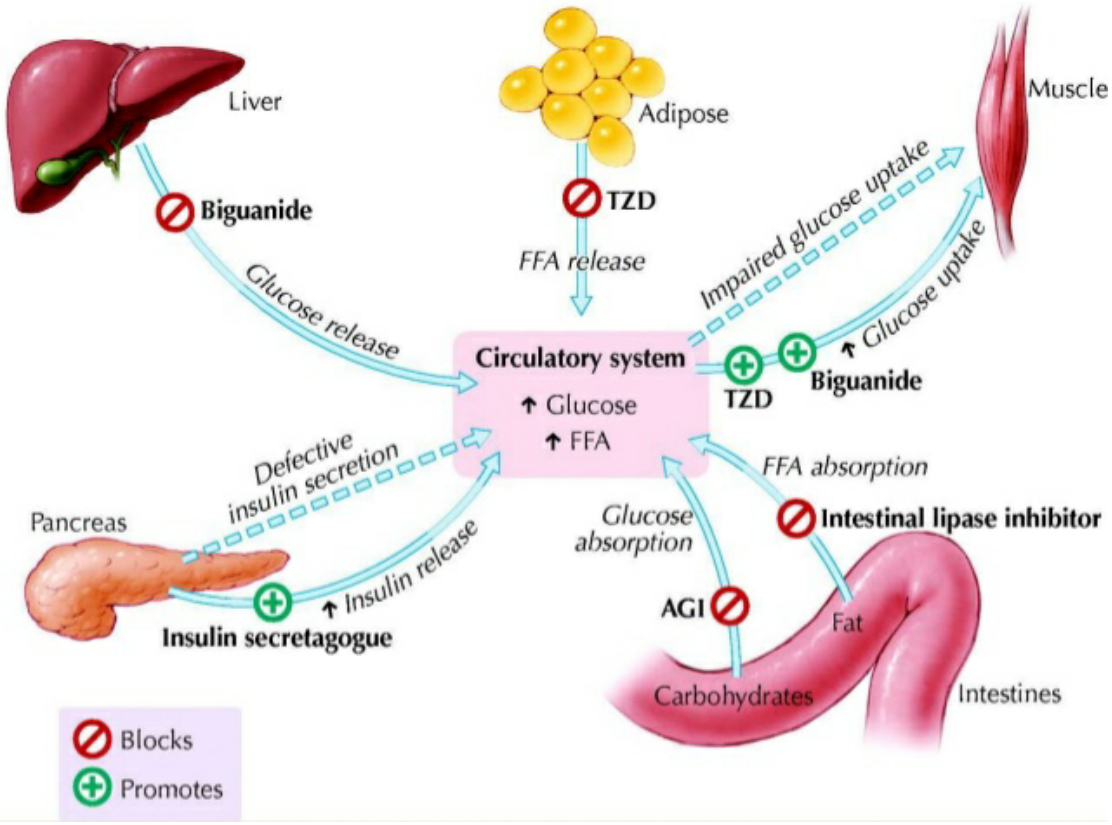
People with GSD IX develop enlarged liver and may have low blood sugar,due to inability to breakdown glycogen

Diagnosis

a) Blood profiling
b) Biopsy of liver

Treatment

It can be prevented by maintaining high carbohydrate(starch foods) diet, adequate amounts of protein in diet and avoiding delayed intake of foods.



How is glycogen storage disease (GSD) treated?

Treatment varies depending on the type of GSD. For types of GSD that involve the liver, treatment is aimed at keeping the right level of glucose in the blood. This is often enough to maintain the cells fuel needs and prevent long-term complications associated with poorly controlled GSD. Treatment consists of taking regular doses of uncooked cornstarch and/or nutrition supplements. Cornstarch is a complex carbohydrate that is difficult for the body to digest; therefore it maintains normal blood sugar levels for a longer period of time than most carbohydrates in food. Eating many small meals that are low in sugar can help keep blood sugar levels normal while preventing excess glycogen storage in the liver.

Carbohydrate solutions may be given continuously during the night to prevent a drop in blood glucose level during sleep, but this carries more risk of severe hypoglycemia compared to using uncooked cornstarch around the clock.

Type IV GSDs with progressive liver disease may have to be considered for liver transplantation after a thorough evaluation.

Can glycogen storage disease (GSD) be prevented?

GSDs are handed down from parents to children through their genes. Therefore, they cannot be prevented. Parents can find out through genetic testing if they carry a gene for a GSD. Both parents must ave a gene for the same type of GSD for a child to inherit the disorder.