Other Disorders

Screening, Technology, and Research in Genetics is a multi-state project to improve information about the financial, ethical, legal, and social issues surrounding expanded newborn screening and genetic testing – http:// www.newbornscreening.info

Disorder name: Gaucher disease
Acronym: GD

This fact sheet contains general information about Gaucher disease. Every child is different and some of this information may not apply to your child specifically. Certain treatments may be recommended for some children but not others. If you have specific questions about Gaucher disease and available treatments, you should contact your doctor.

What is Gaucher disease?

Gaucher disease is an inherited disorder that affects many parts of the body, especially the spleen, liver, bones, and blood. Rarely, in more severe cases, the brain can be affected. People with Gaucher disease have problems breaking down a fat called glucocerebroside (also known as glucosylceramide). Gaucher

disease belongs to the group of diseases called lysosomal storage disorders. There is a wide range in the severity and age of onset for Gaucher disease.

Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are a group of inherited disorders. They are caused by enzymes that do not work properly.

Lysosomes are like recycling centers for cells. They are small sacs filled with enzymes. These enzymes help break down large molecules into smaller molecules that the body can re-use. People with LSDs are missing enzymes or have non-working enzymes. As a result, these people have problems breaking down certain large molecules into usable forms. This leads to a buildup of these molecules, which causes a variety of problems.

The symptoms and treatment vary between LSDs. They can also vary from person to person with the same LSD.

What causes Gaucher disease?

Gaucher disease is caused when an enzyme called “glucocerebrosidase” (GBA), is either missing or not working properly. This enzyme is located in the lysosomes. Its job is to recycle a complex fat (glucocerebroside) that is a normal part of cells.

When the body is unable to breakdown glucocerebroside, it builds up in the lysosomes. This buildup causes the lysosomes to swell and damage the cellular structures around them. The buildup of glucocerebroside in sensitive tissues like the spleen, liver, bone marrow, bone, and other organs causes the symptoms of Gaucher disease.

What are the symptoms of Gaucher disease?

The symptoms of Gaucher disease vary from person to person. Symptoms can begin at different ages. Some symptoms may start in infancy, adulthood, or may not be present at all. Without treatment, in severe cases the symptoms of Gaucher disease may be fatal. It is important to remember that each child is different and may experience symptoms differently.

There are three types of Gaucher disease:

- Type 1 (non-neuronopathic, late-onset)
- Type 2 (acute neuronopathic, infantile-onset)
- Type 3 (subacute neuronopathic, juvenile-onset)

Most individuals with Gaucher disease have type 1, the late-onset non-neuronopathic condition; these individuals tend to have more mild symptoms. While rarer, both the infantile-onset and juvenile-onset types of Gaucher disease have more severe symptoms.

Type 1 (non-neuronopathic, late-onset) Gaucher disease
Type 1 Gaucher disease is the most common type of Gaucher disease, with a wide range of age of onset and symptoms. Individuals with Type 1 Gaucher disease often do not develop symptoms until adulthood, although some people may have symptoms in childhood. Some individuals may never develop any symptoms of Type 1 Gaucher disease.

Symptoms of Type 1 Gaucher disease depend on the individual and their ability to produce the GBA enzyme to prevent glucocerebroside from building up.

Symptoms include:

- Bleeding problems – low blood count, frequent nose bleeds, problems with ability to clot
- Bone problems – fragile bones, frequent broken bones, bone pain
- Enlarged liver and spleen
- Fatigue
- Low blood counts
- Lung disease

It is important for individuals with Type 1 Gaucher disease to be seen by a specialist to help treat, prevent, and manage any symptoms. Individuals with Type 1 Gaucher disease do not get brain and central nervous system symptoms. Enzyme replacement therapy may be helpful in preventing or reducing symptoms in the bones, blood, and liver.

Type 2 (acute neuronopathic, infantile-onset) Gaucher disease
Signs of Type 2 (acute neuronopathic infantile-onset) Gaucher disease usually appear within the first year of the baby's life.
These signs and symptoms may include:

- Developmental disability
- Enlarged liver and spleen
- Poor ability to suck and swallow
- Seizures
- Skin problems
- Spasticity (jerking movements)
- Unusual eye movements
- Lung disease

Type 2 Gaucher disease is the rarest type, making up 1% of all Gaucher disease diagnoses. No successful treatment options exist for Type 2 Gaucher disease.

Type 3 (subacute neuronopathic, juvenile onset) Gaucher disease
Type 3 Gaucher disease typically appears during childhood, and has a slower development of symptoms when compared to Type 2 Gaucher disease.

These signs and symptoms may include:

- Blood disorders
- Bone deformities and frequent breaks
- Developmental delay
- Trouble with coordination
- Enlarged liver and spleen
- Lung disease
- Seizures
- Unusual eye movement

Individuals with Type 3 Gaucher disease can receive enzyme replacement therapy to limit some symptoms. This treatment is not effective at treating symptoms involving the brain and central nervous system. Enzyme replacement therapy may be helpful in preventing or reducing symptoms in the bones, blood, and liver.

What is the treatment for Gaucher disease?

People with Gaucher disease should be treated by a team of specialists who are familiar with the disorder. Which specialists are needed will depend on the person's symptoms. All people with Gaucher disease should be seen by a biochemical genetics doctor (or metabolic genetic specialist). Their team may also include a hematologist (blood doctor), neurologist (brain doctor), gastroenterologist (liver doctor), orthopedist (bone doctor), and genetic counselor. This team can support the family and help manage the symptoms of Gaucher disease.

People with Gaucher disease will have an individualized treatment plan depending on the progression and symptoms of their condition. Certain treatments may be recommended for some children but not others. The following treatments and management are often recommended for children with Gaucher disease:

1. **Bone/Skeletal Support**
   Bone involvement is the most common cause of discomfort for individuals with late-onset Gaucher disease. The associated pain and limitations on mobility can be prevented with certain treatments. An orthopedist (bone doctor) can evaluate and monitor symptoms by measuring the strength of the bones using imaging (such as X-ray or MRI).

2. **Liver Care**
   Abdominal organs, especially the liver, can be affected by Gaucher disease. Cells with an accumulation of glucocerebroside can buildup in the organs and cause them to swell and not function normally. A gastroenterologist (liver doctor) can help monitor and manage symptoms of Gaucher disease.

3. **Psychosocial Support**
   Individual and family counseling, disease education, and participation in patient organizations, advocacy groups, and support groups are important for managing the emotional and psychological impact of Gaucher disease.

4. **Enzyme Replacement Therapy (ERT)**
   Gaucher disease is caused by not having enough of an enzyme called acid glucocerebrosidase (GBA). Enzyme replacement therapy gives people a replacement form of that enzyme intravenously. This new enzyme replaces GBA in people with Gaucher disease. This is a long-term treatment option, but it is not considered a cure. If enzyme replacement therapy is started at the onset of symptoms, it can often prevent or reduce the impact of some Gaucher disease symptoms. It does not prevent or reduce brain and central nervous system symptoms.

5. **Substrate Reduction Therapy (SRT)**
   Substrate reduction therapy aims to decrease the buildup of the fat, glucocerebroside. Substrate reduction therapy is given to individuals with mild to moderate late-onset Gaucher disease for which ERT is not a good option. Substrate reduction therapy is not approved for children or teens, pregnant or breastfeeding women, very elderly patients, or individuals with severe kidney or liver disease.

What happens when Gaucher disease is treated?

Success of treatment for Gaucher disease depends on the type of Gaucher disease an individual has and the progression of the individual's condition.

In children with chronic Type 3 Gaucher disease, ERT may improve and prevent symptoms. ERT may increase bone strength and protect abdominal organs. ERT does not improve symptoms affecting the brain and central nervous system.

In individuals with late-onset Gaucher disease, ERT and SRT can be used to help prevent or improve symptoms.

With early detection and treatment, children with Gaucher disease are more likely to live healthy lives.

What causes the GBA enzyme to be absent or not working correctly?

Genes tell the body to make different enzymes. The GBA gene provides the body the instructions to make the GBA enzyme. People with Gaucher disease have two GBA genes that do not work correctly. Because of the changes, also called variants, in these two GBA genes, the GBA enzyme either does not work properly or is not made at all.

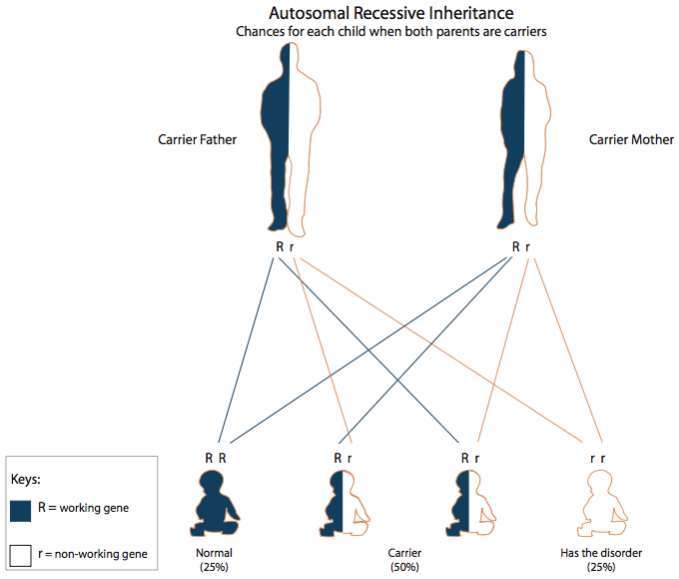
How is Gaucher disease inherited?

Gaucher disease is inherited in an autosomal recessive manner. It affects both boys and girls equally.

In people with Gaucher disease, both GBA genes do not work correctly. These individuals inherit one non-working gene from each parent.

Parents of children with Gaucher disease usually do not have the condition themselves. Instead, each parent has a one non-working gene and one working gene for the GBA enzyme. The parents are called carriers. Carriers do not have Gaucher disease because one of their GBA genes is working correctly. The working GBA gene is able to make enough GBA enzyme for the person to be healthy.

When both parents are carriers, each pregnancy has a 25% (1 in 4) chance of resulting in a child having Gaucher disease (has the disorder). There is a 50% (1 in 2) chance for the child to be a carrier, just like the parents. There is a 25% (1 in 4) chance that the child will have two working genes (normal).



Genetic counseling is available to families who have children with Gaucher disease. Genetic counselors can answer questions about how Gaucher disease is inherited, choices during future pregnancies, and how to test other family members. Ask your doctor about a referral to a genetic counselor.

Is genetic testing available?

A diagnosis of Gaucher disease is usually made based on a doctor's evaluation and genetic testing. Genetic testing for Gaucher disease can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes (variants) in the pair of genes that cause Gaucher disease. If a gene change has been found in other family members, testing can find out if your child has the same gene change.

DNA testing is not always necessary to diagnose your child. It is helpful to know the gene changes in a child with Gaucher disease because it is essential for carrier or prenatal testing, discussed below.

What other testing is available?

Screening Tests

Newborn Screening

Newborn screening for Gaucher disease is done in some states. A blood spot from the baby's heel is used to screen for many different conditions. Newborn screening detects Gaucher disease by looking for GBA enzyme activity. GBA enzymes are active in every healthy newborn's blood. Since babies with Gaucher disease have GBA enzymes that are either not working properly or not working at all, they will have reduced GBA enzyme activity.

If a baby has a positive screen for Gaucher disease through a newborn screening program, it **does not** mean that he or she has Gaucher disease. Low GBA enzyme activity level can sometimes be found in people who never develop Gaucher disease. Therefore, a positive screening result means that further testing must be done to confirm or rule out Gaucher disease. Rarely, there can also be false positives with additional testing.

When one or both parents are known to be carriers of Gaucher disease, newborn screening results are not enough to rule out Gaucher disease in a newborn baby. In this case, more sensitive diagnostic testing should be done in addition to newborn screening, even if the newborn screening result is negative.

Serum Chitotriosidase Concentration

This blood test measures the amount of an enzyme called chitotriosidase in the blood. People with Gaucher disease will often have more chitotriosidase in their

blood than expected. Many other conditions also cause elevated chitotriosidase levels in the blood, so this test cannot be used to make a definite diagnosis of Gaucher disease. However, this test may be used to monitor the progress of treatment of Gaucher disease in affected individuals.

Confirmatory testing
Confirmatory testing is needed for a diagnosis of Gaucher disease. Each person may not need every one of the confirmatory tests listed below.

GBA Enzyme Activity
In this test, a small sample of blood is taken and the amount of GBA enzyme activity is measured. Test results are confirmed, if necessary, by again measuring the GBA enzyme activity in a tissue (usually a skin sample).

Genetic Testing
In the absence of symptoms, genetic testing can be used to determine an individual's specific genetic change. This may help with classifying the type of Gaucher disease an individual has.

Bone Marrow Biopsy
In this test, a small sample of bone marrow is taken. If cells with an accumulation of glucocerebroside are seen in the sample, it can indicate Gaucher disease. This test is not always necessary to diagnose Gaucher disease.

Can you test for Gaucher disease during a future pregnancy?

Prenatal genetic testing for Gaucher disease is only available if a genetic change has already been identified in the family. If not done prior to pregnancy, genetic testing to identify the genetic cause can be performed during the pregnancy. Once a genetic cause has been identified, DNA from the fetus can be tested. The sample for this testing is obtained by either CVS or amniocentesis.

Parents may choose to have testing during pregnancy or wait until birth to have the baby tested. Parents may also choose to use assisted reproductive techniques to decrease the chance that their future children would have Gaucher disease. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing your baby after birth.

Can other members of the family have Gaucher disease or be carriers?

Having Gaucher disease
Each full sibling (same mother and father) of a baby with Gaucher disease has a 25% (1 in 4) chance of also having Gaucher disease. Even older siblings who have not shown any symptoms of the disease could have late-onset Gaucher

disease that has not caused symptoms yet, but may in the future. All siblings of an individual with Gaucher disease should be tested. Not all states offer newborn screening for Gaucher disease. Even if your baby's siblings have had normal newborn screening, they should be tested specifically for Gaucher disease because early treatment can prevent more serious health problems. Talk to your doctor or genetic counselor about testing your other children for Gaucher disease.

Carrier for Gaucher disease

Each full sibling of a baby with Gaucher disease has a 50% (1 in 2) chance of being a carrier. Full siblings who do not have Gaucher disease have a 66% (2 in 3) chance of being a carrier.

If you are a parent of a child with Gaucher disease, your brothers and sisters have a 50% (1 in 2) chance of being a carrier. It is important for other family members to be told that they could be carriers. There is a small chance that they are also at risk to have children with Gaucher disease.

Not all states offer newborn screening for Gaucher disease. This makes it especially important to tell your family members if they are at risk for having a child with the disease.

Can other family members be tested?

Diagnostic testing

Siblings of a child with Gaucher disease should be tested. Talk to your doctor or genetic counselor if you have questions about testing for Gaucher disease.

Carrier testing

If both gene changes (variants) have been found in your child, other family members can have DNA testing to see if they are carriers. If you have questions about carrier testing, ask your genetic counselor or doctor.

How many people have Gaucher disease?

It is estimated that 1 in every 40,000-100,000 live births is a baby with Gaucher disease.

Does Gaucher disease happen more often in a certain ethnic group?

Gaucher disease occurs in people of all ethnicities and races. However, it does occur more often in certain groups. Late onset is most commonly diagnosed in individuals of Ashkenazi Jewish decent. About 1 in every 850 Ashkenazi Jewish

individuals has Gaucher Disease. 1 in 18 Ashkenazi Jewish individuals are carriers for the late onset condition.

Acute infantile onset occurs in all ethnicities and races and is the least common type of Gaucher disease.

Chronic infantile onset occurs more often in individuals of Northern European, Egyptian, or East Asian descent.

Does Gaucher disease go by any other names?

Gaucher disease is also called:

- Glucocerebrosidase Deficiency
- Glucosylceramidase Deficiency
- Cerebroside Lipidosis Syndrome
- Gaucher splenomegaly
- Glucocerebrosidosis
- Glucosyl cerebroside lipidosis
- Kerasin lipoidosis
- Kerasin thesaurismosis
- Lipid histiocytosis (kerasin type)
- Sphingolipidosis 1

Where can I find more information?

National Gaucher Foundation
http://www.gaucherdisease.org

Children's Gaucher Research Fund
http://www.childrensgaucher.org

MedlinePlus
https://medlineplus.gov/genetics/condition/gaucher-disease/

National Organization for Rare Disorders
https://rarediseases.org/rare-diseases/gaucher-disease/

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