



National Institute of Neurological Disorders and Stroke

National Institutes of Health

Reducing the burden of neu-

Lipid Storage Diseases Fact Sheet

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Table of Contents (click to jump to sections)

[What are lipid storage diseases?](#)[What are lipids?](#)[How are lipid storage diseases inherited?](#)[How are these disorders diagnosed?](#)[What are the types of lipid storage disease?](#)[How are these disorders treated?](#)[What research is being done?](#)[Where can I get more information?](#)

What are lipid storage diseases?

Lipid storage diseases, or the lipidoses, are a group of inherited metabolic disorders in which harmful amounts of fatty materials called lipids accumulate in some of the body's cells and tissues. People with these disorders either do not produce enough of one of the enzymes needed to metabolize lipids or they produce enzymes that do not work properly. Over time, this excessive storage of fats can cause permanent cellular and tissue damage, particularly in the brain, peripheral nervous system, liver, spleen, and bone marrow.

[top](#)

What are lipids?

Lipids are fat-like substances that are important parts of the membranes found within and between each cell and in the myelin sheath that coats and protects the nerves. Lipids include oils, fatty acids, waxes, steroids (such as cholesterol and estrogen), and other related compounds.

These fatty materials are stored naturally in the body's cells, organs, and tissues. Minute bodies within the cells called lysosomes regularly convert, or metabolize, the lipids and proteins into smaller components to provide energy for the body. Disorders that store this intracellular material are called lysosomal storage diseases. In addition to lipid storage diseases, other lysosomal storage diseases include the mucolipidoses, in which excessive amounts of lipids and sugar molecules are stored in the cells and tissues, and the mucopolysaccharidoses, in which excessive amounts of sugar molecules are stored.

[top](#)

How are lipid storage diseases inherited?

Lipid storage diseases are inherited from one or both parents who carry a defective gene that regulates a particular protein in a class of the body's cells. They can be inherited two ways:

- ▶ *Autosomal recessive* inheritance occurs when both parents carry and pass on a copy of the faulty gene, but neither parent is affected by the disorder. Each child born to these parents has a 25 percent chance of inheriting both copies of the defective gene, a 50 percent chance of being a carrier, and a 25 percent chance of not inheriting either copy of the defective gene. Children of either gender can be affected by an autosomal recessive this pattern of inheritance.
- ▶ *X-linked (or sex-linked) recessive* inheritance occurs when the mother carries the affected gene on the X chromosome that determines the child's gender and passes it to her son. Sons of carriers have a 50 percent chance of inheriting the disorder. Daughters have a 50 percent chance of inheriting the X-linked chromosome but usually are not severely affected by the disorder. Affected men do not pass the disorder to their sons but their daughters will be carriers for the disorder.

[top](#)

How are these disorders diagnosed?

Diagnosis is made through clinical examination, biopsy, genetic testing, molecular analysis of cells or tissue to identify inherited metabolic disorders, and enzyme assays (testing a variety of cells or body fluids in culture for enzyme deficiency). In some forms of the disorder, a urine analysis can identify the presence of stored material. Some tests can also determine if a person carries the defective gene that can be passed on to her or his children. This process is known as genotyping.

Biopsy for lipid storage disease involves removing a small sample of the liver or other tissue and studying it under a microscope. In this procedure, a physician will administer a local anesthetic and then remove a small piece of tissue either surgically or by needle biopsy (a small piece of tissue is removed by inserting a thin, hollow needle through the skin). The biopsy is usually performed at an outpatient testing facility.

Genetic testing can help individuals who have a family history of lipid storage disease determine if they are carrying a mutated gene that causes the disorder. Other genetic tests can determine if a fetus has the disorder or is a carrier of the defective gene. Prenatal testing is usually done by *chorionic villus sampling*, in which a very small sample of the placenta is removed and tested during early pregnancy. The sample, which contains the same DNA as the fetus, is removed by catheter or fine needle inserted through the cervix or by a fine needle inserted through the abdomen. Results are usually available within 2 weeks.

[top](#)

What are the types of lipid storage disease?

Gaucher disease is the most common of the lipid storage diseases. It is caused by a deficiency of the enzyme glucocerebrosidase. Fatty material can collect in the spleen, liver, kidneys, lungs, brain, and bone marrow. Symptoms may include enlarged spleen and liver, liver malfunction, skeletal disorders and bone lesions that may cause pain, severe neurologic complications, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelets, and yellow spots in the eyes. Persons affected most seriously may also be more susceptible to infection. The disease affects males and females equally.

Gaucher disease has three common clinical subtypes. *Type 1* (or *nonneuropathic* type) is the most common form of the disease. It occurs most often among persons of Ashkenazi Jewish heritage. Symptoms may begin early in life or in adulthood and include enlarged liver and grossly enlarged spleen, which can rupture and cause additional complications. Skeletal weakness and bone disease may be extensive. The brain is not affected, but there may be lung and, rarely, kidney impairment. Patients in this group usually bruise easily and experience fatigue due to low blood platelets. Depending on disease onset and severity, type 1 patients may live well into adulthood. Many patients have a mild form of the disease or may not show any symptoms. *Type 2* (or *acute infantile neuropathic* Gaucher disease) typically begins within 3 months of birth. Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow. Affected children usually die by age 2. *Type 3* (the *chronic neuronopathic* form) can begin at any time in childhood or even in adulthood. Major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, skeletal irregularities, eye movement disorders, blood disorders including anemia, and respiratory problems. Patients often live to their early teen years and often into adulthood.

For type 1 and most type 3 patients, enzyme replacement treatment given intravenously every two weeks can dramatically decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations. Successful bone marrow transplantation cures the non-neurological manifestations of the disease. However, this procedure carries significant risk and is rarely performed in Gaucher patients. Surgery to remove the spleen may be required on rare occasions (if the patient is anemic or when the enlarged organ affects the patient's comfort). Blood transfusion may benefit some anemic patients. Other patients may require joint replacement surgery to improve mobility and quality of life. There is currently no effective treatment for the severe brain damage that may occur in patients with types 2 and 3 Gaucher disease.

Niemann-Pick disease is actually a group of autosomal recessive disorders caused by an accumulation of fat and cholesterol in cells of the liver, spleen, bone marrow, lungs, and, in some patients, brain. Neurological complications may include ataxia, eye paralysis, brain degeneration, learning problems, spasticity, feeding and swallowing difficulties, slurred speech, loss of muscle tone, hypersensitivity to touch, and some corneal clouding. A characteristic cherry-red halo develops around the center of the retina in 50 percent of patients.

Niemann-Pick disease is currently subdivided into four categories. Onset of *type A*, the most severe form, is in early infancy. Infants appear normal at birth but develop an enlarged liver and spleen, swollen lymph nodes, nodes under the skin (xanthomas), and profound brain damage by 6 months of age. The spleen may enlarge to as much as 10 times its normal size and can rupture. These children become progressively weaker, lose motor function, may become anemic, and are susceptible to recurring infection. They rarely live beyond 18 months. This form of the disease occurs most often in Jewish families. In the second group, called *type B* (or juvenile onset), enlargement of the liver and spleen characteristically occurs in the pre-teen years. Most patients also develop ataxia, peripheral neuropathy, and pulmonary difficulties that progress with age, but the brain is generally not affected. Type B patients may live a

comparatively long time but many require supplemental oxygen because of lung involvement. Niemann-Pick types A and B result from accumulation of the fatty substance called sphingomyelin, due to deficiency of acid sphingomyelinase.

Niemann-Pick disease also includes two other variant forms called *types C* and *D*. These may appear early in life or develop in the teen or even adult years. Niemann-Pick disease types *C* and *D* are not caused by a deficiency of sphingomyelinase but by a lack of the NPC1 or NPC2 proteins. As a result, various lipids and cholesterol accumulate inside nerve cells and cause them to malfunction. Patients with types *C* and *D* have only moderate enlargement of their spleens and livers. Brain involvement may be extensive, leading to inability to look up and down, difficulty in walking and swallowing, and progressive loss of vision and hearing. Type *D* patients typically develop neurologic symptoms later than those with type *C* and have a progressively slower rate of loss of nerve function. Most type *D* patients share a common ancestral background in Nova Scotia. The life expectancies of patients with types *C* and *D* vary considerably. Some patients die in childhood while others who appear to be less severely affected live into adulthood.

There is currently no cure for Niemann-Pick disease. Treatment is supportive. Children usually die from infection or progressive neurological loss. Bone marrow transplantation has been attempted in a few patients with type *B*. Patients with types *C* and *D* are frequently placed on a low-cholesterol diet and/or cholesterol lowering drugs, although research has not shown these interventions to change cholesterol metabolism or halt disease progression.

Fabry disease, also known as alpha-galactosidase-A deficiency, causes a buildup of fatty material in the autonomic nervous system, eyes, kidneys, and cardiovascular system. Fabry disease is the only x-linked lipid storage disease. Males are primarily affected although a milder form is common in females, some of whom may have severe manifestations similar to those seen in affected males. Onset of symptoms is usually during childhood or adolescence. Neurological symptoms include burning pain in the arms and legs, which worsens in hot weather or following exercise, and the buildup of excess material in the clear layers of the cornea (resulting in clouding but no change in vision). Fatty storage in blood vessel walls may impair circulation, putting the patient at risk for stroke or heart attack. Other symptoms include heart enlargement, progressive kidney impairment leading to renal failure, gastrointestinal difficulties, decreased sweating, and fever. Angiokeratomas (small, non-cancerous, reddish-purple elevated spots on the skin) may develop on the lower part of the trunk of the body and become more numerous with age.

Patients with Fabry disease often die prematurely of complications from heart disease, renal failure, or stroke. Drugs such as phenytoin and carbamazepine are often prescribed to treat pain that accompanies Fabry disease. Metoclopramide or Lipisorb (a nutritional supplement) can ease gastrointestinal distress that often occurs in Fabry patients, and some individuals may require kidney transplant or dialysis. Recent experiments indicate that enzyme replacement can reduce storage, ease pain, and improve organ function in patients with Fabry disease.

Farber's disease, also known as Farber's lipogranulomatosis or ceramidase deficiency, describes a group of rare autosomal recessive disorders that cause an accumulation of fatty material in the joints, tissues, and central nervous system. The disorder affects both males and females. Disease onset is typically in early infancy but may occur later in life. Children who have the classic form of Farber's disease develop neurological symptoms within the first few weeks of life. These symptoms may include moderately impaired mental ability and problems with swallowing. The liver, heart, and kidneys may also be affected. Other symptoms may include vomiting, arthritis, swollen lymph nodes, swollen joints, joint contractures (chronic shortening of muscles or tendons around joints), hoarseness, and xanthomas which thicken around joints as the disease progresses. Patients with breathing difficulty may require insertion of a breathing tube. Most children with the disease die by age 2, usually from lung disease. In one of the most severe forms of the disease, an enlarged liver and spleen (hepatosplenomegaly) can be diagnosed soon after birth. Children born with this form of the disease usually die within 6 months.

There is no specific treatment for Farber's disease. Corticosteroids may be prescribed to relieve pain. Bone marrow transplants may improve granulomas (small masses of inflamed tissue) on patients with little or no lung or nervous system complications. Older patients may have granulomas surgically reduced or removed.

The **gangliosidoses** are two distinct genetic groups of diseases. Both are autosomal recessive and affect males and females equally.

The **GM1 gangliosidoses** are caused by a deficiency of beta-galactosidase, with resulting abnormal storage of acidic lipid materials in cells of the central and peripheral nervous systems, but particularly in the nerve cells. GM1 has three forms: early infantile, late infantile, and adult. Symptoms of *early infantile* GM1 (the most severe subtype, with onset shortly after birth) may include neurodegeneration, seizures, liver and spleen enlargement, coarsening of facial features, skeletal irregularities, joint stiffness, distended abdomen, muscle weakness, exaggerated startle response to sound, and problems with gait. About half of affected patients develop cherry-red spots in the eye. Children may be deaf and blind by age 1 and often die by age 3 from cardiac complications or pneumonia. Onset of *late infantile* GM1 is typically between ages 1 and 3 years. Neurological symptoms include ataxia, seizures, dementia, and difficulties with speech. Onset of *adult* GM1 is between ages 3 and 30. Symptoms include muscle atrophy, neurological complications that are less severe and progress at a slower rate than in other forms of the disorder, corneal clouding in some patients, and dystonia (sustained muscle contractions that cause twisting and repetitive movements or abnormal postures). Angiokeratomas may develop on the lower part of the trunk of the body. Most patients have a normal size liver and spleen.

The **GM2 gangliosidoses** also cause the body to store excess acidic fatty materials in tissues and cells, most notably in nerve cells. These disorders result from a deficiency of the enzyme beta-hexosaminidase. The GM2 disorders include:

- ▶ **Tay-Sachs disease** (also known as GM2 variant B). Tay-Sachs and its variant forms are caused by a deficiency in the enzyme beta-hexosaminidase A. The incidence is particularly high among Eastern European and Ashkenazi Jewish populations, as well as certain French Canadians and Louisianian Cajuns. Affected children appear to develop normally for the first few months of life. Symptoms begin by 6 months of age and include progressive loss of mental ability, dementia, decreased eye contact, increased startle reflex to noise, progressive loss of hearing leading to deafness, difficulty in swallowing, blindness, cherry-red spots in the retinas, and some paralysis. Seizures may begin in the child's second year. Children may eventually need a feeding tube and they often die by age 4 from recurring infection. No specific treatment is available. Anticonvulsant medications may initially control seizures. Other supportive treatment includes proper nutrition and hydration and techniques to keep the airway open. A much rarer form of the disorder, which occurs in patients in their twenties and early thirties, is characterized by unsteadiness of gait and progressive neurological deterioration.
- ▶ **Sandhoff disease** (variant AB). This is a severe form of Tay-Sachs disease. Onset usually occurs at the age of 6 months and is not limited to any ethnic group. Neurological symptoms may include progressive deterioration of the central nervous system, motor weakness, early blindness, marked startle response to sound, spasticity, myoclonus (shock-like contractions of a muscle), seizures, macrocephaly (an abnormally enlarged head), and cherry-red spots in the eye. Other symptoms may include frequent respiratory infections, murmurs of the heart, doll-like facial features, and an enlarged liver and spleen. There is no specific treatment for Sandhoff disease. As with Tay-Sachs disease, supportive treatment includes keeping the airway open and proper nutrition and hydration. Anticonvulsant medications may initially control seizures. Children generally die by age 3 from respiratory infections.

Krabbe disease (also known as globoid cell leukodystrophy and galactosylceramide lipidosis) is an autosomal recessive disorder caused by deficiency of the enzyme galactosylceramidase. The disease most often affects infants, with onset before age 6 months, but can occur in adolescence or adulthood. The buildup of undigested fats affects the growth of the nerve's protective myelin sheath and causes severe degeneration of mental and motor skills. Other symptoms include muscle weakness, hypertonia (reduced ability of a muscle to stretch), myoclonic seizures (sudden, shock-like contractions of the limbs), spasticity, irritability, unexplained fever, deafness, optic atrophy and blindness, paralysis, and difficulty when swallowing. Prolonged weight loss may also occur. The disease may be diagnosed by its characteristic grouping of certain cells, nerve demyelination and degeneration, and destruction of brain cells. In infants, the disease is generally fatal before age 2. Patients with a later onset form of the disease have a milder course of the disease and live significantly longer. No specific treatment for Krabbe disease has been developed, although early bone marrow transplantation may help some patients.

Metachromatic leukodystrophy, or MLD, is a group of disorders marked by storage buildup in the white matter of the central nervous system and in the peripheral nerves and to some extent in the kidneys. Similar to Krabbe disease, MLD affects the myelin that covers and protects the nerves. This autosomal recessive disorder is caused by a deficiency of the enzyme arylsulfatase A. Both males and females are affected by this disorder.

MLD has three characteristic phenotypes: late infantile, juvenile, and adult. The most common form of the disease is *late infantile*, with onset typically between 12 and 20 months following birth. Infants may appear normal at first but develop difficulty in walking and a tendency to fall, followed by intermittent pain in the arms and legs, progressive loss of vision leading to blindness, developmental delays, impaired swallowing, convulsions, and dementia before age 2. Children also develop gradual muscle wasting and weakness and eventually lose the ability to walk. Most children with this form of the disorder die by age 5. Symptoms of the *juvenile* form typically begin between ages 3 and 10. Symptoms include impaired school performance, mental deterioration, ataxia, seizures, and dementia. Symptoms are progressive with death occurring 10 to 20 years following onset. In the *adult* form, symptoms begin after age 16 and may include impaired concentration, depression, psychiatric disturbances, ataxia, seizures, tremor, and dementia. Death generally occurs within 6 to 14 years after onset of symptoms.

There is no cure for MLD. Treatment is symptomatic and supportive. Bone marrow transplantation may delay progression of the disease in some cases.

Wolman's disease, also known as acid lipase deficiency, is a severe lipid storage disease that is usually fatal by age 1. This autosomal recessive disorder is marked by accumulation of cholesteryl esters (normally a transport form of cholesterol) and triglycerides (a chemical form in which fats exist in the body) that can build up significantly and cause damage in the cells and tissues. Both males and females are affected by this severe disorder. Infants are normal and active at birth but quickly develop progressive mental deterioration, enlarged liver and grossly enlarged spleen, distended abdomen, gastrointestinal problems including steatorrhea (excessive amounts of fats in the stools), jaundice, anemia, vomiting, and calcium deposits in the adrenal glands, causing them to harden.

Another type of acid lipase deficiency is **cholesteryl ester storage disease**. This extremely rare disorder results from storage of cholesteryl esters and triglycerides in cells in the blood and lymph and lymphoid tissue. Children develop an enlarged liver leading to cirrhosis and chronic liver failure before adulthood. Children may also have calcium deposits in the adrenal glands and may develop jaundice late in the disorder.

There is no specific treatment for Wolman's disease or cholesteryl ester storage disease.
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[top](#)

How are these disorders treated?

Currently there is no specific treatment available for most of the lipid storage disorders but highly effective enzyme replacement therapy is available for patients with type 1 Gaucher disease and some patients with type 3 Gaucher disease. Patients with anemia may require blood transfusions. In some patients, the enlarged spleen must be removed to improve cardiopulmonary function. The drugs phenytoin and carbamazepine may be prescribed to help treat pain (including bone pain) for patients with Fabry disease. Restricting one's diet does not prevent lipid buildup in cells and tissues.

[top](#)

What research is being done?

Within the Federal government, the primary supporter of research on neurological disorders is the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health within the U.S. Department of Health and Human Services. As part of its mission, the NINDS conducts research on lipid storage diseases and other inherited neurometabolic disorders. Investigators at the NINDS identified the gene that is altered in the majority of patients with type C and D Niemann-Pick disease. In the year 2000, scientists discovered a second gene that is mutated in a minority of patients with type C Niemann-Pick disease. NINDS researchers have developed highly effective enzyme replacement therapy for Gaucher and Fabry diseases. These researchers are now developing improved research techniques, including a mouse model of Fabry disease. Gene therapy in this model appears to be especially encouraging.

Among other potential therapies for lipid storage diseases under way, NINDS scientists are studying the effectiveness and safety of the medicine called OGT-918, which has been shown to slow the production of the lipid that builds up in Gaucher disease. Scientists hope the drug, which passes through the blood-brain barrier into the brain, will reduce lipid storage and therefore the neurological symptoms of the disease. Other NINDS investigators are evaluating the safety and effectiveness of continued replacement of the enzyme alpha-galactosidase-A in patients with Fabry disease. In a preliminary 24-week clinical trial, this therapy was found to reduce pain, improve renal function, and reverse heart problems among Fabry patients.

NINDS scientists are also studying the mechanisms by which the lipids accumulating in these storage diseases cause harm to the body. The goal of this research is to develop novel approaches to the treatment of these disorders.

Among several current projects being funded by the NINDS, scientists are studying ways to deliver genes and proteins into the brain in animal models of Krabbé disease. Other NINDS-sponsored scientists are examining the possible role of the protein psychosine in the neuroinflammatory response seen in this disease and hope to identify potential therapeutic drugs for use in human trials. Researchers are investigating the mechanisms of intracellular cholesterol delivery and metabolism in Niemann-Pick type C disease and hope to develop a diagnostic tool for the disorder. Other researchers are studying dysfunctional cholesterol processing (seen in Niemann-Pick disease) as a key feature in the development of several neurodegenerative disorders.

[top](#)

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
<http://www.ninds.nih.gov>

Information also is available from the following organizations:

Fabry Support & Information Group
108 NE 2nd Street, Ste. C
P.O. Box 510
Concordia, MO 64020-0510
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Children's Gaucher Research Fund

United Leukodystrophy Foundation