Inherited Metabolic Storage Disorders: Cerebral X-Linked Adrenoleukodystrophy (ALD)

Inherited metabolic storage disorders are a group of inherited diseases in which the lack of an enzyme affects various organs and tissues, including the brain. Enzymes are proteins that play many roles, including to metabolize (break down) substances in the body. In metabolic storage disorders, the body lacks an enzyme needed to metabolize a substance, such as a sugar. Instead, the substance builds up in the body, where it can damage the brain, nervous system, bones, organs and other tissues. Different metabolic disorders affect different enzymes and cause different types and levels of damage.

Metabolic storage disorders are caused by a mutation (mistake) in a gene that affects metabolism. Genes carry an inherited code of instructions that tells the body how to make every cell and substance in the body.

These disorders are rare. Many of them appear in childhood, although some can also appear in adults. A bone marrow or cord blood transplant (also called a BMT) is a treatment option for some of these disorders.

Mucopolysaccharidoses, also called MPS disorders, are a subgroup of metabolic disorders. Some MPS disorders have been treated with transplant:

- Hurler’s syndrome (MPS I) – this is the form of MPS that doctors have the most experience treating with transplant, since 1980
- Maroteaux-Lamy syndrome (MPS VI)
- Sly syndrome (MPS VII)

Leukodystrophies are another subgroup of metabolic disorders, some of which have been treated with transplant:

- Cerebral X-linked adrenoleukodystrophy (ALD)
- Globoid-cell leukodystrophy (GLD) – also called Krabbe disease
- Metachromatic leukodystrophy (MLD)

If you or a family member has an inherited metabolic storage disorder, it is important to talk to a doctor who has experience treating the disorder. These disorders are rare and complex. Early diagnosis and prompt treatment are important. If your doctor has not treated other patients with your disorder, ask him or her to refer you to an expert for consultation. A doctor with experience treating the disorder can discuss whether transplant is a treatment option for you or your family member.

Cerebral X-Linked Adrenoleukodystrophy (ALD) and Transplant

Cerebral X-linked adrenoleukodystrophy (ALD) is an inherited metabolic storage disorder that can cause severe damage to the central nervous system (brain and spinal cord) and the adrenal gland.
Definition of Adrenoleukodystrophy

A Type of Leukodystrophy
ALD is one of a subgroup of metabolic disorders called the leukodystrophies. The leukodystrophies are caused by a variety of gene mutations (mistakes). Genes carry an inherited code of instructions that tells the body how to make every cell and substance in the body. In the leukodystrophies, the gene mutations lead to damage of the myelin.

Myelin is the fatty substance that forms a sheath around the axons that carry signals to and from nerves in the central nervous system (brain and spinal cord). The myelin sheath is similar to the insulation on a wire. It enables the axons to carry signals very quickly. When the myelin sheath is damaged, the signals slow down or may stop completely.

If the signals from the brain and spinal cord have trouble getting to the rest of the body, a person can have problems controlling the body's movements. If the signals between nerves in the brain are slowed or stopped, a person can have problems with memory, learning, speaking and understanding speech, and other mental functions.

Adrenoleukodystrophy
In people with ALD, the disorder affects the body's ability to break down certain fat molecules known as very long chain fatty acids. Very long chain fatty acids are one of the ten substances that make up myelin. In people with ALD, the body does not break down the very long chain fatty acids, so they build up and damage the myelin. Damage to the myelin causes problems with the function of the nervous system. The very long chain fatty acids also affect the adrenal gland. The adrenal gland makes hormones that help control many body functions.

Childhood Cerebral X-linked ALD
There is a wide variation in how severe ALD is and how it affects people. Signs of ALD can appear in people at different ages and cause symptoms ranging from mild to severe. About 30% to 40% of cases of ALD are the most severe form, childhood cerebral X-linked ALD (which is the form discussed here).

Childhood ALD appears in boys between 2 and 10 years of age.

It is called the cerebral form because it damages the brain more severely than other forms of ALD, affecting all mental and body functions.

The disorder is called X-linked because the mutated gene is on the X chromosome, inherited from the mother. Disorders caused by genes on the X chromosome occur only in males. Females are carriers of the mutated gene but do not get the disorder.

Symptoms and Diagnosis of Cerebral X-Linked ALD
The early symptoms of childhood cerebral X-linked ALD include changes in behavior or learning problems. Without treatment, problems with learning, speaking and understanding speech, hearing, seeing, swallowing, walking and other movement can get worse quickly. These symptoms are all caused by damage to the central nervous system. If the damage is not stopped, a boy with the disorder will become unable to control his body or respond to life around him, usually within 6 months to 2 years. Cerebral ALD leads to death within months to several years.

Diagnosis
For boys showing the symptoms described above, a brain scan using magnetic resonance imaging (MRI) shows an abnormal pattern typical of ALD. In boys showing symptoms, the brain MRI is often the first step toward diagnosis.

Doctors can then diagnose ALD using a blood test to check for high levels of very long chain fatty acids. All males in a family affected by ALD should be carefully screened for ALD. A blood test can diagnose ALD even in boys who do not show symptoms and whose brain MRI is normal. Tests for the gene mutation that causes ALD can also be done. Families affected by ALD may want to talk with a genetic counselor about family planning and the chances of having children with ALD.
Treatment Options for Childhood Cerebral X-Linked ALD

For boys with childhood cerebral X-linked ALD, treatment options (all discussed further below) may include:

- Bone marrow or cord blood transplant (also called a BMT) – the only known treatment that can stop the progression of the disease
- Hormone replacement therapy to make up for problems with the adrenal gland function
- Lorenzo’s oil – only if a boy does not yet show signs of the cerebral form of ALD
- Other, newer treatments in clinical trials

Transplant for Cerebral X-Linked ALD

For boys with cerebral X-linked ALD, a bone marrow or cord blood transplant early in the course of the disease can stop the progression of the disease. Though it has serious risks and is not an option for all patients, a transplant can be life-saving and prevent severe disability for some boys with cerebral X-linked ALD. A transplant is not considered a treatment option for other, less severe forms of ALD because it is not clear transplant offers a benefit in these cases.

One of the earliest transplants for X-linked cerebral ALD was reported in 1990. In this case, a boy received a transplant soon after he began showing signs of nervous system damage. He maintained normal mental function (such as memory and the ability to learn) after the transplant. [1] Since that time, doctors have continued to learn about when and how transplant can help boys with X-linked ALD.

Timing of Transplant

Studies show that timing of the transplant is very important. Boys who show early signs of cerebral ALD in MRI scans but have few outward symptoms have a good chance of doing well after transplant. Mild damage may sometimes even be reversed. However, the amount of damage the disorder has already done (amount of myelin already lost) makes a big difference to the outcome of the transplant. Boys who already show major symptoms face higher risks after transplant. Severe damage cannot be reversed, so these boys may have a lower quality of life even if transplant succeeds.

Hormone Replacement Therapy

Boys with ALD may have a life-long need for treatment with hormone replacement therapy. ALD can alter the adrenal glands so that they do not make enough hormones for the body. This can be life-threatening and requires treatment with hormones.

Lorenzo’s Oil and Newer Treatments

Another treatment that has been studied is taking Lorenzo’s oil and eating a low-fat diet. Lorenzo’s oil is made from olive and rapeseed oils. For some boys who do not yet have the cerebral form of ALD, Lorenzo’s oil may reduce or delay severe symptoms. Lorenzo’s oil appears more likely to help boys who have no symptoms of nervous system damage and are younger. However, the benefit of Lorenzo’s oil remains uncertain and it is not a cure. Even boys who appear to benefit are likely to develop the adult form of ALD. Though the adult form is milder than childhood ALD, it is still a serious disease. Studies have shown that Lorenzo’s oil does not help boys who already show symptoms.

Newer Treatments

Researchers are trying to develop other treatments for boys with cerebral ALD. Some other treatment options may be available in clinical trials.
Making Treatment Decisions

If your son has cerebral X-linked ALD, it is important for him to see a doctor who is an expert in treating ALD. If your child’s doctor has not treated other patients with ALD, ask him or her to refer you to an expert for consultation. Since ALD can get worse quickly, it is important to see an expert as soon as possible. If transplant is a treatment option for your child, talk with your doctor about the risks, limits and possible benefits of transplant.

In a family with a history of ALD, some boys can be diagnosed with ALD when there are no signs of central nervous system damage. The cerebral form of ALD is the only one for which a transplant is a treatment option, because it is not clear whether transplant offers a benefit in other forms of ALD. However, doctors have no way to predict which boys with ALD will develop the cerebral form. If your child is diagnosed with ALD before symptoms appear, it is important for him to be watched carefully for signs the ALD is affecting the central nervous system. Your doctor will schedule regular brain MRIs to watch for these signs.

If your child does develop cerebral ALD, getting a transplant early – before the disease progresses and symptoms become severe – can make a difference to outcomes. Your doctor can take steps to be prepared. He or she can check whether your child has any possible donors in your family. Your doctor can also search the National Marrow Donor Program Registry for potential unrelated volunteer donors or cord blood units. That way, if your child develops cerebral ALD and needs a transplant, the first steps of the donor search will be done and your child may be able to move to transplant more quickly.

The NMDP's Office of Patient Advocacy (OPA) continually develops resources and materials to help patients, family members and doctors with questions about marrow or cord blood transplantation. In addition to print, audio and visual materials, OPA has bilingual (Spanish/English) case managers and LanguageLine interpreter services available for callers. All OPA materials and services are free and confidential. Call the OPA toll-free at 1 (888) 999-6743. Outside the United States call (612) 627-8140, or visit marrow.org/patient