Inherited Metabolic Storage Disorders: Metachromatic Leukodystrophy (MLD)

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.
Metachromatic Leukodystrophy (MLD) and Transplant

Metachromatic leukodystrophy (MLD) is an inherited metabolic storage disorder that affects motor skills, balance, vision and mental skills.

Definition of Metachromatic Leukodystrophy

Metachromatic leukodystrophy is one of a group of inherited metabolic storage disorders 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 and causes damage.

A Type of Leukodystrophy

MLD 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.

Metachromatic Leukodystrophy

In people with MLD, the gene mutation affects an enzyme called arylsulfatase A. This enzyme breaks down substances called sulfatides. Sulfatides are one of the ten substances that make up myelin. Without the arylsulfatase A enzyme, sulfatides build up and damage the myelin sheath, causing problems with the central nervous system and peripheral nervous system. The peripheral nervous system is the nerves throughout the body that carry signals to and from the central nervous system.

A person gets MLD when he or she inherits a gene with the mutation from both parents. MLD appears most often in babies and young toddlers, but it also occurs in older children and adults. MLD is rare. About 1 in 100,000 people has this disorder.

Signs and Symptoms of MLD

Late-Infantile MLD

The most common and severe form of MLD is the late-infantile form. The symptoms of the late-infantile form of MLD appear when children are 6 to 24 months old. The first symptoms include problems with walking or other motor skills. Symptoms get worse quickly. Painful muscle cramps and problems with speech, movement and the ability to learn get worse until the child becomes paralyzed and blind. Children with this form of MLD usually die before 10 years of age.

Juvenile MLD

The juvenile form of MLD appears in children between the ages of 4 to 12, sometimes earlier. Early symptoms include problems with learning or with walking. As the disease progresses, symptoms include behavior problems, trouble following directions, and worsening problems with walking and speech. Eventually the child becomes paralyzed and blind. Some children with juvenile MLD survive into adulthood, though others die sooner.
Adult MLD
The adult form of MLD can appear in teenagers or adults of any age. The first symptoms are often changes in personality and poor school or job performance. Adult MLD is often mistaken for other disorders such as schizophrenia or depression. As the disorder progresses, problems with memory and other mental skills, speech, controlling movement and eating get worse slowly. People with adult MLD may sometimes live 10 to 30 years or more after symptoms appear.

Diagnosis
Tests a doctor may use to help diagnose MLD include:

- Blood or skin tests to check for low levels of arylsulfatase A enzyme activity
- Brain scans using magnetic resonance imaging (MRI) to check for abnormalities
- Lumbar puncture (spinal tap) to check the fluid around the spinal cord for high levels of protein
- Urine tests to check for high levels of sulfatides and other signs of possible MLD
- Tests to check the function of the nerves (nerve velocity conduction studies)

Families affected by MLD may want to talk with a genetic counselor about family planning and the chances of having children with the disorder. Early diagnosis may enable early treatment before symptoms occur, which can be important to outcomes.

Transplant for MLD
The only known treatment that can affect the progression of MLD is a bone marrow or cord blood transplant (also called a BMT). The healthy cells received in a transplant can make the arylsulfatase A the body was missing.

Though it has serious risks and is not an option for all patients, a transplant can be life-saving. It can stop damage to the central nervous system, preventing severe mental disability for some people with MLD. A transplant is most likely to benefit a person early in the course of MLD who shows few or no symptoms. Some of the limits of transplant for MLD include:

- Problems that have already appeared will remain after transplant. Damage the disease has already done is not reversed.
- Patients who already have severe symptoms are unlikely to benefit from transplant. Their symptoms are likely to continue to get worse.
- A transplant cannot stop damage to the peripheral nervous system. Problems with controlling movement are likely to continue to get worse after transplant.
- It takes time (sometimes as long as a year) for the transplanted cells to make enough healthy cells to correct a patient’s metabolism. During this time the disorder can continue to cause damage.

The results described here are from reports of individual patients; no larger clinical studies are available. It is a good idea to ask your doctor for help interpreting these data and any other survival outcomes data you find. Your doctor can provide context for these data and discuss your specific situation with you. For more things to consider, see Understanding Survival Outcomes Data.

Making Treatment Decisions
If you or your family member has MLD, it is important to see a doctor who is an expert in MLD. If your doctor has not treated other patients with MLD, ask him or her to refer you to an expert for consultation. If transplant is a treatment option, talk with your doctor about the risks, limits and possible benefits of transplant.

Even after a successful transplant, a patient will face physical problems from MLD. However, a transplant may offer a person with MLD a chance to live a longer life as well as to keep his or her ability to think and learn.
References


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