NATIONAL MARROW DONOR PROGRAM®

Inherited Metabolic Storage Disorders:
Globoid-Cell Leukodystrophy (Krabbe Disease)

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.

Globoid-Cell Leukodystrophy (Krabbe Disease) and Transplant

Globoid-cell leukodystrophy (GLD) is also called Krabbe disease (pronounced crab-A) or Krabbe disease. GLD is an inherited metabolic storage disorder that affects the muscles, vision and mental abilities. It is life-threatening.

Definition of Globoid-Cell Leukodystrophy

A Metabolic Storage Disorder

Globoid-cell leukodystrophy, or Krabbe disease, 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

GLD 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.

Globoid-Cell Leukodystrophy

In people with GLD, the gene mutation affects an enzyme called galactocerebrosidase (GALC). Lack of GALC causes the buildup of a substance that damages cells that make myelin. This results in damage to the central nervous system. A person gets the disorder when he or she inherits a gene with the mutation from both parents. The disorder can appear soon after birth (early-onset GLD or Krabbe disease) or in older children or adults (late-onset GLD). The disorder is rare. About 40 cases of GLD are diagnosed in the United States each year.

Signs and Symptoms of GLD

Early-Onset GLD

Symptoms of early-onset GLD usually appear in babies between 2 and 12 months of age. Symptoms include:

- Unexplained crying
- Fevers
- Stiffness
- Seizures
- Slow development

These symptoms get worse quickly, and children usually die before the age of two years. The early-onset form of the disorder occurs much more often than the late-onset form.

Late-Onset GLD

Late-onset GLD can appear in people of any age. The symptoms include:

- Weakness
- Stiffness
- Problems seeing
- Problems walking
- Loss of mental ability

Without treatment, the symptoms of late-onset GLD get worse and become life-threatening. Symptoms grow worse more slowly in late-onset GLD, but the time for symptoms to become severe varies greatly.

Diagnosis

GLD can be diagnosed by testing a sample of blood or skin cells to measure activity levels of the enzyme GALC. Patients with GLD show very low GALC activity levels. A doctor may also do a lumbar puncture (spinal tap) to get a sample of the fluid around the spinal cord. In patients with GLD, this fluid has very high levels of protein. Families affected by GLD may want to talk with a genetic counselor about family planning and the chances of having children with the disorder.

Transplant for GLD

The only known treatment that has some effect on the progression of the disease is a bone marrow or cord blood transplant (also called a BMT). The healthy cells received in a transplant can make the GALC enzyme the body was missing. 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 people with GLD.

Late-onset GLD (appears in people of any age)
Transplants for late-onset GLD have had a better chance of good results than transplants for early-onset GLD. This is because late-onset GLD gets worse more slowly than early-onset GLD. It takes months for the transplanted cells to make enough healthy cells to correct a patient's metabolism and the disorder can continue to cause damage during that time. The best results in people with late-onset GLD have occurred when they receive a transplant early in the course of the disease, before severe symptoms develop.

Early-onset GLD (appears in babies 2 months to 12 months)
Babies with early-onset GLD may be helped by a transplant if they receive it within the first 1 or 2 months of life. This is before symptoms appear in most cases. Most babies diagnosed early are tested for GLD because an older sibling is affected with the disorder. Early diagnosis can be important to the success of transplants for early-onset GLD. Transplants for babies who are 3 months of age or older and already show symptoms have had poor results.

Transplant Outcomes

Doctors are conducting research to learn about when and how transplant can help people with GLD. The disorder is rare and studies of transplant outcomes for people with GLD have included small numbers of patients.

Making Treatment Decisions

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

More Information on Globoid-Cell Leukodystrophy

You can get further information about GLD from disease-specific organizations such as:

National Institute of Neurological Disorders and Stroke (NINDS): NINDS Krabbe Disease Information Page: http://www.ninds.nih.gov/disorders/krabbe/krabbe.htm

United Leukodystrophy Foundation: Krabbe Disease: http://www.ulf.org/types/krabbe.html

References

1. Krivit W, Shapiro EG, Peters C, et al. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. N Engl J Med. 1998; 338(16):1119-1126.
2. Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med. 2005; 352(20):2069-2081.