United Leukodystrophy Foundation

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FACT SHEET: METACHROMATIC LEUKODYSTROPHY (MLD)

What Causes MLD?

MLD is inherited in an autosomal recessive manner, and is most commonly caused by a mutation in a gene called arylsulfatase A (ASA), also called sulfatide sulfatase. The protein produced by ASA is present in the lysosome, a compartment of the cell that specializes in general "cleanup" of the cell. You may hear MLD referred to as a lysosomal storage disorder, since ASA is a lysosomal enzyme. MLD can also be caused by a defect in Saposin B (also referred to as the cerebroside sulfate activator), which is a protein required for ASA to work properly.

ASA is required for the breakdown of sulfatides, also called glycolipid- cerebroside sulfates, which are fats present in myelin. When ASA is deficient, the sulfatides build up in the myelin to high levels, disrupting the myelin structure and causing demyelination to occur in both the central nervous system and in the peripheral nervous system. The sulfatides will also build up in the visceral organs (such as the kidneys), and will be excreted at high levels in the urine.

Previously, a disorder known as multiple sulfatase deficiency (MSD) was sometimes considered a subset of MLD. While many symptoms of MSD are similar to those of MLD, we have chosen to classify it as a separate disorder. To learn more about MSD, please see our MSD fact sheet.

What are the symptoms of MLD?

There are three forms of MLD, defined by the age of onset of the disease. The late infantile form of MLD is the most common, and produces symptoms between the ages of 1 and 2. The juvenile form generally becomes apparent between the ages of 4 and 12, and the adult form occurs after age 14. As with all the leukodystrophies, the symptoms can vary widely, although in all cases there is a progressive loss of physical and intellectual function over a relatively extended period of time. In general, the earlier the onset, the more rapid the progression of the disease.

Late Infantile MLD

After a period of apparently normal growth and development, skills such as walking and speech may begin to deteriorate. Once clinical symptoms become noticeable, they often appear to progress rapidly over a period of several months, with alternating periods of stabilization and decline. The child eventually becomes bedridden, unable to speak or feed independently. There may be seizures at this stage, which eventually disappear. Contractures are common and apparently painful. The child is still able to smile and respond to parents at this stage, but eventually may become blind and largely unresponsive. Swallowing eventually becomes difficult and a feeding tube becomes necessary. With modern treatment and care, the child may survive for 5-10 years. Death generally occurs as the result of an infection such as pneumonia, as opposed to being a direct result of the MLD. Other symptoms that may be encountered are listed below, along with definitions of the medical terminology as necessary.

- Developmental delay
- Hypotonia: decreased muscle tone

- Esotropia: cross-eyed
- Psychomotor regression
- Clumsiness
- Spasticity: increased reflexes
- Nystagmus: type of abnormal eye movement
- Weakness
- Decreased speech
- Seizures
- Ataxia: loss of the ability to coordinate muscular movement
- Quadriplegia: paralysis from the neck down
- Eventual absence of voluntary functions

Juvenile MLD

Onset is generally between 4-12 years, and the symptoms generally first become apparent during the early years of schooling where a motor disturbance or fall in scholastic performance occurs. The child may have difficulty following directions, and behavioral abnormalities may occur. Symptoms may include incontinence, difficulties in walking and slurred speech. As symptoms advance, children may develop seizures, abnormal postures, tremor, and eventually lose the ability to walk. The final stages of the disease are similar to the late infantile form (see above). An increasing number of patients are living into adulthood.

Adult MLD

Initial symptoms may occur as early as 14 years and as late as 50 years. The initial indications are typically a change in personality, poor job performance and emotional lability. Initial psychiatric diagnoses such as schizophrenia or depression are common. Alcohol and drug abuse may also occur. There is eventually a progressive loss of cognitive and motor functions, usually extending over 1-3 decades.

MLD may also involve the gallbladder. Kidney function is not impaired.

How is MLD diagnosed?

If a child displays some of the symptoms described previously, a series of biochemical evaluations and brain imaging studies can be performed.

Biochemical Evaluations

Because the most common cause of MLD is a deficiency of ASA, a blood sample or skin punch biopsy may be taken, and ASA activity can be measured; a low activity is suggestive of MLD. However, it should be noted that low ASA activity does not necessarily indicate MLD. There is a mutation in the ASA gene known as the "pseudodeficiency allele" that results in a lowering of ASA activity. However, this pseudodeficiency allele does not directly cause MLD. . Roughly 10% of the population carries this pseudodeficiency allele, so biochemical results should be interpreted in conjunction with other tests. Other studies that may be performed include measurement of sulfatides in urine, a test for elevated cerebrospinal fluid protein, slowed nerve conduction, and changes in electrical potential that may be indicative of leukodystrophy.

Prenatal diagnosis for MLD is available.

Brain imaging studies

An MRI (Magnetic Resonance Imaging) may be performed to look for white matter disturbances characteristic of MLD.

How is MLD treated?

Currently, the only treatment for MLD is bone marrow transplantation; this means that cells that produce normal ASA are introduced into the patient, and the normal ASA protein is then taken up into the deficient cells, allowing sulfatides in those cells to be broken down. However, this is only useful for those who are pre-symptomatic or those with very mild neurological manifestations. This highlights the importance of testing asymptomatic brothers and sisters of patients who have MLD. This treatment can slow the disease progress and increase the quality of life for the patient.

How is research on MLD progressing towards better treatments?

Scientists have been working very hard to learn more about MLD, and their work has led to the identification of the genetic defect involved in the disease. Existing studies have focused on gene therapy in a mouse model of MLD. A harmless virus was modified to produce the active ASA protein, and the virus

was then introduced into the mouse. This therapy has been shown to protect mice against some of the deteriorations seen with MLD, including learning ability, behavioral deficits, and some of the neuropathology and neurological impairments. However, the demyelination that is characteristic of MLD in humans is not seen in the mouse model, so it is not clear if this sort of treatment would be able to slow the demyelination process.