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What is Metachromatic Leukodystrophy?

Metachromatic leukodystrophy (MLD) is an inherited disease with a variable age of onset and is characterized by the progressive loss of motor skills and intellectual function. It involves defects in the enzyme called arylsulfatase A (ARSA), which breaks down molecules called sulfatides (a type of lipid found in cell membranes), particularly within the nervous system. Symptoms associated with MLD are due to the build-up of sulfatides that destroy myelin (the protective material that surrounds nerve cells). Metachromatic leukodystrophy is also known as arylsulfatase A deficiency.[1]

What are the symptoms of Metachromatic Leukodystrophy and what treatment is available?

Metachromatic leukodystrophy is a progressive disease that occurs in three types, based primarily on the age of onset.[2]

Type (rate of progression)	Typical Age of Onset	Initial Symptoms	Age at Death
Late-infantile (steady progression)	1-2 years of age	Clumsiness, frequent falls, toe walking, & slurred speech	~3.5 years after onset of symptoms, occasionally second decade of life
Juvenile (slower progression)	4-14 years of age	Decline in school performance & behavioral problems	~10-20+ years after onset of symptoms
Adult (periods of relative stability between periods of decline)	After puberty (~14 years), but may not occur until the 40s-50s	Decline in school or work performance, personality changes, substance abuse issues, emotional changes	~20-30 years after onset of symptoms

Shared symptoms of MLD include [2:]

- Hypotonia (low muscle tone) that progresses with age
- Loss of coordination
- Slurred speech
- Pain in arms and legs
- Peripheral neuropathy (loss of sensation in hands and feet)
- Weak bladder
- Seizures
- Vision and hearing loss
- Nerve damage
- Eventual wheelchair dependence

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There is no cure for MLD. Treatment includes supportive care for symptoms and may include seizure management and physical therapy. Additional therapies, including stem cell transplant, may be considered.[2]

How is Metachromatic Leukodystrophy inherited?

Metachromatic leukodystrophy is an autosomal recessive disease caused by mutations in the *ARSA* gene.[1] An individual who inherits one copy of an *ARSA* gene mutation is a "carrier" and is not expected to have related health problems. An individual who inherits two mutations in this gene, one from each parent, is expected to be affected with MLD.

If both members of a couple are carriers, the risk for an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

Who is at risk for Metachromatic Leukodystrophy?

Metachromatic leukodystrophy can occur in individuals of all races and ethnicities. In the Japanese population, the incidence is approximately 1 in 70,000[3], with a calculated carrier frequency of 1 in 132. In Europe, the incidence is estimated to be 1 in 80,000[4], with a calculated carrier frequency of 1 in 141.

Having a relative who is a carrier or who is affected can increase an individual's risk of being a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

Where can I get more information?

- MLD Foundation: http://www.mldfoundation.org/
- The Evanosky Foundation: http://www.evanoskyfoundation.org
- United Leukodystrophy Foundation: http://ulf.org

References

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4. Lugowska A et al Population Carrier Rates of Pathogenic *ARSA* Gene Mutations: Is Metachromatic Leukodystrophy Underdiagnosed? PLoS ONE 2011; 6(6):e20218.

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