What are leukodystrophies?

Leukodystrophies are a group of genetic disorders that affect the white matter of the central nervous system, which consists of your brain and spinal cord. The white matter is made up of a complex network of axons, which are how nerve cells communicate with each other. Axons are typically insulated by a substance called myelin that helps move these communications along. Leukodystrophies refer to the abnormal development of the white matter, or the progressive breakdown of the white matter. This abnormal development or breakdown occurs due to an underlying genetic condition that impacts the axon, myelin, or other parts of the central nervous system that are important for how the axon or myelin function.

There are several dozen different types of leukodystrophies (over 50 total). Some of the more common types include:

- Metachromatic leukodystrophy (MLD)
- X-linked adrenoleukodystrophy (ALD)
- Pelizaeus-Merzbacher disease (PMD)
- Krabbe disease
- Canavan disease
- Alexander disease

Anywhere from 1 in 6,000-7,000 to 1 in 100,000 individuals are affected with a leukodystrophy.

Because the onset, severity, and progression of different leukodystrophies is extremely variable, it is difficult to provide generalized statements about the signs and symptoms that people with leukodystrophies may experience. Some types of leukodystrophy have a predictable disease progression, while other types are highly variable. For instance, while many symptoms associated with leukodystrophies get worse over time, the rate of this progression can vary. Some forms may have rapid decline and be life shortening, while other types have a more gradual and benign progression. There are some types, although less common, that can show improvement or stabilization over time. Others can appear to be stable, only to have a rapid decline after a triggering event.

The age of onset also varies amongst the different types of leukodystrophy, and sometimes even within the same type of leukodystrophy. Individuals may start to show symptoms anywhere ranging from birth through adulthood. The onset is often broken down into categories:

- Neonatal
- Infantile
- Late infantile
- Juvenile
- Adolescence
- Adulthood

The earlier onset is often associated with more severe and rapid progression and decline, but this too can be variable.

How are leukodystrophies diagnosed?

The diagnosis of leukodystrophy and identifying the specific type of leukodystrophy someone has is based on age of onset of symptoms, brain MRI patterns, detailed examination for both neurological and non-neurological symptoms or features, and biochemical and genetic tests. Due to the use of multi-gene panels and whole exome and genome sequencing, more people are able to receive a diagnosis of their specific type of leukodystrophy compared to the past.

Some neurological symptoms that can be seen in leukodystrophy include:

- Developmental delays or intellectual disability
- Motor impairment, such as delays in reaching motor developmental milestones, onset of abnormal movements or movement disorders, abnormal gait, or changes in muscle tone
- Psychiatric or behavioral disorders; these types of symptoms are usually some of the first that can be seen
- Dysautonomia
- Seizures
- Peripheral neuropathy

Non-neurological symptoms can also be variable, and can affect many of the other body systems. The specific non-neurological symptoms can sometimes be used to help determine the type of leukodystrophy that someone has. However, because the signs and symptoms of the many different types of leukodystrophies overlap, further testing is often needed.

A brain MRI is one of the most helpful tools to diagnose what specific type of leukodystrophy someone has. The type and pattern of lesions that are seen on the brain MRI can help determine if someone has a genetic white matter abnormality (leukodystrophy) or

an acquired (non-genetic) white matter abnormality. This information can be used to help determine specific types of leukodystrophy that may be more likely.

The combination of clinical features, age of onset, and brain MRI findings may allow for a more targeted testing approach with metabolic or genetic testing. If the combination of these things do not point to one specific type of leukodystrophy, broader testing with multi-gene panels or whole exome and genome sequencing could be helpful. It is important to remember that not all individuals with a clinical diagnosis of leukodystrophy will have an identifiable genetic cause. Through the use of multi-gene panels and whole exome and genome sequencing, as many as 70-80% people are able to receive a specific diagnosis. This means for about 20-30% of individuals with leukodystrophy, a genetic cause is not able to be found at this time. As our understanding of genetics continues to progress, this percent will likely continue to decrease.

Are there treatments for leukodystrophy?

For most leukodystrophies there is no known treatment, and medical management is focused on treating the symptoms (both neurological and non-neurological). For some types of leukodystrophy there is treatment available; for instance, hematopoietic stem cell transplantation (HSCT) is an available option for several types such as metachromatic leukodystrophy, Krabbe disease, and cerebral adrenoleukodystrophy. Other forms of treatments being looked at for leukodystrophies include gene therapy, antisense oligonucleotide therapy, and other targeted approaches. However, as with HSCT, the timing of these treatments is crucial. If an individual is treated after development of white matter disease, the treatment may not be as effective and may only stabilize the patient's symptoms.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Resources:

United Leukodystrophy Foundation – ulf.org

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