Leukodystrophy

Synonyms of Leukodystrophy

- hereditary white matter disorders
- inherited leukoencephalopathies

General Discussion

Leukodystrophies are a group of rare, progressive, metabolic, genetic diseases that affect the brain, spinal cord and often the peripheral nerves. Each type of leukodystrophy is caused by a specific gene abnormality that leads to abnormal development or destruction of the white matter (myelin sheath) of the brain. The myelin sheath is the protective covering of the nerve and nerves can't function normally without it. Each type of leukodystrophy affects a different part of the myelin sheath, leading to a range of neurological problems.

Signs & Symptoms

Symptoms of some types of leukodystrophy begin shortly after birth, but others develop later in childhood or even in adulthood. Each type of leukodystrophy affects a different part of the myelin sheath, leading to a range of neurological problems. Leukodystrophy can cause problems with movement, vision, hearing, balance, ability to eat, memory, behavior, and thought. Leukodystrophies are progressive diseases meaning that the symptoms of the disease tend to get worse over time. Some inherited leukoencephalopathies have stable white matter abnormalities.

Magnetic resonance imaging (MRI) has markedly increased the awareness of hereditary white matter diseases associated with the formation of myelin and hypomyelination, in addition to the previously described classic leukodystrophies. New disease entities based on MRI and clinical patterns have been defined through the committed collaboration of neurologists in medical centers around the world. While the following list includes many disorders that have recently been described, it is not complete as there are new leukodystrophies identified each year. With the advances in whole genome sequencing, there will be many more new genetic disorders found including those that affect the white matter of the brain.

Causes

Leukodystrophies are genetic disorders caused by specific gene abnormalities that lead to abnormal development or destruction of the myelin sheath in the nervous system or white matter in the brain. Each type of leukodystrophy follows a particular pattern of inheritance such as autosomal recessive, X-linked recessive or autosomal dominant. Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother.

Recessive genetic disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease but usually will not show symptoms. The risk for two carrier parents to both pass the defective gene and have an affected child is 25%

with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

All individuals carry 10-15 abnormal genes. Parents who are close relatives (consanguineous) have a higher chance than unrelated parents to both carry the same abnormal gene, which increases the risk to have children with a recessive genetic disorder.

Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a new mutation (gene change) in the affected individual (de novo mutation). The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females.

X-linked genetic disorders are conditions caused by an abnormal gene on the X chromosome and manifest mostly in males. Females that have a defective gene present on one of their X chromosomes are carriers for that disorder. Carrier females usually do not display symptoms because females have two X chromosomes and only one carries the defective gene but may display milder symptoms (ex. AMN). Males have one X chromosome that is inherited from their mother and if a male inherits an X chromosome that contains a defective gene he will develop the disease.

Female carriers of an X-linked disorder have a 25% chance with each pregnancy to have a carrier daughter like themselves, a 25% chance to have a non-carrier daughter, a 25% chance to have a son affected with the disease and a 25% chance to have an unaffected son.

If a male with an X-linked disorder is able to reproduce, he will pass the defective gene to all of his daughters who will be carriers. A male cannot pass an X-linked gene to his sons because males always pass their Y chromosome instead of their X chromosome to male offspring.

Affected Populations

The leukodystrophies can affect either adults or children, but are more common in children. Some types of leukodystrophy affect males and females equally but other types predominantly affect males.

Related Disorders

Symptoms of the following disorder can be similar to those of leukodystrophy. Comparisons may be useful for a differential diagnosis:

Multiple sclerosis (MS) is a chronic inflammatory disease affecting the myelin sheath of the brain and spinal cord (central nervous system). It may be progressive, relapsing and remitting, or stable. MS consists of small lesions called plaques that form randomly throughout the brain and spinal cord. These plaques on the myelin sheath prevent proper transmission of nervous system signals. White matter lesions in leukodystrophies tend to be more symmetric and confluent then in MS which may help distinguish the two conditions. Symptoms may include visual and speech problems, numbness, walking difficulty and loss of bladder or bowel control. MS affects both children and adults, and its cause is unknown.

Standard Therapies

Treatment of most leukodystrophies is symptomatic and supportive. Medications and physical therapy may be helpful for spasticity and motor difficulties. Anti-epileptic medications should be provided for seizures and burning paresthesia from peripheral neuropathy may respond to medications for neuropathic pain. Please review the NORD report on the specific type of leukodystrophy for information about successful therapies. Genetic counseling is beneficial for affected individuals and their families.

Investigational Therapies

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government website.

For information about clinical trials being conducted at the National Institutes of Health (NIH) in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/