Pelizaeus-Merzbacher disease

Description

Pelizaeus-Merzbacher disease is an inherited condition involving the brain and spinal cord (central nervous system) that primarily affects males. This disease is one of a group of genetic disorders called leukodystrophies. Leukodystrophies are conditions that involve abnormalities of the nervous system's white matter, which consists of nerve fibers covered by a fatty substance called myelin. Myelin insulates nerve fibers and promotes the rapid transmission of nerve impulses. In particular, Pelizaeus-Merzbacher disease involves hypomyelination, which means that the nervous system has a reduced ability to form myelin. As a result, overall neurological function is reduced.

Pelizaeus-Merzbacher disease is divided into classic and connatal (present from birth) types. Although these two types differ in severity, their features can overlap.

Classic Pelizaeus-Merzbacher disease is the more common type. Within the first year of life, those affected with classic Pelizaeus-Merzbacher disease typically experience weak muscle tone (hypotonia), involuntary movements of the eyes (nystagmus), and delayed development of motor skills, such as sitting or grasping objects. Some individuals are able to walk with assistance. Despite these neurological problems, intellectual and motor skills develop throughout childhood, but development usually stops around adolescence, and these skills are slowly lost (developmental regression). As the condition worsens, nystagmus usually goes away but other movement disorders develop, including muscle stiffness (spasticity), problems with movement and balance (ataxia), head and neck tremors (titubation), involuntary tensing of the muscles (dystonia) , and jerking (choreiform) movements.

Connatal Pelizaeus-Merzbacher disease is the more severe of the two types. Symptoms can begin in infancy and include problems with feeding, poor weight gain and slow growth, high-pitched breathing caused by an obstructed airway (stridor), nystagmus, progressive speech difficulties (dysarthria), severe ataxia, hypotonia, and seizures. As the condition worsens, affected children develop spasticity leading to joint deformities (contractures) that restrict movement. Individuals with connatal Pelizaeus-Merzbacher disease are never able to walk, and many are not able to purposefully use their arms. They also have problems producing speech (expressive language) but can generally understand speech (receptive language).

Frequency

The prevalence of Pelizaeus-Merzbacher disease is estimated to be 1 in 200,000 to 500,000 males in the United States. This condition rarely affects females.

Causes

Mutations in the *PLP1* gene cause Pelizaeus-Merzbacher disease. The *PLP1* gene provides instructions for making proteolipid protein 1 and a modified version (isoform) of that protein called DM20. Proteolipid protein 1 is found primarily in nerves in the central nervous system and DM20 is produced mainly in nerves that connect the brain and spinal cord to muscles (peripheral nervous system). These two proteins are found within the cell membrane of nerve cells, where they make up the majority of myelin and anchor it to the cells.

Most mutations that cause Pelizaeus-Merzbacher disease copy (duplicate) the *PLP1* gene, which results in increased production of proteolipid protein 1 and DM20. Other mutations lead to production of abnormal proteins that are often misfolded. Excess or abnormal proteins become trapped within cell structures and cannot travel to the cell membrane. As a result, proteolipid protein 1 and DM20 are not available to form myelin. The accumulation of excess proteins leads to swelling and breakdown of nerve fibers. Still other mutations delete the *PLP1* gene, which prevents proteolipid protein 1 and DM20 protein production and results in a lack of these proteins in the cell membrane, which causes any myelin that is formed to be unstable and quickly broken down. All of these *PLP1* gene mutations lead to hypomyelination, nerve fiber damage, and impairment of nervous system function, resulting in the signs and symptoms of Pelizaeus-Merzbacher disease.

It is estimated that 5 to 20 percent of people with Pelizaeus-Merzbacher disease do not have identified mutations in the *PLP1* gene. In these cases, the cause of the condition is unknown.

Learn more about the gene associated with Pelizaeus-Merzbacher disease

- PLP1

Inheritance

Pelizaeus-Merzbacher disease is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males, who have only one X chromosome, a mutation in the only copy of the *PLP1* gene in each cell is sufficient to cause the condition. In females, who have two copies of the X chromosome, one altered copy of the *PLP1* gene in each cell can lead to less severe features of the condition, such as muscle stiffness or a decrease in intellectual function, or may cause no signs or symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- Cockayne-Pelizaeus-Merzbacher disease
- HLD1
- Hypomyelinating leukodystrophy, 1
- PMD
- Sudanophilic leukodystrophy

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Pelizaeus-Merzbacher disease (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0205711/)

Genetic and Rare Diseases Information Center

- Pelizaeus-Merzbacher disease (https://rarediseases.info.nih.gov/diseases/4265/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Pelizaeus-Merzbacher disease%22)

Catalog of Genes and Diseases from OMIM

- PELIZAEUS-MERZBACHER DISEASE; PMD (https://omim.org/entry/312080)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Pelizaeus-Merzbacher+Disease%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

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