Phosphoglycerate dehydrogenase deficiency

Description

Phosphoglycerate dehydrogenase deficiency is a condition characterized by an unusually small head size (microcephaly); impaired development of physical reactions, movements, and speech (psychomotor retardation); and recurrent seizures (epilepsy). Different types of phosphoglycerate dehydrogenase deficiency have been described; they are distinguished by their severity and the age at which symptoms first begin. Most affected individuals have the infantile form, which is the most severe form, and are affected from infancy. Symptoms of the juvenile and adult types appear later in life; these types are very rare.

In phosphoglycerate dehydrogenase deficiency there is a progressive loss of brain cells leading to a loss of brain tissue (brain atrophy), specifically affecting the fatty tissue known as myelin that surrounds nerve cells (hypomyelination). Frequently, the tissue that connects the two halves of the brain (corpus callosum) is small and thin, and the fluid-filled cavities (ventricles) near the center of the brain are enlarged. Because development of the brain is disrupted, the head does not grow at the same rate as the body, so it appears that the head is getting smaller as the body grows (progressive microcephaly). Poor brain growth leads to an inability to achieve many developmental milestones such as sitting unsupported and speaking. Many affected infants also have difficulty feeding.

The seizures in phosphoglycerate dehydrogenase deficiency can vary in type. Recurrent muscle contractions called infantile spasms are typical early in the disorder. Without early treatment, seizures may progress to tonic-clonic seizures, which involve a loss of consciousness, muscle rigidity, and convulsions; myoclonic seizures, which involve rapid, uncontrolled muscle jerks; or drop attacks, which are sudden episodes of weak muscle tone.

Individuals with the infantile form of phosphoglycerate dehydrogenase deficiency develop many of the features described above. Individuals with the juvenile form typically have epilepsy as well as mild developmental delay and intellectual disability. Only one case of the adult form has been reported; signs and symptoms began in mid-adulthood and included mild intellectual disability; difficulty coordinating movements (ataxia); and numbness, tingling, and pain in the arms and legs (sensory neuropathy).

Frequency

This condition is likely a rare disorder, but its prevalence is unknown. At least 15 cases have been described in the scientific literature.

Causes

Mutations in the *PHGDH* gene cause phosphoglycerate dehydrogenase deficiency. The *PHGDH* gene provides instructions for making the parts (subunits) that make up the phosphoglycerate dehydrogenase enzyme. Four PHGDH subunits combine to form the enzyme. This enzyme is involved in the production of the protein building block (amino acid) serine. Specifically, the enzyme converts a substance called 3-phosphoglycerate to 3-phosphohydroxypyruvate in the first step in serine production. Serine is necessary for the development and function of the brain and spinal cord (central nervous system). Serine is a part of chemical messengers called neurotransmitters that transmit signals in the nervous system. Proteins that form cell membranes and myelin also contain serine. Serine can be obtained from the diet, but brain cells must produce their own serine because dietary serine cannot cross the protective barrier that allows only certain substances to pass between blood vessels and the brain (the blood-brain barrier).

PHGDH gene mutations result in the production of an enzyme with decreased function. As a result, less 3-phosphoglycerate is converted into 3-phosphohydroxypyruvate than normal and serine production is stalled at the first step. The lack of serine likely prevents the production of proteins and neurotransmitters in the brain and impairs the formation of normal cells and myelin. These disruptions in normal brain development lead to the signs and symptoms of phosphoglycerate dehydrogenase deficiency.

Learn more about the gene associated with Phosphoglycerate dehydrogenase deficiency

- PHGDH

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- 3-PGDH deficiency
- 3-phosphoglycerate dehydrogenase deficiency
- PHGDH deficiency

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: PHGDH deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866174/)

Patient Support and Advocacy Resources

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

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Phosphoglycerate dehydrogenase deficiency%22)

Catalog of Genes and Diseases from OMIM

- PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY; PHGDHD (https://omim.org/entry/601815)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28phosphoglycerate+dehydrogenase+deficiency%5BTIAB%5D%29+OR+%283-phosphoglycerate+dehydrogenase+deficiency%5BTIAB%5D%29+OR+%283-pgdh+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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