pyruvate dehydrogenase deficiency

Pyruvate dehydrogenase deficiency is characterized by the buildup of a chemical called lactic acid in the body and a variety of neurological problems. Signs and symptoms of this condition usually first appear shortly after birth, and they can vary widely among affected individuals. The most common feature is a potentially life-threatening buildup of lactic acid (lactic acidosis), which can cause nausea, vomiting, severe breathing problems, and an abnormal heartbeat. People with pyruvate dehydrogenase deficiency usually have neurological problems as well. Most have delayed development of mental abilities and motor skills such as sitting and walking. Other neurological problems can include intellectual disability, seizures, weak muscle tone (hypotonia), poor coordination, and difficulty walking. Some affected individuals have abnormal brain structures, such as underdevelopment of the tissue connecting the left and right halves of the brain (corpus callosum), wasting away (atrophy) of the exterior part of the brain known as the cerebral cortex, or patches of damaged tissue (lesions) on some parts of the brain. Because of the severe health effects, many individuals with pyruvate dehydrogenase deficiency do not survive past childhood, although some may live into adolescence or adulthood.

Frequency

Pyruvate dehydrogenase deficiency is believed to be a rare condition; however, its prevalence is unknown.

Genetic Changes

The genes involved in pyruvate dehydrogenase deficiency each provide instructions for making a protein that is a component of a group of proteins called the pyruvate dehydrogenase complex. This complex plays an important role in the pathways that convert the energy from food into a form that cells can use. The pyruvate dehydrogenase complex converts a molecule called pyruvate, which is formed from the breakdown of carbohydrates, into another molecule called acetyl-CoA. This conversion is essential to begin the series of chemical reactions that produce energy for cells.

The pyruvate dehydrogenase complex is made up of multiple copies of several enzymes called E1, E2, and E3, each of which performs part of the chemical reaction that converts pyruvate to acetyl-CoA. In addition, other proteins included in the complex ensure its proper function. One of these proteins, E3 binding protein, attaches E3 to the complex and provides the correct structure for the complex to perform its function. Other associated proteins control the activity of the complex: pyruvate dehydrogenase

phosphatase turns on (activates) the complex, while pyruvate dehydrogenase kinase turns off (inhibits) the complex.

The E1 enzyme, also called pyruvate dehydrogenase, is composed of four parts (subunits): two alpha subunits (called E1 alpha) and two beta subunits (called E1 beta). Mutations in the gene that provides instructions for making E1 alpha, the *PDHA1* gene, are the most common cause of pyruvate dehydrogenase deficiency, accounting for approximately 80 percent of cases. These mutations lead to a shortage of E1 alpha protein or result in an abnormal protein that cannot function properly. A decrease in functional E1 alpha leads to reduced activity of the pyruvate dehydrogenase complex.

Other components of the pyruvate dehydrogenase complex are also involved in pyruvate dehydrogenase deficiency. Mutations in the genes that provide instructions for E1 beta (the *PDHB* gene), the E2 enzyme (the *DLAT* gene), E3 binding protein (the *PDHX* gene), and pyruvate dehydrogenase phosphatase (the *PDP1* gene) have been identified in people with this condition. Although it is unclear how mutations in each of these genes affect the complex, reduced functioning of one component of the complex appears to impair the activity of the whole complex. As with *PDHA1* gene mutations, changes in these other genes lead to a reduction of pyruvate dehydrogenase complex activity.

With decreased function of this complex, pyruvate builds up and is converted in another chemical reaction to lactic acid. The excess lactic acid causes lactic acidosis in affected individuals. In addition, the production of cellular energy is diminished. The brain, which requires especially large amounts of energy, is severely affected, resulting in the neurological problems associated with pyruvate dehydrogenase deficiency.

Inheritance Pattern

Pyruvate dehydrogenase deficiency can have different inheritance patterns. When the condition is caused by mutations in the *PDHA1* gene, it is inherited in an X-linked recessive pattern. The *PDHA1* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would usually have to occur in both copies of the gene to cause the disorder. However, in pyruvate dehydrogenase deficiency, one altered copy of the *PDHA1* gene is sufficient to cause the disorder, because the X chromosome with the normal copy of the *PDHA1* gene is turned off through a process called X-inactivation.

Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, such that each X chromosome is active in about half of the body cells. Sometimes X-inactivation

is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation.

Research shows that females with pyruvate dehydrogenase deficiency caused by mutation of the *PDHA1* gene have skewed X-inactivation, which results in the inactivation of the X chromosome with the normal copy of the *PDHA1* gene in most cells of the body. This skewed X-inactivation causes the chromosome with the mutated *PDHA1* gene to be expressed in more than half of cells.

When caused by mutations in the other associated genes, pyruvate dehydrogenase deficiency 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

- ataxia with lactic acidosis
- intermittent ataxia with pyruvate dehydrogenase deficiency
- PDH deficiency
- PDHC deficiency
- pyruvate dehydrogenase complex deficiency

Diagnosis & Management

These resources address the diagnosis or management of pyruvate dehydrogenase deficiency:

- Genetic Testing Registry: Pyruvate dehydrogenase E1-beta deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1867399/
- Genetic Testing Registry: Pyruvate dehydrogenase E2 deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855565/
- Genetic Testing Registry: Pyruvate dehydrogenase E3-binding protein deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855553/
- Genetic Testing Registry: Pyruvate dehydrogenase complex deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0034345/
- Genetic Testing Registry: Pyruvate dehydrogenase phosphatase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1837429/

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Lactic Acidosis
  https://medlineplus.gov/ency/article/000391.htm
- Health Topic: Carbohydrate Metabolism Disorders
  https://medlineplus.gov/carbohydratemetabolismdisorders.html
- Health Topic: Genetic Brain Disorders
  https://medlineplus.gov/geneticbraindisorders.html

Genetic and Rare Diseases Information Center

- Pyruvate dehydrogenase deficiency
  https://rarediseases.info.nih.gov/diseases/7513/pyruvate-dehydrogenase-deficiency

Educational Resources

- Centers for Disease Control and Prevention: Developmental Screening
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/DevelopmentalScreening.pdf
- Disease InfoSearch: Pyruvate dehydrogenase deficiency
  http://www.diseaseinfosearch.org/Pyruvate+dehydrogenase+deficiency/6122
- My Child Without Limits: Developmental Delay
  http://www.mychildwithoutlimits.org/?page=developmental-delay
- Orphanet: Pyruvate dehydrogenase deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=765

Patient Support and Advocacy Resources

- My Child Without Limits: Developmental Delay
  http://www.mychildwithoutlimits.org/?page=developmental-delay
- National Organization for Rare Disorders (NORD): Pyruvate Dehydrogenase Complex Deficiency
  https://rarediseases.org/rare-diseases/pyruvate-dehydrogenase-complex-deficiency/

Genetic Testing Registry

- Pyruvate dehydrogenase complex deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0034345/
- Pyruvate dehydrogenase E1-beta deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1867399/
- Pyruvate dehydrogenase E2 deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855565/
- Pyruvate dehydrogenase E3-binding protein deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1855553/
- Pyruvate dehydrogenase phosphatase deficiency
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1837429/

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22pyruvate+dehydrogenase+deficiency%22

Scientific articles on PubMed

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

OMIM

- PYRUVATE DEHYDROGENASE E1-ALPHA DEFICIENCY
  http://omim.org/entry/312170
- PYRUVATE DEHYDROGENASE E1-BETA DEFICIENCY
  http://omim.org/entry/614111
- PYRUVATE DEHYDROGENASE E2 DEFICIENCY
  http://omim.org/entry/245348

- PYRUVATE DEHYDROGENASE E3-BINDING PROTEIN DEFICIENCY
  http://omim.org/entry/245349
- PYRUVATE DEHYDROGENASE PHOSPHATASE DEFICIENCY
  http://omim.org/entry/608782

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