Pyruvate carboxylase deficiency

Pyruvate carboxylase deficiency is an inherited disorder that causes lactic acid and other potentially toxic compounds to accumulate in the blood. High levels of these substances can damage the body’s organs and tissues, particularly in the nervous system.

Researchers have identified at least three types of pyruvate carboxylase deficiency, which are distinguished by the severity of their signs and symptoms. Type A, which has been identified mostly in people from North America, has severe symptoms that begin in infancy. Characteristic features include developmental delay and a buildup of lactic acid in the blood (lactic acidosis). Increased acidity in the blood can lead to vomiting, abdominal pain, extreme tiredness (fatigue), muscle weakness, and difficulty breathing. In some cases, episodes of lactic acidosis are triggered by an illness or periods without food (fasting). Children with pyruvate carboxylase deficiency type A typically survive only into infancy or early childhood.

Pyruvate carboxylase deficiency type B has life-threatening signs and symptoms that become apparent shortly after birth. This form of the condition has been reported mostly in Europe, particularly France. Affected infants have severe lactic acidosis, a buildup of ammonia in the blood (hyperammonemia), and liver failure. They experience neurological problems including weak muscle tone (hypotonia), abnormal movements, seizures, and coma. Infants with this form of the condition usually survive for less than 3 months after birth.

A milder form of pyruvate carboxylase deficiency, sometimes called type C, has also been described. This type is characterized by slightly increased levels of lactic acid in the blood and minimal signs and symptoms affecting the nervous system.

Frequency

Pyruvate carboxylase deficiency is a rare condition, with an estimated incidence of 1 in 250,000 births worldwide. Type A appears to be much more common in some Algonkian Indian tribes in eastern Canada.

Causes

Mutations in the PC gene cause pyruvate carboxylase deficiency. This gene provides instructions for making an enzyme called pyruvate carboxylase. This enzyme is active in mitochondria, which are the energy-producing centers within cells. It is involved in several important cellular functions, including the generation of glucose, a simple sugar that is the body’s main energy source. Pyruvate carboxylase also plays a role in the formation of the protective sheath that surrounds certain nerve cells (myelin).
and the production of brain chemicals called neurotransmitters that allow nerve cells to communicate with one another.

Mutations in the *PC* gene reduce the amount of pyruvate carboxylase in cells or disrupt the enzyme’s activity. The missing or altered enzyme cannot carry out its essential role in generating glucose, which impairs the body’s ability to make energy in mitochondria. Additionally, a loss of pyruvate carboxylase allows compounds such as lactic acid and ammonia to build up and damage organs and tissues. Researchers suggest that the loss of pyruvate carboxylase function in the nervous system, particularly the role of the enzyme in myelin formation and neurotransmitter production, also contributes to the neurologic features of pyruvate carboxylase deficiency.

**Inheritance Pattern**

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**

- ataxia with lactic acidosis, type II
- Leigh necrotizing encephalopathy due to pyruvate carboxylase deficiency
- Leigh syndrome due to pyruvate carboxylase deficiency
- PC deficiency
- pyruvate carboxylase deficiency disease
- type II ataxia with lactic acidosis

**Diagnosis & Management**

**Formal Diagnostic Criteria**

- ACT Sheet: Increased citrulline
  https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/Citrullinemia.pdf

**Genetic Testing Information**

- What is genetic testing? /primer/testing/genetictesting
- Genetic Testing Registry: Pyruvate carboxylase deficiency

**Research Studies from ClinicalTrials.gov**

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

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Other Diagnosis and Management Resources

- GeneReview: Pyruvate Carboxylase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK6852

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Genetic Brain Disorders
  https://medlineplus.gov/geneticbraindisorders.html
- Health Topic: Mitochondrial Diseases
  https://medlineplus.gov/mitochondrialdiseases.html
- Health Topic: Newborn Screening
  https://medlineplus.gov/newbornscreening.html

Genetic and Rare Diseases Information Center

- Pyruvate carboxylase deficiency
  https://rarediseases.info.nih.gov/diseases/7512/pyruvate-carboxylase-deficiency

Educational Resources

- MalaCards: pyruvate carboxylase deficiency
  https://www.malacards.org/card/pyruvate_carboxylase_deficiency
- Merck Manual Consumer Version: Overview of Hereditary Metabolic Disorders
- Orphanet: Pyruvate carboxylase deficiency
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=3008

Patient Support and Advocacy Resources

- Metabolic Support UK
  https://www.metabolicsupportuk.org/
- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/pyruvate-carboxylase-deficiency/
- Resource List from the University of Kansas Medical Center: Metabolic Conditions
  http://www.kumc.edu/gec/support/metaboli.html
- United Mitochondrial Disease Foundation
  https://www.umdf.org/

Clinical Information from GeneReviews

- Pyruvate Carboxylase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK6852
Scientific Articles on PubMed
- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28pyruvate+carboxylase%5BTIAB%5D%29+AND+%28deficiency%5BTIAB%5D%29%29+OR+%28%28ataxia+with+lactic+acidosis%5BTIAB%5D%29+AND+%28type+II%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

Catalog of Genes and Diseases from OMIM
- PYRUVATE CARBOXYLASE DEFICIENCY
  http://omim.org/entry/266150

Medical Genetics Database from MedGen
- Pyruvate carboxylase deficiency

Sources for This Summary

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