Ornithine translocase deficiency

Ornithine translocase deficiency is an inherited disorder that causes ammonia and other substances to build up (accumulate) in the blood. Ammonia, which is formed when proteins are broken down in the body, is toxic if the levels become too high. The nervous system is especially sensitive to the effects of excess ammonia.

Ornithine translocase deficiency varies widely in its severity and age of onset. Affected infants show signs and symptoms of ornithine translocase deficiency within days after birth. In most affected individuals, however, signs and symptoms of ornithine translocase deficiency do not appear until later in life, with health problems first appearing anytime from childhood to adulthood. Later-onset forms of ornithine translocase deficiency are usually less severe than the infantile form.

Infants with ornithine translocase deficiency may lack energy (be lethargic), refuse to eat, vomit frequently, or have poorly controlled breathing or body temperature. Seizures or unusual body movements are common in these individuals. Some people with this condition have intellectual disability or developmental delay, but others have normal intelligence. Severe cases may result in coma.

Some people with later-onset ornithine translocase deficiency have episodes of vomiting, lethargy, problems with coordination (ataxia), vision problems, episodes of brain dysfunction (encephalopathy), developmental delay, learning disabilities, or stiffness caused by abnormal tensing of the muscles (spasticity). Affected individuals may have chronic liver problems and mild abnormal bleeding.

Individuals with ornithine translocase deficiency often cannot tolerate high-protein foods, such as meat. Occasionally, high-protein meals or stress caused by illness or periods without food (fasting) may cause ammonia to accumulate more quickly in the blood. This rapid increase of ammonia likely leads to the signs and symptoms of ornithine translocase deficiency.

While the signs and symptoms of ornithine translocase deficiency can vary greatly among affected individuals, proper treatment can prevent some complications from occurring and may improve quality of life.

Frequency

Ornithine translocase deficiency is a very rare disorder. More than 100 affected individuals have been described in the scientific literature.

Causes

Mutations in the *SLC25A15* gene cause ornithine translocase deficiency. The *SLC25A15* gene provides instructions for making a protein called mitochondrial
ornithine transporter 1. This protein participates in the urea cycle, which is a sequence of biochemical reactions that occurs in liver cells. The urea cycle breaks down excess nitrogen, made when protein is broken down by the body, to make a compound called urea that is excreted by the kidneys in urine.

Mitochondrial ornithine transporter 1 is located within the mitochondria (the energy-producing centers in cells), where the protein transports a molecule called ornithine so it can participate in the urea cycle.

Mutations in the SLC25A15 gene cause the production of a mitochondrial ornithine transporter 1 with reduced or absent function. As a result, ornithine transport is impaired and the urea cycle cannot proceed normally. This causes, nitrogen to accumulate in the bloodstream in the form of toxic ammonia instead of being converted to less toxic urea and being excreted. Ammonia is especially damaging to the brain, and excess ammonia causes neurological problems and other signs and symptoms of ornithine translocase deficiency. Byproducts of impaired ornithine transport in people with this condition include the accumulation of a substance called ornithine in the blood (hyperornithinemia) and the excretion of a substance called homocitrulline in the urine (homocitrullinuria).

Another version of the mitochondrial ornithine transporter protein is produced by a different gene. While this protein is not as abundant as mitochondrial ornithine transporter 1, it is thought that this other version of the protein may partially compensate for the loss of mitochondrial ornithine transporter 1 and contribute to the late age of onset and mild signs and symptoms in some affected individuals. Other factors, many unknown, also contribute to the variable severity of ornithine translocase deficiency.

Because ornithine translocase deficiency is caused by problems with the urea cycle, it belongs to a class of genetic diseases called urea cycle disorders.

**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**

- HHH syndrome
- hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome
- hyperornithinemia-hyperammonemia-homocitrullinemia syndrome
- hyperornithinemia-hyperammonemia-homocitrullinuria syndrome
- triple H syndrome
Diagnosis & Management

Formal Diagnostic Criteria

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22642880
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3488504/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30982989

Genetic Testing Information

• What is genetic testing?
  /primer/testing/genetictesting

• Genetic Testing Registry: Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

Other Diagnosis and Management Resources

• Baby’s First Test
  https://www.babysfirsttest.org/newborn-screening/conditions/hyperornithinemia-hyperammonemia-homocitrullinuria-syndrome

• GeneReview: Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK97260

• GeneReview: Urea Cycle Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1217

• MedlinePlus Encyclopedia: Hereditary Urea Cycle Abnormality
  https://medlineplus.gov/ency/article/000372.htm

• MedlinePlus Medical Tests: Ammonia Levels
  https://medlineplus.gov/lab-tests/ammonia-levels/

• National Organization for Rare Disorders (NORD) Physician Guide: Urea Cycle Disorders
  https://rarediseases.org/physician-guide/urea-cycle-disorders/
Additional Information & Resources

Health Information from MedlinePlus

• Encyclopedia: Hereditary Urea Cycle Abnormality
  https://medlineplus.gov/ency/article/000372.htm

• 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

• Medical Tests: Ammonia Levels
  https://medlineplus.gov/lab-tests/ammonia-levels/

Genetic and Rare Diseases Information Center

• Ornithine translocase deficiency syndrome

Educational Resources

• MalaCards: hyperornithinemia-hyperammonemia-homocitrullinuria syndrome
  https://www.malacards.org/card/hyperornithinemia_hyperammonemia_homocitrullinuria_syndrome

• Orphanet: Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=415

Patient Support and Advocacy Resources

• Metabolic Support UK
  https://www.metabolicsupportuk.org/

• National Urea Cycle Disorders Foundation
  http://www.nucdf.org/

• Urea Cycle Disorders Consortium
  https://www.rarediseasesnetwork.org/cms/ucdc/Learn-More/Disorder-Definitions

Clinical Information from GeneReviews

• Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK97260

• Urea Cycle Disorders Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1217
Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28ornithine+translocase+deficiency%5BALL%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

Catalog of Genes and Diseases from OMIM

- HYPERORNITHINEMIA-HYPERAMMONEMIA-HOMOCITRULLINURIA SYNDROME
  http://omim.org/entry/238970

Medical Genetics Database from MedGen

- Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16940241

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10369256

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12948741

- OMIM: HYPERORNITHINEMIA-HYPERAMMONEMIA-HOMOCITRULLINURIA SYNDROME
  http://omim.org/entry/238970

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25874378
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358699/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11355015

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27215558
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4921309/

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