Argininosuccinic aciduria

Argininosuccinic aciduria is an inherited disorder that causes ammonia to 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.

Argininosuccinic aciduria usually becomes evident in the first few days of life. An infant with argininosuccinic aciduria may be lacking in energy (lethargic) or unwilling to eat, and have a poorly controlled breathing rate or body temperature. Some babies with this disorder experience seizures or unusual body movements, or go into a coma. Complications from argininosuccinic aciduria may include developmental delay and intellectual disability. Progressive liver damage, high blood pressure (hypertension), skin lesions, and brittle hair may also be seen.

Occasionally, individuals may inherit a mild form of the disorder. These individuals can have an accumulation of ammonia in the bloodstream only during periods of illness or other stress, or mild intellectual disability or learning disabilities with no evidence of elevated ammonia levels.

Frequency

Argininosuccinic aciduria occurs in approximately 1 in 70,000 to 218,000 newborns. Most cases of this condition are detected shortly after birth by newborn screening.

Causes

Mutations in the ASL gene cause argininosuccinic aciduria. This condition belongs to a class of genetic diseases called urea cycle disorders because they are caused by problems with a process in the body called the urea cycle. The urea cycle is a sequence of reactions that occurs in liver cells. This cycle breaks down excess nitrogen, which is made when protein is used by the body, to make a compound called urea. Urea is removed from the body in urine. Breaking down excess nitrogen and excreting it as urea prevents it from accumulating in the body as ammonia.

The ASL gene provides instructions for making an enzyme called argininosuccinate lyase, which is needed for the fourth step of the urea cycle. The specific role of the argininosuccinate lyase enzyme is to start the reaction in which the amino acid arginine, a building block of proteins, is produced from argininosuccinate, the molecule that carries the waste nitrogen collected earlier in the urea cycle. The arginine is later broken down into urea, which is excreted, and ornithine, which restarts the urea cycle.

In people with argininosuccinic aciduria, argininosuccinate lyase is dysfunctional or missing. As a result, the urea cycle cannot proceed normally, arginine is not produced,
and nitrogen is not broken down efficiently. The excess nitrogen accumulates in the blood in the form of ammonia. This buildup of ammonia damages the brain and other tissues and causes neurological problems and other signs and symptoms of argininosuccinic aciduria. It is unclear how a lack of arginine contributes to the features of this condition.

**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**

- Argininosuccinate lyase deficiency
- argininosuccinic acidemia
- Argininosuccinicaciduria
- argininosuccinyl-CoA lyase deficiency
- arginosuccinase deficiency
- ASA
- AS Auria
- ASL deficiency

**Diagnosis & Management**

**Formal Diagnostic Criteria**

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

**Formal Treatment/Management Guidelines**

- New England Consortium of Metabolic Programs: Acute Illness Protocol

**Genetic Testing Information**

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Argininosuccinate lyase deficiency
Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22argininosuccinic+aciduria%22

Other Diagnosis and Management Resources

- Baby's First Test
  https://www.babysfirsttest.org/newborn-screening/conditions/argininosuccinic-aciduria
- GeneReview: Argininosuccinate Lyase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK51784
- 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: Amino Acid Metabolism Disorders
  https://medlineplus.gov/aminoacidmetabolismdisorders.html
- Health Topic: Genetic Brain Disorders
  https://medlineplus.gov/geneticbraindisorders.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

- Argininosuccinic aciduria
  https://rarediseases.info.nih.gov/diseases/5843/argininosuccinic-aciduria
Educational Resources

- MalaCards: argininosuccinic aciduria
  https://www.malacards.org/card/argininosuccinic_aciduria
- Orphanet: Argininosuccinic aciduria
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=23
- Screening, Technology and Research in Genetics
  http://www.newbornscreening.info/Parents/aminoaciddisorders/ASAL.html
- Vanderbilt Children’s Hospital
- Virginia Department of Health

Patient Support and Advocacy Resources

- Metabolic Support UK
  https://www.metabolicsupportuk.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/argininosuccinic-aciduria/
- 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

- Argininosuccinate Lyase Deficiency
  https://www.ncbi.nlm.nih.gov/books/NBK51784
- 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=%28%28argininosuccinic+aciduria%5BTIAB%5D%29+OR+%28argininosuccinate+lyase+deficiency%5BTIAB%5D%29+OR+%28asl+deficiency%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+2160+days%22+AND+5Bbp%5D

Catalog of Genes and Diseases from OMIM

- ARGININOSUCCINIC ACIDURIA
  http://omim.org/entry/207900
Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301396

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12408190

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11148551

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21290785

- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/argininosuccinic-aciduria/

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

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12559843

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