N-acetylglutamate Synthase Deficiency

Subjects: Genetics & Heredity
Contributor: Rita Xu

N-acetylglutamate synthase deficiency is a disorder that causes abnormally high levels of 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 brain is especially sensitive to the effects of excess ammonia.

Keywords: genetic conditions

1. Introduction

The signs and symptoms of N-acetylglutamate synthase deficiency often become evident in the first few days of life. An infant with this condition may be lacking in energy (lethargic) or unwilling to eat, and have difficulty controlling his or her breathing rate or body temperature. Severely affected babies may experience seizures or unusual body movements, or go into a coma. Complications of N-acetylglutamate synthase deficiency may include developmental delay and intellectual disability.

In some affected individuals, signs and symptoms of N-acetylglutamate synthase deficiency do not appear until later in life. Some people with this form of the disorder notice that eating high-protein foods, such as meat, affects how they feel, although they may not know why. In many affected adults, illness or other stress can trigger episodes of vomiting, lack of coordination, headaches, confusion, behavioral changes, or coma.

2. Frequency

N-acetylglutamate synthase deficiency is a very rare disorder. It is estimated to affect fewer than 1 in 2 million people worldwide.

3. Causes

Mutations in the *NAGS* gene cause N-acetylglutamate synthase deficiency. 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.

The *NAGS* gene provides instructions for making the enzyme N-acetylglutamate synthase, which is integral to the first step of the urea cycle.

In people with N-acetylglutamate synthase deficiency, N-acetylglutamate synthase is not available in sufficient quantities, or is not present at all. As a result, the urea cycle is impaired, and nitrogen is not broken down efficiently. The excess nitrogen accumulates in the blood in the form of ammonia. This buildup of ammonia damages tissues in the brain and causes neurological problems and other signs and symptoms of N-acetylglutamate synthase deficiency.

3.1. The Gene Associated with N-Acetylglutamate Synthase Deficiency

- NAGS

4. 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.

5. Other Names for This Condition

- hyperammonemia, type III
- N-acetylglutamate synthetase deficiency
- NAGS deficiency

References

1. Caldovic L, Morizono H, Panglao MG, Cheng SF, Packman S, Tuchman M. Nullmutations in the N-acetylglutamate synthase gene associated with acute neonataldisease and hyperammonemia. Hum Genet. 2003 Apr;112(4):364-8.
2. Caldovic L, Morizono H, Panglao MG, Lopez GY, Shi D, Summar ML, Tuchman M.Late onset N-acetylglutamate synthase deficiency caused by hypomorphic alleles.Hum Mutat. 2005 Mar;25(3):293-8.
3. Cavicchi C, Chilleri C, Fioravanti A, Ferri L, Ripandelli F, Costa C,Calabresi P, Prontera P, Pochiero F, Pasquini E, Funghini S, la Marca G, DonatiMA, Morrone A. Late-Onset N-Acetylglutamate Synthase Deficiency: Report of aParadigmatic Adult Case Presenting with Headaches and Review of the Literature.Int J Mol Sci. 2018 Jan 24;19(2). pii: E345. doi: 10.3390/ijms19020345. Review.
4. Elpeleg O, Shaag A, Ben-Shalom E, Schmid T, Bachmann C. N-acetylglutamatesynthase deficiency and the treatment of hyperammonemic encephalopathy. AnnNeurol. 2002 Dec;52(6):845-9.
5. Häberle J, Schmidt E, Pauli S, Kreuder JG, Plecko B, Galler A, Wermuth B,Harms E, Koch HG. Mutation analysis in patients with N-acetylglutamate synthasedeficiency. Hum Mutat. 2003 Jun;21(6):593-7.
6. Sancho-Vaello E, Marco-Marín C, Gougeard N, Fernández-Murga L, Rüfenacht V,Mustedanagic M, Rubio V, Häberle J. Understanding N-Acetyl-L-Glutamate SynthaseDeficiency: Mutational Spectrum, Impact of Clinical Mutations on EnzymeFunctionality, and Structural Considerations. Hum Mutat. 2016 Jul;37(7):679-94.doi: 10.1002/humu.22995.
7. Schmidt E, Nuoffer JM, Häberle J, Pauli S, Guffon N, Vianey-Saban C, WermuthB, Koch HG. Identification of novel mutations of the human N-acetylglutamatesynthase gene and their functional investigation by expression studies. BiochimBiophys Acta. 2005 Apr 15;1740(1):54-9.