Glutaric Acidemia Type I

Subjects: Genetics & Heredity
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Glutaric acidemia type I (also called glutaric aciduria type I) is an inherited disorder in which the body is unable to process certain proteins properly. It is classified as an organic acid disorder, which is a condition that leads to an abnormal buildup of particular acids known as organic acids.

Keywords: genetic conditions

1. Introduction

Abnormal levels of organic acids in the blood (organic acidemia), urine (organic aciduria), and tissues can be toxic and can cause serious health problems.

People with glutaric acidemia type I have inadequate levels of an enzyme that helps break down the amino acids lysine, hydroxylysine, and tryptophan, which are building blocks of protein. Excessive levels of these amino acids and their intermediate breakdown products can accumulate and cause damage to the brain, particularly the basal ganglia, which are regions that help control movement. Intellectual disability may also occur.

The severity of glutaric acidemia type I varies widely; some individuals are only mildly affected, while others have severe problems. In most cases, signs and symptoms first occur in infancy or early childhood, but in a small number of affected individuals, the disorder first becomes apparent in adolescence or adulthood.

Some babies with glutaric acidemia type I are born with unusually large heads (macrocephaly). Affected individuals may have difficulty moving and may experience spasms, jerking, rigidity, or decreased muscle tone. Some individuals with glutaric acidemia have developed bleeding in the brain or eyes that could be mistaken for the effects of child abuse. Strict dietary control may help limit progression of the neurological damage. Stress caused by infection, fever or other demands on the body may lead to worsening of the signs and symptoms, with only partial recovery.

2. Frequency

Glutaric acidemia type I occurs in approximately 1 in 100,000 individuals. It is much more common in the Amish community and in the Ojibwa population of Canada, where up to 1 in 300 newborns may be affected.

3. Causes

Mutations in the *GCDH* gene cause glutaric acidemia type I. The *GCDH* gene provides instructions for making the enzyme glutaryl-CoA dehydrogenase. This enzyme is involved in processing the amino acids lysine, hydroxylysine, and tryptophan.

Mutations in the *GCDH* gene prevent production of the enzyme or result in the production of a defective enzyme that cannot function. A shortage (deficiency) of this enzyme allows lysine, hydroxylysine and tryptophan and their intermediate breakdown products to build up to abnormal levels, especially at times when the body is under stress.

The intermediate breakdown products resulting from incomplete processing of lysine, hydroxylysine, and tryptophan can damage the brain, particularly the basal ganglia, causing the signs and symptoms of glutaric acidemia type I.

3.1. The gene associated with Glutaric acidemia type I

- GCDH

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

- GA I
- Glutaric acidemia I
- Glutaric acidemia type 1
- Glutaric aciduria I
- Glutaryl-CoA dehydrogenase deficiency

References

1. Basinger AA, Booker JK, Frazier DM, Koeberl DD, Sullivan JA, Muenzer J.Glutaric acidemia type 1 in patients of Lumbee heritage from North Carolina. Mol Genet Metab. 2006 May;88(1):90-2.
2. Boy N, Mengler K, Thimm E, Schiergens KA, Marquardt T, Weinhold N, MarquardtI, Das AM, Freisinger P, Grünert SC, Vossbeck J, Steinfeld R, Baumgartner MR,Beblo S, Dieckmann A, Näke A, Lindner M, Heringer J, Hoffmann GF, Mühlhausen C,Maier EM, Ensenauer R, Garbade SF, Kölker S. Newborn screening: Adisease-changing intervention for glutaric aciduria type 1. Ann Neurol. 2018May;83(5):970-979. doi: 10.1002/ana.25233.
3. Boy N, Mühlhausen C, Maier EM, Heringer J, Assmann B, Burgard P, Dixon M,Fleissner S, Greenberg CR, Harting I, Hoffmann GF, Karall D, Koeller DM,Krawinkel MB, Okun JG, Opladen T, Posset R, Sahm K, Zschocke J, Kölker S;Additional individual contributors. Proposed recommendations for diagnosing andmanaging individuals with glutaric aciduria type I: second revision. J InheritMetab Dis. 2017 Jan;40(1):75-101. doi: 10.1007/s10545-016-9999-9.
4. Gerstner B, Gratopp A, Marcinkowski M, Sifringer M, Obladen M, Bührer C.Glutaric acid and its metabolites cause apoptosis in immature oligodendrocytes: anovel mechanism of white matter degeneration in glutaryl-CoA dehydrogenasedeficiency. Pediatr Res. 2005 Jun;57(6):771-6.
5. Guerreiro G, Faverzani J, Jacques CED, Marchetti DP, Sitta A, de Moura Coelho D, Kayser A, Kok F, Athayde L, Manfredini V, Wajner M, Vargas CR. Oxidativedamage in glutaric aciduria type I patients and the protective effects ofl-carnitine treatment. J Cell Biochem. 2018 Dec;119(12):10021-10032. doi:10.1002/jcb.27332.
6. Hedlund GL, Longo N, Pasquali M. Glutaric acidemia type 1. Am J Med Genet CSemin Med Genet. 2006 May 15;142C(2):86-94. Review.
7. Kölker S, Boy SP, Heringer J, Müller E, Maier EM, Ensenauer R, Mühlhausen C,Schlune A, Greenberg CR, Koeller DM, Hoffmann GF, Haege G, Burgard P.Complementary dietary treatment using lysine-free, arginine-fortified amino acid supplements in glutaric aciduria type I - A decade of experience. Mol GenetMetab. 2012 Sep;107(1-2):72-80. doi: 10.1016/j.ymgme.2012.03.021.
8. Kölker S, Garbade SF, Greenberg CR, Leonard JV, Saudubray JM, Ribes A,Kalkanoglu HS, Lund AM, Merinero B, Wajner M, Troncoso M, Williams M, Walter JH, Campistol J, Martí-Herrero M, Caswill M, Burlina AB, Lagler F, Maier EM, Schwahn B, Tokatli A, Dursun A, Coskun T, Chalmers RA, Koeller DM, Zschocke J,Christensen E, Burgard P, Hoffmann GF. Natural history, outcome, and treatmentefficacy in children and adults with glutaryl-CoA dehydrogenase deficiency.Pediatr Res. 2006 Jun;59(6):840-7.
9. Kölker S, Greenberg CR, Lindner M, Müller E, Naughten ER, Hoffmann GF.Emergency treatment in glutaryl-CoA dehydrogenase deficiency. J Inherit MetabDis. 2004;27(6):893-902. Review.
10. Kölker S, Koeller DM, Okun JG, Hoffmann GF. Pathomechanisms ofneurodegeneration in glutaryl-CoA dehydrogenase deficiency. Ann Neurol. 2004Jan;55(1):7-12. Review.
11. Külkens S, Harting I, Sauer S, Zschocke J, Hoffmann GF, Gruber S, Bodamer OA, Kölker S. Late-onset neurologic disease in glutaryl-CoA dehydrogenase deficiency.Neurology. 2005 Jun 28;64(12):2142-4.
12. Lehnert W, Sass JO. Glutaconyl-CoA is the main toxic agent in glutaryl-CoAdehydrogenase deficiency (glutaric aciduria type I). Med Hypotheses.2005;65(2):330-3.

13. Lindner M, Kölker S, Schulze A, Christensen E, Greenberg CR, Hoffmann GF.Neonatal screening for glutaryl-CoA dehydrogenase deficiency. J Inherit MetabDis. 2004;27(6):851-9. Review.
14. Pokora P, Jezela-Stanek A, Różdżyńska-Świątkowska A, Jurkiewicz E, BogdańskaA, Szymańska E, Rokicki D, Ciara E, Rydzanicz M, Stawiński P, Płoski R,Tylki-Szymańska A. Mild phenotype of glutaric aciduria type 1 in polish patients - novel data from a group of 13 cases. Metab Brain Dis. 2019 Apr;34(2):641-649.doi: 10.1007/s11011-018-0357-5.
15. Screening, Technology and Research in Genetics
16. Shadmehri AA, Fattahi N, Pourreza MR, Koohiyan M, Zarifi S, Darbouy M, SharifiR, Tavakkoly Bazzaz J, Tabatabaiefar MA. Molecular genetic study of glutaricaciduria, type I: Identification of a novel mutation. J Cell Biochem. 2019Mar;120(3):3367-3372. doi: 10.1002/jcb.27607.
17. Strauss KA, Brumbaugh J, Duffy A, Wardley B, Robinson D, Hendrickson C,Tortorelli S, Moser AB, Puffenberger EG, Rider NL, Morton DH. Safety, efficacyand physiological actions of a lysine-free, arginine-rich formula to treatglutaryl-CoA dehydrogenase deficiency: focus on cerebral amino acid influx. MolGenet Metab. 2011 Sep-Oct;104(1-2):93-106. doi: 10.1016/j.ymgme.2011.07.003.
18. Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria,part 1: natural history of 77 patients. Am J Med Genet C Semin Med Genet. 2003Aug 15;121C(1):38-52.
19. Wajner M, Kölker S, Souza DO, Hoffmann GF, de Mello CF. Modulation ofglutamatergic and GABAergic neurotransmission in glutaryl-CoA dehydrogenasedeficiency. J Inherit Metab Dis. 2004;27(6):825-8. Review.