Cerebral folate transport deficiency

Cerebral folate transport deficiency is a disorder that develops from a shortage (deficiency) of the B-vitamin folate (also called vitamin B9) in the brain. Affected children have normal development during infancy, but around age 2 they begin to lose previously acquired mental and movement abilities (psychomotor regression). They develop intellectual disability, speech difficulties, and recurrent seizures (epilepsy). Movement problems such as tremors and difficulty coordinating movements (ataxia) can be severe, and some affected individuals need wheelchair assistance. Affected individuals have leukodystrophy, which is a loss of a type of brain tissue known as white matter. White matter consists of nerve fibers covered by a fatty substance called myelin that promotes the rapid transmission of nerve impulses. Leukodystrophy contributes to the neurological problems that occur in cerebral folate transport deficiency. Without treatment, these neurological problems worsen over time.

Frequency

The prevalence of cerebral folate transport deficiency is unknown. Fewer than 20 affected individuals have been described in the scientific literature.

Causes

Mutations in the \(FOLR1\) gene cause cerebral folate transport deficiency. The \(FOLR1\) gene provides instructions for making a protein called folate receptor alpha. This protein is found within the cell membrane where it attaches (binds) to folate, allowing the vitamin to be brought into the cell. Folate receptor alpha is produced in largest amounts in the brain, specifically in an area of the brain called the choroid plexus. This region releases cerebrospinal fluid (CSF), which surrounds and protects the brain and spinal cord. Folate receptor alpha is thought to play a major role in bringing folate from the bloodstream into brain cells. It transports folate across the choroid plexus and into the CSF, ultimately reaching the brain. In the brain, folate is needed for making myelin and chemical messengers called neurotransmitters. Both of these substances play essential roles in transmitting signals in the nervous system. Additionally, folate is involved in the production and repair of DNA, regulation of gene activity (expression), and protein production.

\(FOLR1\) gene mutations result in a lack of protein or malfunctioning protein. As a result, folate from the bloodstream cannot be transported into the CSF. Without folate, many processes in the brain are impaired, leading to the neurological problems typical of cerebral folate transport deficiency.

The signs and symptoms of cerebral folate transport deficiency do not begin until late infancy because other mechanisms can compensate for this loss. For example, another
A protein called folate receptor beta is responsible for folate transport before birth and in early infancy.

**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**

- cerebral folate deficiency
- FOLR1 deficiency
- neurodegeneration due to cerebral folate transport deficiency

**Diagnosis & Management**

**Genetic Testing Information**

- What is genetic testing? [primer/testing/genetictesting]
- Genetic Testing Registry: Cerebral folate deficiency [https://www.ncbi.nlm.nih.gov/gtr/conditions/C2751584/]

**Other Diagnosis and Management Resources**

- MedlinePlus Encyclopedia: Folic Acid--Test [https://medlineplus.gov/ency/article/003686.htm]

**Additional Information & Resources**

**Health Information from MedlinePlus**

- Encyclopedia: Folate Deficiency [https://medlineplus.gov/ency/article/000354.htm]
- Encyclopedia: Folic Acid--Test [https://medlineplus.gov/ency/article/003686.htm]
- Health Topic: Developmental Disabilities [https://medlineplus.gov/developmentaldisabilities.html]
- Health Topic: Folic Acid [https://medlineplus.gov/folicacid.html]
- Health Topic: Leukodystrophies [https://medlineplus.gov/leukodystrophies.html]
- Health Topic: Speech and Language Problems in Children [https://medlineplus.gov/speechandlanguageproblemsinchildren.html]
Genetic and Rare Diseases Information Center

- Cerebral folate deficiency

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Epilepsy Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page

- NIH Office of Dietary Supplements: Folate
  https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/

Educational Resources

- Centers for Disease Control and Prevention: Facts About Developmental Disabilities
  https://www.cdc.gov/ncbddd/developmentaldisabilities/facts.html

- Centers for Disease Control and Prevention: Folic Acid
  https://www.cdc.gov/ncbddd/folicacid/index.html

- Kennedy Krieger Institute: Developmental Disorders
  https://www.kennedykrieger.org/patient-care/conditions/developmental-disorders

- Kennedy Krieger Institute: Leukodystrophy
  https://www.kennedykrieger.org/patient-care/conditions/leukodystrophy

- KidsHealth from Nemours: Delayed Speech or Language Development

- MalaCards: cerebral folate deficiency
  https://www.malacards.org/card/cerebral_folate_deficiency

  https://www.merckmanuals.com/home/disorders-of-nutrition/vitamins/folate

- Orphanet: Neurodegenerative syndrome due to cerebral folate transport deficiency
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=217382

- Seattle Children's Hospital: Epilepsy Symptoms and Diagnosis
  https://www.seattlechildrens.org/conditions/brain-nervous-system-mental-conditions/epilepsy

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
  http://aaidd.org/

- CURE Epilepsy
  https://www.cureepilepsy.org/
• Resource List from the University of Kansas Medical Center: Developmental Delay/
Mental Retardation
http://www.kumc.edu/gec/support/devdelay.html

• The Arc: For People with Intellectual and Developmental Disabilities
https://www.thearc.org/

• United Leukodystrophy Foundation
https://ulf.org/

Scientific Articles on PubMed

• PubMed
https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28FOLR1%5BTIAB%5D%29+AND+%28cerebral+folate+deficiency%5BTIAB%5D%29+OR+%28cerebral+folate+transport+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

• NEURODEGENERATION DUE TO CEREBRAL FOLATE TRANSPORT
DEFICIENCY
http://omim.org/entry/613068

Sources for This Summary

• Cario H, Bode H, Debatin KM, Opladen T, Schwarz K. Congenital null mutations of the FOLR1
doi: 10.1212/WNL.0b013e3181c679df.
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20018644

• Grapp M, Just IA, Linnankivi T, Wolf P, Lücke T, Häusler M, Gärtner J, Steinfeld R. Molecular
characterization of folate receptor 1 mutations delineates cerebral folate transport deficiency. Brain.
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22586289

• Grapp M, Wrede A, Schweizer M, Hüwel S, Galla HJ, Snaidero N, Simons M, Bückers J, Low PS,
Urlaub H, Gärtner J, Steinfeld R. Choroid plexus transcytosis and exosome shuttling deliver folate
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23828504

Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20668945

• Pérez-Dueñas B, Ormazábal A, Toma C, Torrico B, Cormand B, Serrano M, Sierra C, De Grandis
E, Marfa MP, García-Cazorla A, Campistol J, Pascual JM, Artuch R. Cerebral folate deficiency
syndromes in childhood: clinical, analytical, and etiologic aspects. Arch Neurol. 2011 May;68(5):
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21555636

page 4
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20857335

Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19732866
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771535/

Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24556562

Reprinted from Genetics Home Reference:

Reviewed: September 2014
Published: March 19, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services