Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis is a disorder characterized by abnormal storage of fats (lipids) in many areas of the body. People with this disorder cannot break down certain lipids effectively, specifically different forms of cholesterol, so these fats accumulate in the body in the form of fatty yellow nodules called xanthomas. These xanthomas are most commonly found in the brain and in connective tissue called tendons that attach muscle to bone, which is reflected in the condition name (cerebro-meaning brain and -tendinous referring to tendons).

People with cerebrotendinous xanthomatosis often develop neurological problems in early adulthood that are thought to be caused by an abnormal accumulation of fats and an increasing number of xanthomas in the brain. These neurological problems include recurrent seizures (epilepsy), movement disorders, impaired speech (dysarthria), loss of sensation in the arms and legs (peripheral neuropathy), decline in intellectual function (dementia), hallucinations, and depression. Xanthomas can accumulate in the fatty substance that insulates and protects nerves (myelin), causing the destruction of myelin and disrupting nerve signaling in the brain. Degeneration (atrophy) of brain tissue caused by excess lipid deposits also contributes to the neurological problems.

Xanthomas in the tendons begin to form in early adulthood. The most common areas for xanthomas to develop are tendons in the hands, elbows, knees, neck, and in the Achilles tendon, which connects the heel of the foot to the calf muscles in the leg. Tendon xanthomas may cause discomfort and interfere with tendon flexibility. While many affected people develop tendon xanthomas, these nodules may not be easily visible underneath the skin.

Other features of cerebrotendinous xanthomatosis include clouding of the lenses of the eyes (cataracts) and chronic diarrhea in childhood; a reduced ability to produce and release a digestive fluid called bile (cholestasis), which can lead to a yellowing of the skin or whites of the eyes (jaundice); and progressively brittle bones that are prone to fracture (osteoporosis). People with cerebrotendinous xanthomatosis are also at an increased risk of developing cardiovascular disease or respiratory failure because of lipid accumulation in the heart or lungs, respectively. If untreated, the signs and symptoms related to cerebrotendinous xanthomatosis worsen over time; however, this condition varies greatly among those who are affected.

Frequency

The incidence of cerebrotendinous xanthomatosis is estimated to be 1 per million individuals worldwide. This condition is more common in the Moroccan Jewish population with an incidence of 1 in 108 individuals.
Causes
Mutations in the CYP27A1 gene cause cerebrotendinous xanthomatosis. The CYP27A1 gene provides instructions for producing an enzyme called sterol 27-hydroxylase. This enzyme works in the pathway that breaks down cholesterol to form acids used in the digestion of fats (bile acids), specifically a bile acid called chenodeoxycholic acid.

Mutations in the CYP27A1 gene lead to the production of a nonfunction or abnormal sterol 27-hydroxylase that cannot help form chenodeoxycholic acid. As a result, other molecules are formed by an alternative pathway. A molecule called cholestanol, which is similar to cholesterol, is produced as well as substances called bile alcohols. Cholestanol and bile alcohols are increased in the blood, while blood cholesterol levels are typically normal. In various tissues in the body, including the brain and heart, cholesterol and cholestanol levels are increased. These lipids make up much of the fats found in xanthomas. The accumulation of cholesterol and cholestanol throughout the body's tissues causes the signs and symptoms of cerebrotendinous xanthomatosis.

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 cholesterinosis
- cerebrotendinous cholesterinosis
- cholestanol storage disease
- cholestanolosis
- CTX
- Van Bogaert-Scherer-Epstein disease

Diagnosis & Management
Genetic Testing Information
- What is genetic testing? /primer/testing/genetictesting
Research Studies from ClinicalTrials.gov

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

Other Diagnosis and Management Resources

- GeneReview: Cerebrotendinous Xanthomatosis
  https://www.ncbi.nlm.nih.gov/books/NBK1409

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Cholesterol
  https://medlineplus.gov/cholesterol.html

- Health Topic: Genetic Brain Disorders
  https://medlineplus.gov/geneticbraindisorders.html

- Health Topic: Lipid Metabolism Disorders
  https://medlineplus.gov/lipidmetabolismdisorders.html

Genetic and Rare Diseases Information Center

- Cerebrotendinous xanthomatosis
  https://rarediseases.info.nih.gov/diseases/5622/cerebrotendinous-xanthomatosis

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Lipid Storage Diseases Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Lipid-storage-diseases-Information-Page

- Rare Diseases Clinical Research Network: Sterol & Isoprenoid Research Consortium
  https://www.rarediseasesnetwork.org/cms/stair/Learn-More/Disorder-Definitions

Educational Resources

- MalaCards: cerebrotendinous xanthomatosis
  https://www.malacards.org/card/cerebrotendinous_xanthomatosis

- Orphanet: Cerebrotendinous xanthomatosis
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=909

- Washington Univeristy, St. Louis: Neuromuscular Disease Center
  https://neuromuscular.wustl.edu/ataxia/metatax.html#cx
Patient Support and Advocacy Resources

- Metabolic Support UK  
  https://www.metabolicsupportuk.org/
- National Organization for Rare Disorders (NORD)  
  https://rarediseases.org/rare-diseases/cerebrotendinous-xanthomatosis/
- United Leukodystrophy Foundation  
  http://ulf.org/cerebrtendinous-xanthomatosis-ctx/

Clinical Information from GeneReviews

- Cerebrotendinous Xanthomatosis  
  https://www.ncbi.nlm.nih.gov/books/NBK1409

Scientific Articles on PubMed

- PubMed  
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28cerebrotendinous+xanthomatosis\%5BTIAB\%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- CEREBROTENDINOUS XANTHOMATOSIS  
  http://omim.org/entry/213700

Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17012751
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23759795
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16816916
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24442603
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15061585

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25424010
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264335/

Reprinted from Genetics Home Reference:

Reviewed: September 2016
Published: January 2, 2019

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