LTBL

Subjects: Genetics & Heredity

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Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) is a disorder that affects the brain. LTBL is one of a group of genetic disorders called leukodystrophies, which feature abnormalities of the nervous system's white matter. White matter consists of nerve fibers covered by a fatty substance, called myelin, that insulates nerve fibers and promotes the rapid transmission of nerve impulses.

genetic conditions

1. Introduction

LTBL is characterized by distinct changes in the brain, which can be seen using magnetic resonance imaging (MRI). These abnormalities typically involve white matter in regions of the brain known as the cerebrum and cerebellum. Abnormalities can also be seen in other regions of the brain, including the brainstem, which is the part that connects to the spinal cord. Affected brain regions include the thalamus, midbrain, pons, and medulla oblongata. Thinning of the tissue that connects the left and right halves of the brain (the corpus callosum) also occurs in people with LTBL. In addition, most affected individuals have a high level of a substance called lactate in the brain and elsewhere in the body.

The severity of the condition varies. Mildly affected individuals usually develop signs and symptoms after the age of 6 months. Loss of mental and movement abilities (psychomotor regression), muscle stiffness (spasticity), and extreme irritability are common, and some people with mild LTBL develop seizures. However, after age 2, the signs and symptoms of the condition improve: affected children regain some psychomotor abilities, seizures are reduced or disappear, MRI results become more normal, and lactate levels drop.

Severely affected individuals have features that begin soon after birth. These infants typically have delayed development of mental and movement abilities (psychomotor delay), weak muscle tone (hypotonia), involuntary muscle tensing (dystonia), muscle spasticity, and seizures. Some have extremely high levels of lactate (lactic acidosis), which can cause serious breathing problems and an abnormal heartbeat. Liver failure occurs in some severely affected infants. In severe cases, the signs and symptoms do not improve and can be life-threatening. In some people with LTBL, the features fall between mild and severe.

2. Frequency

LTBL is a rare condition. While its prevalence is unknown, at least 19 cases have been described in the medical literature.

3. Causes

LTBL is caused by mutations in the *EARS2* gene, which provides instructions for making an enzyme called mitochondrial glutamyl-tRNA synthetase. This enzyme is important in the production (synthesis) of proteins in cellular structures called mitochondria, the energy-producing centers in cells. While most protein synthesis occurs in the fluid surrounding the cell nucleus (cytoplasm), some proteins are synthesized in the mitochondria.

During protein synthesis, in either the mitochondria or the cytoplasm, building blocks called amino acids are connected together in a specific order, creating a chain of amino acids that forms the protein. Mitochondrial glutamyl-tRNA synthetase plays a role in adding the amino acid glutamate at the proper place in mitochondrial proteins.

Mutations in the *EARS2* gene likely reduce the amount of mitochondrial aspartyl-tRNA synthetase protein, which hinders the addition of glutamate to mitochondrial proteins. Researchers speculate that impaired protein assembly disrupts mitochondrial energy production. However, it is unclear how a reduction of mitochondrial aspartyl-tRNA synthetase specifically affects certain brain regions, causing LTBL.

3.1. The gene associated with Leukoencephalopathy with thalamus and brainstem involvement and high lactate

- EARS2

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

- combined oxidative phosphorylation deficiency 12
- COXPD12
- LTBL

References

1. Biancheri R, Lamantea E, Severino M, Diodato D, Pedemonte M, Cassandrini D,Ploederl A, Trucco F, Fiorillo C, Minetti C, Santorelli FM, Zeviani M, Bruno C.Expanding the Clinical and Magnetic Resonance Spectrum of Leukoencephalopathywith Thalamus and Brainstem Involvement and High Lactate (LTBL) in a PatientHarboring a Novel EARS2 Mutation. JIMD Rep. 2015;23:85-9. doi:10.1007/8904_2015_434.
2. Danhauser K, Haack TB, Alhaddad B, Melcher M, Seibt A, Strom TM, Meitinger T, Klee D, Mayatepek E, Prokisch H, Distelmaier F. EARS2 mutations cause fatalneonatal lactic acidosis, recurrent hypoglycemia and agenesis of corpus callosum.Metab Brain Dis. 2016 Jun;31(3):717-21. doi: 10.1007/s11011-016-9793-2.
3. Kevelam SH, Klouwer FC, Fock JM, Salomons GS, Bugiani M, van der Knaap MS.Absent Thalami Caused by a Homozygous EARS2 Mutation: Expanding Disease Spectrum of LTBL. Neuropediatrics. 2016 Jan;47(1):64-7. doi: 10.1055/s-0035-1568987.
4. Steenweg ME, Ghezzi D, Haack T, Abbink TE, Martinelli D, van Berkel CG, BleyA, Diogo L, Grillo E, Te Water Naudé J, Strom TM, Bertini E, Prokisch H, van der Knaap MS, Zeviani M. Leukoencephalopathy with thalamus and brainstem involvement and high lactate 'LTBL' caused by EARS2 mutations. Brain. 2012 May;135(Pt5):1387-94. doi: 10.1093/brain/aws070.
5. Taskin BD, Karalok ZS, Gurkas E, Aydin K, Aydogmus U, Ceylaner S, Karaer K,Yilmaz C, Pearl PL. Early-Onset Mild Type Leukoencephalopathy Caused by aHomozygous EARS2 Mutation. J Child Neurol. 2016 Jun;31(7):938-41. doi:10.1177/0883073816630087.