Brain-Lung-Thyroid Syndrome

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Brain-lung-thyroid syndrome is a group of conditions that affect the brain, lungs, and thyroid gland (a butterfly-shaped gland in the lower neck). Brain-lung-thyroid syndrome historically included problems with all three organs, although the designation now encompasses a combination of brain, lung, and thyroid problems. About 50 percent of affected individuals have problems with all three organs, about 30 percent have brain and thyroid problems, and about 10 percent have brain and lung problems. The brain alone is affected in 10 to 20 percent of people with the condition. Such cases are sometimes called isolated benign hereditary chorea.

genetic conditions

1. Introduction

Nearly everyone with brain-lung-thyroid syndrome has brain-related movement abnormalities. Benign hereditary chorea is the most common feature of the syndrome. This feature is associated with involuntary jerking movements (chorea) of the face, torso, and limbs; writhing movements (athetosis) of the limbs; and other movement problems. Individuals with brain-lung-thyroid syndrome can have other abnormalities, such as difficulty coordinating movements (ataxia), muscle twitches (myoclonus), and involuntary muscle contractions that result in twisting and repetitive movements (dystonia). The movement problems typically begin around age 1, although they can begin in early infancy or later in life, and are often preceded by weak muscle tone (hypotonia). They can delay the development of walking. The movement problems usually remain stable and can improve over time. Some affected individuals also have learning difficulties or intellectual disability.

Thyroid problems are the next most common feature of brain-lung-thyroid syndrome. The thyroid gland makes hormones that help regulate a wide variety of critical body functions, including growth, brain development, and the rate of chemical reactions in the body (metabolism). Many affected individuals have reduced thyroid function from birth (congenital hypothyroidism), resulting in lower-than-normal levels of thyroid hormones. Others have a milder condition called compensated or subclinical hypothyroidism, in which thyroid hormone levels are within the normal range, even though the thyroid is not functioning properly. While most people with brain-lung-thyroid syndrome have a normal-sized thyroid, the gland is reduced in size (hypoplastic) or absent (aplastic) in some affected individuals. Although a shortage of thyroid hormones can cause intellectual disability and other neurological problems, it is unclear whether such issues in individuals with brain-lung-thyroid syndrome are due to hypothyroidism or to the brain abnormalities related to the condition.

Lung problems are common in brain-lung-thyroid syndrome. Some affected newborns have respiratory distress syndrome, which causes extreme difficulty breathing and can be life-threatening. Other affected individuals develop widespread lung damage (interstitial lung disease) or scarring in the lungs (pulmonary fibrosis), both of which can also lead to breathing problems. Recurrent lung infections, which can be life-threatening, also occur in people with brain-lung-thyroid syndrome. People with brain-lung-thyroid syndrome have a higher risk of developing lung cancer than do people in the general population.

2. Frequency

Brain-lung-thyroid syndrome is a rare disorder; its prevalence is unknown.

3. Causes

Brain-lung-thyroid syndrome is caused by genetic changes that affect the *NKX2-1* gene, which provides instructions for making a protein called homeobox protein Nkx-2.1. This protein functions as a transcription factor, which means it attaches to DNA and controls the activity (expression) of other genes. By regulating the expression of certain genes during embryonic development, homeobox protein Nkx-2.1 helps direct the development of the brain, lungs, and thyroid gland and promotes their normal function. Mutations in or deletion of the *NKX2-1* gene lead to a reduction in the amount of homeobox protein Nkx-2.1 or impair its function. As a result, the expression of genes controlled by homeobox protein Nkx-2.1 is altered, which impedes the normal development and function of the brain, lungs, or thyroid gland. Problems with these organs underlie benign hereditary chorea, respiratory distress syndrome, congenital hypothyroidism, and other features of brain-lung-thyroid syndrome. It is unclear why all three organs are affected in some individuals with the condition, while only one or two are affected in others.

3.1. The Gene Associated with Brain-Lung-Thyroid Syndrome

- NKX2-1

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In some cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

5. Other Names for This Condition

- BLT syndrome
- brain-thyroid-lung syndrome

- CAHTP
- choreoathetosis, hypothyroidism, and neonatal respiratory distress
- chreoathetosis and congenital hypothyroidism with or without pulmonary dysfunction

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