TUBB4A-related Leukodystrophy

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Contributor: Bruce Ren

TUBB4A-related leukodystrophy is a disorder that affects the nervous system. Leukodystrophies are conditions that involve abnormalities of the nervous system's white matter, which consists of nerve fibers covered by a fatty substance called myelin. Myelin insulates nerve fibers and promotes the rapid transmission of nerve impulses. In particular, *TUBB4A*-related leukodystrophy involves hypomyelination, which means that the nervous system has a reduced ability to form myelin. In some affected individuals, myelin may also break down, which is known as demyelination.

Keywords: genetic conditions

1. Introduction

People with *TUBB4A*-related leukodystrophy have different combinations of signs and symptoms. Some of these combinations are described as separate disorders. However, the features in some affected individuals do not fit into these defined disorders. Researchers now group all of these cases of leukodystrophy, which have the same genetic cause, as *TUBB4A*-related leukodystrophy.

At the most severe end of the *TUBB4A*-related leukodystrophy spectrum is a condition called hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). This disorder begins in infancy or early childhood. Most affected individuals have delayed development of motor skills, such as sitting and walking, and some are never able to walk on their own. In other cases, motor skills develop normally and then are lost in early childhood (developmental regression). In addition, individuals with H-ABC have other movement abnormalities, such as involuntary muscle contractions (dystonia), uncontrolled movements of the limbs (choreoathetosis), muscle stiffness (rigidity), and difficulty coordinating movements (ataxia). These individuals also often have impaired speech (dysarthria), a weak voice (dysphonia), and swallowing problems (dysphagia). Some develop seizures. Learning difficulty is common in individuals with H-ABC.

H-ABC is characterized by particular brain abnormalities, including hypomyelination. In addition, tissue in certain regions of the brain breaks down (atrophies), most prominently in a region called the putamen, which is part of a group of structures that help control movement (the basal ganglia). Atrophy of brain tissue in another region involved in movement called the cerebellum is common, and atrophy of the cerebrum, which controls most voluntary activity, language, sensory perception, learning, and memory, can also occur.

At the mildest end of the *TUBB4A*-related leukodystrophy spectrum is a condition called isolated hypomyelination, which begins at any time from late childhood to adulthood. Individuals at this end of the spectrum have mild hypomyelination and sometimes mild atrophy of the cerebellum, but no problems with the basal ganglia. These individuals can have movement problems, dysarthria, and learning difficulty, although these features are typically milder than in H-ABC.

The features in other individuals with *TUBB4A*-related leukodystrophy fall in between these two extremes. Affected individuals can have varying degrees of hypomyelination and atrophy or impairment of the basal ganglia or other brain regions. Movement problems can also occur. A small group of affected individuals develop muscle stiffness and paralysis of the lower limbs (spastic paraplegia) that slowly worsen. In addition, these individuals may have mild hypomyelination and ataxia without the other movement or learning problems common in H-ABC.

2. Frequency

TUBB4A-related leukodystrophy is a rare disorder, although the exact prevalence of the condition is unknown. At least 70 affected individuals have been described in the medical literature.

3. Causes

TUBB4A-related leukodystrophy is caused by mutations in the *TUBB4A* gene, which provides instructions for making a protein called beta-tubulin (β-tubulin). This protein attaches to another protein called alpha-tubulin (α-tubulin) to form structures called microtubules, which form the framework of cells (cytoskeleton). β-tubulin produced from the *TUBB4A* gene is found primarily in the brain, particularly in the putamen, cerebellum, and white matter. During brain development, microtubules help move nerve cells (neurons) to their proper location (neuronal migration). The microtubules also form scaffolding within neurons that provides structure and aids in the transport of substances.

The mutations that cause *TUBB4A*-related leukodystrophy are thought to alter the structure of the β-tubulin protein, likely impairing the formation or stability of microtubules. While it is unclear how these genetic changes lead to the signs and symptoms of *TUBB4A*-related leukodystrophy, researchers suspect that problems with microtubules impair neuronal migration or the transport of important substances within neurons, which may lead to dysfunction and loss of these cells in the brain, particularly in the putamen, cerebellum, and white matter. Abnormalities in these brain regions underlie the movement, speech, and learning problems that can occur in *TUBB4A*-related leukodystrophy. Researchers do not understand what causes the wide range of severity in this disorder.

3.1 The gene associated with TUBB4A-related leukodystrophy

- TUBB4A

4. Inheritance

TUBB4A-related leukodystrophy is inherited in an autosomal dominant pattern, which means one copy of the altered *TUBB4A* gene in each cell is sufficient to cause the disorder. Most cases of this condition result from new (de novo) mutations in the gene that occur during the formation of reproductive cells (eggs or sperm) or in early embryonic development. These cases occur in people with no history of the disorder in their family. Very rarely, the condition is inherited from a parent with mosaicism. Mosaicism means that some of the body's cells have the gene mutation, and others do not. In these instances, the parent with mosaicism does not show any signs or symptoms of *TUBB4A*-related leukodystrophy.

5. Other Names for This Condition

- TUBB4A-associated hypomyelinating leukoencephalopathies
- TUBB4A-related hypomyelinating leukodystrophy

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