

Infantile-Onset Ascending Hereditary Spastic Paralysis

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Infantile-onset ascending hereditary spastic paralysis is one of a group of genetic disorders known as hereditary spastic paraplegias. These disorders are characterized by progressive muscle stiffness (spasticity) and eventual paralysis of the lower limbs (paraplegia).

genetic conditions

1. Introduction

The spasticity and paraplegia result from degeneration (atrophy) of motor neurons, which are specialized nerve cells in the brain and spinal cord that control muscle movement. Hereditary spastic paraplegias are divided into two types: pure and complicated. The pure types involve only the lower limbs, while the complicated types involve additional areas of the nervous system, affecting the upper limbs and other areas of the body. Infantile-onset ascending hereditary spastic paralysis starts as a pure hereditary spastic paraplegia, with spasticity and weakness in the legs only, but as the disorder progresses, the muscles in the arms, neck, and head become involved and features of the disorder are more characteristic of the complicated type.

Affected infants are typically normal at birth, then within the first 2 years of life, the initial symptoms of infantile-onset ascending hereditary spastic paralysis appear. Early symptoms include exaggerated reflexes (hyperreflexia) and recurrent muscle spasms in the legs. As the condition progresses, affected children develop abnormal tightness and stiffness in the leg muscles and weakness in the legs and arms. Over time, muscle weakness and stiffness travels up (ascends) the body from the legs to the head and neck. Muscles in the head and neck usually weaken during adolescence; symptoms include slow eye movements and difficulty with speech and swallowing. Affected individuals may lose the ability to speak (anarthria). The leg and arm muscle weakness can become so severe as to lead to paralysis; as a result affected individuals require wheelchair assistance by late childhood or early adolescence. Intelligence is not affected in this condition.

A condition called juvenile primary lateral sclerosis shares many of the features of infantile-onset ascending hereditary spastic paralysis. Both conditions have the same genetic cause and significantly impair movement beginning in childhood; however, the pattern of nerve degeneration is different. Because of their similarities, these conditions are sometimes considered the same disorder.

2. Frequency

Infantile-onset ascending hereditary spastic paralysis is a rare disorder, with at least 30 cases reported in the scientific literature.

3. Causes

Infantile-onset ascending hereditary spastic paralysis is caused by mutations in the *ALS2* gene. This gene provides instructions for making the alsin protein. Alsin is produced in a wide range of tissues, with highest amounts in the brain, particularly in motor neurons. Alsin turns on (activates) multiple proteins called GTPases that convert a molecule called GTP into another molecule called GDP. GTPases play important roles in several cell processes. The GTPases that are activated by alsin are involved in the proper placement of the various proteins and fats that make up the cell membrane, the transport of molecules from the cell membrane to the interior of the cell (endocytosis), and the development of specialized structures called axons and dendrites that project from neurons and are essential for the transmission of nerve impulses.

Mutations in the *ALS2* gene alter the instructions for making alsin, often resulting in the production of an abnormally short alsin protein that is unstable and rapidly broken down. It is unclear exactly how *ALS2* gene mutations cause infantile-onset ascending hereditary spastic paralysis. Research suggests that a lack of alsin and the subsequent loss of GTPase functions, such as endocytosis and the development of axons and dendrites, contribute to the progressive atrophy of motor neurons that is characteristic of this condition.

3.1. The gene associated with Infantile-onset ascending hereditary spastic paralysis

- *ALS2*

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

- IAHSP
- infantile onset ascending spastic paralysis
- infantile-onset ascending hereditary spastic paraplegia

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