

Spastic paraplegia type 4 (SPG4) is a rare neurodegenerative disorder. It is caused by mutations in the SPAST gene. SPG4 is the most common type of hereditary spastic paraplegia. It is estimated that, if you count all forms of hereditary spastic paraplegia, the combined prevalence is around 2 to 6 in 100,000 people worldwide. Between 40-50% of these cases would be SPG4.

Symptoms

There are two forms of SPG4: pure and complex. Patients with the pure form of SPG4 experience spasticity and muscle weakness as their primary symptoms. This leads to abnormal gait and walking. People with pure SPG4 also tend to have exaggerated reflexes. Other non-motor symptoms for pure SPG4 patients may include bladder disturbance, defecation disturbance, pain, fatigue, impairment in the arms or hands, and depression. Most cases of SPG4 are considered pure spastic paraplegia.

Complex cases of SPG4 are rare. People with complex SPG4 symptoms may also develop ataxia symptoms. This includes poor balance and coordination. People may also have difficult or unclear speech.

Prognosis

SPG4 symptoms usually begin in young adulthood. However, symptoms can begin at any time between childhood and late adulthood. While the average age at onset of symptoms is 30 years old, cases have been documented in infants up to age 76. The severity of SPG4 symptoms is highly variable. Symptoms vary between patients, even within families. People who have a later onset of symptoms (after age 35) tend to have faster symptom progression.

SPG4 is a progressive disorder. About half of people with SPG4 will eventually need some assistance walking, such as the use of a cane, walker, or rollator. About 10% of people with SPG4 will eventually need to use a wheelchair full-time. Treatments such as physiotherapy and occupational therapy can significantly improve the lives of people with SPG4. Spasticity can be treated through the use of medication such as Baclofen or Tizanidine, or through Botulinum neurotoxin injections. Medication can also be used to manage symptoms related to urinary difficulties, depression, anxiety, or pain management.

Genetics

SPG4 is an inherited genetic disorder. It is caused by an abnormality of a single gene called the SPAST gene. The abnormality can be passed from generation to generation by family members who carry it. Males and females are equally likely to inherit the genes that cause SPG4.

Genetic diseases like SPG4 occur when one of the body's 20,000 genes does not work properly. Genes are microscopic structures within the cells of our bodies that contain instructions for every feature a person inherits from his or her parents. Two copies of each gene are inherited; one copy from the mother and one from the father.

SPG4 is an autosomal dominant disease, meaning that someone will develop symptoms if they inherit at least one mutated copy of the SPAST gene. Each child of someone with SPG4 has a 50% chance of inheriting the gene that causes SPG4. Approximately 80% of SPG4 cases are inherited from a parent. The remaining are caused by de novo mutations that spontaneously develop in a person's DNA when it is being made.

Different types of mutations in the SPAST gene can cause SPG4. Most of these are missense mutations, where a single amino acid of someone's DNA is changed. This changes the function and shape of the SPAST protein. Truncating mutations, which shorten the length of the SPAST protein, can also cause SPG4. While these mutations differ from each other in how they look, they all lead to problems in the SPAST gene and SPAST protein, which results in SPG4.



Gene tests can be performed for diagnostic purposes to determine what kind of Ataxia is within a person or family. Genetic testing can also be done, in some circumstances, even before there are symptoms, to determine whether a person carries the abnormal gene or genes that cause Ataxia. This is called predictive or presymptomatic testing. A gene test can also be used to determine whether a fetus has an abnormal Ataxia gene. This is called prenatal testing. Anyone who is considering a predictive or prenatal test should consult with a genetic counselor to discuss the reasons for the test, the possible outcomes, and how those outcomes might affect the person emotionally, medically, or socially.

Diagnosis

A neurologist is often the most helpful specialist in recognizing symptoms and diagnosing spasticity, paraplegia, and ataxia. A neurologic examination can determine whether a person has symptoms typical of SPG4. Providing a detailed family history of medical conditions is also crucial. There are several potential follow-up tests. MRI brain imaging may be used to confirm cerebellar atrophy. Electromyography (EMG) may be used to test nerve conditions in the limbs.

A definitive diagnosis of SPG4 is established following genetic testing. This confirms that someone has a mutation that causes SPG4 in their SPAST gene.