Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a progressive disease that affects motor neurons, which are specialized nerve cells that control muscle movement. These nerve cells are found in the spinal cord and the brain. In ALS, motor neurons die (atrophy) over time, leading to muscle weakness, a loss of muscle mass, and an inability to control movement.

genetic conditions

1. Introduction

There are many different types of ALS; these types are distinguished by their signs and symptoms and their genetic cause or lack of clear genetic association. Most people with ALS have a form of the condition that is described as sporadic, which means it occurs in people with no apparent history of the disorder in their family. People with sporadic ALS usually first develop features of the condition in their late fifties or early sixties. A small proportion of people with ALS, estimated at 5 to 10 percent, have a family history of ALS or a related condition called frontotemporal dementia (FTD), which is a progressive brain disorder that affects personality, behavior, and language. The signs and symptoms of familial ALS typically first appear in one's late forties or early fifties. Rarely, people with familial ALS develop symptoms in childhood or their teenage years. These individuals have a rare form of the disorder known as juvenile ALS.

The first signs and symptoms of ALS may be so subtle that they are overlooked. The earliest symptoms include muscle twitching, cramping, stiffness, or weakness. Affected individuals may develop slurred speech (dysarthria) and, later, difficulty chewing or swallowing (dysphagia). Many people with ALS experience malnutrition because of reduced food intake due to dysphagia and an increase in their body's energy demands (metabolism) due to prolonged illness. Muscles become weaker as the disease progresses, and arms and legs begin to look thinner as muscle tissue atrophies. Individuals with ALS eventually lose muscle strength and the ability to walk. Affected individuals eventually become wheelchair-dependent and increasingly require help with personal care and other activities of daily living. Over time, muscle weakness causes affected individuals to lose the use of their hands and arms. Breathing becomes difficult because the muscles of the respiratory system weaken. Most people with ALS die from respiratory failure within 2 to 10 years after the signs and symptoms of ALS first appear; however, disease progression varies widely among affected individuals.

Approximately 20 percent of individuals with ALS also develop FTD. Changes in personality and behavior may make it difficult for affected individuals to interact with others in a socially appropriate manner. Communication

skills worsen as the disease progresses. It is unclear how the development of ALS and FTD are related. Individuals who develop both conditions are diagnosed as having ALS-FTD.

A rare form of ALS that often runs in families is known as ALS-parkinsonism-dementia complex (ALS-PDC). This disorder is characterized by the signs and symptoms of ALS, in addition to a pattern of movement abnormalities known as parkinsonism, and a progressive loss of intellectual function (dementia). Signs of parkinsonism include unusually slow movements (bradykinesia), stiffness, and tremors. Affected members of the same family can have different combinations of signs and symptoms.

2. Frequency

About 5,000 people in the United States are diagnosed with ALS each year. Worldwide, this disorder occurs in 2 to 5 per 100,000 individuals. Only a small percentage of cases have a known genetic cause.

Among the Chamorro people of Guam and people from the Kii Peninsula of Japan, ALS-PDC can be 100 times more frequent than ALS is in other populations. ALS-PDC has not been reported outside of these populations.

3. Causes

Mutations in several genes can cause familial ALS and contribute to the development of sporadic ALS. Mutations in the *C9orf72* gene account for 30 to 40 percent of familial ALS in the United States and Europe. Worldwide, *SOD1* gene mutations cause 15 to 20 percent of familial ALS, and *TARDBP* and *FUS* gene mutations each account for about 5 percent of cases. The other genes that have been associated with familial ALS each account for a small proportion of cases. It is estimated that 60 percent of individuals with familial ALS have an identified genetic mutation. The cause of the condition in the remaining individuals is unknown.

The *C9orf72*, *SOD1*, *TARDBP*, and *FUS* genes are key to the normal functioning of motor neurons and other cells. It is unclear how mutations in these genes contribute to the death of motor neurons, but it is thought that motor neurons are more sensitive to disruptions in function because of their large size. Most motor neurons affected by ALS have a buildup of protein clumps (aggregates); however, it is unknown whether these aggregates are involved in causing ALS or are a byproduct of the dying cell.

In some cases of familial ALS due to mutations in other genes, studies have identified the mechanisms that lead to ALS. Some gene mutations lead to a disruption in the development of axons, the specialized extensions of nerve cells (such as motor neurons) that transmit nerve impulses. The altered axons may impair transmission of impulses from nerves to muscles, leading to muscle weakness and atrophy. Other mutations lead to a slowing in the transport of materials needed for the proper function of axons in motor neurons, eventually causing the motor neurons to die. Additional gene mutations prevent the breakdown of toxic substances, leading to their buildup in nerve cells. The accumulation of toxic substances can damage motor neurons and eventually cause cell death. In some cases of ALS, it is unknown how the gene mutation causes the condition.

The cause of sporadic ALS is largely unknown but probably involves a combination of genetic and environmental factors. Variations in many genes, including the previously mentioned genes involved in transmission of nerve impulses and transportation of materials within neurons, increase the risk of developing ALS. Gene mutations that are risk factors for ALS may add, delete, or change DNA building blocks (nucleotides), resulting in the production of a protein with an altered or reduced function. While genetic variations have been associated with sporadic ALS, not all genetic factors have been identified and it is unclear how most genetic changes influence the development of the disease. People with a gene variation that increases their risk of ALS likely require additional genetic and environmental triggers to develop the disorder.

3.1. The genes associated with Amyotrophic lateral sclerosis

- ALS2
- ATXN2
- C9orf72
- CHMP2B
- DCTN1
- FUS
- MATR3
- SETX
- SMN1
- SOD1
- SPG11
- SQSTM1
- TARDBP
- VCP

4. Inheritance

About 90 to 95 percent of ALS cases are sporadic, which means they are not inherited.

An estimated 5 to 10 percent of ALS is familial and caused by mutations in one of several genes. The pattern of inheritance varies depending on the gene involved. Most cases are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with the condition. Some people who inherit a familial genetic mutation known to cause ALS never develop features of the condition. (This situation is known as reduced penetrance.) It is unclear why some people with a mutated gene develop the disease and other people with a mutated gene do not.

Less frequently, ALS 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. Because an affected person's

parents are not affected, autosomal recessive ALS is often mistaken for sporadic ALS even though it is caused by a familial genetic mutation.

Very rarely, ALS is inherited in an X-linked dominant pattern. X-linked conditions occur when the gene associated with the condition is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. In most cases, males tend to develop the disease earlier and have a decreased life expectancy compared with females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

5. Other Names for This Condition

- ALS
- amyotrophic lateral sclerosis with dementia
- Charcot disease
- dementia with amyotrophic lateral sclerosis
- Lou Gehrig disease
- motor neuron disease, amyotrophic lateral sclerosis

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