

Amyotrophic Lateral Sclerosis

Lindsay Zheng, Alice Le, Allegra Panga

Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects individuals with familial history of the disease, and in greater numbers, it affects individuals sporadically. It's a progressive neurodegenerative disease caused by neural mutations, leading to muscle weakness and behavioral and cognitive changes with no cure. Its diagnosis is done through clinical testing, biopsies, spinal taps, MRI, blood, and urine tests, or electromyography tests. Genes that have been linked to ALS include CDorf72, SOD1, TARDBP, and FUS. With no cure, managing symptoms, taking medications such as Riluzole or Edaravone, and practicing physical, speech, nutritional, and respiratory therapy can help individuals with ALS. The future of ALS in medicine is still expanding; new genes connected to amyotrophic lateral sclerosis are still being discovered, and avenues of treatments are still being researched by scientists.

Introduction

The phenotypes of ALS include progressive muscle weakness, which often starts in a limb, along with muscle cramps, twitching, and stiffness. Other symptoms include slurred speech, difficulty swallowing, and, in later stages, breathing difficulties. These symptoms are typically painless and gradually worsen over time. Moreover, some individuals with ALS may experience behavioral changes, such as difficulty with decision-making, or emotional changes, like crying or laughing more easily. Cognitive changes, such as mild executive dysfunction, can also occur in up to half of patients.

90-95% of Amyotrophic lateral sclerosis cases are sporadic, meaning ALS appears in individuals with no family history of the disease, whereas 5-10% of cases of amyotrophic lateral sclerosis are familial, with a known history of ALS. Familial ALS is spread through generations following an autosomal dominant inheritance pattern. The majority of familial ALS cases correlate with the C9orf72 gene, where abnormal hexanucleotide repeat expansions disrupt normal neural functions. The environmental causes of ALS have been recognized, but they are insignificant compared to the familial and sporadic avenues of ALS. In over 95% of sporadic ALS cases, the overproduced, misfolded TDP-43 proteins, located in neurons, the cells located inside of the brain, lead to a falter in regulation of RNA processing and translation. The misfolded proteins lead to incorrectly transcribed mRNA and dysfunctional proteins, and neuron degeneration. Still under research by scientists are additional factors that cause ALS that initially cause damage to neurons. Oxidative stress, mitochondrial dysfunction, immune system abnormalities, environmental exposure, and glutamate excitotoxicity all cause damage to neurons and lead to harmful mutations in genes. The SOD1 gene's mutations lead to the aggregation of toxic proteins and lead to 15% of familial ALS cases in European populations and 30% of familial ALS cases in Asian populations. This gene was also the first gene identified in ALS and is at the center of therapeutic developments towards amyotrophic lateral sclerosis.

Many genes involved in multiple cellular processes, such as autophagy and protein homeostasis, are TARDBP, FUS, VCP, and a host of others, and have been traced to causing ALS. Mutations in these crucial genes negatively affect neurons and facilitate factors that

correlate with familial and sporadic episodes. Genetic therapy is recommended for families with ALS history, and genetic testing is recommended for those cases.

The first gene that was linked to ALS, SOD1, in its mutations, produced a defective form of superoxide dismutase 1 (SOD1) in neurons, transformed into a new toxic cell with a new motive. Mutations in the SOD1 gene are the second most common cause of familial ALS, as they are found in 10-20% of cases, and amount for 1-2% of sporadic ALS cases. Research identified over 150 mutations of the SOD1 gene linked to ALS, all with different ways of affecting the growth of the disease, but all stemming back to expediting the progression of the disease. In North America, the most common mutation is A4V, which means the mutation changes the fourth amino acid in the protein from alanine to valine. This mutation expedites the progression of amyotrophic lateral sclerosis and misfolds its protein, causing it to aggregate inside of neurons and astrocytes and interfere with healthy cells, causing other proteins to misfold or not function properly. Healthy versions of this gene bind to copper and zinc molecules and break down toxic byproducts produced during cell processes. More than 40 genes have been identified to have a link to ALS; four, however, account for 70% of familial ALS in European populations. C9orf72, SOD1, TARDBP, and FUS are the top four genes related to familial amyotrophic lateral sclerosis. The most common genetic cause of ALS is in the C9orf72 gene, with 25-40% of familial cases and 6% of sporadic cases being derived from this gene. C9orf72 is responsible for causing 25% of frontotemporal dementia (FTD), another neurodegenerative disease that some people develop instead of ALS, or alongside ALS. The mutation responsible represents itself as a hexanucleotide repeat expansion, or a six-letter repeated segment of DNA when the gene is expanded. The healthy gene contains six hexanucleotide repeat units, while the mutation has

hundreds to thousands of them. The TARDBP gene has been linked to 4% of familial ALS and 1% of sporadic ALS cases, due to its mutation that causes TDP-43 (transactive response DNA binding protein 43 kDa), the protein this gene creates that attaches to DNA in the nucleus and regulates transcription, processes mRNA, and helps control production of other proteins, to be incorrectly positioned in the cytoplasm instead of the nucleus of motor neurons. When the protein is in the cytoplasm, it aggregates and prohibits the normal function of TDP-43, blocks other cell processes, and becomes toxic and kills its entire cell. Scientists have discovered clumps of defective TDP-43 in the brains and spinal cords of people with ALS, so they suggest it may have a larger role in many forms of ALS.

The FUS gene is responsible for 5% of familial ALS cases and 1% of sporadic ALS cases. The function of this gene was to create a protein called fused in sarcoma; a protein found in the nucleus of most tissues. It is involved in protein production similarly to TDP-43, and they do interact normally in their processes. Mutations of this gene cause the protein to mislocalize out of the nucleus and into the cytoplasm, allowing it to aggregate and cause neuron damage. Researchers are still looking for ways to prevent aggregation of this gene as a way of ALS treatment.

Diagnosis

Currently, there is no single conclusive test that can diagnose ALS, so ALS diagnosis is primarily ruling out other possible conditions that may have caused symptoms common in ALS, like Spinal Muscular Atrophy (SMA) or Multiple Sclerosis (MS). Physicians evaluate patients with the Awaji criteria, which requires signs like progressive muscle weakness, muscle atrophy, and signs of upper and lower motor neuron degeneration to diagnose patients. To do that, they use tools such as MRIs, EMGs, nerve or muscle biopsy, spinal tap, and blood or urine tests.

Diagnosis is usually established following confirmation from two or more of these tests. EMGs are one of the most important tests as they help confirm degeneration of lower motor neurons by identifying signs of active and chronic denervation. Clinic examinations are essential for identifying upper motor neuron degeneration by assessing the patient's family history and testing reflexes. Additional tests like MRI scans and spinal taps rule out other possible diseases and are vital for confirming the diagnosis. The Awaji criteria are a refinement of the El Escorial criteria and considered the main diagnostic guidelines used for official diagnosis of ALS. Awaji criteria place a greater significance on EMG evidence like fasciculation for lower motor neuron degeneration, making it equal weight as clinical examination, which used to be considered a more important diagnostic. EMGs are the primary method for detecting fasciculations, which are spontaneous rapid muscle twitches. By recognizing the importance of fasciculations, it enables earlier diagnosis of ALS even when clinical signs are subtle. This increases the diagnostic sensitivity of the Awaji criteria and allows for earlier access to treatment.

Treatment

ALS treatment focuses on managing symptoms and improving quality of life, as there is currently no ongoing treatment or cure to reverse the damage caused to the motor neurons. Throughout the past several years, a growing number of treatments have been made available, allowing researchers to continue examining more effective options to slow down the progression of ALS in the hopes of further extending patient survival. To ensure supportive healthcare and a favorable quality of life, multi-disciplinary teams of professionals such as physicians, pharmacists, home care and hospice nurses, are readily available to design individualized treatment plans and special equipment aimed at allowing patients to be mobile and comfortable. Treatments include respiratory support, such as non-invasive ventilation in cases where the

muscles responsible for breathing start to weaken; physical and occupational therapy to support ALS patients in maintaining muscle function and movement through low-impact exercises, along with a range of motion exercises; nutritional support, including feeding tubes or nutritionist-prescribed diets to plan specialized, nutritious meals throughout the day; and devices to aid with communication such as computer-based speech synthesizers that utilize eye-tracking devices that allow an individual to use the internet and type on custom screens to communicate. A brain-computer interface (BCI) is a system that allows a patient to communicate and control equipment using only brain activity. However, further research is being conducted to develop a more efficient, mobile BCI for those with severe cases of paralysis or visual impairment. Medications approved by the FDA for ALS treatment plans include riluzole, an oral medication, and provided to reduce damage to motor neurons by decreasing glutamate levels, an amino acid responsible for carrying messages between nerve cells and motor neurons, and Edaravone, an antioxidant prescribed either orally or intravenously, which may help slow disease progression and functional decline.

Future of Research

Future ALS research will focus on genetic therapies, such as RNA interference and gene editing, to correct disease-causing genes, biomarker discovery for earlier diagnosis, and regenerative medicine, including stem cell therapies, to replace damaged cells. In context, Researchers are actively developing gene therapies using techniques like RNA interference to silence genes that cause ALS, which has shown promise in slowing motor function loss in preclinical models. Technologies like CRISPR are being explored to correct gene mutations associated with ALS, with the potential for developing curative therapies. Researchers are investigating microRNAs and long non-coding RNAs (lncRNAs), which are RNA molecules that

originate from DNA but are not translated into proteins, as potential biomarkers for diagnosis and disease monitoring. Clinical trials are evaluating the safety and efficacy of stem cell therapies, which could replace damaged cells or secrete neuroprotective factors to support motor neurons.

Whereas treatments for the C9orf72 gene are still under development by scientific researchers. In recent years, the FDA approved Tofersen, today known as Qalsody, a treatment for ALS, which the RNA produced from mutated SOD1 genes to stop the production of toxic SOD1 genes from being made, but more genetically targeted treatments are being developed. Researchers continue to find genes that are linked to ALS, but it varies depending on the techniques used for identification, similar supporting studies of specific genes, whether the biological effects of genes are known, and the fact that genetic risk factors vary for different ethnic populations.

Conclusion

Around 30,000 Americans are currently living with ALS, causing most of them to live life in wheelchairs as their motor neurons are damaged and die, leading to muscle atrophy all over their body. While most cases are sporadic with no known cause, some of them are linked to specific genetic mutations. These mutations disrupt essential cellular processes that result in progressive motor neuron degeneration and lead to devastating traits like trouble speaking, paralysis, and even difficulty breathing and can lead to early death. Significant advances in genetic research have identified mutations in C9orf72, SOD1, TARDBP, and FUS that contribute to ALS's onset and progression. Despite all the advances in finding the cause, more

effort needs to be made in the diagnosis of ALS as there is currently no single test that can accurately diagnose it. Rather, a wide variety of diagnostic tools including EMGs and clinical evaluations are considered in the Awaji criteria, the primary criteria used to establish the existence of ALS and rule out other conditions. There is no cure for ALS, and current treatment focuses on managing symptoms as well as slowing the progression of disease. This emphasizes the importance of more research into approaches like gene-targeted therapy and biomarkers to diagnose earlier, create more effective treatments, and ultimately improve the outcome for patients living with ALS.

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