Overview of Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rare, progressive neurological disease characterized by the degeneration of motor neurons. These motor neurons, or nerve cells, control voluntary muscles which are used for actions such as swallowing, talking, breathing, and walking. A continuous decline of the nerve cells eventually leads to their death. When they die, the ability of the brain to initiate and control muscle movement is lost. Therefore, patients in the later stages of the disease may become totally paralyzed. Most ALS patients die of respiratory failure within 3 to 5 years of disease onset. ALS typically does not affect the senses, nor does it alter cognition.

According to the National ALS Registry, the disease affects about 5 people per 100,000 in the United States. Although ALS can strike at any age, it is often diagnosed between 55 and 65 years of age. ALS is slightly more common in men than women. In addition, Caucasians and non-Hispanics are most likely to develop the disease, but ALS affects people of all races and ethnic backgrounds.

Researchers do not know what causes ALS but estimate 90% of cases occur spontaneously without a known family history or associated environmental risk factors. About 5 to 10% of the cases are believed to be genetic, resulting from the mutations of certain genes that lead to motor neuron breakdown. In these cases, the disease runs in families and gets passed down through genetic changes.

Not all ALS patients experience the same symptoms or the same sequences or patterns of disease progression. However, the gradual onset of increased muscle weakness is the most common initial symptom of the disease. Additional early symptoms may include tripping, dropping things, abnormal fatigue of the arms or legs, slurred speech, muscle cramps and twitches and uncontrollable periods of laughing or crying. More severe symptoms can include shortness of breath, difficulty breathing, chewing, and swallowing, weight loss, as well as the inability to stand or walk independently. Anxiety and depression are also common because ALS patients usually remain able to reason and are aware of their loss of function. Ultimately, progressive muscle weakness and paralysis will be experienced by all ALS patients. When breathing muscles are affected, ALS patients will need permanent ventilatory support to assist with breathing.

There is no single test to diagnose ALS. Healthcare providers conduct physical and neurological exams to test reflexes, muscle strength, and other responses. Muscle and imaging tests such as electromyography (EMG), a nerve conduction study (NCS), or a magnetic resonance imaging (MRI), as well as blood and urine tests may be done to rule out other diseases and confirm the diagnosis.

Currently, there is no treatment to reverse damage to motor neurons or cure ALS. Therefore, available drug therapy is utilized to alleviate symptoms, prevent complications, and slow disease progression. Medications may be prescribed to help manage muscle cramps, stiffness, excess saliva, unwanted episodes of crying or laughing, pain, depression, sleep disturbances, or constipation. A limited number of ALS specific medications are also available. Rilutek® (riluzole) was the first FDA-approved drug available to treat ALS in 1995 and works by blocking the release of glutamate. Too much glutamate is believed to injure nerve cells. It works to prolong survival by a few months and slow the progression of ALS. Riluzole is also available in an oral film formulation (Exservan™) and thickened liquid (Tiglutik) for use when swallowing becomes difficult. Radicava™ (edaravone) was approved in 2017 and works by removing toxic molecules and lowering oxidative stress. It may reduce nerve damage and slow the decline in physical function by one-third. Relyvrio™ is a combination of two drugs, sodium phyenylbutyrate and taurursodiol, which act to prevent nerve cell death by blocking stress signals in cells. It was approved to treat ALS in 2022. Earlier this year, Qalsody™(tofersen) was approved to treat ALS associated with a mutation in the superoxide dismutase 1 (SOD1) gene. Approximately 2% of ALS cases are associated with

mutations in this gene. Qalsody was approved under the FDA's accelerated approval pathway. In the next couple of years, additional therapy options may be approved. The FDA is scheduled to review NurOwn® (debamestrocel) at the end of 2023. NurOwn is a cell therapy designed to deliver growth factors in the spinal fluid to reduce neuroinflammation. Several more investigational therapies are in phase III trials with the potential for approval in 2024 or 2025.

In addition to drug therapy, supportive health care provided by a multidisciplinary team of health care professionals can work to keep patients mobile, comfortable, and independent for as long as possible. Physical therapy can help patients stay mobile while reducing discomfort associated with stiff muscles, cramps, and fluid retention. A dietician can counsel patients on eating a healthy, balanced diet as well as recommend food options when swallowing becomes difficult. Speech therapists can help patients maintain verbal communication for as long as possible. They can also teach ways to communicate nonverbally. Splints, braces, grab bars, reach devices, and wheelchairs can also help to prolong the independence of ALS patients.

While a wealth of new scientific understanding about the physiology of ALS has occurred in recent years, much remains to be discovered and is the focus of current research. Ongoing studies are seeking to understand the mechanisms that selectively trigger motor neurons to degenerate in ALS, which may lead to effective approaches to halt this process. Other clinical research studies are working to identify additional genes that may cause or put a person at risk for either genetic or spontaneous ALS. In addition, a large-scale collaborative research effort with both public and private organizations is analyzing genetic data from thousands of individuals with ALS to discover new genes involved in the disease. Scientists are also working on the development of disease biomarkers that help identify the presence or rate of progression of a disease or the effectiveness of a therapeutic intervention. Finally, numerous investigational treatments are in development that include gene therapies, antibodies, as well as cell-based therapies.

The number of ALS cases is expected to rise to nearly 380,000 worldwide by 2040, partially due to the aging population. Therefore, optimization of current therapeutic approaches and the development of new treatment options is extremely relevant. A number of factors including environmental, genetic, and age-related changes can lead to motor neuron cell death causing impairment and paralysis in different parts of the body. As a result, finding suitable therapy to slow down or possibly stop disease progression remains challenging. Until satisfactory treatment is available, supportive therapy remains important to keep ALS patients mobile and living as independently as possible. Fortunately, the vast amount of ongoing ALS research provides the hope of improved future care and therapy for patients and their families.

References

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