



AMYOTROPHIC LATERAL SCLEROSIS

by *Bill Wojciechowski, MS, RRT*

When baseball fans hear the name of the disease amyotrophic lateral sclerosis (ALS), they automatically have thoughts of Lou Gehrig, the great New York Yankee first baseman. Because of his prominence, Lou Gehrig's name has become synonymous with ALS and as most know, ALS removed Gehrig from the Yankee's lineup unexpectedly after he had played 2,130 consecutive games (13 seasons).

Despite ALS being a devastating disease, some people, for example, physicist Dr. Stephen Hawking, have managed to carve out productive lives. Ordinarily, people diagnosed with ALS succumb within 10 years. Most die within five.

ALS is a progressive neuromuscular disorder that affects primarily voluntary muscles. Consequently, the muscles become progressively weaker. In Gehrig's case, he collected only four hits in the first eight games of the 1939 season, and often stumbled running to cover first base for infield ground balls. By early May of that year, he was out of baseball.

When the muscles of ventilation become affected in ALS, respiratory failure is generally inevitable

Etiology

The two forms of ALS are familial (genetic) and sporadic. Sporadic ALS is responsible for 90% to 95% of all ALS cases, whereas the familial form accounts for the remaining 5% to 10%. Sporadic ALS has no known cause. Familial, on the other hand, is linked to a mutation of the enzyme called superoxide dismutase 1 (SOD1) and with an over-stimulation of motor neurons by the neurotransmitter glutamate. Environmental factors, e.g., neurotoxins and heavy metals, are believed to play a role in the incidence of ALS, but none have been definitively identified.

Epidemiology

In the United States, the incidence of ALS is approximately five cases per year per 100,000 population. Whites are diagnosed more frequently than non-whites. ALS most frequently strikes between the ages of 40 and 70 years. Nonetheless, younger and older people can sometimes be stricken. Men are more often afflicted than women by a ratio of 1.5 to 1.0.

The belief is that ALS is geographically evenly distributed; however, collections of people have been reported to have contracted this motor neuron disease. The largest cluster appears to be among

the Chamorro or Chamoru people of Guam among whom the incidence sometimes exceeds 140 per year per 100,000 population.

Pathophysiology

ALS affects motor neurons arising from the brain, brainstem, and spinal cord. These neurons are responsible for voluntary muscle activity. ALS afflicts both upper and lower motor neurons. The upper motor neurons originate in the brain and brainstem, and the lower motor neurons arise from the spinal cord. The motor neurons from the brain and brainstem control muscles involved in eye, head and neck movements, feeding, speech and facial expressions. In terms of the lower motor neurons, ALS affects the anterior horn cells of the spinal cord, leading to limb weakness.

The bulbar region of the brain may also be affected. These regions include the cerebellum, medulla, and pons. Patients with bulbar involvement demonstrate difficulty speaking (dysarthria), chewing, and swallowing (dysphagia).

Biochemical Expression

The superoxide dismutase 1(SOD1) gene provides instructions for making the enzyme called superoxide dismutase which is normally abundant in cells throughout the body. This enzyme normally neutralizes the oxygen radical called the superoxide anion. When superoxide anion levels are uncontrolled, they damage cells. Superoxide anions are cytotoxic metabolites and are byproducts of normal aerobic respiration, particularly from energy-producing reactions occurring in the mitochondria.

Why motor neurons in the brain and spinal cord are particularly sensitive to SOD1 mutations is unknown. Studies have demonstrated several ways in which this altered enzyme may cause the death of motor neurons. These possibilities include (1) accumulation of harmful superoxide anions, (2) increased production of other types of neurotoxic radicals, (3) abnormal mitochondria unable to supply the high energy demands of motor neurons, (4) acceleration of programmed cell death (apoptosis), (5) formation of aggregates of malformed superoxide dismutase that are neurotoxic, or (6) continuous stimulation of nerve cells causing them to "burn out" and die. The latter process is termed excitotoxicity.

As neurons transmit impulses to each other and to their target receptors (voluntary muscles), they release messenger molecules called neurotransmitters. Glutamate, a neurotransmitter, binds with receptors at various synapses. Ordinarily, glutamate is quickly released from its receptor sites and removed from these nerve cell junctions. Research has shown that prolonged excitation of a

nerve cell is toxic to that neuron. In ALS, glutamate remains bound longer to its receptor at the synapse causing over-excitation of the cell receiving the impulse. Over-stimulation and over-excitation damage the neurons along the motor neuron pathway.

Clinical Manifestations

Early manifestations are often so subtle that the symptoms are overlooked. Eventually, the person experiences clumsiness, stumbling, muscle twitching, and cramping. Progressively, the person displays proximal (head or neck) and/or distal (hands or feet) skeletal muscle weakness. Bulbar dysfunction is characterized by slow, slurred speech along with uttering short phrases and inappropriate pauses. Dysphagia is accompanied by longer eating times and drooling. Fasciculations (twitching) of the tongue and tongue wasting are common. Weight loss follows as eating becomes more labored. Emotional lability, sometimes described as the pseudobulbar effect, is the occurrence of sudden and unpredictable episodes of crying, laughing, or other emotional displays and outbursts. Degeneration of bulbar motor neurons attributes to exaggerated expressions of emotion. Bulbar involvement also features difficulty closing the jaw and with voluntary coughing.

When the muscles of ventilation (diaphragm and external intercostal muscles) become affected in ALS, respiratory failure is generally inevitable, requiring a tracheotomy and mechanical ventilation. Before commitment to mechanical ventilation, these patients tend to experience dyspnea, difficulty sleeping, ineffective cough, expiratory muscle weakness, and accessory muscle use.

Because ALS affects only the motor neurons, a person's cognitive function remains intact. Therefore one's intelligence, personality, and memory are not impaired.

Diagnosis

No laboratory tests diagnose ALS. Ultimately required for diagnosis are signs and symptoms of both upper and lower motor neuron involvement attributable to no other causes. An abnormal Babinski reflex occurs when upper motor neuron damage has developed. The Babinski reflex presents when the great toe flexes toward the top of the foot and the other toes fan out after the sole of the foot has been firmly stroked. Electromyography and nerve conduction velocity tests are also performed. Abnormal



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findings from these tests may merely indicate damage to peripheral nerves or myopathy, and offer nothing specific toward the diagnosis of ALS. Magnetic resonance imaging (MRI) studies are done to investigate if the presence of a brain or spinal cord tumor or a herniated disk is responsible for the patient's complaint of muscle weakness. Nothing explicit regarding ALS appears on an MRI. Nonetheless, results of electrophysiological studies are linked to upper and lower motor neuron dysfunction and are considered within the context of the patient's complaints.

Because Lyme disease features signs and symptoms similar to ALS, Lyme disease serology should be performed. Other neurological conditions such as multiple sclerosis, post-polio syndrome, and spinal muscular atrophy can mimic the signs and symptoms of ALS.

Treatment

ALS is not curable; the treatment is essentially palliative. Rilutek (riluzole) has demonstrated promise among ALS patients. Pharmacologically, Rilutek has an inhibitory effect on pre-synaptic glutamate release, minimizing the over-stimulatory effect of glutamate. Rilutek appears to be neuroprotective against the damaging effects of excitotoxic mechanisms. Newly diagnosed patients often benefit from exercise regimens and physical therapy. However, once the muscles of ventilation are affected, the patient requires mechanical ventilation. Initially, at this point, non-invasive positive pressure ventilation may provide the patient's ventilatory needs. As the patient's condition deteriorates, tracheotomy and invasive mechanical ventilation ensue.

Because no testing is available to definitively diagnose ALS, and because a number of diseases mimic ALS, the patient should seek a second opinion.

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