



## Understanding Amyotrophic Lateral Sclerosis (ALS)

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**Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease in the United States,** is a neurodegenerative disease of the upper and lower motor neurons. In most countries around the world, it is called amyotrophic lateral sclerosis or ALS. In the United Kingdom, Australia, New Zealand and South Africa, it's known as motor neuron disease (MND). Internationally, the disease is termed ALS/MND and is referred to as a neurodegenerative, or neuromuscular, disease.

Dr. Jean-Martin Charcot, the French neurologist renowned as "The Father of Neurology", published the first description of the clinical and pathological features of ALS in 1874. Based on his findings of the spinal cord and muscles at autopsy, he named the disease "Amyotrophic Lateral Sclerosis." "Amyotrophic" means loss of muscle, "lateral" refers to the nerve tracts that run down both sides of the spinal cord, and "sclerosis" refers to the hard scar tissue that remains after nerves have disintegrated.

### Classical ALS

**ALS is characterized by the degeneration and loss of motor neurons, which are the motor nerve cells in the spinal cord (anterior horn cells), brain stem (selected cranial nerves) and brain (motor or cerebral cortex)** that contract skeletal muscles and control voluntary movements of the muscles that move the body. Gradually, motor neurons die,

resulting in progressive weakness and functional loss of the involved muscles. The muscles affected may include muscles of the limbs and trunk, as well as those for speaking and swallowing, although not everyone experiences speech and swallowing problems. Likewise, not all individuals lose the ability to walk or to use their hands and arms. One-third of the cases begin with the onset of weakness in an arm; another one-third, weakness begins in a leg; and approximately one-fourth to one-third, people first develop weakness in the bulbar (speech or swallowing) muscles. Invariably, however, ALS results in progressive respiratory muscle weakness and loss of the ability to breathe — unless breathing support is used.<sup>1</sup>

**Classical ALS is characterized by the involvement of both the upper and lower motor neurons.** Damage to the upper motor neurons (in the motor cortex of the brain) causes muscle spasticity and stiffness, loss of muscle strength, and loss of dexterity. Damage to the lower motor neurons (in the brain stem and spinal cord) results in muscular weakness, atrophy (muscle wasting), and fasciculations (fine, rapid, flickering twitches of a muscle) and muscle cramps.

**Typically, in ALS, the sensory system and bladder, bowel, and sexual functions are not affected.** A small number of people, however, may have abnormal bladder function. This suggests the possibility of an abnormality of the involuntary autonomic neurons. In addition, the mental faculties usually remain intact. Dementia may occur, but it is rare. Targeted at

"upper middle age" adults, the average age range of onset is 55 to 65 years, although any adult, young or old, can get ALS. Men get the disease somewhat more often than women, although there is no difference at older ages.

### Pattern of Progression

**Which muscles lose function depend on which motor neurons are involved. Muscular weakness initially begins in one group of muscles, and then gradually spreads to other groups of muscles, striking in a random, but predictable, fashion.<sup>2</sup>** The pattern of muscle deterioration and rate of progression vary widely among persons with ALS. Thus, over a period of months or years, for those who experience the onset of difficulty in walking, using their hands and arms, or in talking or swallowing, the progression of loss of movement in those muscle groups is predictable. In some people, the disease progresses very slowly, while others experience a more rapid progression. Occasionally, some people who have a typical progression may appear to stabilize<sup>2</sup> and cease to progress for a very long time. However, what is predictable is that breathing problems will occur, either early or late, in the disease course. That means some people with ALS, who are walking, talking or having good use of their upper extremities, could have breathing failure and die (if untreated) within several months after the onset of the disease. Periodic pulmonary evaluation and consultation help prevent unexpected respiratory failure and hasty decision-making; this also helps in the planning of timely interventions and the prediction of patient outcomes. Despite the concern people have

of the future, many with ALS never experience severe disability.

### How ALS is Diagnosed

In diagnosing ALS, a medical history, with physical and neurological examinations, is done by a neurologist. The electromyogram (EMG) is a diagnostic test that is done to determine abnormal nerve and muscle activity. In this test, electrodes are inserted into the muscles to measure electrical signals. The clinical examination and tests also rule out other conditions that might mimic motor neuron disease. The clinical evidence of upper and lower motor neuron signs, according to the criteria (El Escorial) that was established by the World Federation of Neurology, determines the certainty of the diagnosis. The diagnostic categories for ALS are: [1] Clinically Definite ALS; [2] Clinically Probable ALS; [3] Clinically Probable — Laboratory Supported ALS; [4] Clinically Possible ALS.<sup>3</sup>

### Sporadic ALS and Familial ALS

**Sporadic ALS can strike anyone, anywhere in the world.** ALS is not contagious. Ninety to 95% of all ALS is without any family history and is called Sporadic ALS. However, **approximately 10% of all people who have ALS are found to have a family history of the disease, called Familial ALS (FALS).** For a diagnosis of FALS, it must be identified clinically in another member of the family.<sup>4</sup> FALS is inherited as an autosomal dominant trait, with a high penetrance after the sixth decade. An autosomal dominant inheritance pattern means that the gene flaw is on an autosome, a chromosome (DNA) that is not the sex (X or Y) chromosome, and a person needs to inherit a

flawed gene from only one parent to cause the disease. About 15% to 20% of those with FALS have a mutation in the Cu/Zn superoxide dismutase (SOD1) gene on chromosome 21.<sup>5</sup>

### The Three Clinical Subtypes of Motor Neuron Disease

**Some persons are diagnosed to have a clinical variant form of motor neuron disease, which may later evolve eventually into classical ALS. These three clinical subtypes of motor neuron disease include:**<sup>6</sup>

- 1. Progressive bulbar palsy (PBP)** is due to destruction of the motor neurons in the brain stem (referred as "bulbar involvement") and causes weakness of the speech and swallowing muscles.
- 2. Progressive muscular atrophy (PMA)** is due to destruction of the lower motor neurons of the spinal cord and, on occasion, of the brain stem. This results in weakness and wasting of the limbs, trunk, and sometimes, the bulbar muscles.
- 3. Primary lateral sclerosis (PLS)**

is due to destruction of upper motor neurons in the motor cortex of the brain. PLS is considered the UMN form of ALS. PLS causes muscle spasticity and may be slowly progressive over many years.

### Prevalence of ALS

ALS is presumed to occur as frequently as multiple sclerosis<sup>7</sup>, twice that of muscular dystrophy<sup>7</sup>, and three times more common than myasthenia gravis.<sup>8</sup> Except for a few clusters, it is also believed to have a uniform prevalence world-wide. Based on patients attending their clinics and residing in their local counties, only a very few centers have sought to determine trends in the

incidence of ALS.<sup>9</sup> Thus, epidemiological studies to determine the incidence of ALS, in most regions of the United States and worldwide, have never been done. Since 1990, the prevalence of ALS has probably risen sharply due to: more precise diagnosis of the disease; improved management of care; the advent of nasal ventilation (breathing support) that can significantly prolong survival in ALS; and the increase in population, particularly the rapid escalation of the "baby boomer generation" reaching the average age range of the disease onset. Therefore, ALS is most assuredly more common than described in the literature.

### Only One Approved Drug for ALS

**Although there is no known treatment to slow or stop the progression of the disease, experimental drugs are always being investigated through clinical drug trials.** For the past 20 years there have been numerous trials of experimental drugs. To date, all clinical trials of potential ALS drugs have failed, with the exception of riluzole, which was approved by the Federal Drug Administration (FDA) in 1996. Riluzole, called Rilutek (trade name), became available by prescription in tablet form. Riluzole, an ant glutamate compound (Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville, PA), is the first drug that showed possible therapeutic effect, but its benefit is limited. The theory is that riluzole may inhibit the action of glutamate, an excitatory neurotransmitter that may contribute to motor neuron degeneration. It was reported that riluzole extends survival a few months in people with ALS.<sup>10</sup> Nevertheless, studies did not reveal that riluzole had any effect on breathing function or quality of life. Because of the high cost and

limited benefit, many physicians do not prescribe Rilutek, unless patients have insurance benefits to cover the cost. Despite use of the drug, ALS patients continue to have progression of muscle weakness. Another consideration is that optimal use of nasal ventilation can usually prolong survival longer than taking Rilutek.

### “Cure” Vs. Treatment of ALS

**The cause and prevention of ALS, including a treatment to stop or retard its progression remain unknown,** although research efforts in exploring the mysteries of the relentless disease are being vigorously pursued. Nevertheless, because the central nervous system (brain, brain stem and spinal cord) cannot be re-generated, people with ALS who are paralyzed and presently waiting for a “cure,” should not presume this means reversal of their paralysis. **Cure is defined as the “return of one’s previous state or strength.”** Therefore, to discover a genuine “cure” for ALS would mean to find a treatment that would regenerate (regrow, restore) motor neurons for muscles to regain their strength. Unless science first discovers a way to regenerate neurons in human beings, whereby there is the evidence of people paralyzed from the neck down with a spinal cord injury regaining the ability to walk, a “cure” for ALS or any paralyzing disease with the manifestation of reversal of paralysis, appears unrealistic. To “cure” ALS, myriads of motor neurons would need to be regenerated, and, unfortunately, more than 50% of the motor neurons are already lost by the time of diagnosis.

In summary, making life support decisions should not be based on fundraising campaigns for a cure

and new reports or drugs in the news. Ethically, people with ALS have the right to know the difference between the meaning of “cure,” and treatment to slow or stop disease progression.

### Survival

Nowadays, survival varies greatly in people with ALS, particularly because of the number getting better care and the more prevalent use of some form of breathing support (use of a ventilator). Traditionally, people with ALS used non-assisted ventilation, except for tracheostomy ventilation prior to the advent of nasal ventilation. Thus, 50% of ALS individuals (those who do not use breathing support) die within three years of the disease onset.<sup>2</sup> At some point in the disease course, respiratory impairment will occur and eventually progress. Respiratory failure is the primary cause of death in ALS. However, respiratory failure can be prevented and treated. Unlike other diseases, living or dying is a choice. In other words, ALS itself is not fatal when a ventilator is used successfully and complications are avoided. Methods of mechanical ventilation, used to relieve symptoms and prolong survival, include nasal (noninvasive) ventilation or tracheostomy (invasive) ventilation.

### Life Choices

Persons who can talk, or have the ability to adequately swallow their saliva, are the best candidates for nasal ventilation, which can be easily applied with a nasal mask and headgear. Through optimal use, nasal / oral ventilation can alleviate respiratory symptoms and prolong survival temporarily, until bulbar impairment becomes severe.<sup>1</sup> Individuals who are intolerant of nasal ventilation

need to know that tracheostomy ventilation is an alternative to respiratory failure and dying. However, people should know that tracheostomy (invasive) ventilation is long-term life support, and those who choose this option can live for many years.

People with ALS need accurate, understandable and necessary information on all the options for breathing and living, the need for timely interventions and optimal management of care. Everyone should know that ALS ultimately results in progressive respiratory muscle weakness, that breathing failure can be prevented, and that all people should have the choice to live — or if they so choose, to stop life-sustaining treatment. The goal is for people with ALS and their loved ones to have the best life possible.

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***“An independent, nonprofit organization whose mission is improving the care of people with ALS through research and education of nurses and care providers.”***