

Section 1

ALS OVERVIEW

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a progressive, degenerative disease of the nervous system. It is one of a group of diseases, called motor neuron diseases (MND), in which specialized nerve cells that control movement of the voluntary muscles gradually cease functioning and die. These nerve cells, called motor neurons, carry impulses from the brain to the brainstem and the spinal cord. The impulses are then carried to the muscles. The muscles respond to these messages by coordinated relaxation or contraction corresponding to willed movement. In ALS and other motor neuron diseases, motor neurons gradually deteriorate. Because the nerve cells that stimulate them have died, the muscle tissues waste away. This results in progressive muscle weakness, atrophy, and often spasticity, or excess muscle tone. Only the motor neurons are affected. Other nerve cells, such as sensory neurons that bring information from sense organs to the brain, remain healthy.

SYMPTOMS

The early symptoms of ALS vary in different patients, depending on which part of the central nervous system (the brain and spinal cord) the disease affects first. Upper motor neurons travel from the surface of the brain (the cortex) down to the brainstem and/or to the spinal cord. Within the brainstem or spinal cord, the upper motor neuron connects with a lower motor neuron. The lower motor neuron leaves the brainstem or spinal cord and travels to the muscle that it controls. ALS may involve damage to either upper or lower motor neurons, but it usually affects both kinds of neurons.

The symptoms and clinical features of the disease depend on the location of the affected neurons. Speech and swallowing impairments are called bulbar symptoms. They indicate that neurons in the brainstem are affected. Weakness of the respiratory muscles, muscle weakness, and loss of mobility in the arms and legs are called somatic symptoms. They indicate spinal cord involvement. In classical ALS, a mixture of upper and lower motor neurons are involved, with both bulbar and somatic symptoms. Early symptoms of ALS can include weakness, clumsiness, fatigue, stiffness, muscle twitching, cramping, and difficulty in chewing, swallowing, speaking, or breathing.

Lower Motor Neuron Symptoms

Weakness and muscle wasting are common when lower motor neuron involvement predominates. The patient or physician usually notices fasciculation, or muscle twitching. Fasciculation is a sign of muscle irritability, as the normal action of the lower motor neuron on the muscle is impaired. The sole involvement of lower motor neurons can be seen in a form of ALS called progressive muscular atrophy. Fasciculation is described as "benign" if there is no muscle weakness, atrophy, or impairment of motor function. Fasciculation is described as "pathologic" when it occurs in ALS with other symptoms.

Upper Motor Neuron Symptoms

Spasticity, or stiffness, in the lower limbs, face, or jaw indicates upper motor neuron involvement. Spasticity in the legs often produces severe walking difficulties. The patient may complain of heaviness, fatigue, stiffness, or lack of coordination of any affected limb. Reflexes are very brisk, or exaggerated. Outbursts of laughter or crying with minimal provocation can occur. This is called emotional lability and is referred to as a pseudo-bulbar affect. Both brisk reflexes and emotional lability involve the inability to inhibit reflexes.

Primary lateral sclerosis (PLS) characteristically involves progressive spasticity, difficulty in walking, and pseudo-bulbar affect related to upper motor neuron involvement of bulbar and somatic muscles. In progressive bulbar palsy, an ALS variant, speech, swallowing, and behavioral symptoms predominate, related to upper and lower motor neuron involvement.

CLINICAL COURSE

Weakness of the bulbar and somatic muscles produces a decline in speech, swallowing, and limb strength and function. The ALS patient usually remains alert throughout the course of the illness and retains normal sensation, vision, and bowel function. Bladder function is impaired in a small percentage of patients. Generally, ALS is not a physically painful condition. Discomfort can result from immobility and joint contractures, a shortening of muscles resulting in deformity. The problems are related to advancing muscle weakness and the inability to change positions easily. Proper positioning, exercise, physiotherapy, and medications can help keep patients comfortable.

While most patients do not have loss of intellectual function, some may have subtle changes in mood, behavior, or personality. In a small minority of patients, more significant changes in behavior and judgment suggest a form of dementia.

Patients with significant bulbar involvement may require help to improve communication or ensure safe and adequate nutrition. A gastrostomy (feeding) tube may be suggested in the following situations: recurrent pneumonia, high risk of aspiration (inhaling food or liquids into the lungs), inadequate nutrition, rapid weight loss, or extended feeding time. A wide range of devices and techniques can address problems with communication. Ultimately, ALS may result in respiratory decline, requiring consideration of respiratory support, including non-invasive ventilation such as a BiPAP, or a tracheostomy and a ventilator.

Each ALS patient is unique in regard to the rate and characteristics of the progression of the disease. The Lois Insolia ALS Center provides a multidisciplinary approach to patient care, including an individualized treatment plan guided by the patient's personal preferences and wishes. Although the clinical progression can vary greatly, 50 percent of those diagnosed will succumb to the illness within five years of the onset of symptoms.

DIAGNOSIS

A patient who might have ALS is usually evaluated by a neurologist, a doctor who specializes in disorders of the nervous system. The diagnosis of ALS is "clinical" in nature. That is, it is determined by what the doctor hears and sees. A series of tests are usually ordered to exclude conditions that can mimic ALS. Testing for conditions that might mimic ALS is important because many of these conditions are treatable. Once the diagnosis of ALS is confirmed, the neurologist and the Lois Insolia ALS Center staff provide information and resources to the patient and family, and an individualized plan of care for the patient is established.

Three kinds of diagnostic tests are usually performed: imaging studies, electrodiagnostic studies, and fluid and tissue analysis.

Imaging studies, such as X rays, CT (Computerized Tomography) and/or MRI (Magnetic Resonance Imaging) scans, and myelography, are performed to exclude any structural abnormality of the nervous system.

The EMG (electromyogram), which records the electrical activity of muscle, and the NCV (nerve conduction velocities), which quantifies a nerve's ability to transmit electrical impulses, are electrodiagnostic studies. They evaluate the integrity of muscles and peripheral nerves.

Fluid analysis includes the evaluation of blood, urine, and occasionally cerebrospinal fluid. These fluids are screened for potential metabolic, endocrine, immunologic, infectious, and toxic abnormalities. Tissue analyses, including muscle and/or nerve biopsy, are occasionally indicated to establish the diagnosis or to exclude other neuromuscular conditions.

In addition, approximately 2–3percent of all ALS cases are due to mutations in the gene for Cu, Zn, Superoxide dismutase (SOD1). Genetic testing for SOD1 is available.

In general, patients with ALS will not have significant abnormalities on imaging studies and fluid analysis, but will show characteristic results on electrodiagnostic studies and muscle biopsy.

Although the diagnostic work-up is extensive, the tests are generally not risky or painful. Once the diagnosis of ALS has been established, the short- and long-term care of the patient and family can be planned. Professionals who care for ALS patients believe a multidisciplinary approach is most appropriate. A therapeutic team of professionals, trained in a variety of disciplines, ensures optimal patient and family care. This team includes practitioners in neurology, nursing, social work, speech, nutrition, genetic counseling, and occupational and physical therapies. Such care is provided by the Lois Insolia ALS Center, a nationally-recognized patient-care facility.

CAUSES

Each year, two new ALS cases per 100,000 people are diagnosed. At any given time, approximately 30,000 people afflicted with ALS are living in the United States. Most patients are between 50 and 60 years of age, although the disease can strike at any age. Men are affected slightly more frequently than women. Some studies have identified areas that at certain times have

had greater than expected numbers of cases. This has occurred in the past in the western Pacific islands and in parts of Japan and Australia. Other areas in the continental United States have been reported but have not stood up to careful epidemiological investigations.

Familial ALS accounts for 10 percent of all ALS cases. Researchers investigate the genetic basis of ALS by studying families in which a number of members have the disease. Such research has identified two genes that cause ALS. One such gene is on chromosome 21 (the copper-zinc superoxide dismutase, or SOD1, gene). It accounts for about 20 percent of the familial ALS cases, or 3 percent of all ALS cases. Development of a mouse model of ALS, which has mutant SOD1 genes in its chromosomes, has enhanced our understanding of how ALS develops. The mouse model also serves as an important “testing ground” for newly developed therapies. The second gene, called ALSIN, causes ALS and PLS in children. Molecular genetic investigation is likely to uncover additional genes and their products that will account for the majority of familial ALS cases. The identification of additional genes and gene products will significantly advance our understanding of sporadic (non-familial) ALS. In addition, the search for a genetic predisposition in sporadic ALS is being investigated.

For several years, scientists have investigated naturally-occurring toxic chemicals as a possible cause of ALS. The presence of abnormal amounts of glutamate, a chemical that occurs naturally in the brain, has been observed in ALS patients. Glutamate helps carry messages from one nerve cell to another. Normally, after glutamate does its work, it is removed by another chemical, called a transporter. If the transporter doesn't properly remove the glutamate, excess glutamate might remain in the nervous system. This is postulated to over-stimulate motor neurons and result in their death. The glutamate hypothesis is one basis for riluzole therapy. Riluzole is a chemical that, among other actions, reduces the amount of glutamate released into the nervous system, thus reducing damage to the motor neurons. Currently, the only FDA-approved drug for the treatment of ALS is Rilutek, which is the brand name for riluzole.

OTHER THEORIES

Viruses and abnormalities of the immune system are other possible causes of ALS. A virus or foreign substance may trigger the immune system, which normally fights infection. The immune system may then attack the body's own nervous system (an autoimmune process). Immune system abnormalities and autoimmune diseases may be more frequent in ALS patients and their relatives. However, specific and consistent abnormalities are difficult to identify and related trials have not shown success in the treatment of ALS.

A large number of ALS patients may have abnormal antibodies. However, it is not clear which of the antibodies produce disease and which are associated with the disease process but do not actually cause disease. As noted above, a viral "triggering" agent of motor neuron disease has been suggested. This hypothesis has been generated because certain viruses such as the polio virus or the West Nile virus can cause an acute infection of the motor neurons. This has led to the idea that ALS might be a persistent viral infection, resulting in progressive motor disability. However, no virus has been seen or otherwise identified in autopsy material from ALS patients. It is true that many polio survivors begin to deteriorate years after the acute phase of their illness. However, the cause of this progressive, post-polio muscular atrophy is unclear. Post-polio patients do not appear to have greater risk for ALS.

Neurotrophic factors, or chemicals that affect the growth of neurons, are found throughout the nervous system. One theory of ALS suggests that a deficiency of growth factors results in reduced survival and eventual degeneration of motor neurons. Nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), and insulinlike growth factor (IGF-1) all promote motor neuron survival in tissue culture and in animal models of motor neuron disease. However, clinical trials using neurotrophic factors in ALS have had generally negative results. Overall, the neurotrophic factors do not appear to be effective in treating ALS.

Many other possible causes and associations have been suggested, including environmental toxins, premature aging, endocrine factors, heavy metal poisoning, and various nerve abnormalities. No single cause has yet explained the variety of motor neuron disorders or ALS. Many interacting factors are probably involved in the clinical and pathological abnormalities in ALS.

More recently the subcellular organelle called a mitochondrion has been implicated in motor nerve cell death in some experiments. Mitochondria are the energy factories of the motor neuron. Not only could there be energy failure for some reason but in addition there are at least two potential toxic things that could come out of mitochondria. All mitochondria normally produce some free radicals sometimes called reactive oxygen species. In excess free radicals can kill cells. Nature has evolved several ways to handle free radicals including the SOD enzyme. It is possible these detoxifying systems could be overwhelmed. Another possible mitochondrial explanation goes by the name of apoptosis. This is a cell suicide pathway that is triggered by enzymes called caspases. One of these is produced by the mitochondria.

Another area of interest is the way the disease spreads. It seems to stick with the first limb for a while, progress there and then usually but not always spread to another limb. This has led some investigators to think that there is a problem with the supporting cells in the nervous system called glia or astrocytes (because they are star shaped). The thought there is that it may be the neighborhood that matters as much as the neuron itself.