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Amyotrophic Lateral Sclerosis: Lou Gehrig's Disease

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Amyotrophic lateral sclerosis (ALS), commonly called Lou Gehrig's disease, is a progressive neuromuscular condition characterized by weakness, muscle wasting, fasciculations and increased reflexes. Approximately 30,000 Americans currently have the disease. The annual incidence rate is one to two cases per 100,000. The disease is most commonly diagnosed in middle age and affects more men than women. It usually presents with problems in dexterity or gait resulting from muscle weakness. Difficulty in speaking or swallowing is the initial symptom in the bulbar form of the disease. Over a period of months or years, patients with ALS develop severe, progressive muscular weakness and other symptoms caused by loss of function in both upper and lower motor neurons. Sphincter control, sensory function, intellectual abilities and skin integrity are preserved. Patients become completely disabled, often requiring ventilatory support and gastrostomy. Death usually occurs within five years of diagnosis and is attributed to respiratory failure or cachexia. The etiology of the disease is unknown. Current research is focused on abnormalities of neuronal cell metabolism involving glutamate and the role of potential neurotoxins and neurotrophic factors. New drugs are being developed based on these theories. Current management involves aggressive, individualized alleviation of symptoms and complications.

Amyotrophic lateral sclerosis (ALS) was first described in 1869.[1] It is frequently referred to as "Lou Gehrig's disease" in memory of the famous baseball player who died of ALS in 1941.[2] ALS is defined as adult-onset, idiopathic, progressive degeneration of anterior horn cells and upper and lower motor neurons resulting in progressive muscle weakness, wasting and fasciculations.[3-5(pp9-15)] The clinical picture varies, depending on the location and progression of the pathologic changes. Diagnostic criteria of the World Federation of Neurology (the "El Escorial criteria")[6] can help define and classify ALS (*Table 1*).

Illustrative Case 1

Bulbar Form

Relatives of a 61-year-old woman reported that she appeared to have difficulty concentrating during long discussions. Apart from longstanding thyroid and estrogen supplementation, her medical history was unremarkable. Review of systems, a mental status examination and a physical assessment were normal. The patient was a psychologist who usually read several books a week and had an active social life, including competitive bridge and vigorous daily exercise. She had no symptoms of depression, or mental or intellectual difficulties, and denied alcohol or substance abuse. She believed her family's concerns were unwarranted but eventually conceded that her voice "just wore out" during prolonged conversations.

Speech therapy evaluation demonstrated moderate to severe weakness of laryngeal muscles. Within a month, the patient had slurred speech, difficulty in swallowing liquids and fasciculations of the tongue. During the next year, she lost the ability to

speak or swallow, and developed weakness and fasciculations in her shoulders, arms and upper trunk. Communication was complicated by multiple daily episodes in which the patient laughed or wept inappropriately and switched from one emotion to the opposite within a few minutes. She became cachectic despite use of a gastrostomy tube and experienced increasing problems with balance, respiration, nutrition and hydration.

The patient died approximately 20 months after the onset of symptoms. Although cachectic, mute and almost totally immobile toward the end of her illness, she remained intellectually uncompromised and had no problems with bladder or bowel dysfunction or skin breakdown.

Illustrative Case 2

Spinal Form

A 53-year-old woman developed an unusual gait related to "calf stiffness." After several months of progressive weakness, she developed a right foot drop. Within 15 months, she also described difficulty in writing, weakness of the right hand and arm, and diffuse muscle twitching with painful muscle cramps. Assessment confirmed weakness of all limbs, more marked on the right side, with muscle atrophy. Reflexes were hyperactive and fasciculations were observed in the right leg.

Within two years, the patient became severely disabled because of generalized weakness. She experienced no sensory problems, intellectual deterioration or skin breakdown in spite of her degree of immobility. Difficulty in swallowing necessitated the use of a gastrostomy tube for feeding. The patient died of respiratory failure approximately three years after reporting the initial symptoms.

TABLE 1
Diagnostic Criteria for ALS

Positive features

- Definite ALS
  - --LMN and UMN signs in three to four regions
  - -- Evidence of progression
- Probable ALS
  - LMN and UMN signs in at least two regions with UMN above LMN signs and evidence of progression
- Possible ALS
  - --LMN and UMN in one region
  - --UMN in two regions
  - --LMN above UMN signs
  - --LMN and UMN signs but no evidence of progression
- Suspected ALS
  - --LMN signs in two to three regions

Negative features

- Findings inconsistent with diagnosis of ALS
- Neuroimaging, EMG, clinical or other evidence of an alternative disease explaining signs or symptoms
- Lack of progression to other body regions
- Cognitive decline
- Sphincter abnormalities
- Sensory dysfunction
- Visual decline

ALS=amyotrophic lateral sclerosis; LMN=lower motor neuron; UMN=upper motor neuron; EMG=electromyographic.

Adapted from Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci 1994; 124(Suppl):96-107.

Pathology

Atrophy of the anterior horn cells and replacement of the large motor neurons by fibrous astrocytes (gliosis) causes the affected anterior and lateral columns of the spinal cord to become hard, hence the term "lateral sclerosis."[4] Large neurons tend to be affected before small ones,[7] but the general distribution of pathologic findings within the spinal cord should correlate with the clinical findings. In the brain, atrophic changes may be found in the motor and premotor cortex.[4,7] Peripheral nerves show secondary degeneration of axons and myelin.[1] Surviving motor axons develop collateral branches to attempt reinnervation of muscles. The denervated muscles display various stages of atrophy.[1]

Cellular abnormalities and inclusion bodies have been described in the degenerating neurons, but none of these changes are pathognomonic of ALS.[4]

Epidemiology

Between 25,000 and 30,000 Americans may currently have ALS. The estimated prevalence is up to six cases per 100,000 of the adult population, with an annual incidence of one to two cases per 100,000. The peak age of onset is between 55 and 75 years, with a male preponderance of 1.5 to 2.0:1.[8] Recently, a modest increase in incidence has been noted, along with a

tendency for the condition to present at younger ages.[9]

Most patients die within five years of diagnosis,[2,8] but 8 to 22 percent survive for at least 10 years.[8] The prognosis tends to be worse for older patients and those with the bulbar form of the disease.[10] Although most U.S. cases are sporadic, familial and geographic clusters of ALS occur.

Etiology

ALS may have a multifactorial etiology or may result from a number of different neuronal insults. The major lines of investigation include genetic, viral, autoimmune[11] and neurotoxic hypotheses.

Leading theories concern neurotoxicity relating to abnormalities of calcium and amino acids (especially glutamate) essential to neurotransmission. Excessive entry of these compounds into the neurons damages cell metabolism, resulting in pathologic changes. Neuronal damage could similarly result from oxidative processes that produce hydroxyl radicals. Clinical trials of medications that attempt to reverse these processes are under way. Other hypothetic causes of ALS include neurotoxicity from various metals, chemicals or foods,[12] and, conversely, deficiency of neurotrophic agents (poorly understood proteins that enhance neuronal maintenance and growth).[4,13]

An intriguing theory that brings together several factors holds that ALS develops when vulnerable persons are exposed to a neurotoxin at times of strenuous physical activity.[14] For example, bursts of maximal muscle strength in athletes could create conditions that would deliver such a toxin to the anterior horn cells.

The mechanisms responsible for ALS operate long before the onset of symptoms. An estimated one third of motor neurons must be destroyed before muscle atrophy becomes apparent.[10]

Clinical Features

The classic presentation of ALS is insidious, progressive, asymmetric muscular weakness and atrophy along with neurologic signs, particularly fasciculations and hyperreflexia.[4] The clinical picture depends on the area of the nervous system that is damaged. The disease begins with equal frequency in upper and lower limbs (30 to 40 percent of cases each). Bulbar symptoms are the initial manifestations in 19 to 25 percent of cases.[10,15]

Patients with lower limb onset may complain of tripping, stumbling or awkwardness when walking or running. Those with upper limb onset may first notice difficulty in actions such as buttoning clothes, picking up small objects or turning keys. Speech problems, such as slurring, hoarseness or decreased volume, are the most common presentations in the bulbar form of ALS.

Classic signs of ALS include asymmetric muscle weakness, hyperreflexia, fasciculations and muscle atrophy.

As symptoms progressively worsen and spread, muscle atrophy becomes apparent and upper motor neuron symptoms such as spasticity complicate gait (in lower limb involvement) and manual dexterity (in upper limb involvement). Fasciculations in the affected limbs or the tongue cause "twitching," which may be embarrassing to the patient. Muscle pain may be caused by clonus or hyperreflexia. Many patients complain of muscle cramps. As the disease progresses, immobility from weakness and spasticity predisposes the patient to painful joint complications. Primary neuropathic pain does not occur in ALS.

Patients with the bulbar form of ALS develop problems in swallowing that are worse for saliva and liquids than for solids. The combination of excessive salivation (sialorrhea) and difficulty in swallowing leads to drooling. Bulbar ALS also causes a variety of speech problems, such as dysarthria (articulation) and dysphonia (volume). These patients may also develop an exaggerated emotional response ("pseudobulbar affect") consisting of frequent, brief episodes of laughter or tears that alternate rapidly.

Patients with ALS often experience fear, anxiety and depression. Weight loss is characteristic, and often the extent of cachexia cannot be explained by muscle atrophy or nutritional difficulties.

The patients progress to a state of profound disability, and many eventually require ventilatory assistance and interventions such as gastrostomy for nutrition. Death is usually caused by respiratory failure.

In spite of the widespread devastating effects of ALS, certain functions are conspicuously unaffected; extraocular muscle movement, bladder and bowel control, sensory function and skin integrity are usually preserved. The characteristic absence of pressure ulcers even in cachectic, bedridden patients may result from complex, poorly understood skin changes.[16]

Diagnosis

The diagnosis of ALS is clinical, based on the characteristic signs of progressive weakness, atrophy, fasciculations and hyperreflexia affecting several regions of the body. The early differential diagnosis may include musculoskeletal, neurologic or systemic conditions. In one study, 8 percent of the patients were given an erroneous diagnosis of ALS, and one half of those patients had treatable conditions.[17]

Each patient should undergo a diagnostic process based on the most probable explanation for the signs and symptoms. Extensive testing may be unnecessary. The diagnostic process consists of a history and physical examination, repeated at regular intervals, to document progressive hyperreflexia, fasciculations, and upper and lower motor neuron involvement. Electromyographic testing is used to document denervation and to distinguish benign fasciculations from those of ALS. Targeted laboratory, radiographic and special investigations may be necessary to enable exclusion of other causes of symptoms *(Table 2)*.[1,15,18] The diagnostic strategy requires balancing the need for certainty against the discomfort and potential adverse effects of excessive testing. Patients and families may request referral to specialty centers or additional testing to eliminate uncertainty.

TABLE 2
Differential Diagnosis of ALS

Spinal cord lesions	Examples: tumors, lymphoma, syringomyelia, vascular malformations
Spinal bone lesions	Examples: spondylosis, cervical rib, metastatic tumors
Infections	Examples: HIV, syphilis, myelitis, poliomyelitis, Lyme disease
Endocrine disorders	Examples: hyperthyroidism, hyperparathyroidism, diabetic radiculopathy
Toxins	Examples: lead, mercury
Other	Examples: postpolio syndrome, Huntington's disease, Friedreich's ataxia, sarcoidosis, multiple sclerosis, polymyositis, myasthenia gravis, muscular dystrophies

ALS=amyotrophic lateral sclerosis; HIV=human immunodeficiency virus.

Information from references 1, 15 and 26.

Management

The management of ALS is a complex and demanding team effort requiring individualized therapy and continual adaptation of medications and therapies. In addition to conventional sources, World Wide Web sites such as those maintained by the American Academy of Neurology, the ALS Association, the World Federation of Neurology and the national ALS associations of several countries provide valuable information and support. However, the unregulated format of the Internet may also include sites that provide unscientific information or promote unproven treatments.

Disease-Modifying Drugs

The only agent currently labeled for the treatment of ALS is riluzole (Rilutek). At least one other drug (mecasermin) is under consideration by the U.S. Food and Drug Administration. Clinical trials of other drugs are in progress.

Riluzole is believed to decrease glutamate release. One large study[19] reported that 56.8 percent of patients treated with 100 mg of riluzole daily were alive without tracheostomy after 18 months, compared with 50.4 percent of patients who received a placebo, a clinically small but statistically significant difference. Previously, a smaller study[20] reported a significant improvement in survival, but most of those patients had the bulbar form of ALS. Any positive effect on functional abilities from the use of riluzole is unclear, and no studies have reported that the drug halts the disease process.[21] Adverse effects include asthenia, nausea, dizziness, elevation of liver enzymes and granulocytopenia.[21-23]

The monthly cost for riluzole is approximately $600. The manufacturer (Rhône-Poulenc Rorer; telephone, 1-800-340-7502) has established programs to assist patients in gaining access to this drug and other support services.

Symptomatic Treatments

Various symptomatic treatments may be helpful.[5(pp321-8),15,24] Frequent, close contact with the patient and the family helps the physician gauge the significance of individual symptoms and the possible benefit of treatment compared with the risk of adverse side effects.

Spasticity may be relieved by use of baclofen (Lioresal), in a dosage of 10 to 25 mg three times daily, diazepam (Valium), in a dosage of 2 to 15 mg three times daily, or dantrolene (Dantrium), gradually titrated to a dosage of 50 to 100 mg four times daily. Unfortunately, these drugs can increase weakness and cause sedation, dizziness and other adverse effects.

Pain may result from muscle contractures and secondary effects on joints. Muscle cramps occur in almost all patients and may cause severe pain and sleep disturbance. Physical therapy can ameliorate many of the painful symptoms of ALS. Nonsteroidal anti-inflammatory agents and anticonvulsive medications such as carbamazepine (Tegretol), in a dosage of 200 mg three times daily, or phenytoin (Dilantin), in a dosage of 300 mg at bedtime, may be useful. Early use of amitriptyline (Elavil), in a dosage of 50 to 150 mg at bedtime, or nortriptyline (Pamelor), in a dosage of 50 to 75 mg at bedtime, may potentiate analgesic medications. The traditional treatment of cramps with quinine is no longer recommended because of the risk of reactions.[25] Fasciculations may be reduced by decreasing caffeine and nicotine intake. Lorazepam (Ativan) may relieve severe fasciculations.

Drooling may be one of the most distressing symptoms for patients with bulbar ALS. When excess saliva spills into the airway, bronchospasm can result. Mechanical suction devices are useful in preventing aspiration. Medications that suppress sialorrhea include anticholinergic drugs such as atropine, in a dosage of 0.4 mg four times daily, or scopolamine (Transderm-Scop), one 0.5-mg transdermal patch applied every three days. Some antihistamines, such as diphenhydramine (Benadryl), in a dosage of 25 to 50 mg three times daily, may also be helpful in suppressing sialorrhea.

Tricyclic antidepressants are widely used in the treatment of ALS because of their multiple effects. Amitriptyline, in a dosage of 5 to 100 mg at bedtime, can provide antidepressant and antisialorrheic actions as well as nocturnal sedation, potentiation of analgesia and possible weight gain. Doxepin (Sinequan) and imipramine (Tofranil) have similar actions. Tricyclic agents have potential hypotensive, cardiac, sedative and anticholinergic side effects. The selection of agent and dosage requires balancing the desired effects and potential adverse effects.

Depression and anxiety are common in ALS and require individualized therapy. Supportive counseling is appropriate for all patients and their families, and antidepressant medication may also be helpful. An adequate dosage of a tricyclic agent may relieve the patient's depression, with the advantage that the side effects (dry mouth, sedation and weight gain) actually help to counter symptoms of ALS. Selective serotonin reuptake inhibitors such as fluoxetine (Prozac), in a dosage of 20 mg once or twice daily, are effective but have the potential adverse effects of insomnia and agitation. Benzodiazepines may relieve anxiety and insomnia but can cause daytime sedation.

Supportive Therapies

Supportive therapies play a crucial role in the care of patients with ALS.[5(pp360-463),15] Physical therapy should begin early and should be adapted to the patient's needs throughout the course of the disease. Exercises to promote strength, range of motion and endurance may dominate the early therapy program. Heat, massage or transcutaneous electrical nerve stimulation may be added later to relieve pain. Electric stimulation of muscles has been used to try to increase muscle strength and induce movement, but this can be painful. In addition to carrying out the therapy program, physical therapists can help patients and families select and use equipment ranging from simple splints and neck supports to complex, multiple supportive devices and wheelchairs.

Occupational therapists can provide support and special equipment or environmental adaptations to maximize function. Associations for persons with disabilities (especially those with ALS and muscular dystrophy) can assist in finding equipment appropriate for each patient.

Speech therapists and communications specialists are particularly important to patients with the bulbar form of ALS. Patients and families can learn techniques to convey the maximum information with minimal effort shortly after diagnosis. Good communication also involves use of nonverbal modalities. The choice of equipment to assist communication is expanding rapidly because of computers, but weakness of the hands often limits choices.

Speech pathologists can also assist patients who have problems in swallowing. Modified barium studies may provide specific information to guide advice, such as use of the chin tuck (swallowing in a head-down position) to minimize choking and coughing.

The diagnosis of ALS is clinical and is based on history and physical examinations, repeated at regular intervals, documenting the classic signs of the disease.

All ALS patients require intensive nutritional support. Patients with swallowing problems require frequent, high-energy meals presented in a soft, moist consistency for ease in swallowing. Both liquids and dry foods can be difficult to swallow. Collaboration among the patient, caregivers, nutritionist and speech therapist is required to provide food that is nutritionally appropriate, appetizing and manageable for the patient; the aim is to prevent mealtime from being a frustrating occasion.

Discussion of percutaneous endoscopic gastrostomy (PEG) tube placement should be initiated early; placement should be presented as a positive option rather than a sign of failure. Many patients and families need time to adjust to this strategy and may be helped by information from patient associations. Modern PEG techniques have low morbidity, and tubes may be placed while the patient can still swallow, to enhance nutrition and avoid exhaustion. Nutritionists and home health nurses can provide essential support to families in managing PEG tubes and achieving adequate nutrition.

Many patients have a great fear of being unable to breathe, particularly at night. Symptoms usually begin with nocturnal dyspnea and orthopnea, and signs of poor nocturnal oxygenation, such as morning headache, frequent waking, nightmares and daytime sleepiness. Although mucolytics, expectorants, theophylline, antibiotics and oxygen can contribute to respiratory management, ventilatory support should be anticipated and the options explored before clinical respiratory failure develops. Pulmonary consultants and respiratory therapists can help patients and families learn about the many approaches, and the indications for and implications of each alternative. As with gastrostomy, patients need time to consider various options and require objective information. Patient associations and organizations can be very helpful. It is believed that fewer than 5 percent of patients eventually use long-term ventilatory support.[26]

Final Comment

The experience of ALS is unique to each patient and family. In addition to various health professionals, families often work with counselors, social workers and others to address adjustment, mental health, disability, and financial and other concerns. Fears of "getting lost in the system," loss of privacy and abandonment are common. Family physicians are well positioned to support ALS patients. Important aspects of care include ensuring that one person is the point of contact so that messages are promptly dealt with and communication is enhanced; providing home visits; making sure that covering physicians are well informed about the patient; and anticipating crises by preparing written instructions for situations such as respiratory failure and by addressing resuscitation and other end-of-life decisions. Some patients and families place great value on access to the latest information, referral to specialist centers and assistance in enrolling in experimental studies.

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