

Primer of Amyotrophic Lateral Sclerosis

General: Amyotrophic lateral sclerosis (ALS) is also known as Lou Gehrig's disease after the NY Yankee's baseball player who had the disease. It was fully described clinically and pathologically by the French neurologist J-M Charcot in 1886, and he gave it the name of amyotrophic lateral sclerosis. It is the most common form of motor neuron disease of adults. The incidence is 2-4:100,000.

Clinical features: ALS is a disease of adults (age range 20 to 80's) with a median age of symptom onset in the mid 50's. It is characterized by degeneration of upper and lower motor neurons that causes weakness and loss of function. Loss of upper motor neurons results in degeneration of the lateral corticospinal tract. Loss of lower motor neurons results in thinning of the ventral roots and atrophy of muscle. Thus the term "amyotrophic lateral sclerosis" connotes loss of lower and upper motor neurons.

Weakness typically starts focally (in a limb or with bulbar function) and progresses to involve all muscles. ALS is inexorably progressive, and shortens life by eventually weakening the diaphragm. The rate of

progression varies, and the median time to death from respiratory failure is 2-5 years from symptom onset, although there are rare long-surviving patients.

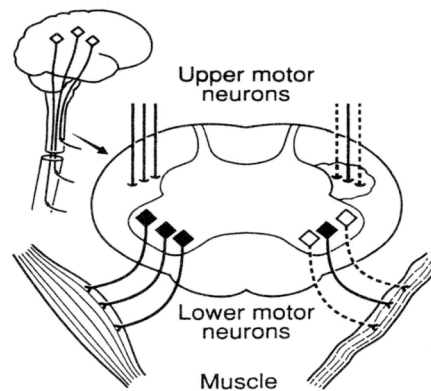


Diagram of upper motor neurons in cerebral cortex and lower motor neurons in brainstem and spinal cord.

Genetics: For 95% of patients the disease is sporadic, and for 5% it follows an autosomal dominant hereditary pattern. Mutations in the Cu/Zn superoxide dismutase 1 (SOD 1) gene have been described for only 15% of hereditary forms. Candidate genes have been proposed for the remaining 85% of familial ALS, but definite genes have not been identified.

Diagnosis: The diagnosis of ALS is clinical, based on a history of progressive symptoms and signs related to upper and lower motor loss with no other explanation. An EMG study is the most helpful test to confirm lower motor

neuron loss in a diffuse pattern, including subclinical denervation in strong muscles. Laboratory blood tests and imaging studies may help to exclude alternative diagnoses.

Strictly speaking, ALS involves degeneration of both upper and lower motor neurons. Some patients have greater loss of upper or greater loss of lower motor neurons. These differences in degree of upper and lower motor neuron loss do not change the progressive prognosis. In these circumstances, the more general term 'motor neuron disease' is appropriate.

Symptoms and signs of upper motor neuron loss:

| |
|---|
| UPPER MOTOR NEURON SYMPTOMS |
| Difficulties with speech Difficulties with swallowing Slowed and more difficult movements Stiffness of walking Ease of laughing or crying, Increase yawning Urinary urgency |
| UPPER MOTOR NEURON SIGNS |
| Spastic dysarthria Dysphagia Spastic gait Pathologic tendon reflexes Pathologic reflexes Labile affect |

Symptoms and signs of lower motor neuron loss:

| |
|--|
| LOWER MOTOR NEURON SYMPTOMS |
| Weakness Shrinkage of muscles Ease of muscle cramps Twitches of muscle Increased fatigue |
| LOWER MOTOR NEURON SIGNS |
| Muscle atrophy Fasciculations Weakness Needle EMG findings of active neurogenic denervation |

Pathogenesis: The cause of upper and lower motor neuron death is not known. Despite identification of SOD 1 mutations the pathogenesis of this form of ALS is not known. There are a number of theories with substantial support, including glutamate excitotoxicity, oxidative stress-free radical formation, mitochondrial dysfunction, abnormal protein aggregation, and abnormalities of neurofilaments. These theories are not mutually exclusive, and there may be a cascade of cellular events, ultimately leading to cell death. In sporadic ALS, there are likely to be genetic susceptibilities and environmental factors, although none have been identified.

Treatment: There is one FDA approved drug for ALS, riluzole (Rilutek®) that is felt to reduce glutamate release. It has been shown to prolong survival compared to placebo. The prolongation is modest, three to five months.

Management: Symptom management and optimizing independence of function is the primary goal. Symptoms that can be readily treated include sialorrhea, muscle cramps, urinary urgency, and labile affect. Functions that can be supported with equipment include ankle-foot orthoses (AFOs), walkers, raised seats and chairs, wheelchairs, hospital beds and lifts for transfers. Communication can be aided by computers. The role of nutrition is important, and gastric feeding tubes can preserve

weight when dysphagia limits nutritional intake. Non-invasive ventilation can ease nocturnal desaturations and shortness of breath and may prolong survival. Invasive positive pressure ventilation prolongs survival indefinitely, but does not stop progression, but patients on artificial ventilation can become locked in. Patients are best managed in multidisciplinary clinics that include a spectrum of therapists. The caregiver must be considered because of the great demands placed on them as the patient becomes weaker. Hospice has a prominent role toward the latter part of the disease. Patients usually pass away peacefully.

15 November 2006