Amyotrophic Lateral Sclerosis (ALS) — Causes and Symptoms

Actors, musicians, and TV anchors have done it. Even politicians and former US presidents have participated in the social media craze and have dumped a bucket of ice water on their heads: the “ice bucket challenge” went viral in the summer of 2014. But the disease that this campaign was supposed to raise awareness for has been largely unknown to the public. So here you will find an overview of the most important facts about the condition called Amyotrophic Lateral Sclerosis (ALS).

Definition

ALS: a degenerative disease of the central nervous system
Amyotrophic lateral sclerosis (ALS) is a degenerative disease of the central nervous system that leads to a progressive **damage to upper and lower motor neurons**.

The death of affected motor neurons leads to denervation and atrophy of the corresponding muscles, (therefore the term amyotrophy). The loss of motor neurons results in thinning of the corticospinal tracts in the lateral columns of spinal cord and resulting gliosis imparts a particular firmness to the lateral columns (therefore the term lateral sclerosis).

**Reminder:** The motor system is represented on CNS level by the primary motor cortex located in the precentral gyrus (upper motor neurons), which sends efferent nerve fibers through the corticospinal tract to the alpha motor neurons (lower motor neurons) of the anterior horns of the spinal cord.

### Epidemiology

With a global incidence rate of 2-3/100,000, it is a relatively rare disease. The peak of incidence falls in the 5th to 7th decade of life, with **men more often affected** than women.

### Causes of ALS

**Mostly sporadic occurrence of ALS**

Most cases of the disease (90 %) are sporadic. The other 10 % are so-called familial ALS cases (autosomal dominant inheritance), caused by a variety of genetic mutations. An important role can be attributed to mutations of the gene for cytosolic Cu-Zn **superoxide dismutase** (SOD1), which is located on the q arm of chromosome 21 (**SOD1 mutation**). This enzyme is responsible for detoxifying free superoxide radicals.

Other proteins that have been a research focus are the RNA-binding proteins FUS and
TDP-43. Elevated levels of both proteins can be found in the cytosol of affected neurons. Usually the distal extremities are the first to be affected and patient presents with asymmetric weakness.

A toxic overstimulation of the affected neurons (excitotoxicity) by the neurotransmitter glutamate is also being discussed as a potential cause. This theory is corroborated by reports about the mechanism of action of riluzole, the only authorized and demonstrably effective medication for ALS, which supposedly inhibits the release of glutamate from the synapses.

Note: 90% of cases occur sporadically. Only 10% are of genetic origin, with mutations mainly affecting the cytosolic Cu-Zn superoxide dismutase (SOD1), which is responsible for detoxifying free superoxide radicals. Furthermore, glutamate excitotoxicity is being discussed as a potential causative factor of ALS.

Symptoms of ALS

ALS affects muscle functions

The clinical presentation of ALS is characterized by the simultaneous occurrence of symptoms caused by either the upper or lower motor neurons.

Affected patients complain of muscle cramps, muscle weakness of the upper and lower extremities (usually starting at the distal end) and of the trunk, muscle atrophies (usually starting with the small muscles of the hand), and involuntary and sometimes painful muscular contractions (fasciculations). Over the course of the disease, bulbar symptoms such as fasciculations and weakness of the lingual muscles, weakness of mimic muscles, dysphagia with (pseudo)ptyalism, dysarthria, and pathological laughing and crying can occur.

Furthermore, cognitive deficits like frontotemporal dementia have been observed. The life-threatening aspect of the condition is, however, the respiratory insufficiency that develops at a progressed stage of the disease and which involves dyspnea and an increased risk of bronchopulmonary infections.

Note: Damage to the cortical motor neurons (upper motor neurons) leads to spastic paresis, pyramidal signs, and overresponsive reflexes (hyperreflexia). The destruction of alpha motor neurons (lower motor neurons) becomes noticeable as flaccid paralysis, fasciculations, and muscle atrophies.

Diagnosis of ALS

Diagnosis of exclusion for ALS

Diagnosing amyotrophic lateral sclerosis is done by a diagnosis of exclusion. In accordance with the so-called El Escorial criteria postulated by the World Federation of Neurology (WFN) in 1998, a diagnosis is only confirmed when at least 3 body regions (out of bulbar, cervical, thoracic, and lumbosacral motor neurons) show clinical and electrophysiological signs of motor neuron damages (upper and lower motor neurons). However, the practicability of these criteria is controversial since a secure diagnosis is only possible in an already progressed stage of the disease.
Extensive neurological examinations with regard to the above-mentioned findings are essential and so are comprehensive **electrophysiological work-ups:**

- **Electromyogram (EMG):** The muscular denervation caused by the destruction of the lower motor neurons manifests as an increase in spontaneous activity of the affected muscle fibers which translates to fasciculation potentials and positive sharp waves on the EMG.

- **Electromyoneurography (ENG):** A sign of axonal damage, reduced amplitudes of the compound motor action potentials can be found. Initially, the nerve conduction velocity (NCV) is not impaired but it can diminish with the progression of the disease.

In accordance with standard recommendations, further differential diagnosis procedures should include an MRI in order to rule out spinal causes (e.g., myelopathy, radiculopathy) and extensive **laboratory testing:**

- Inflammation marker (ESR, CRP)
- Electrolyte panel, blood glucose
- Differential blood count
- **Liver** function tests (GOT, GPT)
- Thyroid levels (TSH, T3, T4)
- Vitamin B12 (methylmalonic acid, homocysteine)
- Total serum protein test and immunoelectrophoresis-serum test
Within the scope of follow-up care, lung function (vital capacity) and body mass index (BMI) should be assessed. In case of high incidences of ALS within a family, **genetic testing** should determine the presence of the above-mentioned mutations (SOD1, TDP-43, FUS).

**Note:** ALS is a diagnosis of exclusion. Essential examinations include comprehensive neurological testing, electromyogram, electromyoneurography, and genetic testing for cases of familial ALS.

# Treatment of ALS

## Medication and symptom management for ALS

As of yet, no causal treatment for ALS exists. The only first medication that has been proven effective is the glutamate antagonist **riluzole**; several studies have shown that it can prolong survival time. The second drug approved for ALS is Edaravone. Edaverone acts due to its antioxidant action, and is administered via recurring monthly 10-day series of daily intravenous infusions. Beyond this, the management of symptoms is at the center of treatment approaches. This includes:

- Physical therapy and ergotherapy for the strengthening of the muscles; reducing spasms; improving ventilation and maintaining the remaining muscular functions
- Speech therapy for dysphagia and dysarthria. In cases of severe dysphagia, the insertion of a PEG might be considered.
- Treating muscle cramps: magnesium, quinine sulfate, carbamazepine
- Effective pneumonia prophylaxis: mucolytics, tapping massage, a beta blocker (propranolol), ipratropium bromide, possibly antibiotic treatment
- Treatment of respiratory insufficiency: oxygen, non-invasive ventilation, invasive ventilation and tracheostomy (only with the consent of the patient)
- Treatment of hypersalivation: anticholinergic drugs (scopolamine patches, atropine drops), botulinum injection into the parotid gland
- Treatment of dyspnea: morphine, benzodiazepine (lorazepam, midazolam)
- Treatment of depressive symptoms/labile affect: amitriptyline, SSRI
- Pain treatment according to the WHO pain ladder
- Effective thrombosis prophylaxis with low molecular weight heparin
- Provision of aids as needed (Foot drop splints, cough assist device etc.)

**Note:** As of yet (2014), there is no causal treatment for ALS. The only authorized medication riluzole (a glutamate antagonist) has been shown to prolong survival time.

# Prognosis of ALS

ALS is a progressive and fatal disease. **Median survival is 3-4 years from the time of diagnosis.** However, a slower progression with longer survival is possible.

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