

Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease causing a progressive loss of motor neurons. The disease prevalence is 5-9 per 100 000. The revised Airlie House criteria define four categories of certainty in making the diagnosis: clinically definite ALS; clinically probable ALS; probable, laboratory-supported ALS and possible ALS. These criteria are mainly based on the number of regions in the central nervous system (bulbar, cervical, thoracic, lumbosacral) affected by upper motor neuron (UMN) and lower motor neuron (LMN) symptoms. Age at disease onset varies widely, but peak incidence is between 40 and 60 years. In about two-thirds of the patients ALS begins with usually asymmetric limb involvement (muscle weakness and wasting). Bulbar onset (dysarthria and dysphagia) is observed in about one-third of the patients. The disease is relentlessly progressive with increasing disability and handicap and leads generally to death resulting from respiratory failure in approximately 3-5 years. The diagnosis is mainly clinical. Ancillary investigations (electrophysiological, neuroimaging and laboratory studies) are used to exclude other diseases. To date, ALS is an incurable disease, but Riluzole has been proven to increase survival. Symptomatic management include rehabilitation therapy, respiratory assistance, antispasticity agents. The etiology is likely multifactorial, involving both genetic and environmental factors. Motor neuron death is believed to arise from mutations in superoxide dismutase 1 gene (SOD1) on chromosome 21. Abnormal neurofilament metabolism, glutamate transporter dysfunction, mitochondrial dysfunction and altered responses to growth factors may play a role. Familial ALS (FALS) accounts for 5-10% of cases, and mutations in SOD1 are present in 15-20% of families with FALS.

Keywords

Amyotrophic lateral sclerosis, ALS, motor neurone disease, SOD1

Disease name and synonyms

Amyotrophic lateral sclerosis (ALS) is also known as Lou Gehrig's disease, named after a

famous sportsman in the USA who suffered from the disease. As Charcot was the first to describe the clinical picture in detail, this disorder is also known as Charcot's disease.

Diagnostic criteria/Definition

ALS is a neurodegenerative disease causing a progressive loss of motor neurons.

According to the revised *Airlie House criteria* (being a revision of the former El Escorial criteria), the diagnosis of ALS requires:

the presence of:

- evidence of lower motor neuron (LMN) degeneration by clinical or electrophysiological examination;
- evidence of upper motor neuron (UMN) degeneration by clinical examination;
- and progression of the motor symptoms within a region* or to other regions, as determined by history or examination.

the absence of:

non-motor signs and symptoms such as signs of disturbed sensation, autonomic failure, cerebellar or extrapyramidal signs, disturbed vision or impaired eye movements; electrophysiological or neuroimaging evidence of another disease process that might explain the clinical signs.

* There are four regions: bulbar, cervical, thoracic and lumbosacral.

The revised Airlie House criteria allow for four categories of certainty in making the diagnosis, mainly based on the number of regions affected by UMN and LMN symptoms:

clinically definite ALS

- the presence of clinical UMN and LMN signs in at least three different regions.

clinically probable ALS

- the presence of clinical UMN and LMN signs in two or more different regions with at least some UMN signs rostral to the LMN signs.

probable, laboratory-supported ALS

- the presence of clinical UMN and LMN signs in one region with electrophysiological evidence of LMN signs in two or more regions, after exclusion of other causes by neuroimaging studies, electrophysiological and laboratory investigations;
- the presence of clinical UMN signs in one region with electrophysiological evidence of LMN signs in two or more regions, after exclusion of other causes by neuroimaging studies, electrophysiological and laboratory investigations.

possible ALS

- the presence of clinical UMN and LMN signs in only one region, after exclusion of other causes by neuroimaging studies, electrophysiological and laboratory investigations;

- the presence of clinical UMN signs in two or more regions, after exclusion of other causes by neuroimaging studies, electrophysiological and laboratory investigations;
- the presence of clinical LMN signs rostral to UMN signs, with no electrophysiological evidence of LMN signs in other regions, after exclusion of other causes by neuroimaging studies, electrophysiological and laboratory investigations.

Epidemiological features

There are about 1-3 incident cases per 100 000 per year, and ALS has a prevalence of 5-9 per 100 000. 50% survival rate ranges from 36 to 48 months (95% confidence interval [CI]) after onset of symptoms

**Excluded diseases and differential diagnosis
Other motor neurone diseases**

- familial ALS
- familial "ALS-plus" syndromes, a combination of motor neuron disease with extrapyramidal signs and/or cognitive deficit (frontal lobe dysfunction)
- primary lateral sclerosis (PLS), a pure UMN syndrome
- progressive spinal muscular atrophy (PSMA), a pure LMN syndrome
- adult onset hereditary spinal muscular atrophy, a pure LMN syndrome
- focal/segmental spinal muscular atrophy, a pure LMN syndrome
- post-polio syndrome, a pure LMN syndrome

Other neuromuscular diseases

- multifocal motor neuropathy, a pure LMN syndrome with conduction blocks on electrophysiological examination
- myopathies, e.g. inclusion body myositis (muscle biopsy required)
- myasthenic syndromes

Other degenerative diseases

- syringomyelia or syringobulbia (MRI required)
- cervical myelopathy (MRI required)

Infectious diseases

- neuroborreliosis (CSF-examination required)
- HIV infection

Metabolic disorders

- thyroid and parathyroid disorders
- hexosaminidase deficiency (< 35 years of age)
 - Radiation plexopathy or myelopathy
 - Benign fasciculations

Clinical description

Age at disease onset varies widely but peak incidence is between 40 and 60 years.

In about two-thirds of the patients, ALS begins with usually asymmetric limb involvement. Bulbar onset is noted in about one-third of the patients. Bulbar ALS affects relatively more middle-aged women. Onset with weakness of paraspinal muscles at the cervical level gives rise to a dropped head, and at the thoracic level, to a bent spine. Onset with weakness of respiratory muscles is exceptional.

In limb-onset ALS there is often insidious muscle weakness and wasting in one region, for example distal paresis in the leg, making early and accurate diagnosis difficult. ALS can be recognised as such only when symptoms progress and spread to other regions.

In bulbar-onset ALS early symptoms include dysarthria and dysphagia. On neurological examination a combination of LMN signs (e.g. atrophy, fasciculations) and UMN signs (e.g. hyperreflexia, extensor plantar response, pathological crying or laughing) can be found. Cognition is usually unaffected, although there is increasing evidence that ALS patients sometimes show deficits on tests of executive functions and verbal fluency (Abrahams *et al*, 2004).

Usually, the disease is relentlessly progressive with increasing disability and handicap and leads to death in approximately 3-5 years, although there are a few patients (especially younger patients) who have lived with the disease for 10-20 years. Death results from respiratory failure.

Management including treatment

To date, ALS is an incurable disease.

Riluzole (50 mg bidaily) is the only medication with a very modest effect on disease progression. It was proven to increase survival by 3 months.

Rehabilitation physicians usually co-ordinate the care for an ALS patient within a multidisciplinary team, encompassing occupational therapy, physiotherapy, speech therapy, dietician, and psychological support. Main goals in ALS are palliation, timely arrival of assistive devices such as wheelchair or speech computer, and support for the patient and his or her caregivers.

Symptomatic management in ALS may include the use of painkillers, agents against spasticity, against cramps, amitriptyline or radiotherapy of the parotid glands against sialorrhoea. The possibility of a percutaneous endoscopic gastrostomy (PEG) should be discussed in patients with dysphagia, before it leads to severe weight loss or aspiration pneumonia. Safety of a PEG procedure is dependent on vital capacity and should preferably take place before vital capacity falls below 50% of the expected value. However well controlled data on this subject are lacking. . Death usually results from respiratory

failure and pros and cons of non-invasive positive pressure ventilation and invasive ventilation should be discussed at an early stage with the patient and his or her caregiver. Due to the fatal course of the disease, end-of-life issues such as euthanasia and physician-assisted suicide are important subjects of discussion for many patients in advanced disease stages.

Etiology

The etiology is likely multifactorial, involving both genetic and environmental factors.

Motor neuron death is believed to arise from mutations in *superoxide dismutase 1* gene (*SOD1*), mapped to chromosome 21. Abnormal neurofilament metabolism, glutamate transporter dysfunction, mitochondrial dysfunction and altered responses to growth factors may play a role.

The disease is inherited in 5-10% of cases leading to familial ALS (FALS) and mutations in *SOD1* are present in 15-20% of families with FALS. Two additional ALS loci have been identified on chromosome 16q12.1-q12.2 and 20 (Abalkhail *et al*, 2003; Ruddy *et al*, 2003, Sapp *et al*, 2003). A newly identified mutation in the *peripherin* gene (12q12-q13) may cause a small percentage of ALS cases, providing further support to the view that neurofilament disorganisation may be involved in pathogenesis (Gros-Louis *et al*, 2004).

Recently attention was drawn to the role of vascular endothelial growth factor (VEGF) which is essential in angiogenesis and which has also been implicated in neuroprotection (Lambrechts *et al*, 2003). Reduced levels of VEGF predispose mice and humans to ALS. In a mouse ALS model VEGF treatment increased life-expectancy by 30% (Azzouz *et al*, 2004).

Environmental exposures during the Gulf war have been proposed as the explanation for an increased incidence of ALS in Gulf War veterans (Haley 2003, Horner *et al*, 2003).

Diagnostic methods

ALS diagnosis is mainly clinical. Ancillary investigations (electrophysiological, neuroimaging and laboratory studies) are used to exclude other diseases. To diagnose a case of "definite" or "probable" ALS, as defined in the revised Airlie House criteria, physical neurological examination is sufficient. In the diagnosis of "possible" or "probable, laboratory-supported" ALS, laboratory and electrophysiological investigations, and often also MRI scan of the brain and/or spine are needed to exclude alternative diagnoses.

Genetic counseling

FALS is often, but not always, inherited as an autosomal dominant trait. Childhood-onset ALS usually follows an autosomal recessive trait.

Mutations in genes others than *SOD1* have been found but most of these cannot be tested on a routine basis. In other pedigrees, loci have been mapped but the genes have as yet not been identified. The number of FALS cases might be underestimated as family history is not always thoroughly explored, sometimes unknown, and because penetrance is not complete. Most, but not all, pedigrees with FALS show a penetrance of 85% by the age of 85 years. All of the above mentioned factors complicate the process of genetic counseling.

If a mutation in the *SOD1* gene is found, counseling is quite straightforward. In families carrying an unknown mutation but following a clear cut autosomal dominant or recessive inheritance pattern, members can be informed about their chances to develop FALS, but not about the age at onset.

While providing genetic counseling, one should keep in mind that an effective therapy for ALS is still lacking.

Unresolved questions

Despite several hypotheses on etiology, the exact cause of ALS is still unknown. The study of the complex relationship between genomics and phenotype is essential (Veldink *et al*, 2004). There is still no effective therapy available. Stem- cell therapy is worked on but is still at a preclinical stage (Silani *et al*, 2004). Palliative care is only recently addressed and thus is not yet evidence-based. Knowledge on quality of life and end-of life issues is also lagging behind.

References

- Abalkhail** H, Mitchell J, Habgood J, Orrell R, *et al*. A new familial amyotrophic lateral sclerosis locus on chromosome 16q12.1-16q12.2. *Am J Hum Genet*. 2003;73:383-9
- Abrahams** S, Goldstein LH, Simmons A *et al*. Word retrieval in amyotrophic lateral sclerosis: a functional magnetic resonance imaging study. *Brain* 2004;127(pt 7):1507-17
- Andersen** PM, Sims KB, Xin WW, *et al*. Sixteen novel mutations in the Cu/Zn superoxide dismutase gene in amyotrophic lateral sclerosis: a decade of discoveries, defects and disputes. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2003;4:62-73
- Andersen** PM. Genetics of sporadic ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2001;2 (suppl 1):S37-S41
- Azzouz** M, Ralph GS, Storkebaum E, Walmsley LE, *et al*. VEGF delivery with retrogradely transported lentivector prolongs survival in a mouse ALS model. *Nature*. 2004;429:413-7
- Bach** JR. Amyotrophic lateral sclerosis. Prolongation of life by noninvasive respiratory aids. *Chest* 2002;122:92-98
- Bensimon** G, Lacomblez L, Meininger V and the ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Engl J Med* 1994;330:585-91
- Brooks** BR. Natural history of ALS: symptoms, strength, pulmonary function, and disability. *Neurology* 1996;47 (suppl 2):S71-S82
- Carver** AC, Vickrey BG, Bernat JL *et al*. End-of-life care. A survey of US neurologists' attitudes, behavior, and knowledge. *Neurology* 1999;53:284-293
- Eisen** A. Amyotrophic lateral sclerosis is a multifactorial disease. *Muscle Nerve* 1995;18:741-752
- Gros-Louis** F, Lariviere R, Gowing G, Laurent S, Camu W, Bouchard JP, Meininger V, Rouleau GA, Julien JP. A frameshift deletion in peripherin gene associated with amyotrophic lateral sclerosis. *J Biol Chem*. 2004 Aug 17 [Epub ahead of print]
- Haley** RW. Excess incidence of ALS in young Gulf War veterans. *Neurology* 2003;61:750-6
- Horner** RD, Kamins KG, Feussner JR *et al*. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 2003;61:742-9
- Hand** Ck, Rouleau GA. Familial amyotrophic lateral sclerosis. *Muscle Nerve* 2002;25:135-159
<http://www.wfnals.org/>
- Lambrechts** D, Storkebaum E, Morimoto M *et al*. VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death. *Nat Genet* 2003;34:383-94
- Leigh** PN, Ray-Chaudhuri K. Motor neuron disease. *J Neurol Neurosurg Psychiatry* 1994;57:886-96
- Mathus-Vliegen** EMH, Louwense ES, Merkus MP, Tytgat GNJ, de Jong, JMBV. PEG in patients with ALS and impaired pulmonary function. *Gastrointest Endosc* 1994;40:463-469
- Miller** RG *et al*. Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review). *Neurology* 1999;52:1311-1323
- Miller** RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2000;(2) CD001477
- Moss** AH, Casey P, Stocking CB *et al*. Home ventilation for amyotrophic lateral sclerosis: outcomes, costs, and patient, family and physician attitudes. *Neurology* 1993;43:438-443
- Rowland** LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001;344:1688-1700

Ruddy DM, Parton MJ, Al-Chalabi A, Lewis CM et al. Two families with familial amyotrophic lateral sclerosis are linked to a novel locus on chromosome 16q. *Am J Hum Genet.* 2003;73:390-6

Sapp PC, Hosler BA, McKenna-Yasek D, Chin W, et al. Identification of two novel loci for dominantly inherited familial amyotrophic lateral sclerosis. *Am J Hum Genet.* 2003;73:397-403.

Silani V, Cova L, Corbo M et al. Stem-cell therapy for amyotrophic lateral sclerosis. *Lancet* 2004;364:200-2

Stambler N, Charatan M, Cedarbaum JM and the ALS CNTF Treatment Study Group. Prognostic indicators of survival in ALS. *Neurology* 1998;50:66-72

Traynor BJ, Codd MB, Corr B *et al.* Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria. *Arch Neurol* 2000;57:1171-1176

Veldink JH, van den Berg LH, Wokke JH. The future of motor neuron disease: The challenge is in the genes. *J Neurol* 2004;251:491-500

Veldink JH, Wokke JHJ, van der Wal G *et al.* Euthanasia and physician assisted suicide among patients with amyotrophic lateral sclerosis in the Netherlands. *J Engl J Med* 2002;346:1638-1644

Worms PM. The epidemiology of motor neuron diseases: a review of recent studies. *J Neurol Sci* 2001;191:3-9