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El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder involving primarily motor neurons in the cerebral cortex, brainstem and spinal cord. The variability in clinical findings early in the course of ALS and the lack of any biological diagnostic marker make absolute diagnosis difficult and compromise the certainty of diagnosis in clinical practice, therapeutic trials and other research purposes.

The El Escorial criteria[1] for the diagnosis of ALS have been widely accepted, but it was felt that they should be revised in order to increase their sensititvity. The criteria described below represent the result of a three-day workshop, convened at Airlie Conference Center, Warrenton, Virginia on 2–4 April, 1998 by the World Federation of Neurology Research Committee on Motor Neuron Diseases.

This consensus document, reviewed, amended and ultimately accepted by all workshop participants, has been placed on the WFN ALS website (www.wfnals.org) where additional clinicians, researchers involved in ALS research, as well as appropriate scientific review bodies and concerned voluntary organizations, have reviewed it, prior to formal publication.

Requirements for the diagnosis of ALS

The diagnosis of ALS requires:
(A) the **presence** of:

- (A: 1) evidence of **lower motor neuron (LMN) degeneration** by clinical, electrophysiological or neuropathologic examination,
- (A: 2) evidence of **upper motor neuron (UMN) degeneration** by clinical examination, and
- (A: 3) **progressive spread of symptoms or signs** within a region or to other regions, as determined by history or examination,

together with:
(B) the **absence** of

- (B:1) **electrophysiological or pathological evidence of other disease processes** that might explain the signs of LMN and/or UMN degeneration, and
- (B:2) **neuroimaging evidence of other disease processes** that might explain the observed clinical and electrophysiological signs.

Clinical studies in the diagnosis of ALS

A careful history, physical and neurological examination must search for clinical evidence of UMN and LMN signs

in four regions (brainstem, cervical, thoracic, or lumbosacral spinal cord) of the central nervous system (CNS). Ancillary tests should be reasonably applied, as clinically indicated, to exclude other disease processes. These should include electrodiagnostic, neurophysiological, neuroimaging and clinical laboratory studies .

Clinical evidence of LMN and UMN degeneration is required for the diagnosis of ALS

The clinical diagnosis of ALS, without pathological confirmation, may be categorized into various levels of certainty by clinical assessment alone, depending on the presence of UMN and LMN signs together in the same topographical anatomic region in either the brainstem (bulbar cranial motor neurons), or the cervical, thoracic, or lumbosacral spinal cord (anterior horn motor neurons). The terms **Clinically Definite ALS** and **Clinically Probable ALS** are used to describe these categories of clinical diagnostic certainty on clinical criteria alone:

Clinically Definite ALS is defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.

Clinically Probable ALS is defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

The terms **Clinically Probable ALS – Laboratory-supported** and **Clinically Possible ALS** are used to describe these categories of clinical certainty on clinical and criteria or only clinical criteria:

Clinically Probable ALS – Laboratory-supported is defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Clinically Possible ALS is defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS – Laboratory-supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

Clinically Suspected ALS may be suspected in many settings, where the diagnosis of ALS could not be regarded as sufficiently certain to include the patient in a research study. Hence, this category is deleted from the revised El Escorial Criteria for the Diagnosis of ALS.

Clinical types and patterns of ALS

There are a number of ALS and ALS-like syndromes that must be recognized:

1. **Sporadic ALS** – ALS occurring alone or present incidentally with other preexisting disease processes
2. **Genetically-determined (familial, hereditary) ALS** – ALS, present in one or more generations, associated with different modes of inheritance and defined pathogenic mutations such as superoxide dismutase-1 (SOD1) mutations or hexoseaminidase A/B deficiency.

   ALS may occur as a genetically determined disease. In some cases, the pathogenic mutation has been determined, e.g. mutations of the SOD1 gene. When there is a family history of such a defined pathogenic mutation, the diagnosis may be upgraded to **Clinically Definite Familial ALS – Laboratory-supported:** ALS presenting with progressive upper and/or lower motor neuron signs in at least a single region (in the absence of another cause for the abnormal neurological signs).

   However, in genetically determined cases where the gene has not been identified (even if linkage is established), the criteria for the diagnosis of sporadic ALS apply.
3. **ALS-Plus Syndromes** – ALS present in association with clinical features of other neurological diseases which develop in addition to the phenotype of ALS which develop in parallel with the ALS, e.g. extra-pyramidal features or dementia. (Appendix 1)
4. **ALS with Laboratory Abnormalities of Uncertain Significance** – ALS present in association with laboratory-defined abnormalities that are of uncertain significance to the pathogenesis of ALS. (Appendix 2)
5. **ALS-Mimic Syndromes** – These syndromes occur as a consequence of other, non-ALS pathogenic processes, and do not represent other forms of ALS. ALS-Mimic Syndromes include the post-poliomyelitis syndrome, multifocal motor neuropathy with or without conduction block; endocrinopathies, especially hyperparathyroid or hyperthyroid states; lead intoxication; infections; and paraneoplastic syndromes.

Electrophysiological studies in the diagnosis of ALS

Patients in whom the diagnosis of ALS is considered on clinical grounds **should have electrophysiological studies** performed to:

- **confirm LMN dysfunction in clinically affected regions**,
- **detect electrophysiological evidence of LMN dysfunction in clinically uninvolved regions** and
- **exclude other pathophysiological processes**.

These electrophysiological studies should be performed by qualified physicians according to established standards. It is essential to interpret the electrophysiological results in conjunction with the clinical and other ancillary findings. (Appendix 3)

	Brainstem	Cervical	Thoracic	Lumbosacral
Lower motor neuron signs weakness, atrophy, fasciculations	• jaw, face, • palate, • tongue, • larynx	• neck, arm, hand, • diaphragm	• back, • abdomen	• back, abdomen, • leg, foot
Upper motor neuron signs pathologic spread of reflexes, clonus, etc.	• clonic jaw jerk, • gag reflex, • exaggerated snout reflex, • pseudobulbar features, • forced yawning, • pathologic DTRs, • spastic tone	• clonic DTRs, • Hoffmann reflex, • pathologic DTRs, • spastic tone, • preserved reflex in weak wasted limb	• loss of superficial abdominal reflexes, • pathologic DTRs, • spastic tone	• clonic DTRs, • extensor plantar response, • pathologic DTRs, • spastic tone, • preserved reflex in weak, wasted limb

Table 1
Lower motor neuron and upper motor neuron signs in four CNS regions

Neuroimaging studies in the diagnosis of ALS

Neuroimaging studies should be selected in order to **exclude other conditions** which may cause UMN and/or LMN signs that may simulate sporadic ALS. (Appendix 4)

There are no neuroimaging tests which provide positive support for the diagnosis of ALS, although there are neuroimaging methods (e.g. MRI spectroscopy) that may in the future be used to support the diagnosis of UMN involvement. Rarely, brain T_2-weighted MRI may show increased signal in the corticospinal tracts.

Clinical laboratory studies in the diagnosis of ALS

The diagnostic process employed to confirm the diagnosis of sporadic ALS, when the diagnosis is uncertain, includes repeated clinical examinations to document progression, repeated electrophysiological and/or neuroimaging examinations to exclude structural disorders and clinical laboratory examinations to exclude other disorders or support the diagnosis of ALS-Plus Syndromes, ALS-Mimic Syndromes, or ALS with Laboratory Abnormalities of Uncertain Significance. (Appendix 5)

Neuropathological studies in the diagnosis of ALS

The diagnosis of sporadic ALS may be **supported or excluded by muscle and/or biopsy studies** in the living patient.

The diagnosis of sporadic ALS may be **proven or excluded by autopsy** examination. (Appendix 6)

References

1. Subcommittee on Motor Neuron Diseases of World Federation of Neurology Research Group on Neuromuscular Diseases, El Escorial "Clinical Limits of ALS" Workshop Contributors. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci 1994; 124: 96–107.

Glossary

Definite	specific clinical and exclusionary criteria met; no other diagnosis possible on basis of clinical distribution or laboratory findings
Dementia	progressive deterioration of specific cognitive functions
Extrapyramidal	clinical features localizable to basal ganglia and/or midline cerebellum
Hyperreflexia	spread of deep tendon reflex outside stimulated territory
Minor	subjective and objective complaints confirmed by examination (utilization of instrumental sensory testing may increase the detection of sensory abnormalities)
Onset	time of first subjective symptom noticed by patient which later is confirmed by examination
Possible	specific clinical and exclusionary criteria met
Probable	specific clinical and exclusionary criteria met
Radicular	distribution conforming to particular nerve root
Region	brainstem, cervical, thoracic or lumbosacral spinal cord levels (regional involvement is defined by either right or left sided signs)
Required	necessary or sufficient
Segment	single brainstem or spinal cord level
Spread	involvement of new anatomic segments or regions in the central nervous system
Support	neither necessary nor sufficient, but may suggest
Systemic	non-central nervous system
Weakness	decreased isometric strength
Worsening	increased weakness of muscles in previously affected segment

APPENDIX 1: ALS-Plus and ALS-Mimic Syndromes

ALS-Plus Syndromes and ALS-Mimic Syndromes must meet the clinical, electrophysiological and neuroimaging criteria for Clinically Possible, Clinically Probable or Clinically Definite ALS. The predominant presentation in ALS-Plus Syndromes and ALS-Mimic Syndromes is that seen in sporadic ALS, but includes one or more features such as:

1. Geographic clustering (including disorders seen in the Western Pacific, Guam, Kii Peninsula, North Africa, Madras, etc).
2. Extrapyramidal signs (bradykinesia; cogwheel rigidity; tremor; familial or sporadic).
3. Cerebellar degeneration (spinocerebellar abnormalities; familial or sporadic).
4. Dementia (familial or sporadic; frontal lobe type; Creutzfeldt-Jacob amyotrophic form).
5. Autonomic nervous system involvement (clinically significant abnormal cardiovascular reflexes; bowel or bladder control problems; familial or sporadic).
6. Objective sensory abnormalities (decreased vibration; sharp/dull discrimination; blunting of cold sensation; familial or sporadic).
7. Ocular movement abnormalities (supranuclear; nuclear; familial or sporadic).
8. ALS mimics (delayed post-poliomyelitis; multifocal motor neuropathy with or without conduction block; endocrinopathies; lead intoxication; infections).

APPENDIX 2: ALS with Laboratory Abnormalities of Uncertain Significance (ALS-LAUS) Syndromes

ALS with Laboratory Abnormalities of Uncertain Significance (ALS-LAUS) must meet the clinical, electrophysiological and neuroimaging criteria for Clinically Probable or Clinically Definite ALS. ALS-LAUS have laboratory-defined features which may be relevant to the development of the ALS phenotype. In some patients correction of the associated abnormality may result in alteration of the disease course. Such patients need special consideration in the context of research studies.

ALS-LAUS includes patients with Clinically Definite or Clinically Probable ALS associated with:

1. Monoclonal gammopathy (monoclonal gammopathy of unknown significance, Waldenstrom's macroglobulinemia, osteosclerotic myeloma, etc).
2. Autoantibodies (high-titer GMI ganglioside antibody; etc).
3. Nonmalignant endocrine abnormalities (hyperthyroidism, hyperparathyroidism, hypogonadism, etc).
4. Lymphoma (Hodgkin's and non-Hodgkin's lymphoma). Cases of sporadic ALS associated with cancer of the lung, colon or thyroid and insulinoma, are currently thought not to be causally related to the neoplasm.
5. Infection (HIV-1, HTLV-1, varicella-zoster, brucellosis, borrelliosis, cat-scratch disease, syphilis etc).
6. Exogenous toxins (e.g. lead, mercury, aluminum).

APPENDIX 3: Employing electrophysiological studies in the diagnosis of ALS

ALS may be most reliably identified when the clinical and electrophysiological changes involve a sufficient number of regions so that other possible causes of similar EMG abnormalities are highly unlikely. The electrodiagnostic (EMG / NCV) examination is thus an extension of the clinical examination used to identify LMN dysfunction.

Electrophysiological features of LMN dysfunction

Conventional EMG studies

The features of LMN dysfunction in a particular muscle are defined by electromyographic concentric needle examination to provide evidence of active and chronic denervation including fibrillations and fasciculations. Nerve conduction studies are also required to exclude motor neuropathy.

Signs of **active denervation** consist of:

1. **fibrillation potentials**
2. **positive sharp waves**

Signs of **chronic denervation** consist of:

1. **large motor unit potentials** of increased duration with an increased proportion of polyphasic potentials, often of increased amplitude
2. **reduced interference pattern with firing rates higher than 10 Hz** unless there is a significant UMN component, in which case the firing rate may be lower than 10 Hz
3. **unstable motor unit potentials**.

The combination of active denervation findings and chronic denervation findings is required but the relative proportion may vary from muscle to muscle.

Fasciculation potentials

Fasciculation potentials are a characteristic clinical feature of ALS. Their presence in EMG recordings is helpful in the diagnosis of ALS, particularly if they are of long duration and polyphasic, and when they are present in muscles in which there is evidence of active or chronic partial denervation and reinnervation. Their distribution can vary. Their absence raises diagnostic doubts, but does not preclude the diagnosis of ALS. Fasciculation potentials of normal morphology occur in normal subjects (benign fasciculations), and fasciculation potentials of abnormal morphology occur in other denervation disorders, e.g. motor neuropathies.

Quantitative EMG studies

In addition to conventional EMG examination, signs of chronic partial denervation can also be demonstrated with other techniques, including

1. single fiber EMG,
2. macro EMG,
3. turns/amplitude analysis and decomposition EMG,
4. quantitative motor unit potential analysis
5. motor unit number estimates (MUNE).

Topography of active and chronic denervation and reinnervation

The EMG signs of LMN dysfunction required to support a diagnosis of ALS should be found in at least two of the four CNS regions: brainstem (bulbar / cranial motor neurons), cervical, thoracic, or lumbosacral spinal cord (anterior horn motor neurons).

- For the **brainstem** region it is sufficient to demonstrate the EMG changes in **one muscle** (e.g. tongue, facial muscles, jaw muscles])
- For the **thoracic spinal cord** region it is sufficient to demonstrate the EMG changes either in the **paraspinal muscles** at or below the T6 level or in the **abdominal muscles**.
- For the **cervical and lumbosacral spinal cord** regions, **at least two muscles** innervated by different roots and peripheral nerves must show EMG changes.

Nerve conduction studies

Nerve conduction studies are required for the diagnosis principally to define and exclude other disorders of peripheral nerve, neuromuscular junction and muscle that may mimic or confound the diagnosis of ALS. These studies should generally be normal or near normal.

- The motor conduction times should be normal unless the compound muscle potential is small.
- The sensory nerve conduction studies can be abnormal in the presence of entrapment syndromes and coexisting peripheral nerve disease.
- Lower extremity sensory nerve responses can be difficult to elicit in the elderly.

Electrophysiological features compatible with UMN involvement include:

1. Up to 30% increase in central motor conduction time determined by cortical magnetic stimulation
2. Low firing rates of motor unit potentials on maximal effort.

Electrophysiological features suggesting other disease processes include:

1. Evidence of motor conduction block.
2. Motor conduction velocities lower than 70%, and distal motor latencies over 30%, of the lower and upper limit of normal values, respectively.
3. Sensory nerve conduction studies that are abnormal. Entrapment syndromes, peripheral neuropathies and advanced age may render sensory nerve action potentials difficult to elicit in the lower extremities.
4. F-wave or H-wave latencies more than 30% above established normal values.
5. Decrements greater than 20% on repetitive stimulation.
6. Somatosensory evoked response latency greater than 20% above established normal values.

7. Full interference pattern in a clinically weak muscle.
8. Significant abnormalities in autonomic function or electronystagmography.

APPENDIX 4: Employing neuroimaging studies in the diagnosis of ALS

In patients with Clinically Definite ALS with bulbar or pseudobulbar involvement, neuroimaging studies are not essential. In all other patients, appropriate neuroimaging studies should be performed to rule out structural lesions that may explain the observed signs and symptoms. Neuroimaging features that cast doubt on the diagnosis of ALS or may be confounding factors in interpretation of diagnostic or clinical trial results include the following:

1. significant bony abnormalities on plain X-rays of skull or spinal canal that might explain clinical findings.
2. significant abnormalities of head or spinal cord MRI suggesting intra- or extra-parenchymal processes. However, abnormalities confined to the corticospinal tract are consistent with ALS.
3. significant abnormalities of spinal cord myelography with/without CT or CT alone suggesting lesions as noted above.
4. significant abnormalities on spinal cord angiography suggesting vascular malformations.

APPENDIX 5: Employing clinical laboratory studies in the diagnosis of ALS

The demonstration of the presence of a pathogenetically relevant gene mutation can assist in the diagnosis of ALS (such as SOD1). There are no clinical laboratory tests which confirm the diagnosis of non-genetically determined ALS. Clinical laboratory tests that may be abnormal in otherwise typical ALS:

- Muscle enzymes (serum creatine kinase (unusual above ten times upper limit of normal), ALT, AST, LDH)
- Hypochloremia, increased bicarbonate (related to advanced respiratory compromise)
- Serum creatinine (related to loss of skeletal muscle mass)
- Elevated CSF protein (unusual above 100 mg/dl)

Clinical laboratory tests that may be abnormal in ALS with Laboratory Abnormalities of Uncertain Significance (ALS-LAUS) and ALS-Mimic Syndromes:

- Autoantibodies (including antineuronal)
- Hormonal abnormalities
- Bone marrow / lymph node biopsy (lymphoma may be associated with CSF protein >1g/dl)
- Evidence of infection
- Blood and urine lead/mercury levels
- Hexoseaminidase A/B

Clinical laboratory features inconsistent with the diagnosis of ALS:

There is no clinical laboratory finding which, if present with the proper clinical and electrophysiological signs of ALS and appropriate neuroimaging studies, rules out the diagnosis of ALS.

APPENDIX 6: Employing neuropathology studies in the diagnosis of ALS

Pathological studies in the living patient with sporadic ALS

Indications for biopsy

Biopsies of the skeletal muscle, peripheral nerve and other tissues are not required for the diagnosis of ALS, unless the clinical, electrophysiological or laboratory studies have revealed changes that are atypical for ALS (e.g. inclusion body myositis). In addition, the muscle biopsy may be used to demonstrate LMN involvement in a body region that had not been shown to be involved by other techniques.

Muscle biopsy

Features required for the diagnosis:

1. Evidence of chronic denervation/reinnervation in an affected muscle.

Features that are compatible with, and do not exclude, the diagnosis:

1. Scattered hypertrophied muscle fibers.
2. No more than a moderate number of target or target-oid fibers.
3. Fiber type grouping of no more than mild-to-moderate extent.
4. The presence of a small number of necrotic muscle fibers.

Features that rule out the diagnosis or suggest the presence of additional disease:

1. Significant monoclonal gammopathy, infiltration with lymphocytes and other mononuclear inflammatory cells.
2. Significant arteritis.
3. Significant numbers of muscle fibers involved with the following structural changes: necrosis; rimmed vacuoles; nemaline bodies; central cores; accumulation of mitochondria (ragged red fibers).
4. Large fiber type grouping.
5. Giant axonal swellings from accumulation of masses of neurofilaments, but not of PAS positive bodies, in intramuscular nerves.

Pathological studies at autopsy other than in cases surviving for prolonged periods on life support systems

Gross pathological changes

Features required for the diagnosis:

There are no positive diagnostic features on gross pathological examination.

Features that rule out the diagnosis of ALS or suggest the presence of additional disease:

1. Plaques of multiple sclerosis.
2. A focal cause of myelopathy.

Light microscopic studies

Features required for the diagnosis:

1. Some degree of loss of both of the following neuronal systems: large motor neurons of the anterior horns of the spinal cord and motor nuclei of the brainstem (V motor, VII motor, IX and X somatic motor, and XII); and large pyramidal neurons of the motor cortex and/or large myelinated axons of the corticospinal tracts.
2. The following cellular pathological changes in the involved neuronal regions described above: neuronal atrophy with relative increase in lipofuscin and loss of Nissl substance. There should be evidence of different stages of the process of neuronal degeneration, including the presence of normal-appearing neurons, even in the same region.
3. Evidence of degeneration of the corticospinal tracts at the same level.

Features that strongly support the diagnosis:

1. Lack of pathological change in the motor neurons of cranial nerves III, IV and VI, the intermediolateral column of the spinal cord, and Onuf's nucleus.
2. The occurrence of one or more of the following cellular pathological changes in the involved neuronal systems described above:

- Ubiquinated intracytoplasmic inclusions in the motor neurons (skeins, Lewy body-like structures)
- Bunina bodies
- Aggregates of neurofilaments in perikarya of the motor neurons (hyaline conglomerate inclusions)
- Axonal spheroids with accumulation of masses of neurofilaments, Wallerian-like degeneration in the anterior roots.

Features that are compatible with, and do not exclude, the diagnosis:

Variable involvement of Clarke's nucleus and the spinocerebellar tracts; posterior root ganglia, the posterior columns of the spinal cord and peripheral sensory nerves; the brainstem reticular neurons and the anterolateral columns of the spinal cord; the thalamus; subthalamic nucleus; and the substantia nigra.

Features that rule out the diagnosis or suggest the presence of additional disease:

Major pathological involvement of other parts of the nervous system, including: cerebral cortex other than the motor cortex; basal ganglia; substantia nigra; cerebellum; cranial nerves II and VIII; dorsal root ganglia.

The following cellular pathological changes in the involved neuronal systems described above:

- Extensive central chromatolysis;
- Extensive active neuronophagia;
- Neurofibrillary tangles;
- The presence of abnormal storage material;
- The presence of significant spongiform change;
- The presence of perivascular inflammatory cell infiltration.

Electron microscopic studies

Features required for the diagnosis:

Ultrastructural studies are not required for the diagnosis of ALS.