# DIAGNOSTIC CRITERIA OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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**ABSTRACT**

The revised El Escorial Criteria (EEC) are the gold standard of ALS diagnosis.They are very specific although insensitive and not suitable for early diagnosis. Therefore the Awaji Criteria have been developed which put more emphasis on EMG findings than the EEC, especially on fasciculation potentials. The Awaji Criteria regard fasciculation potentials as sign of active denervation in an otherwise typical clinical context of ALS. Recent publications confirm that the Awaji Criteria have a higher sensitivity than the EEC in the diagnosis of ALS without increasing the rate of false positive diagnoses.

**Key words:** amyotrophic Lateral Sclerosis, El Escorial Criteria, Awaji Criteria

## INTRODUCTION

Amyotrophic lateral sclerosis is a fast progressing motor neuron disease with a medium survival of 3 to 5 years after first symptoms. The onset of the disease is insidious and symptoms may be disregarded by the patient for several weeks or months. The first physicians consulted are usually general practitioners, orthopedic surgeons or rheumatologists and only rarely neurologists. Even in countries with well developed health care system it takes a year on the average before the diagnosis is made (Dengler 1999). The knowledge of ALS among lay people as well as health care professionals is poor in most European countries while in the United States ALS is widely known as Lou Gehrig´s disease. Up to now the diagnosis ALS is still a clinical one and EMG is the most important technical test to support the diagnosis. Laboratory tests and imaging including MRI do not yield diagnostically positive results, but are necessary to exclude other potentially better treatable diseases. This article summarizes the diagnostic criteria as they are currently used internationally. It is not the aim of this article to provide a comprehensive clinical description of the disease, of its treatment or of the newest research results. It will mainly focus on the clinical and on the clinical-neurophysiological criteria of the disease.

Gold standard of the ALS diagnosis are the El Escorial Criteria as revised in 1998 (Brooks et al. 2000). These criteria are mainly based on clinical findings although they appreciate results of electrophysiological studies. The El Escorial Criteria (EEC) are, however, fairly rigid and allow a diagnosis only relatively late in advanced stages of the disease. This has been critisized particularly by experts active in treatment trials of ALS as it appears reasonable to include patients in earlier stages of the disease when the EEC do not yet allow a diagnosis. For this reason, several experts in the field of ALS and of electromyography suggested a new set of diagnostic criteria (de Carvalho et al. 2008), the so-called Awaji-criteria, which are based on the El Escorial criteria, but modify some of their statements to EMG findings and therefore increase the diagnostic sensitivity.

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## SOME CLINICAL PRINCIPLES OF ALS

ALS is characterized by degeneration of the cortical motor neurons and their axons (upper motor neuron) and of the motor neurons in the cranial nerve nuclei and in the spinal cord (lower motor neuron) with the exception of the oculomotor and the sphincter muscles. There have been numerous debates on whether the upper or the lower motor neuron is first affected by the disease process (Dengler 2010).

Upper motor neuron signs are preserved or exaggerated tendon reflexes in the presence of muscle atrophy and weakness. The muscle tone may be increased corresponding to spasticity more in the lower than the upper extremities. In about 30 % of the cases a Babinski sign may be observed. Signs of corticobulbar involvement are increased masseter reflexes, pathological laughing, crying and yawning which are also called pseudobulbar affect. Many patients, however, do not show signs of the upper motor neuron in early stages of the disease.

Signs of the lower motor neuron are muscle atrophy, weakness and fasciculations. In early stages of the disease, patients frequently speak of clumsiness and not so often of weakness.

The onset of ALS is usually focal and asymmetrical, in somewhat more than 30% of the cases in the upper extremities, in about one third in the lower extremities and in about 25% in the bulbar region. A special phenotype is the so called Flail-Arm-syndrome with an onset of muscle weakness in the proximal upper extremities while the legs may be spared for a long time. The Flail-Leg-syndrome with onset of the symptoms in the proximal lower extremities is observed less frequently. These two phenotypes are characterized by an overall better prognosis, i.e. longer survival.

Another special phenotype is progressive bulbar palsy. A distinction between pseudobulbar and bulbar involvement may be difficult and the leading clinical signs are dysarthria and dysphonia in conjunction with dysphagia, atrophy and fasciculations of the tongue and sialorrhea. These patients frequently also show a pseudobulbar affect. The survival is shorter than that of patients with disease onset in the extremities.

Signs of an involvement of the autonomic nerve system such as reduced perfusion of the extremities, decrease of the heart frequency variability or changes detected in the electrocardiogram can be observed. Sensory disturbances and pain are not typical for ALS although they have been described. Relevant sensory deficits raise doubts concerning the diagnosis. Respiratory insufficiency develops in the late stages of the disease and is a hallmark of the terminal phase. Loss of body weight frequently occurs early in the disease and may be caused by muscle wasting, dysphagia and by hypermetabolism.

Very recently, an association between ALS and frontotemporal dementia has been increasingly discussed (Morita et al. 2006). While many patients show mild frontal signs, about 25% may develop manifest frontotemporal dementia. Depression may develop during the course of the disease and may, at least, in some patients, become a relevant clinical aspect.

It is not clear whether Primary Lateral Sclerosis (PLS), a disease with selective upper motor neuron signs, is a variant of ALS or a distinct disease. A considerable portion of these patients, however, develop signs of the lower motor neuron over years. Progressive muscular atrophy (PMA) is characterized by pure lower motor neuron signs and is otherwise resembling ALS. It has been suggested to regard PMA as a variant of ALS (Kim et al. 2009).

## THE EL ESCORIAL CRITERIA INITIATED BY THE WFN

In order to standardize the diagnosis of ALS the El Escorial Criteria (EEC) have been developed in 1994 following the older Airlie-House-Criteria. The EEC have been revised in 1998 (Brooks et al. 2000). The EEC are mainly clinical and form the gold standard of ALS diagnosis. They are, however, relatively rigid and are not suitable for early diagnosis. They are important for scientific classification and so far for recruitment into clinical trials, but not for clinical praxis. According to the EEC, the diagnosis of ALS requires the presence of A-criteria and the absence of B-criteria:

**A-criteria:**

A1: Degeneration of the lower motor neuron approved by clinical, electrophysiological or neuropathological examination.

A2: Degeneration of the upper motor neuron approved by clinical examination.

A3: Progressive dissemination beyond typical nerve supply areas.

**B-criteria:**

B1: Electrophysiological or neuropathological findings typical for other diseases which could explain the degeneration of the upper and lower motor neuron.

B2: Findings in imaging studies which can explain the clinical symptoms.

The diagnosis ALS requires an extensive historyand a thorough clinical and electrophysiological examination. The electrophysiological tests can demonstrate the involvement of the lower motor neuron in affected and frequently also in clinically not affected body regions. The EEC define four body regions to be evaluated:

- brain stem (bulbar),
- cervical (neck and upper extremities),
- thoracal (trunk, abdominal wall)
- lumbosacral (lumbar spine and lower extremities).

The classification according to the revised EEC distinguishes between:

### Clinically definite ALS

Proof of both, lower and upper motor neuron signs in at least 3 body regions.

### Clinically probable ALS

Proof of both, lower and upper motor neuron signs in at least 2 body regions. The upper motor neuron signs have to be demonstrated rostrally to the region of the lower motor neuron signs.

### Clinically probable – laboratory supported ALS

Clinical signs of the lower and the upper motor neuron in 1 body region only. Additionally there are electromyographic signs of active and chronic degeneration in at least 2 extremities.

### Possible ALS

Signs of lower and upper motor neuron in 1 body region only or upper motor neuron signs in 2 or more body regions.

The old version of the EEC additionally contained the category "clinically suspected ALS" which has been deleted in the revised version.

### Electrophysiology in the revised EEC

The revised EEC appreciate electromyographic and electroneurographic findings in the appendix 3 "employing Electrophysiological Studies in the Diagnosis of ALS". The EEC state that EMG/NCV examination is an extension of the clinical examination used to identify LMN dysfunction which can be defined by electromyographic concentric needle examination to provide evidence of active and chronic denervation. Signs of active denervation consist of fibrillation potentials and positive sharp waves while fasciculation potentials are not mentioned in this context.

Signs of chronic denervation consist of large motor unit potentials of increased duration with an increased proportion of polyphasic potentials often of increased amplitude (see Fig. 1), 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 and unstable motor unit potentials (see Fig. 2). The EEC also state that the combination of active

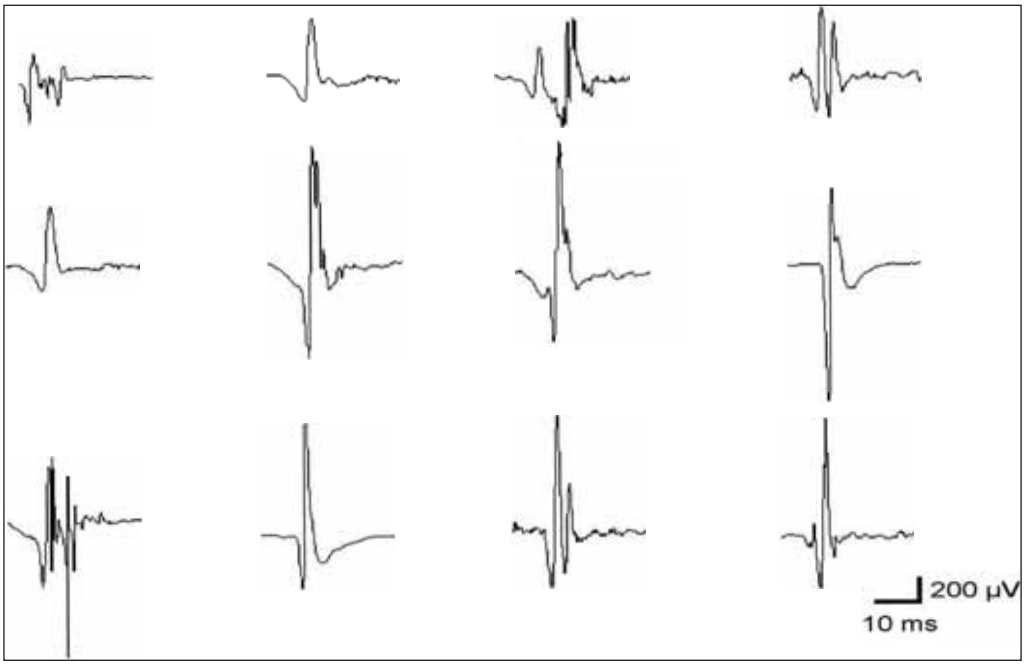


***FIGURE 1.*** *Motor Unit Action Potentials obtained from the biceps muscle of a patient with early ALS at slight innervation. Amplitudes are frequently higher than 1 mV and the configuration is frequently polyphasic.*

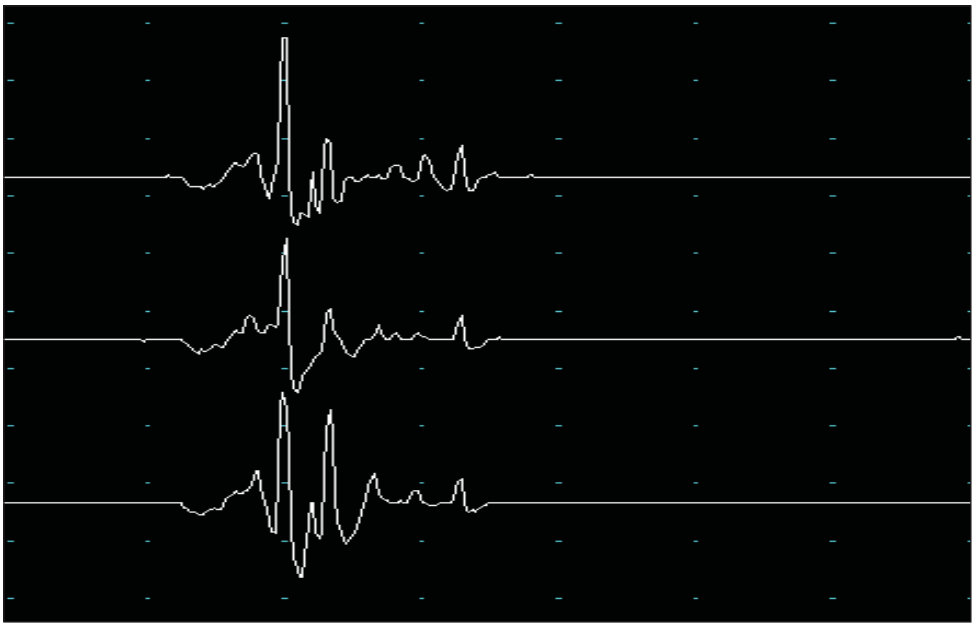

***FIGURE 2**. Unstable MUAP in the tibialis anterior muscle of a patient with ALS.The configuration of the potential changes from discharge to discharge. Concentric needle electrode; filter setting 1 kHz to 10 kHz; calibration: 5 ms / Div. and 100 uV / Div.*

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

Fasciculation potentials are mentioned in the revised EEC as a characteristical clinical feature of ALS, but are not used for clinical or electromyographical diagnosis. Their presence in EMG is considered helpful in the diagnosis of ALS, especially if they reveal a neurogenic configuration (long duration and polyphasicity) (see Fig. 3) and when they are present in muscles in which there is evidence of active or chronic partial denervation and reinnervation.

### Nerve Conduction Studies

The EEC point out that nerve conduction studies are required in the diagnosis of ALS to exclude motor neuropathy or other disorders of peripheral nerve, neuromuscular junction and muscle that may

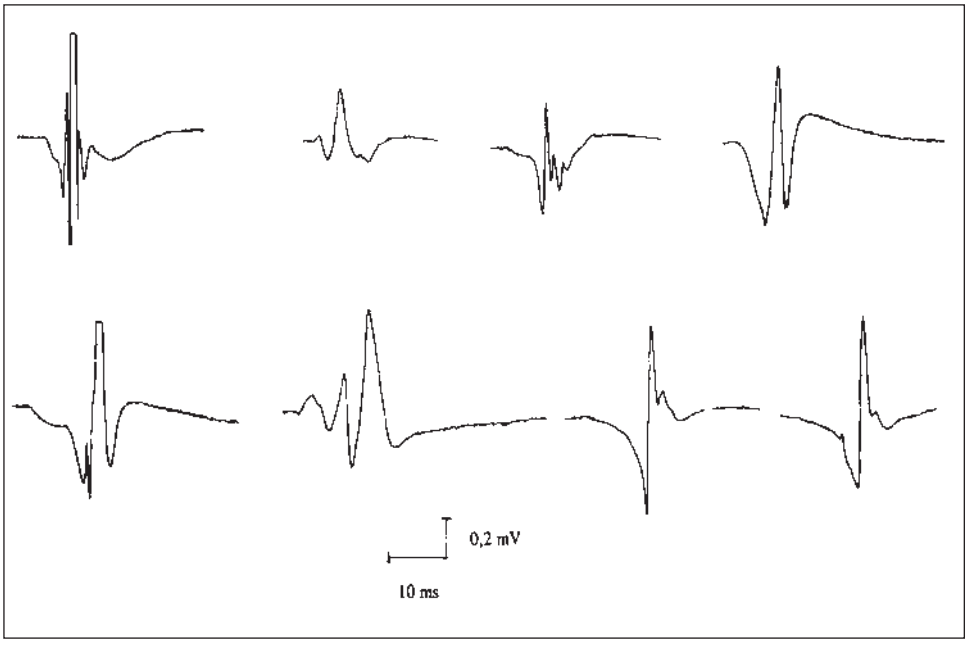


***FIGURE 3.** Fasciculation potentials in the vastus lateralis muscle of a patient with ALS. Note the neurogenic configuration of most of these potentials !*

mimic or confound the diagnosis of ALS. In this context it is worth to mention that an especially difficult differential diagnosis can be multifocal motor neuropathy with conduction blocks (MMN) (see Fig. 4). The EEC state that motor conduction times should be normal unless the compound muscle potential is small. Sensory nerve conduction studies should be normal although they can be changed in the presence of entrapment syndromes and coexisting other peripheral nerve disease. In addition, lower extremity sensory nerve responses can be abnormal in the elderly.

### New EMG-Criteria for the diagnosis of ALS. The Awaji Criteria initiated by the IFCN.

As described above the revised EEC appreciate the role of EMG and NCS in the diagnosis of ALS. Many ALS/ EMG experts, however, were not satisfied with the EEC as they are very specific on one side, but too rigid and insensitive on the other side to make an early diagnosis. Patient can die from motor neuron disease without ever reaching the diagnostic level of probable or definite ALS according to the EEC. In addition, the EEC do not fully use the diagnostic potential of EMG, in particular, they do not use the presence of fasciculation potentials diagnostically. Therefore, a group of ALS/ EMG experts critisized the EEC and initiated a conference to discuss the role of EMG in ALS diagnosis with support by the IFCN. Their conclusions have been published (de Carvalho et al. 2008) and have become known as "Awaji Criteria".

### Statements of the Awaji Criteria

First of all, the general statements of the EEC were adopted. The clinical and electromyographical anomalies required by the EEC were confirmed. Signs of denervation in EMG, however, were regarded as equivalent to clinical signs of the lower motor neuron and it was suggested to delete the category „laboratory supported probable ALS" and to use only the category „probable ALS".

The essential difference between the EEC and the Awaji Criteria is that the latter regard fasciculation potentials in muscles with chronic neurogenic EMG-changes in a clinical context fitting with ALS as sign of „active denervation" even in the absence of fibrillation potentials and positive waves. This improves the sensitivity of EMG studies considerably without increasing the rate of false positive diagnoses as has recently been demonstrated (Boekestein et al. 2010; de Carvalho and Swash 209; Chen et al. 2010 ). ALS experts know very well that one frequently finds muscles in typical

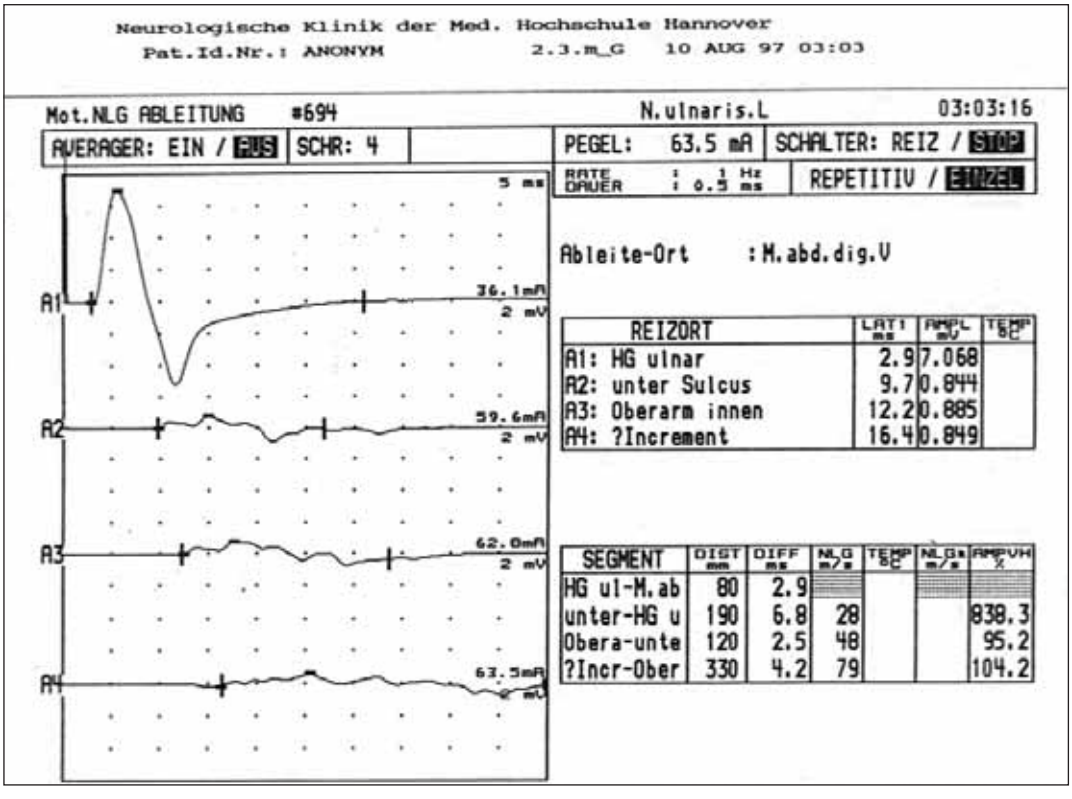


***FIGURE 4.*** *Conduction study of the left ulnar nerve in a patient with multifocal motor neuropathy (MMN). There is a partial conduction block between the elbow and the wrist with a decrease of the motor response by more than 50 % and with signs of chronodispersion.*

ALS which do not show fibrillation potentials and positive waves, but fasciculation potentials and chronic neurogenic changes (Dengler 2008).

### Upper motor neuron signs in the Awaji Criteria, the role of TMS

There was a long discussion among the experts on the diagnostic role of transcranial magnetic stimulation (TMS) in ALS. Finally, it was concluded that TMS may be helpful and that changes of central motor conduction times to arm or leg muscles or side to side differences in the size of motor evoked potentials (MEP) may point to upper motor neuron involvement. There was, however, considerable uncertainty as to the specificity and sensitivity of TMS and it was regarded not possible to make a clear statement to the relevance of TMS in the diagnosis of ALS at the moment. The new Triple

***TABLE 1.*** *Obligatory and facultative ancillary tests in the diagnosis of ALS as suggested in the European Guidelines (Andersen et al. 2007)*

| **Tests** | | **obligatory** | | **facultative** |
|---|---|---|---|---|
| **Blood** | | | | |
| BSR | | X | | |
| CrP | X | | | |
| cell count | X | | | |
| GOT/GPT/LDH | X | | | |
| TSH, FT3, FT4 | X | | | |
| Vit B12, Folate | X | | | |
| Elphor | | X | | |
| Immunology | | X | | |
| CK | X | | | |
| Creatinine | X | | | |
| Electrolytes | | X | | |
| Glucose | | X | | |
| ACE | | | | X |
| Lactate | | | | X |
| Hexosaminidase A und B | | | X | |
| Gangliosid GM-1-AB | | | | X |
| antineuronal AB | | | X | |
| RF, ANA, anti-DNA | | | X | |
| Anti-AChR, Anti-MUSK | | | X | |
| Bakteriology (Borreliosis etc.) | | | X | |
| Virology (HIV etc.) | | | | X |
| DNA-Tests (SOD-1; Kennedy S.) | | | X | |
| **Urin** | | | X | |
| **CSF** | | | X | |
| **Clinical Neurophysiology:** | | | | |
| EMG | | X | | |
| NCS | | X | | |
| MEP | | | | X |
| **Imaging depending on the site of onset of symptoms** | | | | |
| MRI: head, neck, thoracal, lumbar | X | | | |
| Thorax X rays | | X | | |
| **Biopsies:** | | | | |
| muscle | | | | X |
| nerve | | | | X |
| bone marrow | | | | X |
| lymph nodes | | | | X |

Stimulation Technique (TST) (Rösler et al. 2000; Kommisarov et al. 2004, Krampfl et al. 2004) was considered very sensitive in detecting upper motor neuron lesions although the experience available with the use of this method in ALS was regarded too limited. Similarly, MRI is clearly necessary in the diagnosis of ALS to exclude other potentially treatable disorders, but is currently too insensitive to detect early signs of upper motor neuron involvement in individuals with ALS at a significant rate.

### The European guidelines initiated by the EFNS

A frequent question in the context of ALS diagnosis is which laboratory tests are obligatory and which are facultative. A very useful summary of the ancillary tests for ALS diagnosis is provided by the European Guidelines initiated by the EFNS and published in 2005 (Anderson et al. 2007) (see Table 1). A revision of these guidelines is in preparation.

## CONCLUSION

Since the revised EEC are relatively rigid and insensitive in the diagnosis of ALS the new Awaji Criteria have been developed. In essence, they consider fasciculation potentials as sign of active denervation in an otherwise typical clinical context of ALS. Recent publications confirm that the Awaji Criteria have a higher sensitivity than the EEC in the diagnosis of ALS without increasing the rate of false positive diagnoses.

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