Electrodiagnosis of Motor Neuron Disease

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KEYWORDS
• Motor neuron disease • Amyotrophic lateral sclerosis • Awaji criteria
• Electrodiagnosis

KEY POINTS
• ALS, a relentlessly progressive disorder of upper and lower motor neurons and the most common form of motor neuron disease, is examined here as a model for the electrodiagnosis of all motor neuron disease.
• Electrodiagnostic testing in ALS should be guided by the clinical manifestations noted on physical examination.
• The most sensitive and specific criteria for the diagnosis of ALS are the principles of the revised El Escorial criteria combined with the Awaji modifications to the diagnostic categories of the revised El Escorial criteria.
• Nerve conduction study and needle electromyography remain the most important diagnostic testing for ALS. The former is used primarily to help rule out other disorders, and the latter to establish evidence for widespread active denervation and chronic reinnervation.

CLINICAL FEATURES OF AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of upper motor neurons (UMN) and lower motor neurons (LMN). It has a worldwide incidence of approximately 1.5 per 100,000, with a male/female ratio of approximately 1.5.1 Although occasional patients present before the age of 25, the incidence increases after age 40 and does not clearly decline in the elderly population.2 Approximately 10% of cases are familial and include autosomal recessive, X-linked, and...
autosomal-dominant patterns, with autosomal-dominant being most common. The first causative mutation reported was a point mutation in the gene that encodes SOD1; since this discovery in 1993, more than 75 other mutations have been described. Most recently, a hexanucleotide repeat expansion of the chromosome 9 open reading frame 72 (C9orf72) gene has been described, and is likely to be the most common mutation in familial cases with or without frontotemporal dementia. A total of 90% of cases of ALS remain sporadic or idiopathic.

The only clear risk factor is increasing age, but this is too nonspecific to be clinically useful. Sporadic ALS has been linked to cigarette smoking, military service, agricultural or factory work, and periods of heavy muscle use, but a definite causal relationship with any one factor has not been established. Multiple genetic risk factors have been identified in sporadic ALS, including duplication of the survival motor neuron 1 gene and trinucleotide repeat expansion of the ataxin 2 gene. Hexanucleotide repeat expansions of the C9orf72 gene are not only associated with familial ALS, but may be found in approximately 5% to 7% of apparently sporadic cases.

The cause of sporadic ALS is unknown, and many of the multiple genetic defects that cause ALS do so in a manner that is still obscure. The finding that mutations in SOD1 cause ALS has raised the question of the role of oxidative stress in ALS, because SOD1 is a ubiquitous free radical scavenger in neural and nonneural tissue. However, it is clear that SOD1 mutations cause disease as a result of a toxic gain of function, rather than reduction of activity of the SOD1 protein. Mitochondrial dysfunction has been noted early in genetic models, and likely plays a role in the disease pathway. Excitotoxicity by excessive activation of glutamate receptors has been shown in a variety of models, caused at least in part by reduction in glutamate uptake in areas of the brain damaged by ALS. This leads to increased intracellular calcium, which triggers damage to mitochondria and nucleic acids, and ultimately neuronal death. Protein misaggregation has been noted pathologically, and several recently discovered causative mutations in the genes for fused in sarcoma (FUS), TAR DNA binding protein-43 (TDP-43), and potentially C9orf72 result in abnormal protein being deposited in the cytoplasm of motor neurons. Because these genes have a major role in RNA trafficking, impairment of this function has been suggested as a potential cause of ALS.

Riluzole (Rilutek), which reduces glutamate-induced excitotoxicity, is the only drug that has been shown to affect the course of ALS. Death usually occurs through respiratory muscle insufficiency or complications from dysphagia, with a median survival from time of diagnosis of 3 to 5 years. Approximately 10% of patients with ALS may live beyond 10 years, but the relentlessly progressive nature of this disease, the significant morbidity, and impact on family and society is common to all.

The clinical presentation of ALS is varied, given the number of body segments and predominance of UMN versus LMN symptoms and signs that are possible. We speak of ALS affecting four body segments, referring to motor neurons involved in a cranio-bulbar, cervical, thoracic, or lumbosacral distribution. A fundamental quality of ALS is the presence of UMN and LMN findings that spread without remission to ultimately involve multiple body segments, often in a predictable pattern. UMN findings include muscle spasticity, defined as increased tone in the muscle that renders it resistant to stretch and causes stiff and slow movement with little weakness, and heightened deep tendon reflexes. An interesting feature of UMN dysfunction is pseudobulbar affect. This manifests with sudden outbursts of involuntary laughter or crying that is often excessive or incongruent to mood, caused by loss of voluntary cortical inhibition to brainstem centers that produce the facial and respiratory functions associated with those behaviors, through bilateral corticobulbar lesions, or through interruption of corticocerebellar control of affective displays.
Clinical features resulting from loss of LMNs are flaccid weakness, muscle atrophy, hyporeflexia, muscle cramps, and fasciculations, which may be visible as brief twitching under the skin or in the tongue. LMN loss in axial muscles may result in abdominal protuberance or impaired ability to hold the body or head upright against gravity. LMN loss to the diaphragm results in dyspnea or orthopnea that usually disturbs sleep. Flaccid weakness affecting bulbar muscles may present as slurred, nasal, or hoarse speech; dysphagia; or drooling. The initial clinical presentation of ALS may start in any body segment, and may manifest as UMN, LMN, or both, with a pattern of spread from one body segment to others that is often predictable. In time, UMN and LMN findings develop in the same body segment, if they did not start concurrently. Asymmetric limb weakness, often distal with hand weakness or foot drop, is the initial presentation in 80% of patients, with bulbar symptoms, such as dysarthria or dysphagia, in most of the rest.

Extraocular motor neurons are spared until very late in the disease. Autonomic symptoms are not typical, but multifactorial constipation and urinary urgency from a spastic bladder may occur late in the course. Sensory symptoms, such as distal limb paresthesias, may occur in 20% of patients, but usually with a normal clinical sensation examination. Cognitive symptoms in the form of frontotemporal dementia or dysfunction may be present in anywhere from 15% to 50% of patients. This may manifest as subtle impairment of language, judgment, or personality. Mutations involving certain genes, including TDP-43, FUS, and C9orf72, are associated with a higher likelihood of cognitive impairment.

**ELECTRODIAGNOSIS**

ALS is a clinical diagnosis, but is supported by electrophysiologic study, which can either help to rule out other possible diagnoses or show characteristic abnormalities in body areas not yet clinically affected. The electrophysiologic studies that are in common practice, such as needle electromyography (EMG) and nerve conduction studies (NCS), directly identify LMN pathology, and at best may suggest UMN pathology by the observation of decreased activation on EMG. How do needle EMG and nerve conduction testing, together referred to as electrodiagnostic testing (EDX), support the diagnosis of ALS? EDX primarily helps rule out other causes of similar symptoms (Table 1) and uncovers subclinical LMN loss, which can speed time to diagnosis and increase diagnostic sensitivity.

Review of the diagnostic criteria for ALS illustrates the importance of uncovering subclinical LMN loss with EDX, particularly with EMG. The El Escorial World Federation of Neurology criteria, first proposed in 1994 and revised in 2000 (Tables 2 and 3), is still in effect, with two key modifications proposed in December 2006 during a consensus conference in Awaji-shima, Japan, sponsored by the International Federation of Clinical Neurophysiology.

Using EMG to uncover subclinical LMN dysfunction in the form of active denervation with compensatory chronic reinnervation in the same muscle can change the diagnosis of ALS from “Clinically Possible ALS” to “Laboratory Supported Clinically Probable ALS.” A limitation of the revised El Escorial criteria is that it is not sufficient to demonstrate LMN dysfunction by EMG alone in a limb, but that the category of “Laboratory Supported Clinically Probable ALS” requires a demonstration of LMN by physical examination in one limb. Another limitation is that the revised El Escorial criteria restricts EMG evidence of acute denervation to fibrillations or positive sharp waves, which may not be as demonstrable in bulbar muscles and those muscles of normal bulk and strength. These limitations have contributed to the fact that 22% of patients...
die from ALS without being assigned a level of certainty about the disease higher than the "Clinically Possible ALS" category.31

To increase the sensitivity for detection of a probable or definite diagnosis of ALS, the Awaji criteria were recently proposed (Table 4). Using these criteria, EMG findings of LMN dysfunction, specifically active denervation with chronic reinnervation in a muscle, are assigned equal diagnostic significance to the findings of LMN dysfunction on physical examination. This eliminates the need for the category of “Laboratory Supported Clinically Probable ALS” and is based on the observation that EMG is an extension of the physical examination in detecting features of denervation and reinnervation.

Although no change was suggested to the general principles of the revised El Escorial criteria (see Table 2), the Awaji criteria stipulates that the diagnostic categories of ALS should be defined by clinical or electrophysiologic evidence of LMN dysfunction, and UMN dysfunction, in specified numbers of body segments. Specifically, this means that in using the Awaji criteria, individual muscles that show active and chronic denervation with reinnervation electrophysiologically may be used to help diagnose

### Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Presentation</th>
<th>Distinguishing Features</th>
<th>Role of Electrodiagnostic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical radiculomyelopathy</td>
<td>LMN dysfunction at the level of stenosis with UMN findings below</td>
<td>Neck pain and radicular sensory symptoms in arms</td>
<td>No EMG findings in bulbar or thoracic paraspinal muscles</td>
</tr>
<tr>
<td>Concomitant cervical and lumbar stenosis</td>
<td>Like cervical radiculomyelopathy, but with LMN findings also in lumbosacral myotomes</td>
<td>Neck and back pain, radicular sensory symptoms in the arms and legs</td>
<td>No EMG findings in bulbar or thoracic paraspinal muscles</td>
</tr>
<tr>
<td>Benign fasciculation syndrome</td>
<td>Frequent fasciculations, diffuse or focal; cramps</td>
<td>Normal neurologic examination</td>
<td>No EMG findings other than fasciculation potentials</td>
</tr>
<tr>
<td>Multifocal motor neuropathy with conduction block</td>
<td>LMN limb weakness, often upper extremities</td>
<td>Not myotomal, often in patients younger than 45 yr old</td>
<td>Conduction block in motor nerve NCS nonentrapment sites</td>
</tr>
<tr>
<td>Inflammatory myopathies</td>
<td>LMN limb weakness, dysphagia</td>
<td>IBM: finger flexor, quadriceps weakness Polymyositis or dermatomyositis: proximal muscle weakness</td>
<td>Fibrillation potentials/ positive sharp waves; small amplitude and short duration motor unit potentials and occasionally neuropathic MUPs (IBM only) with normal or early recruitment</td>
</tr>
</tbody>
</table>

Abbreviations: IBM, inclusion body myositis; MUPs, motor unit potentials.
ALS in conjunction with the clinical examination, obviating the need to demonstrate needle EMG changes in an entire limb. One other change from revised El Escorial criteria is that using Awaji criteria, in the presence of chronic neurogenic findings on EMG in a patient with a clinical history suggestive of ALS, fasciculation potentials are equivalent to fibrillation potentials and positive sharp waves in denoting acute denervation, especially if the fasciculation potentials have unstable or complex morphology. Studies evaluating the utility of the Awaji modifications compared with the revised El Escorial criteria for the diagnosis of ALS suggest improved sensitivity from 28% to 61% with no change in specificity, which remains at 96%.32–35

Electrodiagnosis of ALS begins with the recognition of a clinically suggestive history and examination. The role of NCS is to help rule out other causes of similar symptoms, as required by the general principles outlined in the revised El Escorial criteria for the diagnosis of ALS and endorsed by the Awaji consensus group (see Table 2). The role

<table>
<thead>
<tr>
<th>Category of ALS</th>
<th>UMN Findings</th>
<th>LMN Findings</th>
<th>Additional Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically definite</td>
<td>3</td>
<td>+ 3</td>
<td></td>
</tr>
<tr>
<td>Clinically probable</td>
<td>2</td>
<td>+ 2</td>
<td>Some UMN signs rostral to the LMN signs</td>
</tr>
<tr>
<td>Clinically probable Laboratory supported</td>
<td>1</td>
<td>+ 1</td>
<td>OR 0</td>
</tr>
<tr>
<td>Clinically possible</td>
<td>1</td>
<td>+ 1</td>
<td>OR 0</td>
</tr>
<tr>
<td>Definite familial Laboratory supported</td>
<td>1</td>
<td>+ 1</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Body segments are craniobulbar, cervical, thoracic, and lumbosacral.
of needle EMG is to establish concomitant acute denervation and compensatory chronic reinnervation in specific body segments, according to the specifications set out by the Awaji modifications to the revised El Escorial criteria (see Table 4). The following is a summary of features of NCS and EMG that are most relevant to ALS.

NERVE CONDUCTION STUDIES

Because the fundamental pathology in the disease is motor neuron loss resulting in retrograde axonal degeneration followed by reinnervation, features that are not seen on NCS in ALS include the following:

- Evidence of demyelination or conduction block on motor nerve conduction. Evidence for demyelination suggests pathology at the level of the myelinated axon rather than the motor neuron. Demyelination is characterized by prolonged distal latencies or slowing of conduction velocity, with the caveat that loss of larger and faster motor axons may cause a mild prolongation of distal latency (but not more than 130% the upper limit of normal) or mild slowing of conduction velocity (but not less than 75% the lower limit of normal). Conduction block of motor nerves in areas not associated with entrapment, with sparing of sensory nerves, suggests multifocal motor neuropathy with conduction block, an immune-mediated demyelinating neuropathy that is responsive to intravenous

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**Table 4**  
Awaji modifications to the diagnostic categories of the revised El Escorial criteria

<table>
<thead>
<tr>
<th>Category of ALS</th>
<th>UMN Findings</th>
<th>LMN Findings</th>
<th>Additional Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body Segments&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Body Segments&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>on Physical Examination</td>
<td>on Physical Examination</td>
<td>And/or Electrophysiologic Testing&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clinically definite</td>
<td>3</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>Clinically probable</td>
<td>2</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Clinically possible</td>
<td>1</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>Definite familial</td>
<td>1</td>
<td>+</td>
<td>+ Documented</td>
</tr>
<tr>
<td>Laboratory supported</td>
<td>1</td>
<td>+</td>
<td>genetic mutation</td>
</tr>
</tbody>
</table>

<sup>a</sup> Body segments are craniobulbar, cervical, thoracic, and lumbosacral.

<sup>b</sup> Electrophysiologic examination:

- Evidence of acute denervation in the form of fibrillation potentials and positive sharp waves
- Evidence of chronic reinnervation in the form of voluntary motor unit potentials of increased amplitude, increased duration, or polyphasia, that may exhibit decreased recruitment (if there is concomitant UMN dysfunction, a decreased recruitment pattern may not be clear)
- Evidence of chronic reinnervation as above, with evidence of acute denervation in the form of fasciculation potentials, preferably of complex morphology, or instability when studied with a high band pass filter and trigger delay line, which suggests their origin from reinnervated motor units.

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immunoglobulin. Conduction block, as distinguished from normal temporal dispersion, is defined as a drop in the compound muscle action potential (CMAP) area of greater than 50% between proximal and distal stimulation sites.

- Abnormalities of sensory nerve conduction. Sensory nerves are not typically affected in ALS. Sensory nerve conduction abnormalities in a patient with motor neuron disease suggests a diagnosis of X-linked bulbospinal muscular atrophy, also known as Kennedy disease. Kennedy disease is a slowly progressive form of spinal muscular atrophy, found in men in their third to fifth decade with LMN degeneration in proximal limb and bulbar muscles. Unlike other motor neuron diseases, Kennedy disease is associated with low amplitude or absent sensory nerve action potentials (SNAPs) caused by degeneration of dorsal root ganglia. SNAP abnormalities should also prompt consideration of other diagnoses, including plexopathies and peripheral and multiple entrapment neuropathies. It is also possible for a patient with ALS to have an unrelated peripheral neuropathy or entrapment neuropathy.

Features on NCS that are consistent with the diagnosis of ALS include the following:

- Normal or reduced CMAP amplitudes. Reduced CMAP amplitude reflects axonal loss, but does not distinguish between lesions at the motor neuron, nerve root, plexus, or peripheral nerve. Loss of larger, faster motor neurons may cause prolongation of distal latency up to but not beyond 130% of the upper limit of normal, or decrease in conduction velocity but not less than 75% of the lower limit of normal.

- Normal SNAP amplitudes. Although expected in ALS, this may be seen in cervical or lumbar radiculopathies, and because these lesions are proximal to the dorsal root ganglia.

- Normal F wave latencies. F waves, representing antidromic stimulation of 1% to 5% of the motor neurons in the anterior horn of the spinal cord, are often normal early in the course of ALS. As the disease progresses and motor neurons are lost from the anterior horn, F response abnormalities begin to be seen. Impersistence, defined by less than 50% of F waves obtained per number of stimulations, and repetition of similar F wave morphologies from stimulation of the same motor units, reflect the decreased pool of motor units overall from motor neuron loss. If the largest and fastest motor units are lost, F wave latency may be slightly prolonged. F wave abnormalities are actually more likely to occur in radiculopathy rather than motor neuron disease, but cannot be used reliably to distinguish between the two.

**RECOMMENDATION FOR NCS**

At a minimum, NCS of a patient with suspected ALS should include testing of at least one motor nerve with F wave study and one sensory nerve in an upper and lower extremity on the most symptomatic side. If suspicion is high for multifocal motor neuropathy with conduction block, multiple upper and lower extremity nerves should be studied, with stimulation as proximal as is feasible.

**NEEDLE EMG**

The hallmark of ALS on needle EMG is chronic and active loss of LMNs innervating muscles with multiple nerve root innervation and spread within an initial body segment and to other body segments. Although NCS is used primarily to help rule out other causes of the same clinical symptoms, such as neuropathy and radiculopathy, needle
EMG is primarily used to establish evidence of ongoing denervation and chronic compensatory reinnervation. EDX is particularly helpful in uncovering subclinical evidence of this process, so needle EMG should not be limited to the testing of muscles or body segments where LMN dysfunction is clinically apparent.

Evidence for acute denervation in ALS on needle EMG includes the following:

- **Fibrillations and positive sharp waves.** In ALS, these waveforms reflect the spontaneous depolarization of a denervated muscle fiber at rest. Although they are pathologic, they are also seen in other denervating conditions, such as radiculopathy and axonal neuropathies, and myopathies in which muscle necrosis occurs, such as polymyositis.

- **Fasciculation potentials.** These potentials reflect the spontaneous and involuntary discharge of a single motor unit, and as such may arise from the motor neuron or its axon, and are considered the hallmark of ALS. However, they may be a benign finding in normal muscles, in the setting of a serially normal neurologic examination and no other findings suggestive of acute or chronic denervation on EMG, as in the case of benign fasciculation syndrome (see Table 1). Unfortunately, there is no definitive way to distinguish between pathologic and benign fasciculation potentials. However, pathologic fasciculation potentials usually have a more regular activation frequency and a morphology of motor unit potentials (MUPs) characterized by increased amplitude, polyphasia, and duration. Pathologic fasciculation potentials are also commonly complex or unstable, with peaks appearing or disappearing with sustained observation. Yoked discharges appearing more than 10 milliseconds after the initial discharge are also suspicious for a pathologic process. As such, these complex and unstable fasciculation potentials are given equal weight as a sign of denervation as fibrillations and positive sharp waves when seen in the context of chronic neurogenic changes on EMG, in the Awaji modified criteria for the diagnosis of ALS (see Table 4).

Evidence for chronic denervation in ALS on needle EMG includes the following morphologic changes of MUPs:

- **Increased duration.** Increased duration results from the reinnervation process of collateral axonal sprouting, because duration reflects the number of muscle fibers within the motor unit, which increases as motor units with intact axons reinnervate adjacent muscle fibers from a denervated motor unit.

- **Increased polyphasicity.** MUPs are commonly polyphasic in ALS, although in very slowly progressive disease, polyphasic motor units may be rare. Polyphasis is defined by greater than four phases in a MUP and may occur normally up to 10% of the MUPs in any given muscle, and up to 25% in the deltoid. Polyphasis beyond this normal range is a sign of dyssynchrony of the muscle fibers firing within the motor unit, reflecting the process of reinnervation through collateral sprouting from adjacent normal axons after denervation within a motor unit.

- **Increased amplitude.** Amplitude increases in a chronically reinnervated muscle because of an expansion of the territory of the motor unit. Depending on the rate of progression of the disease process, abnormally small MUPS can also be seen, which reflect the inability of individual axons to support the normal number of nerve sprouts. This is often a reflection of a diseased axon just before death of the associated neuron.

- **Decreased recruitment.** Decreased recruitment of motor units reflects the loss of MUPs and manifests as increased firing of an inappropriately low number of
MUPs when the muscle is called on to generate a greater force of contraction. With motor neuron dropout, a common observation is that a reduced number of rapidly firing motor units is noted when subjects exert maximum or near maximum strength. This is a subjective finding, but often a sensitive and early indicator of neurogenic change. Decreased recruitment of motor units is often an early and sensitive indicator of LMN abnormality.

- **MUP instability.** This is often reflective of rapid loss of motor units and is not always seen. It may reflect more aggressive disease. MUP instability is noted subjectively when a voluntarily activated unit changes with respect to number of peaks or amplitude of individual peaks from potential to potential. This can be characterized more objectively by measuring jitter and blocking of MUPs with a trigger delay line. MUP instability, while common, is not specific to the diagnosis of ALS.38

**RECOMMENDATIONS FOR NEEDLE EMG TESTING**

At a minimum, needle EMG study of a patient with suspected ALS should include testing of at least three limbs, sampling muscles innervated by at least two different nerve roots, and peripheral nerves and proximal and distal muscles. Additionally, testing should be performed on at least one bulbar muscle, such as a facial muscle, the masseter muscle, or tongue. Finally, needle EMG should be done on at least two thoracic paraspinal muscles.

**OTHER ELECTRODIAGNOSTIC TOOLS**

Motor unit number estimation (MUNE), a sensitive technique for identifying lower motor unit loss, particularly before the onset of clinical weakness, is not yet widely performed and is used primarily in the research setting. MUNE can be used as marker for disease progression in ALS, because it can be linked to important outcomes, such as survival.39–41 A recently described standardized technique for multipoint incremental MUNE generates highly reproducible data, and can be rapidly performed on basic EDX equipment with minimal discomfort to the patient through use of low stimulus intensities.42 When studied as percent change from baseline, this measurement of decline in ALS compares favorably with the more commonly used Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

Transcranial magnetic stimulation (TMS) physiologically evaluates UMN function. A brief magnetic pulse is directed to the motor cortex, which induces an electric current that is capable of exciting corticomotor neurons or interneurons. The activation of these cells creates a motor volley recordable in the extremities as a motor evoked potential. Central motor conduction time is derived by subtracting peripheral conduction time from the total response latency. Prolongation may reflect loss of corticospinal axons.43,44 Peripheral conduction time can be estimated using F waves, or directly measured by stimulating ventral roots at their origin using a magnetic stimulator. Similar studies can be performed using routine electrical stimulation, but needle-stimulating electrodes must be used to approach the ventral root and this procedure is usually perceived as uncomfortable by patients. Another parameter of TMS that is associated with ALS is shortening of the cortical silent period recorded from muscle during voluntary contraction.45,46 The cortical silent period duration is evoked by asking a subject to tonically contract the muscle from which recordings are being made. Stimulation of motor cortex induces a period of suppression of the tonic contraction known as the cortical silent period. This is a function of cortical inhibitory interneurons activated during voluntary contraction. Reduced cortical inhibition has
also been reported in ALS, measured by pairing two magnetic stimuli at varying latencies and looking at inhibition of the second response by the first as a function of time between the two stimuli.\textsuperscript{47–49}

TMS can be used to measure short interval intracortical inhibition (SICI) and shows a reduction in inhibition in ALS, suggesting cortical hyperexcitability from ion channel dysfunction. SICI is the increase in TMS stimulus required to generate a constant motor evoked potential, when a conditioning stimulus representing a selected percentage of the resting motor threshold is first applied. Reduction in SICI across a variety of subthreshold stimuli correlates with reductions in resting motor threshold and increase in motor evoked potential/CMAP ratio, suggesting that the decreased net central inhibition that results in cortical hyperexcitability is mediated through reduced inhibitory cortical interneurons and excessive intracortical excitation.\textsuperscript{50,51}

Threshold tracking techniques are applicable to the study of LMNs in ALS.\textsuperscript{52} A criterion response from a mixed nerve is selected, such as percentage of the maximal motor response. Then the stimulus intensity required to maintain that criterion response is measured while varying stimuli duration (strength-duration relationship) or before or after administering a hyperpolarizing or depolarizing conditioning stimulus below the threshold for activation (latent addition if the conditioning stimulus is brief, and threshold electrotonus if it is prolonged). The differences in axonal membrane excitability observed with threshold tracking reflect nodal and internodal processes across ion channels. Prolonged strength-duration time constants and latent addition reflect persistent sodium channel conductance, whereas threshold electrotonus provides information on internodal processes, such as reduction of fast potassium conduction.\textsuperscript{53,54} LMN hyperexcitability may be appreciated with threshold tracking techniques before clinical manifestations of spontaneous axonal activity, such as fasciculation potentials, are seen. At present time, threshold tracking is primarily a research tool to investigate the basic mechanisms of hyperexcitability in ALS, and thus target therapies. It is not specific enough to contribute to diagnosis, and has not been studied in relation to rate of progression, but prolonged strength-duration time constant and latent addition have been linked to decreased survival in ALS.\textsuperscript{55}

SUMMARY

ALS is a disease diagnosed primarily on clinical grounds, because specific imaging abnormalities or other biomarkers have not been clearly identified. Clinical neurophysiology, as an extension of the neurologic examination, has proved useful in helping to establish a diagnosis, by eliminating possible disease mimics and providing evidence of abnormalities in body areas that may yet be clinically unaffected. Electrodiagnosis begins with an understanding of the clinical features of the disease, because clinical correlation is important to an accurate interpretation of the electrophysiologic findings. To improve the sensitivity of the electrophysiologic evaluation, the Awaji criteria has been proposed as a modification to the revised El Escorial criteria, which is currently accepted as the gold standard for the diagnosis of ALS. The Awaji criteria incorporate needle EMG findings of ongoing denervation and reinnervation in LMNs in a fashion similar to that of the El Escorial criteria but assigns increased importance to the presence of fasciculation potentials. NCS are primarily used to help rule out other diseases that could mimic ALS, such as multifocal motor neuropathy. Although techniques have been developed to evaluate abnormalities of corticomotor neurons and to quantify loss of LMNs, they remain primarily research tools and have not yet influenced clinical practice.
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