ABSTRACT: The clinical electrodiagnostic medicine (EDX) consultant asked to assess patients with suspected amyotrophic lateral sclerosis (ALS) has a number of responsibilities. Among the most important is to provide a clinical assessment in conjunction with the EDX study. The seriousness of the diagnoses and their enormous personal and economic impact require a high-quality EDX study based on a thorough knowledge of and experience with motor neuron diseases (MNDs) and related disorders. Clinical evaluation will help determine which of the EDX tools available to the EDX consultant should be applied in individual patients. Although electromyography (EMG) and nerve conduction study are the most valuable, each of the following may be helpful in the assessment of selected patients based on their clinical findings: repetitive nerve stimulation, motor unit number estimate, single-fiber EMG, somatosensory evoked potential, autonomic function test, and polysomnography. The pertinent literature on these is reviewed in this monograph. The selection and application of these EDX tools depend on a thorough knowledge of the MNDs and related disorders.

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ELECTRODIAGNOSTIC STUDIES IN AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISORDERS

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Following is an overview of motor neuron diseases (MNDs). This overview will introduce the MNDs, but only an in-depth study of the disorders and pertinent literature will enable an electrodiagnostic medicine (EDX) consultant to provide a full range of help. Most MNDs are diffuse system degenerations of unknown etiology that selectively destroy upper and/or lower motor neurons.99,112 Although many are diffuse, sporadic, and progressive, a small proportion is hereditary11,126 or focal.61 Amyotrophic lateral sclerosis (ALS) is the most common MND in adults; spinal muscular atrophy (SMA) is the most common in children.57,69 The underlying molecular genetic defect has been identified in one form of hereditary ALS with an abnormal form of the enzyme superoxide dismutase.5 The locus of the abnormal gene has been determined in childhood SMA and in Kennedy’s syndrome (bulbospinal neuronopathy).63,64,107 The World Federation of Neurology (El Escorial) criteria classify other MNDs into mimic, coexisting, and variant disorders.36 “Motor neuron disease mimic disorders” are disorders in which the motor neurons are secondarily involved, such as spondylotic myelopathy, spinal cord arteriovenous malformation, exposure to exogenous toxins, lymphoma, other cancers, monoclonal and dysimmune gammopathies, vasculitis, motor polyradiculopathy, multifocal motor neuropathy (MMN) with conduction block, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), hyperthyroid and hypothyroid states, Creuzfeldt–Jakob disease, and acute infections.3,8,56,73,82,110,119 Acute viral infections that involve the motor neurons are polio, herpes zoster, and some coxsackie viruses.58,98 Other hereditary degenerations, such as Friedreich’s ataxia and multisystem atrophy (Shy–Drager syndrome) can also have motor neuron involvement. Anterior horn cells (AHCs) can be damaged in association with other syndromes.
with neoplasms, radiation, asthma, and hypoglycemia.24,81,121,139 “Motor neuron disease coexisting disorders” occur in patients who have a pre-existing neurologic disease superimposed on ALS, such as diabetic neuropathy or ulnar neuropathy. “Motor neuron disease variant disorders” occur in patients with ALS in whom the autonomic, sensory, or another component of the nervous system is involved along with the motor system. Electrodiagnostic medicine testing is particularly important for identifying and distinguishing the coexisting diseases and some of the mimic disorders (Table 1).

With the identification of underlying mechanisms of the MND, options for therapy have become available. Some have already been shown to have small benefits, but many others are being investigated. The ability of EDX studies to quantify the lower motor neuron damage makes these studies an integral part of clinical therapeutic trials.

A number of disorders may resemble a MND, especially those with focal cord involvement such as syringomyelia, tumors of the spinal cord, spinal cord arteriovenous malformations, infarction, or congenital dysplasias of the spinal cord. The most common cause of localized cord damage that can mimic MND is bony spine disease, such as cervical and lumbar spondylosis, which impinges on the spinal cord or nerve roots. The EDX consultant must attempt to differentiate these problems from MND. This can be quite difficult because both spondylotic myelopathy and MND may be focal at onset and remain asymmetrical.

With the exception of “variant” disorders, MNDs do not show clinical involvement of the sensory or other components of the nervous system. Some forms of MND selectively affect the upper motor neurons as in primary lateral sclerosis; some selectively affect the lower motor neurons, as in progressive SMA; others, such as Kennedy’s syndrome, have specific distributions. The most common disorder, ALS, involves both upper and lower motor neurons.

Table 1. Disorders sometimes mistaken for ALS that must be considered during electrodiagnostic evaluation.

<table>
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<tr>
<td>Cervical spondylosis</td>
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<td>Motor polyradiculopathy</td>
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<td>Multifocal motor conduction block</td>
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<td>Peripheral neuropathy</td>
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Involvement of upper motor neurons results in weakness without atrophy. Reflexes are hyperactive, and pathologic reflexes are present. Spasticity is common; with involvement at different levels, there may be spastic dysarthria with pseudobulbar palsy, or spastic gait. Damage to upper motor neurons is manifest on needle electromyography (EMG) only as abnormalities of motor unit discharge patterns.

In contrast, lower motor neuron damage in ALS produces both clinical and electrophysiological abnormalities. Degeneration of AHCs and their peripheral axons results in loss of muscle innervation. Denervated muscle becomes weak, flaccid, and atrophic, the typical signs of lower MND. The nerve terminals of remaining intact motor units retain their capacity for collateral sprouting and will reinnervate the denervated muscle fibers. Weakness and atrophy do not occur as long as the reinnervation can keep pace with the loss of AHCs. Up to one half of the motor neurons innervating a muscle may be lost in ALS before clinical signs of weakness or atrophy are found.27 As more motor neurons progressively die, compensation fails and weakness develops. After poliomyelitis, as another example of the capability of collateral sprouting, a few motor neurons that sprout to reinnervate denervated muscles can maintain normal strength when 90% of the neurons have been lost. The regenerating axons are irritable and often discharge spontaneously, resulting in fasciculations, especially after exercise.

**AMYOTROPHIC LATERAL SCLEROSIS**

**Clinical.** The major determinant of ALS is progressive loss of motor neurons. The loss of motor neurons usually begins in one area, is asymmetrical, and later becomes evident in other areas. The first signs of ALS may be either upper or lower motor neuron loss. Recognition of upper motor neuron involvement depends on clinical signs; the electrophysiological changes that occur with upper motor neuron damage are neither specific nor sensitive enough to provide help.

In contrast, EDX testing is of major help in identifying lower motor neuron involvement; lower motor neuron abnormalities are typically evident on electrodiagnostic testing before they are clinically recognizable. Needle EMG and nerve conduction studies (NCSs) can assist in both identifying the presence of and documenting the progression of the loss of lower motor neurons that occurs in ALS, thus minimizing the common occurrence of early misdiagnosis.10,16 However, the variations in the findings among patients with ALS require better definition of the criteria for diagnosis.9
The World Federation of Neurology has classified ALS into definite (upper motor neuron and lower neuron signs at three levels); probable (upper motor neuron and lower motor neuron signs at two levels), possible (upper and lower motor neuron signs at one level or upper motor neuron signs at two levels), and suspect (lower motor signs at two levels or upper motor neuron signs at one level). Although these criteria are appropriate for clinical diagnostic purposes, they have been modified to allow earlier entry of patients into clinical trials, by requiring lower motor neuron findings in only two limbs. The "levels" for the classification are bulbar, cervical, thoracic, and lumbosacral. The electrophysiological changes that occur with ALS at each of these levels result in abnormal motor unit potentials (MUPs) and abnormal spontaneous electrical activity. The MUP changes that occur in ALS include impaired MUP recruitment, unstable MUPs, and abnormal MUP size and configuration. A number of abnormal spontaneous discharges can occur with ALS, especially fibrillation potentials and fasciculation potentials.

**Needle Electromyography.** The increase in muscle force that occurs with increased effort results from a combination of the number of MUPs that are activated, and the rate of activation of individual MUP. Motor unit potential recruitment is the orderly activation of more motor units as the effort and firing rate of individual units increases (Fig. 1). The primary EMG finding in ALS is the abnormal MUP recruitment that results from the loss of AHCs. The orderly pattern of MUP recruitment is preserved in ALS, but the number of MUPs recruited with increasing effort is reduced. Recruitment frequency, one measure of recruitment, is the rate of discharge of one MUP when an additional MUP begins to discharge. In ALS, the recruitment frequency is increased because fewer AHCs are available to be activated as effort increases. When recruitment is reduced from a loss of AHCs, the number of MUPs firing at any given firing rate is reduced. The relationship between the number of active MUPs and their firing rate is the major EDX measure in the assessment of MNDs. Quantitative measurements of MUP recruitment in ALS, although difficult to make, have shown a marked reduction.

As the number of AHCs in the motor neuron pool innervating a muscle are lost in a MND, fewer MUPs can be activated. When the disorder has destroyed all the AHCs for a muscle, there are no MUPs under voluntary control. Just before that stage, a single motor unit may be found firing at rates of up to 50-Hz. With a severe loss of motor units, only two or three potentials are found firing at frequencies of 20-Hz. Occasionally, if motor units with a high threshold for activation are lost first, apparently normal recruitment may be seen with two or three MUPs firing at rates under 10 per second; but then additional units are not recruited with increased effort (Fig. 2).

Such patterns of poor MUP recruitment must be distinguished from poor activation, a pattern in which a few MUPs are firing at slow rates. Poor activation may be caused by upper motor neuron weakness, pain, or poor cooperation and is not a sign of lower MND. The differentiation of poor activation from poor recruitment is best made by: (1) the rate of firing of individual MUPs (slow in poor activation and rapid in poor recruitment) or (2) the ratio of
the rate of MUP firing to the number of MUPs that are active.

The assessment of recruitment is usually subjective and more difficult than the identification of MUP changes or fibrillation potentials. Motor unit potential quantitation, such as “peak ratio analysis,” can help distinguish a neurogenic process, especially in muscles with continuous activity, such as the tongue. Nonetheless, EDX consultants can readily become proficient at recruitment assessment by training their hearing to make quantitative estimates of: (1) the rate of individual MUP discharge and (2) the number of active MUPs. Motor unit number estimates (MUNE), described below, is a method that more objectively measures the number of remaining AHCs.

The MUPs of intact AHCs change their appearance, as collateral sprouts from their nerve terminals reinnervate denervated muscle fibers in ALS. Sprouting nerve terminals have slower conduction, and they may show block of conduction or release of smaller amounts of acetylcholine at the neuromuscular junction. Motor unit potentials that include such recently reinnervated muscle fibers will therefore show variation in configuration of the MUP from moment to moment on needle EMG. Increased jitter and blocking on single-fiber EMG (SFEMG) are seen for the same reasons and may be the first sign of denervation and reinnervation. Motor unit potentials variation is a sign of active disease, and, even though it is an attempt at recovery of function, in ALS, it is a poor prognostic sign that signifies a more rapidly progressive disease (Fig. 3).

The MUPs of reinnervated muscle fibers have less synchrony of firing of the component single fiber potentials because of nerve terminal conduction slowing and the slowing of muscle fiber conduction in recently reinnervated, atrophic muscle fibers. Asynchronous firing of muscle fiber potentials results in an increase in polyphasic MUPs (MUPs with more than four phases), an early finding in virtually all patients with ALS. Increased fiber density on SFEMG also reflects the reinnervation of muscle fibers by remaining motor units. Fiber density measurements estimate the number of muscle fibers innervated by one AHC. Fiber density increases as ALS progresses until late in the disease, when it begins to fall because AHCs are no longer able to support the increased numbers of muscle fibers.

As collateral sprouting brings more muscle fibers into a motor unit, the MUP increases in duration and amplitude. Motor unit potentials increase in size with greater synchrony of firing as maturing collateral nerve terminals develop faster conduction and reinnervated muscle fibers regain their size. Increased MUP duration and amplitude are often the easiest measures for the EDX consultant to recognize, and they are an important clue to the presence of a neurogenic process. Long-duration, high-amplitude MUPs cannot be taken alone as evidence of ALS, because the same MUP changes can be seen as residuals of an old neurogenic process. A severe neurogenic disorder with residual weakness may be associated with residual fibrillation potentials. Nonetheless, the finding of unstable MUPs or fibrillation potentials is strong evidence of an ongoing process.

The axons and cells of motor neurons sprouting to reinnervate denervated muscle are irritable, firing spontaneously or with a low threshold. Irritability of lower motor neurons is manifested by fasciculation potentials. Fasciculation potentials occur in a number of disorders and in normal individuals. Fasciculations are prominent in most patients with ALS and can be an important clue that a patient may have the disease. However, they are nonspecific and are of no significance if not accompanied by fibrillation potentials or the appropriate MUP changes. Fasciculation potentials with no other associated EDX abnormalities (“benign fasciculations”) do not evolve into ALS. Fasciculation potentials in ALS become long-duration, polyphasic, and unstable as the disease progresses, just as the MUPs do. Fasciculation potentials in ALS are generated in the AHC early and in the nerve terminal late in the disease. They arise from motor units that are still intact and will therefore disappear in muscles that have lost all their innervation. Occasional patients with definite ALS have no fasciculation potentials. Prominent fasciculation potentials may be so dense that they obscure the baseline and make it difficult to identify...
fibrillation potentials. Auditory recognition of the slow, ticking sound of fibrillation potentials is then more reliable than visual recognition.

The most reliably recognized abnormalities on EMG in ALS are fibrillation potentials, the spontaneous discharge of single muscle fibers that have lost their innervation (Fig. 4). Fibrillation potentials can be readily recognized by their slow, regular firing pattern. Infrequently, fibrillation potentials may discharge irregularly but can still be distinguished from irregular end-plate spikes in that fibrillation potentials do not have the short interpotential intervals (<70 ms) seen with end-plate spikes. Careful search for fibrillation potentials is essential to the identification of ALS. Early in the course of involvement of a muscle by ALS, or in patients with slow progression of their disease, collateral sprouting produces nearly complete reinnervation of denervated fibers. In these patients, fibrillation potentials are limited in number and scattered in distribution, making them difficult to find. In slowly progressing ALS, fibrillation potentials do not become prominent until up to one third of the AHCs are lost.80 In patients with primarily bulbar involvement, if fibrillation potentials cannot be found elsewhere, examination of the tongue, masseter, or facial muscles is important.

Complex repetitive discharges are spontaneous, regularly firing, time-locked, multispike potentials that may be seen on needle EMG examination with chronic denervation (Fig. 4). Complex repetitive discharges occur in ALS of longer duration as well as in other chronic neurogenic atrophies and have no special significance. Rarely, myotonic discharges that wax and wane in amplitude and frequency may be seen in association with prominent fibrillation potentials.37 Patients with ALS rarely have other iterative discharges, such as grouped discharges and doubles. These also implicate nerve terminal irritability but have no other significance.

The selection of muscles for needle EMG study is an important consideration in the evaluation of a patient with suspected ALS.79,134 The number of muscles examined in an ALS patient should be minimized, while obtaining sufficient information to make the correct diagnosis (Table 2). Fibrillation potentials are best seen in weak, atrophic muscles. Examining such muscles first to confirm the presence of a neurogenic process facilitates a needle EMG examination. Identification of definite ALS requires the presence of abnormalities (reduced recruitment, large MUPs, and fibrillation potentials) in at least three levels of the neuraxis. It is usually best to first select muscles in the most clinically involved limb, testing proximal and distal muscles innervated by different nerve roots and peripheral nerves (Table 3). It is important when faced with a potentially diffuse process not to spend time attempting to look for a root or peripheral nerve distribution of apparently focal abnormalities. It is far more efficient and easier on the patient to move to another limb or to cranial muscles after clear abnormalities are found in two muscles with different innervation in one limb.

It is often necessary to test less common muscles to identify and characterize ALS. Thoracic paraspi-
nal muscles are particularly useful for showing multilevel involvement and may require testing at two or more levels to find the fibrillation potentials. Tho- racic paraspinal muscle involvement suggests earlier respiratory involvement. If thoracic paraspinal muscles are involved, identifying abnormalities at two additional levels (one arm and one leg) is sufficient to confirm the lower motor neuron involvement of definite ALS. Other muscles that are also sometimes helpful are the tongue, masseter, intercostal, and diaphragm muscles. Respiratory muscles are particularly helpful in patients presenting with respiratory difficulty for assistance in both diagnosis and treatment. Although the anal sphincter remains clinically uninvolved in almost all ALS patients, testing should be considered if there is incontinence of stool, because it may show abnormalities on needle EMG testing.

Focal weakness and atrophy without pain or sensory loss, and preserved reflexes suggest ALS. Testing clinically normal limbs will often provide the evidence of a diffuse neurogenic disorder, typical of ALS. However, some patients do not have the multilevel fibrillation potentials typical of ALS, even after testing paraspinal and bulbar muscles. Although such patients may have a monomelic amyotrophy (see later), plexus damage, or localized spinal cord disease, ALS cannot be excluded. The presence of minimally abnormal MUPs, unstable MUPs, or abnormal SFEMG should be sought, because they may be the earliest signs of involvement in other regions.

**Nerve Conduction Studies.** Although the major electrophysiological changes in ALS are found on needle EMG, NCSs are an important part of the assessment of a patient with suspected ALS to exclude other possible causes, especially MMN. As a muscle in a patient with ALS loses its innervation, the compound muscle action potential (CMAP) falls in amplitude. Low-amplitude CMAPs are therefore directly related to the severity of the disease and can provide data for judging prognosis. Low-amplitude CMAPs may occur in myopathies but not with disuse. An initial positive deflection of the CMAP due to dispersion of the end-plate region is often seen with very low CMAPs and may not be improved with repositioning the active electrode.

Measurement of motor conduction is of major importance in recognizing peripheral neuropathies, mononeuropathies, and polyradiculopathies that may resemble ALS clinically. Conduction velocity (CV) may be slightly slowed and distal and F-wave latencies slightly prolonged in patients with ALS but not as prominently as in neuropathy or polyradiculopathy. A mild reduction in CV occurs in ALS from relative loss of larger, faster-conducting fibers; the remaining, smaller fibers conduct at their normal, slower rate. The reduction in CV does not fall below 70% of the lower limit of normal. The amount of slowing is proportional to the reduction in CMAP amplitude (Fig. 5). Ulnar nerves in ALS do not appear to be more susceptible to localized entrapment than in normal subjects, but ulnar neuropathy can aggravate the impairment from ALS if not recognized.

Search for conduction block is of particular importance in suspected ALS patients with primarily lower motor neuron findings to exclude potentially treatable disorders such as MMN with conduction block. A single axon with intact conduction along its entire length except at a local site through which the action potential cannot pass is said to have a conduction block. A classic example is the conduc-
Conduction block in an axon when a local anesthetic prevents the generation of an action potential. The CMAP can be elicited distal, but not proximal, to the block. The CMAP therefore is full amplitude distal to the block and absent proximal to the block. Conduction block in the axons of a whole nerve is seen as an abrupt change in CMAP amplitude or area with stimulation at different sites along the nerve. Stimulation at short intervals along the nerve can precisely identify the location of the block.

Conduction block can be reliably assessed only in motor axons. There are pitfalls to the accurate detection of focal conduction block. When the CMAP amplitude is reduced to less than 50%, phase cancellation and the mild slowing in some nerves often results in an amplitude difference between proximal and distal sites of stimulation that is more than that seen in normal individuals. This finding is not uncommon in ALS and may suggest the presence of a conduction block. Compound muscle action potential area measurements are helpful in identifying conduction block because dispersion causes less change in area than amplitude between proximal and distal sites of stimulation that is more than that seen in normal individuals. This finding is not uncommon in ALS and may suggest the presence of a conduction block. Compound muscle action potential area measurements are helpful in identifying conduction block because dispersion causes less change in area than amplitude between proximal and distal sites of stimulation that is more than that seen in normal individuals.

Repetitive Stimulation. The instability of neuromuscular transmission in collateral nerve terminal sprouts in ALS is manifest on repetitive stimulation as a decrement with stimulation at slow rates. Although decrements of up to 28% may be seen, the decrement is usually less than 10% (Fig. 6). The decrement may have the same characteristics as that of myasthenia gravis (MG): maximal after three to five stimuli, repair after brief exercise, and enhancement several minutes after exercise. It is therefore not possible by electrophysiological testing to determine whether MG coexists in patients with ALS. Because repetitive stimulation and SFEMG may be abnormal in ALS, only a large decrement in muscles with a normal CMAP would suggest a primary neuromuscular junction disorder. A decrement often becomes evident during NCSs by an inability to obtain a CMAP of stable amplitude.
**Motor Unit Number Estimates (MUNEs).** Determination of MUNEs is a quantitative method of assessing loss of AHCs but it is less commonly used than is MUP recruitment. The number of motor units in a muscle is estimated in MUNEs by (1) measuring the size of the CMAP evoked by supramaximal nerve stimulation and (2) dividing the supramaximal CMAP by the average size of single motor unit potentials (S-MUPs). Estimates of the size of S-MUPs can be made by measuring "all" or "none" responses at threshold stimulation, from the size of F waves, from spike-triggered surface averages, or from measurements of CMAP variance. Motor unit number estimates can be most reliably used in neurogenic processes, where the reliability increases as the disease progresses. The method is most readily performed in distal muscles that lend themselves to surface stimulation and recording techniques but requires 5 to 10 min per nerve for full assessment. Reproducibility is now comparable with that for CMAP.

Motor unit number estimates have shown that reinnervation by collateral sprouting can prevent reduction in strength and CMAP amplitude with loss of up to half the motor units in a slowly progressive ALS. The loss of motor units measured by MUNEs in individual muscles is rapid over a few months and more gradual for the remaining motor units (Fig. 7). In ALS, some of the S-MUPs seen on MUNEs are much larger than others, indicating much more collateral sprouting and increase in size (Fig. 8). Motor unit number estimates quantitation is the most reliable method to measure the loss of motor neurons in clinical trials.

**Other Studies with Limited Application in ALS.**

Some uncommon electrophysiological studies can provide insight into clinical phenomena. Comparison of macro-EMG and twitch forces has shown that the late deterioration of strength in patients with ALS results from a decline in force of surviving motor units as well as from loss of motor neurons and corticospinal degeneration. The fatigue in ALS results from a combination of factors. Polysomnography can help elucidate the problems of sleep-disordered breathing in selected patients.

Other electrophysiological methods are useful primarily for elucidating the pathophysiology of ALS, in addition to, at times, ruling out mimic disorders. There have been reports of abnormalities of somatosensory evoked potentials in ALS. Studies of populations of ALS patients have shown...
an increase in the mean values for the median N20 and tibial P38 scalp somatosensory evoked potential. Such changes in a patient with ALS therefore may be related to the primary disease rather than a secondary disorder. Somatosensory evoked potential changes are of diagnostic help only when they clearly demonstrate the presence of another disorder.

Recent studies of transcranial motor evoked potentials (MEPs) have shown distinct abnormalities of threshold, cortical inhibition, latency, and motor control, whereas the cortical silent period is normal. Abnormalities of excitatory postsynaptic potentials have been shown with peristimulus time histogram testing with MEPs. These studies are of interest in helping to better define the nature of the disease but are not as yet of clinical diagnostic value. Primary lateral sclerosis shows distinct changes on MEPs. Threshold tracking that tests axonal membrane excitability can show changes in axonal membrane excitability. This promising new method has shown some changes in ALS that are of uncertain clinical significance. One report of abnormal stapedial reflex excitability suggests that ALS involves the motor neurons of the stapedius muscle. H-reflex abnormalities have also been reported.

Only a very small proportion of patients with ALS has clinical evidence of impaired autonomic function. Nonetheless, autonomic function testing shows that up to 30% of patients show mild, but definite, abnormalities on one or more sympathetic and parasympathetic tests of autonomic function, especially in the leg; autonomic testing should be considered in patients with such symptoms.

### Diagnosis

With careful attention given to the technical details of needle EMG and NCS, electrodiagnostic testing can be extremely useful in identifying and characterizing ALS (Table 2). The typical NCS and needle EMG findings in a patient with ALS are low CMAPs with normal nerve conduction, poor MUP recruitment, and widespread fibrillation potentials with MUPs of increased duration and amplitude. Some decrement on repetitive stimulation, varying MUPs, and abnormal jitter and blocking are common. Finding this combination of changes in individual muscles demonstrates the presence of a progressing neurogenic process. The distribution of such changes defines the likelihood of ALS. In association with multilevel upper motor neuron signs, the following criteria can be used to interpret the distribution of lower motor neuron findings where the levels are bulbar, cervical, thoracic, and lumbo-sacral; definite ALS, three levels; probable ALS, two levels; possible ALS, one level; and suspected ALS, two levels without upper motor neuron signs.

A paucity of findings in individual muscles may require a number of muscles to be tested to identify abnormalities at a single level (cranial, cervical, thoracic, lumbo-sacral); but even when findings are unequivocal, at least two muscles of different spinal nerve and peripheral nerve innervation should be tested at each level. It is best to avoid muscles that are frequently involved in common disorders, such as carpal tunnel syndrome and ulnar neuropathy.

One of the most important tasks of the EDX consultant is to rule out the presence of other diseases that may resemble ALS (Table 1). The disorders to be particularly concerned about include cervical or lumbar spine disease, peripheral neuropathy, polyradiculopathy, and multifocal motor conduction block. Normal motor and sensory NCSs make the presence of a peripheral neuropathy very unlikely. Normal F-wave and blink reflex latencies make it less likely that the disorder is a motor polyradiculopathy, but it can never be entirely ruled out by needle EMG.

If the clinical signs are predominantly lower motor neuron with some preservation of reflexes, then multifocal motor conduction block should be sought with additional conduction studies. Prominent weakness and fasciculation in forearm muscles require careful search for conduction block in that limb. The most important clue to the presence of a conduction block is a normal CMAP with marked weakness in that muscle. If that is present, then proximal stimulation should be applied in search for proximal conduction block. Bilateral ulnar, median, peroneal, and tibial motor conduction studies including F waves and proximal stimulation may be needed to identify the block. Identification of a conduction block becomes more difficult as stimulation proceeds more proximally. Root stimulation is particularly difficult, and it requires well-defined normal values for comparison. Although the conduction block may appear at any level, the median nerve in the forearm is a common site rarely susceptible to other disorders. The best evidence of multifocal motor conduction block is a localized region of CMAP amplitude drop or slowing over a few centimeters, demonstrated by “inching” or near-nerve needle stimulation.

Some patients with ALS may have low-amplitude sensory nerve action potentials with mild slowing of sensory conduction. Nonetheless, the presence of sensory changes should suggest other disorders.

Localized spinal cord disease from spondylosis is differentiated by the distribution of abnormalities—
widespread in ALS, localized to the upper or lower limbs in spondylosis. In the patient with spinal cord damage due to bony disease along the entire spine, bulbar signs would be needed to identify ALS. Complete certainty is not possible by needle EMG alone. For example, patients with syringomyelia of the entire cord can show all the typical needle EMG findings of a MND. Some clinical considerations in designing the plan for EDX testing of a patient with suspected ALS are listed in Table 3.

Rate of Progression. The mechanisms underlying differences in rate of progression, and thereby of prognosis, are yet to be defined, but needle EMG findings can assist in the definition of prognosis. Although there have been few published studies, experience has demonstrated that the severity and rate of progression of the disease can be judged from the needle EMG as well as clinical criteria. Both severity of needle EMG abnormalities and their distribution are important in this judgment. Poor MUP recruitment is strong evidence of a neurogenic process, and an otherwise entirely normal needle EMG would suggest an acute process (possibly toxic or infectious). Among the electrophysiological measures, decline in MUNEs and mean CMAP amplitude are most directly correlated with rapid progression to a fatal outcome because CMAPs less than 20% of normal for age in ALS indicate severe motor neuron loss. Examples of additional evidence of rapid progression are moderate-intensity fibrillation potentials in all limb muscles, low MUNEs, varying MUPs, and a decrement on repetitive stimulation. In 30 patients with moderately severe, progressing ALS, individual needle EMG criteria were no better than individual clinical signs in predicting time to death; prediction of time to death was best judged from a combination of clinical and EMG findings (Table 4). The assessment of clinical trials is significantly enhanced by electrophysiological quantitation.

OTHER MOTOR NEURON DISEASES

Bulbospinal Neuronopathy (Kennedy’s Syndrome).

An x-linked, slowly progressive form of MND symmetrically involving bulbar and spinal motor neurons is associated with testicular atrophy and gynecomastia. The age of onset is younger than for most ALS patients. However, both patients with Kennedy’s syndrome and those with ALS, who do not have classic findings, may be misdiagnosed. The unique genetic defect has been demonstrated to be a CAG expansion repeat; the age of onset is earlier with longer lengths of repeats. Genetic testing should be considered whenever the possibility of that diagnosis exists.

Although the electrophysiological findings are similar to those of ALS, greater symmetry of findings and clear bulbar abnormalities are helpful in distinguishing the disorders. Nerve conduction studies are generally normal except for reduced CMAPs and MUNEs, but some patients have shown sensory nerve abnormalities. A higher proportion of Kennedy’s syndrome patients have reduced sensory nerve action potentials than do ALS patients. On needle examination, there is marked reduction in recruitment with large MUPs and scattered fibrillation potentials.

Spinal Muscular Atrophy. The major MNDs in childhood are the autosomal recessive SMAs. Their genetic defects are allelic variations on a single gene resulting in different severity and rates of progression. Type 1 (Werdnig–Hoffmann disease), is a rapidly progressing, more often fatal disorder with onset before 6 months of age; type 2, with an onset from 6 to 18 months of age, is a more slowly progressive and relatively benign disorder. Type 3, with onset after 18 months of age, often presents in adolescence and has a long survival with ambulation throughout most of adult life. Some adults with SMA are those with type 3. Others who have onset in adulthood may be autosomal dominant or recessive, but the gene loci have not been identified. All forms of SMA have prominent proximal weakness.

The needle EMG findings in Werdnig–Hoff-
mann disease are similar to those in ALS, with poor recruitment (loss of MUPs), large MUPs, and fibrillation potentials. Needle EMG findings are among the most relevant to confirm AHC disease in this disorder. The number of fibrillation potentials varies not only with the severity of Werdnig–Hoffmann disease but also with the diligence of the EDX consultant in searching for them in a small child. This is somewhat easier with conscious sedation, but electronic storage and subsequent review of all needle EMG recordings should be standard for children. Frequently, review of the recording immediately after completing the needle EMG shows fibrillation potentials, varying MUPs, or other MUP changes that were not appreciated during the recording. The reported incidence of fibrillation potentials has varied up to 100%. Large MUPs are seen in Werdnig–Hoffmann disease, but more low-amplitude, short-duration, varying MUPs are seen in this SMA than in ALS and are due to reinnervation; these MUPs should not suggest an additional myopathy. Fasciculation potentials are seen in only 35% or fewer of children with Werdnig–Hoffmann disease, much less than in patients with ALS.

Low CMAPs with mild slowing of CV and small decrements on repetitive stimulation are also seen in children. Most studies have shown sensory conduction to be normal. More benign forms of SMA in children and adults may be mistaken for muscular dystrophy. The needle EMG results can be extremely helpful in making an accurate diagnosis for SMA. The needle EMG findings are those of a chronic neurogenic process with poor recruitment and large MUPs. The severity of findings increases with the duration of the disease. Early in the disease, muscle cramps and minimal needle EMG abnormalities may be the only findings. If the duration of clinical disease is over a year, impairment of recruitment and large MUPs are widespread and prominent. Fascillation potentials in SMA are infrequent and scattered in contrast to their prominence in ALS. The fibrillation potentials may be of such low amplitude and short duration that they are difficult to distinguish from baseline noise. True fasciculation potentials are generally infrequent, but they must be distinguished from contraction fasciculation, the potentials (or twitches) of large motor units in muscles that are not completely relaxed. This differentiation can be made only by recognizing the irregular firing pattern of true fasciculations, as opposed to the semirhythmic pattern of MUP firing. Many forms of iterative discharge can occur in SMA.

Complex repetitive discharges are more common in SMA than in ALS. Neurotonic discharges (rapidly waning potentials firing at 150- to 300-Hz) are seen in some patients with long-standing SMA.

Motor unit potentials in SMA are usually of long duration and high amplitude. Polyphasic MUPs, although less common than in ALS, may include separate, time-locked components called “satellites,” or “linked potentials.” These late components are the action potentials of atrophic single muscle fibers, of split fibers or of muscle fibers innervated by a long, thin nerve terminal. In the late stages of SMA, short-duration, low-amplitude MUPs may be found, especially in weight-bearing muscles such as the anterior tibial and gastrocnemius muscles. These small MUPs are typically associated with histologic changes of the type seen in a myopathy. Nerve conduction studies of motor and sensory fibers in SMA are normal. Compound muscle action potential amplitudes are not as low as those seen in ALS and are often normal. Responses to repetitive stimulation are also usually normal.

Needle EMG diagnosis of SMA is usually not difficult in the patient with atrophic muscles, normal conduction, poor MUP recruitment, and large MUPs. The major distinction is usually a chronic myopathy, which would have small, rather than large, MUPs. However, in the late stages of SMA and some myopathies, severe degeneration of muscle can result in MUP similarities that may make it difficult to distinguish them by needle EMG. Chronic inflammatory myopathies may show large, long-duration MUPs, suggesting a neurogenic process. Atrophic muscle in neurogenic disease that has been chronically overworked may show the changes of a myopathy, both on needle EMG and histology. In these patients, it is better to study less severely involved muscles, which are less likely to have changes resembling a myopathy. In the patient with a widespread, chronic, wasting disease, caution must be used in interpreting needle EMG findings that are not clear-cut.

Rare, focal forms of MNDs have been described that remain limited to one extremity, “monomelic.” The needle EMG findings are like those of SMA but are limited to the involved extremity. Their benign, but insidious, course is reflected on needle EMG by low CMAP amplitude, normal sensory potentials, marked impairment of MUP recruitment, and very large MUPs. On needle EMG, they cannot be distinguished from spinal cord disease due to syringomyelia, spondylitis, or other focal disorders.
Multisystem Disorders with Prominent Lower Motor Neuron Involvement. Hexosaminidase A deficiency is an autosomal recessive, adult-onset disorder with widespread basal ganglia, cerebellar, and cortical cell loss in addition to AHC loss. Significant AHC loss also is common in Machado–Joseph, polyglucosan body, and Parkinson-dementia complex disorders. All show needle EMG changes of a chronic, slowly progressing motor system disease.

Poliomyelitis. Needle EMG in acute poliomyelitis is characterized by poor MUP recruitment at the onset of weakness, followed by the development of fibrillation potentials in widespread muscle groups after 2 to 4 weeks. The fibrillation potentials subside as reinnervation by surviving motor units proceeds during recovery. In muscles with too few motor units to effect adequate reinnervation, fibrillation potentials can persist indefinitely. These fibrillation potentials become extremely small as the muscle fibers atrophy and may be easily overlooked. The reinnervated motor units result in MUPs that are among the largest seen in any disorder, up to 20 mV in amplitude and 30 ms in duration. The muscles that remain weak and atrophic after recovery have very few or only one motor unit under voluntary control. However, virtually all muscles including the clinically normal muscles show abnormal recruitment, large MUPs, and increased fiber density. Scattered fibrillation potentials with evidence of ongoing reinnervation are seen in weak muscles in the absence of clinical evidence of either progression or “post-polio syndrome.” The reduced number of motor units predisposes patients with poliomyelitis to increasing impairment with either minor axonal damage or with the loss of motor units with aging.

The pathophysiology of late progression of old poliomyelitis is unknown. Most patients do not show distinct needle EMG findings. The normal loss of MUPs with aging in muscles with only a limited number of motor units left by the disease may contribute. Needle EMG in late progression of poliomyelitis is generally similar to old poliomyelitis without progression. There are scattered fibrillation potentials, reduced recruitment, and large MUPs. Needle EMG and NCSs therefore are not of help in specifically identifying late progression of poliomyelitis. The EDX testing is most helpful in demonstrating other superimposed diseases such as an ulnar neuropathy. Because large MUPs are present in all atrophic muscles, with fibrillation potentials in some of them, it is difficult to reliably identify a new neurogenic disorder in a patient with needle EMG residuals of poliomyelitis.

Motor unit number estimates have also demonstrated that muscles with normal strength and CMAP amplitude after poliomyelitis often have moderate to marked loss of motor units. In comparison with normal subjects, the rate of loss of motor units appears to be higher in patients with the residuals of poliomyelitis.

Except for a reduction in CMAP in proportion to muscle atrophy, motor and sensory NCSs remain normal in poliomyelitis. Some apparent slowing may be seen in an atrophic extremity, if the limb temperature is low, as is frequently the case.

REFERENCES


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