

# The Electrophysiology of the Motor Neuron Diseases

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## KEYWORDS

- Amyotrophic lateral sclerosis • Spinal muscular atrophy
- Primary lateral sclerosis • El Escorial criteria
- Progressive muscular atrophy • Multifocal motor neuropathy

Charcot is credited with the first descriptions of amyotrophic lateral sclerosis (ALS) in the 1860s.<sup>1</sup> He named the disease based on the pathologic features of muscle atrophy (amyotrophy) and sclerosis of the cortical spinal tracts (or lateral columns) in the spinal cord. In the early British literature the disease came to be known as *motor neuron disease*, and since that time the two terms are generally considered synonymous. The illness gained particular notoriety in the United States around 1940 when Lou Gehrig, the famous baseball player for the New York Yankees, was diagnosed with and died of the disease. In the United States, the disease soon became widely known in the lay literature eponymously as Lou Gehrig's disease.

Lou Gehrig offers a unique perspective in ALS that is not possible in most other cases. His baseball statistics offer a nearly daily assessment of his physical abilities. In analyzing these, one can observe when his physical decline began. A review of his batting average indicates that in 1939, his last full year of baseball, a steady and continuous decline occurred in his batting average<sup>2</sup>; this was a full year before the onset of his symptoms in 1940. This fact highlights the difficulty facing experimental treatment trials in ALS; the disease is already well established and advanced before presentation, limiting the potential impact of any disease-modifying therapy.

Also interesting historically was Lou Gehrig's participation in a clinical trial studying the effects of vitamin E in the treatment of ALS. Lou Gehrig was a patient of Dr Wechsler's in New York and appears as index case #4 in Wechsler's publication of this clinical trial.<sup>3</sup> In his case description, Wechsler identifies the classic features of ALS, including the upper motor neuron features of spasticity, slowness of movements, and hyperreflexia, and the lower motor neuron features of atrophy, weakness, and fasciculations. The only missing clinical feature from his description is the asymmetric focal onset that is characteristic of the disease.

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Over time, the motor neuron syndromes have been further classified into ALS and other much less common forms, including primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), spinal muscular atrophy (SMA), and X-linked spinobulbar atrophy (SBMA; also known by its eponym, Kennedy disease). The clinical features of each are reviewed in **Table 1**. The clinical syndrome of ALS is characteristic. The role of nerve conduction studies and needle electromyography (collectively referred to as *EMG*) is often straightforward. The objective of EMG is to confirm the clinical suspicion while excluding certain mimic syndromes. As with other ancillary tests, no pathognomonic findings are seen on EMG, but in the proper clinical context it can be diagnostic. Because of its ability to investigate alternative etiologies and provide supportive evidence, EMG is the single most important ancillary testing in evaluating ALS.

## SUMMARY

1. Motor neuron disorders can be separated into ALS, PLS, PMA, SMA, and SBMA. Each has a unique phenotype and prognosis.
2. Motor neuron disease and ALS are considered synonymous terms.

## ALS

ALS is the most common of all the motor neuron disorders. Pathologically it can be distinguished by the gliosis and neuronal loss within the motor cortex and the anterior horns of the spinal cord. More recently, pathologic aggregation of the proteins TAR DNA-binding protein 43 (TDP-43) and ubiquilin 2 has been identified in most sporadic cases of ALS.<sup>4,5</sup> This pathology is indistinguishable from that of ubiquitin-positive frontotemporal dementia (u-FTD), raising suspicion that these two disorders may represent separate phenotypes of a common underlying cause.

The incidence of ALS is 1.5 to 2.0 cases per 100,000 population per year.<sup>6</sup> The incidence rate increases with age up to approximately 80 years, followed by a sharp decline in the most senior years. The median survival from diagnosis is approximately 18 months. Age of onset is the most significant prognostic variable.<sup>6</sup> Patients who are younger when diagnosed have a better long-term survival than those who are older. A minority (5%–10%) of cases will live beyond 5 years after diagnosis. The only treatment currently approved by the U.S. Food and Drug Administration (FDA) is riluzole. Two randomized controlled studies showed a dose-dependent mean survival benefit

**Table 1**  
Clinical features of the motor neuron disorders

	Onset	Bulbar Involvement	Fasciculations	Lower Motor Neuron Features	Upper Motor Neuron Features
ALS	Asymmetric and focal	Prominent	Prominent	Prominent	Prominent
PMA	Asymmetric and focal	Less prominent	Prominent	Prominent	Absent
PLS	Symmetrically usually in lower limbs	Prominent in later stages	None	Absent	Prominent
SMA	Symmetrically in proximal limbs	Less prominent	Variable	Prominent	Absent
SBMA	Symmetrically in proximal limbs	Prominent	Very prominent	Prominent	Absent

of approximately 4 months that did reach significance.<sup>7,8</sup> Approximately 5% to 10% of cases are familial, with most being autosomal dominant. A variety of mutations are now known to be associated with this disorder, the most common of which are mutations with the *SOD* (Cu/Zn) gene.

## EMG IN ALS

ALS most commonly presents with a classic phenotype of focal onset weakness. Typically it will begin in one hand, one leg, or with dysarthria. In a small minority of cases it may begin with dyspnea (pulmonary onset) or in a generalized fashion. The disease generally evolves into contiguous body regions as it progresses, resulting in the classic lower motor neuron signs (weakness, atrophy, and fasciculations) in combination with the upper motor neuron signs (spasticity, hyperreflexia, and slowness of movements) within the same body region. These symptoms occur while sparing the sensory modalities and other neurologic systems. In these classical cases, EMG serves as an extension of the neurologic examination and is used to confirm the distribution of the lower motor neuron involvement. In less classical cases, EMG is valuable for excluding other mimic syndromes, such as the other motor neuron diseases, other peripheral neuropathies, and neuromuscular disorders.

ALS is a disorder that begins focally and spreads contiguously, and EMG findings will reflect that evolution. In classic cases, nerve conduction studies provide little supportive evidence for the diagnosis. The sensory nerve action potentials are normal for age and the compound muscle action potentials (CMAPs) may be reduced in amplitude, reflective of the loss of motor axons from the death of the anterior horn cells. Because of the loss of motor axons, the motor nerve conduction velocities and distal latencies may be mildly delayed, but only modestly. No evidence should be present of motor conduction block. Sensory conduction velocities and distal latencies should remain normal.

In established cases, needle EMG will identify the classic features of fibrillation potentials, fasciculation potentials, and large, complex, unstable motor unit potentials with reduced recruitment diffusely in all body regions. Early in the disease, however, these abnormalities may be identified only in the affected regions, begging the question of how diffuse the abnormalities need to be on EMG to confirm a diagnosis.

In 1998, a consensus conference was held in El Escorial, Spain, to establish standard inclusion criteria for ALS clinical trials.<sup>9</sup> These criteria are known as the *El Escorial criteria* and have become the standard on which the diagnosis of ALS is based. These criteria allow for a level of diagnostic certainty (from possible to definite) based on the number of regions clinically involved. The body is divided into four regions: bulbar, cervical, thoracic, and lumbar. Involvement of each region on EMG requires the presence of fibrillation and fasciculation potentials and neurogenic motor unit potentials in at least two muscles innervated by separate nerves and myotomes. In the proper clinical setting, one region of involvement is classified as possible ALS; two regions, probable; and three or four regions, definite ALS. The *El Escorial criteria* were subsequently revised to allow for EMG data alone to support the diagnosis, with the additional diagnostic category of "probable ALS—laboratory-supported." The EMG components of the *El Escorial criteria* are summarized in [Table 2](#).

In 2006, a follow-up consensus conference held in Awaji, Japan, resulted in further revision of the diagnostic criteria.<sup>10</sup> These criteria are known as the *Awaji criteria* and differ from the revised *El Escorial criteria* in the equating fasciculation potentials with fibrillation potentials. In the *Awaji criteria*, a region can be included as affected in the presence of either fasciculation or fibrillation potentials (in contrast to the revised *El*

<b>Level of Certainty</b>	<b>Regions Involved</b>
Possible ALS	1 region
Probable ALS	2 regions
Probable ALS–laboratory-supported	1 region clinically; 1 electrodiagnostically
Definite ALS	3 or 4 regions

Regions include bulbar, cervical, thoracic, and lumbar.

Involvement requires two muscles affected innervated by two separate nerves in two separate myotomes.

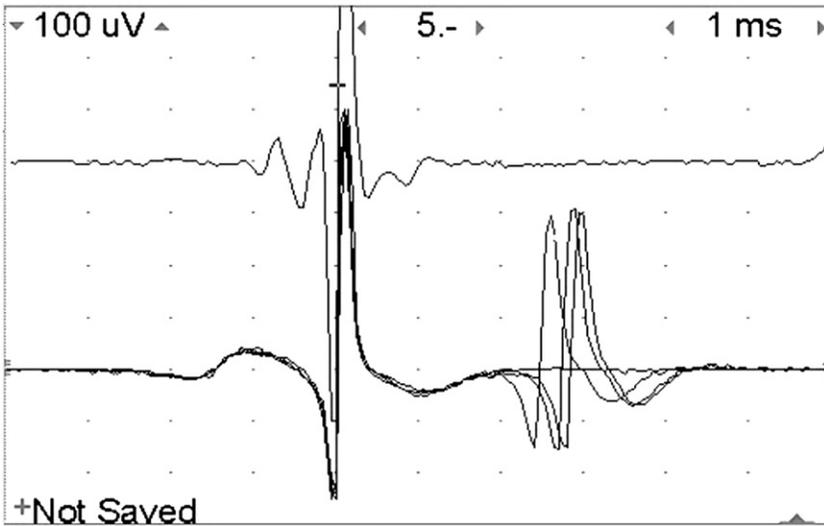
Escorial criteria, which require the presence of both). The Awaji criteria remain under investigation and have not yet replaced the revised El Escorial criteria as the standard for diagnosis. A concern regarding the Awaji criteria is an unacceptable loss of specificity if they are adopted for general use, although studies have not yet found the drop in specificity to be problematic.<sup>11</sup>

### **EARLIEST CHANGES ON EMG IN ALS**

In advanced cases of ALS, the EMG findings of fibrillation and fasciculation potentials and large complex motor unit potentials are found diffusely. In these circumstances, the diagnosis can be easily confirmed. However, in earlier cases, when the process is just beginning, the findings are much more subtle. To address the earliest abnormalities on needle EMG, data from the animal models can be reviewed. Animal studies have shown that the earliest detectable morphologic changes of the motor unit occur while the anterior horn cell is still viable. At this stage, a dying back of the terminal motor axons occurs, followed by reinnervation through axonal sprouting.<sup>12</sup> This remodeling of the terminal motor unit results in a series of immature terminal axon sprouts that do not conduct the nerve action potential reliably. This process results in instability of the motor unit potential and blocking of the action potential to individual muscle fibers, creating the visual and auditory appearance of significant motor unit instability and blocking, even in motor units of normal amplitude and duration (**Fig. 1**). As the motor unit remodeling becomes more established, the fiber density begins to increase (**Fig. 2**). Fiber density is the electrophysiological equivalent of fiber type grouping on muscle pathology, and is the hallmark of reinnervation within the muscle. As the disease progresses and the anterior horn cells are lost, the more typical changes in motor unit potentials that are associated with ALS will appear, including long duration, increased complexity, and reduced recruitment. Motor unit instability remains a prominent feature, and motor unit variability remains highly visible and audible throughout the course of ALS. The nerve conduction and needle EMG findings in ALS and other mimic syndromes are summarized in **Table 3**.

#### ***Fasciculations***

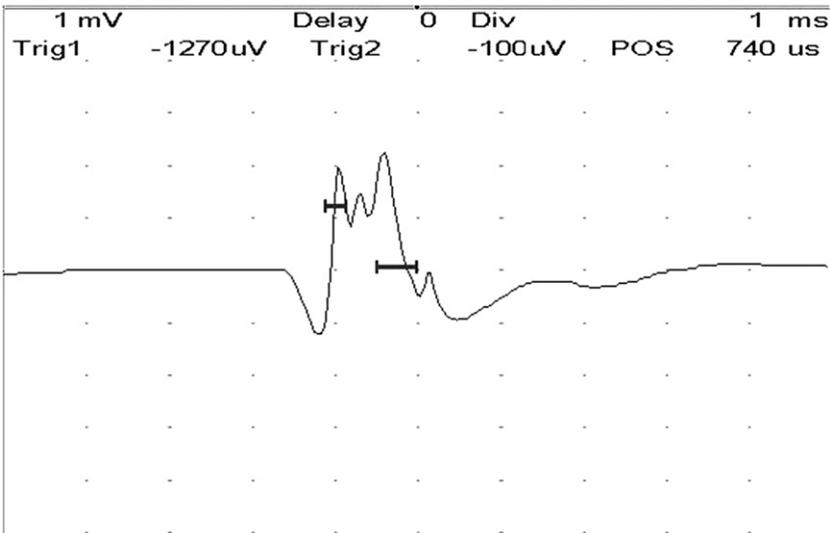
Fasciculations are commonly associated with ALS and other motor neuron disorders. Fasciculations represent random action potentials of a single, isolated motor unit potential. They are involuntary and spontaneous, and occur in widely distributed within the muscle. Fasciculations are not specific for ALS; they occur in other disorders, and occasionally in people of normal health. One study that followed more than 100



**Fig. 1.** Single-fiber analysis of early involvement of the motor unit potential in ALS. Note the significant jitter and blocking in an otherwise normal motor unit potential.

subjects with clinical and electromyographic fasciculations but no other signs of denervation failed to identify any cases of ALS at a mean follow-up of 5 years.<sup>13</sup>

However, ALS clearly has a strong association with fasciculations, and these play an important role in the diagnosis of ALS. Nearly all patients with ALS will have clinical and electromyographic fasciculations during the course of their illness. When examining for fasciculations, the muscle must be completely at rest. Muscle twitches that occur



**Fig. 2.** Single motor unit potential by a single fiber, indicating four muscle fibers in this muscle region. Normal fiber density ranges from one to three in most motor unit potentials. The gain of the image is set at 1 mV per division with a sweep speed of 1 msec per division.

	<b>Motor NCS</b>	<b>Sensory NCS</b>	<b>Fibrillation</b>	<b>Fasciculation</b>	<b>MUP</b>
ALS	Normal to low amplitude	Normal	Prominent	Prominent	Large and unstable
PMA	Normal to low amplitude	Normal	Prominent	Prominent	Large and unstable
SBMA	Usually normal, may be low amplitude	May be reduced in amplitude	Present	Prominent	Large and stable
SMA	Usually normal, may be low amplitude	Normal	Present	Present	Large and stable
PLS	Normal	Normal	Absent	Absent	Normal but may have poor activation
IBM	Usually normal, may be low amplitude	Normal	Prominent	Absent	Mixed large and small
MFMN	Conduction block present	Normal	Present	Present	Large and stable
Hirayama disease	Normal to low amplitude	Normal	Present	Present	Large and stable

*Abbreviations:* IBM, inclusion body myositis; MFMN, multifocal motor neuropathy; MUP, motor unit potential; NCS, nerve conduction study.

without relaxation (so-called contraction fasciculations) do not impart the same pathologic implications that resting fasciculations do. Also, on needle EMG, fasciculations that occur with needle movement lose their specificity. When examining for fasciculations, either clinically or with EMG, the muscle should be relaxed and observed for a minimum of 30 seconds. During this time the needle should not be moved and should remain at rest. The density and frequency of fasciculation potentials do not impart any known prognostic significance, however; merely their presence in the proper clinical situation, along with other findings of acute denervation, is strongly supportive of an ALS diagnosis.

Why fasciculations are so prominent in ALS is not well-known. Evolving evidence shows that within the neuron, one of the earliest metabolic derangements to occur is dysfunction of the mitochondria.<sup>14</sup> The mitochondria has three key functions that are relevant to the pathogenesis of ALS: calcium buffering and calcium-related excitotoxicity; apoptosis regulation; and energy metabolism. Energy failure is now known to occur early in ALS.<sup>15</sup> The motor neuron consumes a considerable amount of energy to maintain the neuron's resting membrane potential and to maintain normal excitability for the transmission of the nerve action potential. Maintaining this resting membrane potential is an energy-dependent process. In the setting of a compromised energy supply, the resting membrane potential will drift. During this drift, the resting potential may reach threshold and spontaneously activate the voltage-gated sodium channels, thus triggering an action potential of that motor axon. This action potential will then cause activation of the entire motor unit, resulting in a single isolated motor unit potential or fasciculation. Because the energy state and resting membrane potential vary, these action potentials occur randomly and spontaneously.

## SUMMARY

1. ALS presents as a focal disorder, with mixed upper and lower motor neurons, and spreads contiguously.
2. The diagnosis of ALS has been standardized through the El Escorial criteria.

## OTHER MOTOR NEURON DISORDERS

### *PLS*

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PLS is an uncommon variant of motor neuron disease. It occurs with pathologic loss of the cortical motor neurons only, sparing the anterior horn cells of the spinal cord. Whether PLS represents a disorder unique from ALS or is simply a phenotypic variant remains a matter of debate.<sup>16</sup> The strongest argument favoring a phenotypic variant is from the familial forms of ALS. The PLS phenotype is now well described in familial forms of ALS.<sup>17</sup> The coexistence of these two phenotypes from the same genetic mutation strongly favors separate phenotypes of a common origin. Regardless, patients with PLS are known to have a much more indolent progression with a much longer survival than those with ALS. PLS should be distinguished from upper motor neuron-onset ALS, in which evolution to lower motor neuron involvement typically occurs in the first year. Some clinical features help make this distinction. First, a very high proportion of PLS begins symmetrically in the lower extremities, with the onset of a spastic gait, and then ascends. Conversely, upper motor neuron-predominate ALS begins in a focal asymmetric manner and can occur in any region of the body. PLS will progress indolently, whereas upper motor neuron-predominate ALS typically progresses more rapidly. Fasciculations are notably absent in PLS, whereas they are present in upper motor neuron-predominate ALS.

PLS tends to evolve very slowly over several years, and is overall associated with much better survival than ALS. After years of involvement, a small proportion of patients with PLS may develop lower motor neuron involvement and convert to an ALS phenotype, but this is uncommon. More commonly, after years of indolent progression, the disease tends to plateau, followed by years of relative stability. The timing of this is variable, and in some patients with PLS the neurologic deficits remain modest, whereas in others severe quadriplegia and spastic bulbar palsy may develop.

Neurophysiology testing is an important ancillary test for all patients who present with progressive spastic paraparesis. In PLS, the nerve conduction studies and needle EMG are generally normal or merely indicate poor voluntary activation. Changes consistent with denervation early in the disease are concerning for upper motor neuron-predominate ALS, and patients should be counseled appropriately. Given the prognostic significance, follow-up studies at a later date, including serial electrodiagnostic testing, should be performed to make this distinction definitively.

Early PLS may be difficult to distinguish from hereditary spastic paraparesis (HSP). Most patients with PLS have no family history, and a family history consistent with HSP should prompt genetic counseling and testing. In contrast to PLS, most forms of HSP do not evolve to include the upper limbs or bulbar regions.

### *PMA*

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PMA is a lower motor neuron disorder that is otherwise phenotypically indistinguishable from ALS. Like ALS, it starts in a focal region and spreads to contiguous regions. Muscle atrophy, weakness, and fasciculations are prominent, but upper motor neuron signs are absent. As with PLS, it remains debated whether PMA is a distinct disorder from ALS or merely a phenotypic variant. Independent autopsy studies support a common origin for PMA and ALS. Postmortem studies in PMA have consistently

shown subclinical loss of cortical motor neurons and sclerosis of the lateral columns.<sup>18</sup> Recent pathology studies have confirmed a common TDP-43 pathology in PMA and ALS.<sup>19</sup> Because PMA is a lower motor neuron disorder, nerve conduction studies and needle EMG in PMA are indistinguishable from those in ALS. Classical ALS and PMA are differentiated through clinical examination and the lack of upper motor neuron signs.

### **SMA**

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SMA is a hereditary lower motor neuron disorder. It is now known to be caused by a deletion in the survival motor neuron gene (*SMN1*) on chromosome 5q.<sup>20</sup> Genetic testing is now commercially available for this genetic mutation. Onset ranges from infancy to early adulthood. SMA type 1, also known by its eponym Werdnig-Hoffmann disease, is the most common form, with infantile onset, and is usually fatal within the first year of life. SMA type 2 has its onset in toddlers, usually before 2 years of age. The overall prognosis is better than that for type 1, but these children typically never achieve the ability to walk. SMA type 3 (Kugelberg-Welander syndrome) has its onset later in childhood and has a more indolent course generally thought to be compatible with a normal life expectancy. SMA type 4 is the rarest form and has its onset in young adulthood. The distinction between the four types is somewhat arbitrary. It is now known that the age of onset and the severity of the phenotype is associated with the number of copies present for the modifier gene *SMN2*; the larger the copy number of the *SMN2* gene, the later the onset of disease and the more benign the clinical course.<sup>21</sup> Phenotypically, all four types share several common clinical features. All four have symmetric proximal-predominate weakness. Bulbar weakness is common in SMA type 1 but is not a prominent feature in the other types. Loss of reflexes early in the disease is typical.

Electrodiagnostic testing in SMA will reveal the underlying pathology and distribution of disease. As with the other motor neuron disorders, fibrillation and fasciculation potentials are noted. Motor unit potentials are large but tend to be less complex and more stable because of the more indolent and chronic nature of the disorder. The distribution of findings follows the clinical distribution of weakness. The changes are greatest in the proximal limbs and paraspinal muscles, with less-prominent changes distally. The EMG findings also tend to be symmetric. On nerve conduction studies, the sensory nerve action potentials remain unaffected and normal for age. The CMAPs appear similar to those in other motor neuron disorders. The CMAPs may be reduced in amplitude, reflective of the loss of motor axons from the death of the anterior horn cells. Because of the loss of motor axons, the motor nerve conduction velocities and distal latencies may be mildly delayed, but only modestly. No evidence should be present of motor conduction block.

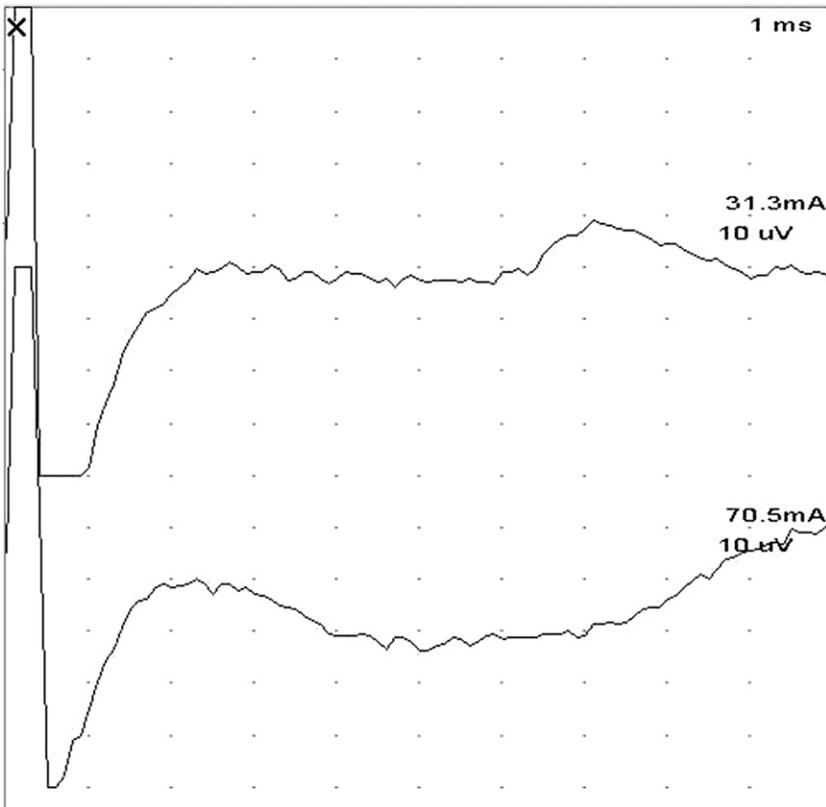
### **SBMA**

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SBMA is an X-linked inherited disorder that occurs almost exclusively in men. Rarely, female carriers may have mild clinical manifestations. The responsible mutation is a trinucleotide repeat within the androgen receptor gene on the X-chromosome.<sup>22</sup> This genetic mutation is also commercially available for testing. How a mutation in the androgen receptor results in degeneration of the lower motor neurons is unknown. Other clinical manifestations include partial androgen insensitivity with gynecomastia and testicular atrophy in many affected men. The neurologic manifestations result from slow degeneration of the anterior horn cells and the bulbar motor neurons. This degeneration results in the clinical manifestations of a flaccid bulbar palsy and symmetric weakness of the proximal limb muscles.

Fasciculations are prominent, particularly around the facial muscles. In contrast to ALS, no upper motor neuron signs are present. The age of onset is variable and can occur at any time during adulthood.<sup>23,24</sup> Survival in SBMA is only modestly reduced.<sup>24</sup>

On electrodiagnostic testing, the needle EMG shows the fibrillation and fasciculation potentials. As with SMA, the motor unit potentials are large and may have some increased complexity. In contrast to ALS, the motor unit potentials are stable, indicative of the chronic indolent nature of the disease. As with SMA, the needle examination findings are most prominent in the proximal limb muscles, symmetrically. On nerve conduction studies, the CMAPs may be reduced in amplitude, reflective of the loss of motor axons from the death of the anterior horn cells. Because of the loss of motor axons, the motor nerve conduction velocities and distal latencies may be mildly delayed, but only modestly. No evidence should be present of motor conduction block. Although these patients do not report any sensory symptoms, sensory nerve action potentials on nerve conduction studies often show a loss of amplitude (Fig. 3). This feature is unique among the motor neuron disorders.



**Fig. 3.** Sural sensory nerve action potential with stimulation at the ankle and calf while recording posterior to the lateral malleolus. In this young patient with SBMA, no elicitable nerve action potential is seen from either site.

## SUMMARY

1. PLS and PMA are currently considered phenotypic variants of ALS, both with a more benign prognosis.
2. SMA is a unique genetic disorder associated with deletions in the survival motor neuron gene and a variable age of onset and prognosis.
3. SBMA is a unique genetic disorder associated with a trinucleotide repeat in the androgen receptor gene, a variable age of onset, and only modestly reduced survival.
4. Unique features of the clinical examination and electrodiagnostic testing help differentiate the motor neuron disorders.

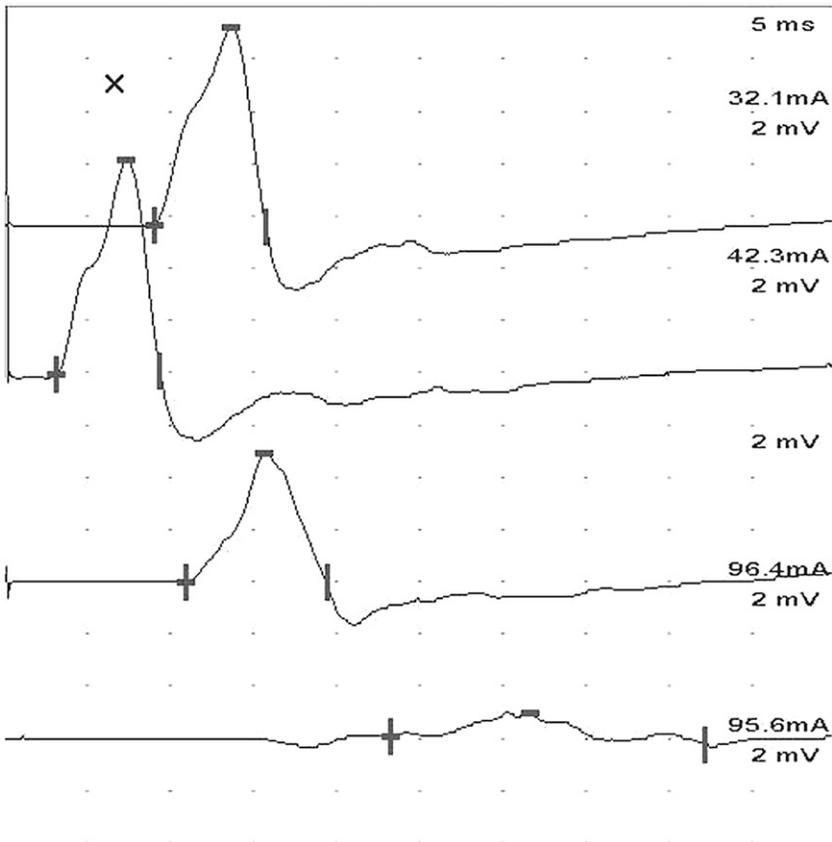
## OTHER MIMIC SYNDROMES

### *Multifocal Motor Neuropathy*

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Multifocal motor neuropathy is a rare peripheral neuropathy that affects the motor axons exclusively. The disorder is characterized by focal or multifocal regions of conduction block along the length of the axon. The pathology at these sites is indeterminate, and whether this is caused by focal demyelination or an ion channel disorder is unclear. In either case, a blocking of the action potential results clinically in weakness and conduction block on motor nerve conduction studies. The disorder is believed to be immune-mediated, and a proportion of these cases are associated with a marked titer of antiganglioside antibodies, which can be clinically tested. This syndrome typically begins unilaterally with hand weakness. Early in the course little muscle atrophy occurs, but in established cases the muscle atrophy will appear because of secondary axonal loss from the local inflammatory attack of the nerve. Fasciculations are common, which contributes to the misdiagnosis of motor neuron disease in many patients. This syndrome has a particular predilection for the radial motor nerve, and prominent finger extensor or wrist extensor weakness should raise suspicion for this disorder. Uncommonly, the disorder may begin distally in a lower extremity. The disorder rarely affects proximal muscles and almost never has bulbar involvement. In contrast to ALS, no upper motor neuron signs are apparent. The natural history is for periods of slow, indolently progressive weakness that occurs over years. Although inflammatory, it is believed to be resistant to most immunotherapies, except intravenous gammaglobulin (IV Ig), which is the mainstay of therapy. With IV Ig, patients may experience prolonged periods of stability, but many patients become IV Ig-dependent,<sup>25</sup> and eventually many experience slow indolent progression despite the treatment.<sup>25</sup>

Electrodiagnostic testing is critical to the diagnosis of this disorder. The needle EMG findings may be similar to those of the motor neuron disorders, with fibrillation and fasciculation potentials and large complex motor unit potentials. The nerve conduction studies, however, are the key to diagnosing this disorder. In multifocal motor neuropathy, the motor nerve conduction studies are critical. The identification of areas of motor conduction block is the hallmark of this disorder and these must be examined for carefully. Often the areas of conduction block are in the proximal nerve segments, which may not be identified on routine conduction studies. Therefore, motor nerve conduction studies should be performed proximally through the plexus or even the root, with needle stimulation, if this disorder is suspected. Routine conduction studies at distant sites may miss the area of conduction block that is critical to the diagnosis (**Fig. 4**). Given the predilection of this disorder for the radial nerve, a radial motor conduction study should also be considered when investigating for areas of conduction block.



**Fig. 4.** Ulnar motor conduction study in multifocal motor neuropathy, indicating conduction block in the proximal segment. Routine nerve conduction studies at the wrist and elbow would have missed this area of conduction block.

### ***Inclusion Body Myositis***

Inclusion body myositis (IBM) is an adult-onset inflammatory myopathy that is commonly mistaken for a motor neuron disease. This mistake arises from the needle EMG of IBM, which shows a mixed pattern of small and large complex motor unit potentials. The larger neurogenic-appearing motor unit potentials deceptively suggest a primary neurogenic process, and the clinical disorder is often mistakenly interpreted as motor neuron disease. Despite the neurogenic-appearing motor unit potentials, whether IBM has a neurogenic component is of debate. Currently, researchers believe the larger motor unit potentials seen are merely reflective of the chronic nature of the illness, but this remains speculative. Despite the presence of an inflammatory exudate on muscle biopsy, the disorder does not seem to be immunoresponsive, and no effective treatment is known.

Clinically, IBM has a rather classic presentation. Patients typically report slowly progressive weakness of either the proximal lower extremities (most notable on stairs or rising from low seated positions) or reduction of hand grip strength. Often the process is so indolent that patients cannot date the onset of the illness accurately. When questioned in retrospect, often subtle problems can be identified many years

before the weakness was first noted. The weakness tends to be symmetric, although it may be asymmetric in a minority. On examination, weakness and atrophy are notable primarily in the quadriceps muscles and the deep finger flexors of the hands, and is most prominent in the flexor pollicis longus and flexor digitorum profundus. Fasciculations are absent and no upper motor neuron signs are present.

A high clinical suspicion is critical for interpreting the electrodiagnostic testing. The nerve conduction studies will seem similar to those of the motor neuron diseases, with sparing of the sensory nerve action potentials and normal- to reduced-amplitude CAMPs. The needle examination is most challenging. Mixed populations of large and small complex and unstable motor unit potentials are seen in this disorder. If IBM is suspected, the examiner must look carefully throughout the muscle to properly identify this pattern of involvement. Fibrillation potentials tend to be diffuse and prominent, and fasciculation potentials should be absent.

### ***Hirayama disease***

Hirayama disease is a rare disorder that was initially described in the Japanese literature<sup>26</sup> and subsequently has been described in non-Asian populations. It has also been referred to as *Sobue's neuropathy*, *juvenile focal amyotrophy*, and *monomelic motor neuron disease*. Clinically it presents with unilateral (or at least markedly asymmetric) weakness and atrophy within the C8 and T1 myotomes, with preservation of sensation and absence of pain. It occurs almost exclusively in young, athletic patients, and has a very strong male predominance. The weakness tends to progress for several years before stabilizing. Recent literature suggests that flexion MRI scans of the cervical spine will show an expanded dorsal epidural space.<sup>27</sup> How this translates into anterior horn cell loss and why it is so specific to the lower cervical myotomes is unknown. Hypotheses include venous congestion and secondary ischemia to the anterior horn cells, and compression from the dilated epidural space.<sup>28-31</sup> However, neither is fully adequate in explaining the clinical presentation. This disorder lacks upper motor neuron features, but fasciculations may be prominent. Throughout its course, it tends to remain asymmetric, and complete plegia of the hands is uncommon. Fortunately, patients can be reassured that it does not spread to other regions. Cervical decompression has been reported with mixed results.<sup>31-33</sup>

### **SUMMARY**

1. Multifocal motor neuropathy is an important disorder to distinguish from ALS given its more benign prognosis and treatable nature.
2. IBM is commonly mistaken for ALS given the unique needle EMG features. The clinical pattern of weakness should suggest this disorder and should be examined for carefully on needle EMG.

### ***Other Neurophysiology Techniques***

#### ***Motor unit number estimates***

Motor unit number estimates (MUNEs) represent an attempt to quantitate the number of motor units innervating a muscle or muscle group. A variety of techniques been developed to accomplish this estimation. However, all techniques share a common formula for calculating the MUNE. The supramaximal CMAP for a muscle or muscle group is divided by average size of the individual motor unit potentials as recorded from the surface electrodes. This calculation results in a unitless number that estimates the number of motor axons innervating that muscle group. The difference between the techniques is how the size of the average motor unit potential is

calculated. Quantitating the number of motor units in the motor neuron diseases has obvious advantages. Studies have shown that a decrease in the MUNE counts correlates well with disease progression, and the MUNE has been used as an outcome measure in several ALS clinical trials.<sup>34</sup> Its value in following patients with ALS is its rate of change over time, requiring sequential measurements. Currently, the MUNE techniques are time-consuming, and whether MUNE as a prognosticating factor adds information beyond other clinical measures in ALS is unclear. Furthermore, MUNE is only informative for the muscle examined, providing no information for other regions of the body that may not be evolving at the same rate.

### **Central motor conduction time**

Electrodiagnostic testing is very effective at interrogating the lower motor neuron involvement in ALS. However, a paucity of ancillary testing has been performed for the upper motor neurons. In some patients, imaging will show abnormal signal in the corticospinal tracts. However, this only occurs in a minority of patients in whom the upper motor neuron signs are obvious clinically, limiting its diagnostic value. Stimulation of the motor cortex, either magnetically or electrically, and observing the CMAP responses in the periphery is one method described to interrogate the upper motor neurons.<sup>35</sup> The central motor conduction time is reportedly delayed in ALS with loss of the upper motor neurons. The central motor conduction time is obtained through determining the CMAP latency with cortical stimulation. Because this latency incorporates both central and peripheral conduction times, the peripheral conduction time must be subtracted away to obtain the central conduction time. The peripheral conduction time can either be estimated from the F-wave latency or from root stimulation. From the F-wave latency, the peripheral conduction latency can be derived from the following formula<sup>36</sup>:

$$\text{Peripheral conduction latency} = (\text{CMAP distal latency} + \text{F-wave latency} - 1)/2$$

The central conduction time then represents the motor evoked potential latency with the peripheral conduction latency subtracted away:

$$\text{Central conduction time} = \text{motor evoked potential latency} - \text{peripheral conduction latency}$$

In ALS with upper motor neuron involvement, a delay has been shown in the central conduction time. Magnetic stimulation motor evoked potentials are not FDA-approved in the United States, and motor evoked potentials induced by electrical stimulation require sedation, increasing the risk and complexity of the procedure. As with imaging, abnormalities in the central motor conduction time are typically present in patients with readily apparent upper motor neuron signs on clinical examination, causing the technique to be of little clinical use. Therefore, this technique is not widely used in general clinical practice.

### **Neurophysiology index**

The neurophysiology index (NPI) was developed as a quantitative measure of disease severity in ALS. The initial intent was as a surrogate outcome measure to be used in ALS clinical trials.<sup>37</sup> It is derived from the CMAP amplitude, distal latency, and F-wave frequency. The formula for calculating the index is:

$$\text{NPI} = (\text{CMAP amplitude}/\text{distal latency}) \times \text{F-wave frequency} \%$$

One limitation of the NPI is that it does not represent a specific biologic process, and change in the NPI has no inherent clinical significance. It is not useful as a diagnostic measure, and therefore is not widely used in general clinical practice.

### ***Electrical impedance myography***

Electrical impedance myography (EIM) is a novel and innovative technique being investigated in ALS.<sup>38</sup> This technique bears little resemblance to traditional neurophysiology testing. In EIM, a low-intensity, high-frequency alternative current (AC) is applied through a muscle while the voltage patterns are recorded with surface electrodes overlying the muscle of interest. In diseased muscle, changes are seen in the phases and impedance of the underlying muscle tissue. Currently this technique is not capable of distinguishing diseases diagnostically, but the results do change in a predictable manner with disease progression. A disadvantage of the technique is that it requires special equipment and cannot be performed with standard commercially available neurophysiology equipment. What role this technique will have in the evaluation of neuromuscular disorders is uncertain.

### **SUMMARY**

1. MUNE refer to a group of methods to estimate the number of remaining motor units innervating a muscle group.
2. Loss of the MUNE over time correlates well with ALS progression.
3. Central motor conduction time is a neurophysiology parameter that can be used to interrogate for upper motor neuron involvement.
4. EIM is a new and novel neurophysiology technique currently being investigated in the evaluation of the motor neuron disorders.

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