Motor Neuron Diseases

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Etiology

Motor neuron diseases (MND) are very challenging to diagnose, and it is imperative that the correct diagnosis is reached early after the onset of symptoms, because of the poor prognosis associated with the disease. Amyotrophic Lateral Sclerosis (ALS) is the most frequent form of MND. It causes gradual dysfunction of the upper motor neurons (UMN) and lower motor neurons (LMN). The median survival of ALS is about 2–3 years after onset of symptoms, typically related to respiratory muscle weakness/failure. However, because the disease is variable, there are a few exceptions, with some patients living past the typical estimated life expectancy.

UMN symptoms comprise spasticity, weakness, and pathologic hyperreflexia, and the expression of symptoms varies between patients depending on which motor neurons are affected. LMN signs include fasciculations, cramps, muscle atrophy and weakness. ALS patients are typically diagnosed in late middle age (average age of about 55 years at diagnosis), but more cases have been diagnosed as being genetic/familial affecting much younger adult patients as well. ALS is typically more common in men than in women, but this is rapidly changing as the incidence can equal between men and women with increasing age. Genetic influence plays an important role as more gene mutations are found, some linked with environmental risk factors causing degeneration of the motor neurons. ALS cases were initially described and studied by Jean-Martin Charcot in 1869 as a pure motor neuron disease with a very distinct pathology, and the term amyotrophic lateral sclerosis was later introduced in his 1874 research paper. Nowadays, ALS is considered a multi-systemic disease that can be at times associated with non-motor symptoms, causing dysfunction of the fronto-temporal lobes, cerebellar circuits (as may sometimes be seen in Madras MND), autonomic nervous system, basal ganglia [1], dorsal columns, and even cases described as related to idiopathic sensory neuropathy [2]. Rare forms of ALS that can be inherited in endemic areas and which can present with ALS-Parkinsonism-Dementia complex have also been reported. Madras motor neuron disease (MMND) is another rare subtype of motor neuron disease presenting typically in the young, having weakness and wasting of limb muscles, together with multiple lower cranial nerve palsies and sensorineural hearing loss. Infrequently, there may be cerebellar involvement, with cerebellar atrophy described in at least 1 case [3].

A small percentage of ALS patients may manifest with frontotemporal dementia (FTD) with cognitive deficits, personality changes, and

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behavioral changes (up to 50% of ALS patients with at least some of these features). Even though the majority of cases of ALS are sporadic, now it is considered a genetically heterogeneous disorder with a complex genetic etiology [4]. The most frequently mutated disease genes discovered are: *C9ORF72*, *SOD1* (the first gene mutation identified for ALS), *NEK1* (sporadic and familial cases), *TDP-43* (mostly dominant forms of inheritance cases), and *FUS* (mostly dominant inheritance pattern). *C9ORF72* DNA expansion gene accounts for more ALS cases with a genetic influence (seen in up to ~40%), including a predisposition to developing FTD, and to a lesser extent seen in sporadic cases (up to ~7%). More genes have been discovered that are associated with the development of ALS, and having an understanding of their role in the disease will affect future therapeutic avenues. Nevertheless, there are limitations with genetic testing in patients with suspected family history of ALS, mostly because of variable expression and incomplete penetrance of the genes [4]. ALS has been linked to excessive stimulation of glutaminergic NMDA (activation of glutamate receptors causing elevation of neuronal intracellular calcium, leading ultimately to cell death) and AMPA (*alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate*) receptors, impaired axonal transport, increased oxidative stress, glial cell dysfunction, reactive astrocytes, among other hypotheses, ultimately leading to motor neuron degeneration [5].

Primary Lateral Sclerosis (PLS) selectively affects the UMN with a clinical presentation of spasticity, pathologic hyperreflexia, weakness, and even pseudobulbar affect [6]. It affects about 1–3% of patients diagnosed with MND, with also a slight male predominance. Symptoms can take years to progress; most commonly exhibiting progressive paraplegia, spastic bulbar weakness, or hemiplegia [7]. Overlaps with other diseases have also been documented [8]. The Pringle criteria suggests that the diagnosis is based on clinical findings, appropriate laboratory testing (infectious, metabolic, or toxic), EDX results not meeting El Escorial criteria, and at least 3 years of observation. This is to ensure that the correct diagnosis is made, as it can be easily mistaken with other diseases/mimics. Lack of LMN involvement on EDX, structural lesions on imaging, or family history of hereditary forms of spastic paraplegia, will make the diagnosis of PLS more convincing. Typically, the prognosis of PLS is better when compared to classic ALS. The etiology is considered mostly similar to ALS with a potential combination of genetic and environmental factors.

Progressive Muscular Atrophy (PMA) is another subtype of MND presenting with purely LMN symptoms of: fasciculations, cramps, reduced/absent reflexes, flaccid muscle weakness, and atrophy. It also carries a better prognosis than ALS. Appropriate diagnostic testing and close clinical observation are needed because some patients with initial physical examination suggestive of PMA could progress to develop UMN signs, hence eventually meeting El Escorial criteria for ALS. EDX evaluation is important to differentiate between PMA and multifocal motor neuropathy with conduction block (MMNCB), which is another disorder mostly affecting the motor fibers with sparing of the sensory fibers. MMNCB is an immune-mediated demyelinating motor neuropathy, and it is imperative for it to be excluded during EDX testing and laboratory investigation (associated with GM1 ganglioside antibody). This is especially important since most MMNCB, patients show improvement with immune-modulating therapies (particularly IV immunoglobulin).

Progressive Bulbar Palsy (PBP) presents with selective damage of the motor nerves supplying the bulbar muscles, affecting speech and swallowing, and may affect the facial muscles as well. Most cases are sporadic and some familial ones have been described. Diagnosis is usually delayed because the initial symptoms are mistaken as gastrointestinal or ENT-related conditions. Patients can present with tongue muscle atrophy with fasciculations, drooling, spastic speech, and brisk facial reflexes. It can remain limited to the bulbar muscles, but in some cases, it may be the initial presentation of the ALS type of MND. Close clinical observation and EDX information over time are integral parts of securing the diagnosis. A small study published in 2016 suggested early changes on imaging that could potentially assist in the future when distinguishing among the different MND variants. The study proposed early disease changes seen in diffusion tensor imaging

(DTI) and magnetic resonance spectroscopic (MRS) studies in patients with bulbar-onset and limb-onset ALS. Extra-motor involvement by the corpus callosum is a feature seen in bulbar-onset patients, when compared to limb-onset ALS, and can suggest poor outcome in such patients [9].

Anatomy

The upper motor neurons (pyramidal tracts) originate in the brain's primary motor cortex, and those tracts carry voluntary motor activity from the cortex to the lower motor neurons. These tracts will descend in the spinal cord to synapse with the lower motor neurons at each spinal nerve root level. Each of those axons will innervate several fibers of a skeletal muscle. The major UMN/pyramidal pathway is the corticospinal tracts, which travel down the anterior horn to connect with interneurons and exit the spinal cord to convey voluntary muscle control to the extremities and trunk. The other pyramidal pathway is the corticobulbar tract, which connects to the cranial nerve motor nuclei, like the nucleus ambiguus (supplying motor fibers of the vagus and glossopharyngeal nerves), and motor fibers of the trigeminal, facial, and accessory nerves. Damage to the nucleus ambiguus will affect speech and swallowing because of its control on the pharynx, larynx, and soft palate muscles. Once the nerve exits the spinal cord or brainstem (in the case of cranial nerve motor nuclei) it becomes a lower motor neuron. Electrodiagnostic evaluation (EDX) will specifically assess the function of the lower motor neurons. ALS affects both the upper and lower motor neurons (see Figs. 9.1 and 9.2), and remains a clinical diagnosis. EDX will assist in detecting lower motor neuron dysfunction, with upper motor neuron involvement primarily assessed during physical examination.

From a histopathological point of view, astrocytes are vital in supporting and repairing the nervous tissue, and when they become reactive, they promote motor neuron autophagy. It has been stipulated that motor neuron degeneration has been linked to a reactive state of astrocytes, at times triggered by environmental factors like traumatic central nervous system injuries; however, not fully understood. Hence, increased risk for ALS has also been associated with history of traumatic brain injuries [10]. Typically, ALS starts with symptoms affecting one body segment, and depending on the location and degree of spinal cord motor neuron loss, progressive weakness will ultimately involve adjacent myotomes. The disease will continue to spread to other extremities, or bulbar muscles, producing weakness and respiratory complications, leading to death. Prompt diagnosis is paramount in order to offer available treatment to slow the disease

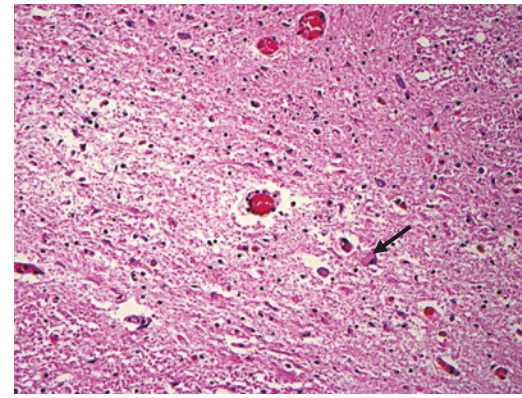

Fig. 9.1 Hematoxylin and eosin stained slide showing loss of neurons in the anterior horn cell region with reactive astrocytes (arrow represents a motor neuron). Courtesy of Dr. Richard Prayson/Section Head of Neuropathology at Cleveland Clinic

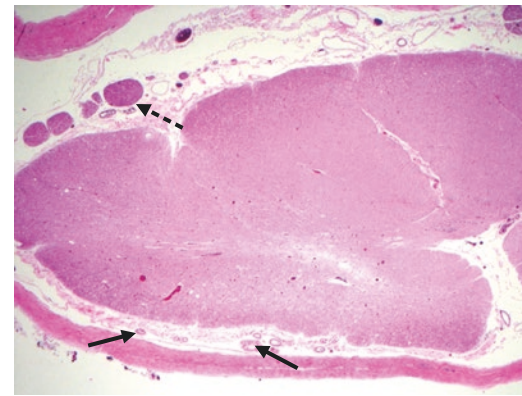

Fig. 9.2 Hematoxylin and eosin stained slide of the cervical spinal cord with atrophy of the anterior spinal rootlets (solid arrows) when compared to the posterior rootlets (dashed arrow). Courtesy of Dr. Richard Prayson/Section Head of Neuropathology at Cleveland Clinic

progression. Two FDA-approved medications are available for the treatment of ALS: Riluzole and Edaravone. Riluzole may modulate and inhibit glutamate neurotransmission, decreasing glutamate-related excitotoxicity. Edaravone has been associated with decreasing oxidative stress. Free radicals/oxidative stress have been linked to motor nerve cell death, increasing the risk of ALS development.

Clinical Features

Motor neuron diseases can be very difficult to diagnose because they can share clinical features, at its earliest presentation, with other diseases/mimics. At onset, the majority of ALS patients will have subtle features of weakness in either an upper or lower extremity. Symptoms then evolve to muscle atrophy, and continue to spread to other myotomes. Depending on the location of motor neuron involvement, it can clinically mimic a mononeuropathy such as at the ulnar nerve, or a lumbar radiculopathy presenting with foot drop. The clinical absence of sensory symptoms should indicate to the clinician that a motor neuron process could be the etiology. If bulbar motor nerves are involved at presentation, then the patients may have spastic and/or flaccid speech, dysarthria, dysphagia, leading to the development of tongue atrophy with fasciculations and drooling. Most of these cases are initially extensively evaluated by other specialists looking for other causes of dysphagia and dysarthria.

The revised El Escorial criteria (see Table 9.1) were published to assist in the correct diagnosis of ALS. Based on the guidelines, there has to be clinical evidence of disease progression, and absence of alternative causes. Signs of upper and lower motor neuron involvement must be present, which may include that supported by electrophysiological evaluation. Neuroimaging is always recommended to exclude mimics. The revised El Escorial criteria classify cases as: suspected, possible, probable, or definite ALS. Appropriate laboratory evaluations are needed to rule-out other etiologies when the diagnosis is in question. At times, repeating EDX testing is required to discern disease progression. This can be considered in cases where the initial symptoms are bulbar, and the patient starts to develop new symptoms spreading to other limbs. Clinical examinations should be performed at least every 6 months for progression. Four regions have been established to describe the involvement/spread of clinical symptoms: bulbar, cervical, thoracic, and lumbosacral. The diagnosis becomes more evident when the features spread within the same region, or involve other regions. Moreover, if there is sensory, sphincter, or autonomic dysfunction, then alternative diagnoses should be considered. A detailed neurological examination, family history, past medical history, medications/toxin exposure history, and onset/evolution of symptoms review need to be carefully taken into consideration when diagnosing MND. More importantly, electrophysiological studies are always recommended to confirm a lower motor neuron process, and are essentially equivalent to clinical LMN findings. Primary Lateral Sclerosis (PLS) often presents as progressive leg weakness, cramps, and stiffness. The disease course is prolonged, and has a better prognosis than ALS. On examination, patients will develop pathologic hyperreflexia and marked spasticity. Some patients can develop cognitive changes and pseudobulbar affect and dysarthric speech. At least 3 years are required for clinical observation, looking for progression or development of features suggestive of LMN involvement, according to The Pringle criteria. EDX evaluation must show lack of a LMN process. Progressive Muscular Atrophy (PMA) also has a prolonged course of symptom development. On physical examination, the patients will show: reduced or absent reflexes, fasciculations, muscle weakness, and ultimately muscle atrophy. Limited forms of the disease have also been described, like flail arm or leg syndromes. The clinician needs to perform close observation over time, looking for UMN signs or features that meet El Escorial criteria, to exclude the possibility of disease progression to classic ALS. Progressive Bulbar Palsy (PBP) presents with early symptoms of speech, drooling, and swallowing dysfunction. Patients can develop tongue and facial weakness with atrophy and fasciculations. Generally, the symptoms remain lim-

Table 9.1 World Federation of Neurology El Escorial criteria for ALS

LMN signs	UMN signs	Regions	Clinically definite	Clinically probable	Clinically possible	Clinically suspected
– Weakness – Atrophy – Fasciculations	– Spasticity – Pathologic hyperreflexia – Extensor plantar response – Pseudobulbar features	**-Bulbar (craniobulbar)** **-Cervical** **-Thoracic** **-Lumbosacral**	**UMN and LMN features:** →bulbar and at least 2 other spinal regions OR →3 spinal regions →absence of other possible etiologies	**UMN and LMN features:** → 2 regions →some UMN signs must be rostral to (above) LMN signs → "Clinically probable, laboratory-supported ALS": UMN signs in 1 or more regions coupled with LMN signs by EMG in at least 2 regions →absence of other possible etiologies	→UMN and LMN signs in 1 region OR →UMN signs in 2 or more regions OR →UMN and LMN signs in 2 regions without UMN signs rostral to the LMN signs →absence of other possible etiologies	→LMN *or* UMN signs only in 1 or more regions →absence of other possible etiologies

Based on the revised El Escorial criteria ("Clinically Suspected" category carried forward from the original criteria). On electromyography, cervical and lumbar region requires involvement of at least 2 muscles innervated by different nerve roots. Bulbar and thoracic region requires involvement of at least 1 muscle per region. *ALS* Amyotrophic lateral sclerosis; *UMN* upper motor neuron; *LMN* lower motor neuron; *EMG* electromyography

ited to the bulbar muscles, but in some cases, it can be the initial presentation of ALS.

Clinically, if there is evidence of widespread LMN process (at least 2 or more regions), then ALS should be suspected, provided that the appropriate diagnostic testing (neuroimaging, laboratory, or genetic testing if warranted) was performed to exclude other possible etiologies. Cognitive testing should also be considered to assess ALS variants like FTD-ALS. More forms of ALS are being described leading to the belief that it is a multi-systemic disease. It has to be recognized that ALS can be associated, in some cases, with mild sensory, autonomic, and cerebellar, among other symptoms.

Differential Diagnosis

Motor neuron diseases have a myriad of symptoms that can be confused with many other diseases at onset [11]. Using the revised El Escorial criteria can assist in the proper clinical evaluation of ALS and its mimics. All of these patients should undergo EDX evaluation, laboratory testing, and neuroimaging studies to exclude other disease possibilities. Requesting imaging studies is very important because a structural lesion can present with both UMN and LMN features. Some examples of structural lesions are: cervical compressive myelopathy/myeloradiculopathy, brainstem or spinal cord tumors, also tandem UMN lesions with LMN lesions from plexopathy, or polyradiculopathy, among others. However, some of these examples may have sensory loss clinical features, and should alert the clinician against the case for ALS. Laboratory studies are recommended to exclude metabolic, toxic (organic pesticides, lead, mercury, arsenic, among others), infectious, or nutritional causes. Vitamin B12 deficiency, thyroid dysfunction, copper deficiency, hyperparathyroidism, heavy metals toxicity, vitamin E deficiency, Lyme disease, HIV myelopathy, and tropical spastic paraparesis (human T-lymphotropic virus type 1 infection), are some other examples. Some of them can present with largely UMN symptoms, like HIV myelopathy and tropical spastic paraparesis. EDX testing can only complement the physical examination, and should not be used in isolation to diagnose ALS. As previously mentioned, EDX evaluation will specifically assess the function of the lower (not upper) motor neurons. One caveat of EDX testing can be seen in multiple sclerosis patients when the plaque involvement is near/at root exit zones, and the patient also has a more typical central nervous system lesion(s). Clinically, the patient will express UMN and LMN involvement, mimicking a motor neuron disease process. Although rare, it may present on EDX testing as a pure LMN process, like a polyradiculopathy. Clinical examination, onset of symptoms review, and neuroimaging will certainly aid in differentiating between the two entities. Post-polio syndrome should be easy to assess, because of prior history of infection and slow muscle weakness and atrophy progression over many years.

Often patients present to the neurologist with muscle twitching or fasciculations, having great concern about the implications of this isolated symptom. In these cases, fasciculation potentials are often detected on EDX evaluation in the absence of any other significant changes. Close clinical observation over time would typically confirm benign fasciculation syndrome, rather than a more sinister motor neuron process. In particular, lack of unequivocal weakness or progressive muscle atrophy suggests a benign disorder like this.

Certain muscle diseases may mimic a disorder of motor neuron dysfunction. This raises the importance of appropriate laboratory including electrodiagnostic testing, and in some cases muscle biopsy to confirm a diagnosis. Inclusion body myositis (IBM) is an idiopathic inflammatory disorder that can present with asymmetric limb weakness (typically, deep finger flexors and quadriceps muscles), with some difficulties in swallowing due to bulbar muscle involvement. IBM can share some EDX features with ALS, hence ideally a muscle biopsy should be performed in suspected cases for diagnosis confirmation. Oculopharyngeal muscular dystrophy is another muscle disease that can present with progressive muscle weakness of the throat, facial, ocular, and eyelid muscles. It can mimic bulbar-onset ALS, specifically when the extraocular muscle symptoms are very subtle at onset. In this case, genetic testing will help in the evaluation. Isolated neck extensor myopathy is one of the etiologies of dropped head syndrome that will show signs of electrical "irritability" on needle electro-

myography testing in the cervical paraspinal muscles, and can be confused with MND at onset. However, it is usually limited and does not spread to other myotomes, such as in ALS. Diseases of the neuromuscular junction may present with LMN features. Myasthenia gravis may present with bulbar symptoms, and at onset can be mistaken for bulbar-onset ALS. To assist in differentiation, blood evaluation [e.g. for acetylcholine receptor and MuSK (muscle-specific kinase) antibodies], and repetitive nerve stimulation on electrodiagnostic testing (or single fiber EMG), can be performed to establish the diagnosis of myasthenia gravis. One should not rely only on symptom improvement with cholinesterase inhibitors to differentiate between them, because some MND patients may express transient symptom improvement with these medications.

Immune-mediated processes should always be investigated further because some could be potentially treatable. Multifocal motor neuropathy with conduction block (MMNCB) presents with a lower motor neuron dysfunction, and needs to be excluded from the progressive muscular atrophy MND variant. MMNCB is a purely motor demyelinating neuropathy that is slowly progressive, and also begins distally as in many ALS cases. Clinically, they can be differentiated by more multifocal individual motor nerves being affected in MMNCB, rather than progressively involving adjacent myotomal distributions as in ALS/MND. Anti-GM1 antibody presence, and motor conduction block (between distal and proximal motor segments) on EDX evaluation, are typical of MMNCB patients. The distinction between these two processes must be made clear because a trial of intravenous immunoglobulin therapy should be considered in MMNCB patients. Stiff person syndrome patients will develop painful cramps and spasticity, thus clinically mimicking a UMN disease. Typically, it affects the truncal muscles, but there are other variants that are segmental or limited to a limb. Blood evaluation for glutamic acid decarboxylase (GAD) antibodies, and paraneoplastic testing, should be performed to exclude underlying malignancy.

Hereditary spastic paraparesis, spinal muscular atrophy, Kennedy's disease (spinal and bulbar muscular atrophy), and hexosaminidase A deficiency (Tay-Sachs disease), are examples of hereditary diseases that may present with some features of MND clinically or electrodiagnostically. Hereditary spastic paraparesis can present with UMN disorder, whereas spinal muscular atrophy will present as slowly progressive muscle weakness because of anterior horn cell/LMN involvement. Kennedy's disease patients will manifest with muscle cramps, tongue weakness/fasciculations, speech disturbance, and limb weakness. There is dysfunction of the motor neurons at the brainstem and spinal cord, which can be confused with classic ALS, but these patients will also show endocrine dysregulation, and genetic testing will confirm the diagnosis. Hexosaminidase A deficiency/adult or late-onset patients can express speech and swallowing problems, but prominent psychiatric and cognitive deficits can differentiate it from bulbar-onset ALS.

Paraneoplastic processes can also manifest with clinical features of MND. Lymphoma can present with lower extremity LMN features. Radiation therapy can manifest with muscle weakness and atrophy, even many years after radiation exposure, and clinically exhibits a pure LMN process. EDX evaluation will be important in this case because myokymic discharges are very commonly seen in radiation-induced processes, particularly plexopathy.

Electrodiagnostic Evaluation

Nerve Conduction Studies

Nerve conduction studies and needle electromyography play an important role in the diagnostic process of motor neuron diseases, but essentially can only evaluate the presence of lower motor neuron dysfunction. Therefore, ALS is a clinical diagnosis, supported by the presence of UMN dysfunction (signs disclosed on neurological exam) and LMN dysfunction (exam and/or EDX findings). EDX evaluation will also serve to exclude potentially treatable alternative etiologies, including a demyelinating motor/motor-predominant polyneuropathy. Careful testing of several motor nerves should be performed to increase the probability of finding a motor con-

duction block or focal/segmental demyelination. At times, proximal nerve stimulation can be considered, or contralateral studies, to look for pertinent features including motor conduction block. In addition, if the late-responses are abnormal and the motor studies are normal, contralateral or proximal motor nerve studies are recommended.

Upper and lower extremities must be assessed on nerve conduction studies (NCS). Features of motor axonal loss are classic findings of LMN involvement in ALS. Decreased compound muscle action potentials (CMAP), with relatively normal distal latencies and conduction velocities are typical findings seen with motor axonal loss. If there is involvement of the largest and fastest conducting axons, then there could be mild slowing of the conduction velocities; however, not to the degree seen in a demyelinating process. Only the fastest conducting fibers are measured on conduction velocities and latency testing on NCS. If there is marked motor axonal loss, the CMAP will drop, but the distal latencies and conduction velocities should remain essentially normal (or almost normal), because there will be a few of the fastest conducting fibers still left unaffected. These fibers can only drop to ~75% of the lower limit of normal conduction velocity because these myelinated fibers cannot conduct slower than this range. Distal latencies can be prolonged, but will not be greater than ~130% of the upper limit of normal. Applying these concepts to the evaluation of MND is important to exclude a demyelinating neuropathy. When there is a complete motor conduction block, there is a drop of more than 50% of the CMAP amplitude or area, when comparing the distal and proximal stimulation sites (with or without associated temporal dispersion). This tends to become marked when the nerve is studied utilizing a long distance between stimulation sites. Sensory nerve conduction studies should be normal in MND/ALS, except in those cases where there is a superimposed process like a mononeuropathy or polyneuropathy, in which case relevant investigations should be performed looking for other etiologies.

Routine motor studies should be performed on the following nerves: median (recording at abductor pollicis brevis; stimulating at the wrist and antecubital fossa), ulnar (recording at the abductor digiti minimi; stimulating at the wrist and at below-elbow and above-elbow sites), peroneal (fibular) (recording at extensor digitorum brevis; stimulating at the ankle, below the fibular neck, and lateral popliteal fossa), and tibial (recording at abductor hallucis; stimulating at the ankle and popliteal fossa). Consider peroneal (fibular) motor studies recording at the tibialis anterior muscle if the peroneal (fibular) motor study recording at the extensor digitorum brevis muscle is abnormal. If the CMAP amplitudes are low at the median/abductor pollicis brevis or ulnar/abductor digiti minimi, a brief post-exercise stimulation should be performed to evaluate the presence of a presynaptic disorder of neuromuscular junction transmission. The ulnar/first dorsal interosseous muscle response is also recommended, especially as it pertains to the demonstration of a "split-hand pattern" which may be seen in ALS.

Sensory nerve action potential (SNAP) studies should include the following nerves: median (stimulating at the wrist; recording at second digit), ulnar (stimulating at the wrist; recording at fifth digit), radial (stimulating at the forearm; recording at base of the thumb), superficial peroneal (fibular) (stimulating at the lateral leg; recording at the ankle), and sural (stimulating at the posterior portion of the calf; recording at the posterior ankle). Late responses are important and should include: F-waves (median, ulnar, peroneal (fibular), and tibial nerves), and tibial H-reflexes. Any abnormality should be compared to the contralateral side. More proximal motor nerve stimulation could be considered looking for conduction block, but may be limited due to location and supramaximal stimulation pitfalls at the axilla or Erb's point. Late responses could also be minimally abnormal in MND/ALS, mostly reflecting the reduced number of motor neurons available for the response, but are not typically expected to be absent or significantly delayed, as may be seen in a severe polyradiculopathy.

Needle Electrode Examination

Needle electromyographic assessment must be comprehensive and must show evidence of widespread denervation and re-innervation, specifically in the majority of the four regions discussed previously, and in at least two muscles of different spinal nerve root innervation within each limb region.

Table 9.2 Recommended muscle selections for needle electrode examination- motor neuron disease protocol

Upper extremity	Lower extremity	Craniobulbar	Paraspinal muscles
→first dorsal interosseous →abductor digiti minimi →abductor pollicis brevis →flexor pollicis longus (if question of inclusion body myositis) →extensor indicis proprius →pronator teres →biceps brachii →triceps →deltoid	→tibialis anterior →medial gastrocnemius →tibialis posterior or flexor digitorum longus →rectus femoris or vastus lateralis →gluteus medius	→tongue **Consider:** →sternocleidomastoid →masseter →facial muscles	→cervical **→thoracic (must be performed- typically, mid or low thoracic levels)** →lumbosacral

Abnormal spontaneous activity (fibrillation, positive sharp wave, and/or fasciculation potentials) are usually very prominent in a motor neuron disease process. However, fasciculation potentials alone are not sufficient to be considered as evidence of active/ongoing denervation, as they can be seen in other diseases, or may be a benign finding in some cases. Nonetheless, in MND, fasciculation potentials tend to be large with multiple turns and/or phases comprising a complex "bizarre-appearing" morphology. Noteworthy is the added pathological/diagnostic significance that is conferred by fasciculation potentials when there is superimposition of chronic motor axon loss changes in the same muscle (added diagnostic yield from the Awaji criteria, compared to the revised El Escorial criteria). Complex repetitive discharges (CRDs) can be seen in chronic lower motor neuron processes, but are not a particularly common feature in MND. Abnormal needle EMG findings must show involvement of different myotomes, with careful evaluation of possible sparing of individual nerves that could suggest another process, such as MMNCB.

Careful evaluation of motor unit action potentials (MUAPs) are key in the assessment of a lower motor neuron process. Features of chronic axon loss will be manifested by MUAP configurational changes- high amplitude, long duration, and may include increased polyphasia. There is often evidence of motor unit instability, as typically evidenced by "moment-to-moment amplitude variation". Decreased recruitment would also reflect the loss of motor units. Recruitment analysis will be essential when differentiating a lower motor neuron process from a myopathic process (including one with overalapping denervation/neurogenic) features. With LMN lesions, recruitment is reduced (including the rapid firing frequency of affected MUAPs), but in myopathies there is typically "early" recruitment (of MUAPs which are polyphasic, but short in duration and low in amplitude).

The recommended protocol for needle electromyography should include at least two limbs (distal and proximal muscles of different spinal nerve root innervation), thoracic paraspinal muscles (typically at the mid and low thoracic levels), and may also include craniobulbar muscles (important when excluding the possibility of superimposed cervical or lumbosacral polyradiculopathy). Active/ongoing denervation findings in the thoracic paraspinal muscles are commonly seen in most patients with MND/ALS, and several segments should be examined to increase diagnostic yield. Please refer to Table 9.2 for our recommended protocol of muscle selection for needle electrode examination in motor neuron disease cases.

Electrodiagnostic Pitfalls and Limitations

Sensory nerve action potentials are essential when demonstrating that there is definite electrodiagnostic evidence of a motor neuron process. As mentioned previously, SNAPs are expected to be normal in lower motor neuron disease. However, if the patient has a superimposed mononeuropathy, or polyneuropathy (or plexopathy), then the results can seem confounding because of reduced SNAPs. In this case, history, physical examination, and additional testing may assist in the differential diagnostic investigation. Motor nerve studies must be evaluated with cau-

tion, because the examiner has to specifically exclude MMNCB. If there is any indication of selective motor nerves being affected, with sparing of other individual motor nerves, MMNCB (or multifocal motor neuropathy) has to be considered. Since a complete motor conduction block has been established as greater than 50% drop in CMAP amplitude or area between distal and proximal nerve stimulation sites, there needs to be vigilance to prevent spurious responses with similar changes. Accordingly, if supramaximal nerve stimulation was not achieved (or if there are technical factors related to large body habitus), then responses may exhibit a motor conduction block pattern, leading to misdiagnosis. For example, a patient can be misdiagnosed as having a demyelinating polyneuropathy, when the underlying pathological entity is actually motor neuron disease. This can result from improper testing of nerve conduction responses, and the inability to acquire the SNAPs correctly, and consequently documenting an abnormal or absent response which should otherwise be present. Therefore, proficiency in nerve conduction studies is of paramount importance.

Again, at times it is recommended to repeat electrodiagnostic testing after several months to confirm progression of disease over time and to ascertain the diagnosis. Moreover, cervical and lumbosacral polyradiculopathies can manifest with the same nerve conduction features of a lower motor neuron disease, mostly because the SNAPs are normal (lesions are proximal to the dorsal root ganglia). However, in these patients, sensory symptoms and signs are typically present, contrasting with MND patients.

Late responses are not expected to be significantly abnormal in most cases of MND/ALS. This finding can be seen in the late or end stages of the disease, as more motor neurons become affected and can't contribute to the late response. As more of the largest and fastest the constituent fibers are affected, the F-wave latencies are expected to be progressively prolonged. Significant abnormalities of the late responses are commonly seen in a polyradiculopathy, and this feature could assist the electromyographer when making the distinction between this entity and MND, but it is generally not considered sufficient, especially as an isolated finding.

Needle electromyography also has some limitations during the evaluation of a lower motor neuron disease process. Accordingly, the assessment has to be comprehensive and should involve sufficient coverage of the majority of regions (craniobulbar, cervical, thoracic, and lumbosacral). There should be the aforementioned electrical evidence of active/ongoing and chronic axon loss (i.e. overlapping features of denervation and reinnervation), spanning different nerve roots/myotomes, which cannot be reasonably explained by any other etiologies. Thoracic paraspinal muscles are of paramount importance when differentiating motor neuron disease from a polyradiculopathy, as typically they will be abnormal in MND. In contrast, a polyradiculopathy is commonly seen at the cervical and lumbar regions, and is much less likely at the thoracic region. Moreover, some fasciculations can be seen during the needle EMG of patients with a polyradiculopathy (or any other neurogenic process), and need careful interpretation. Fasciculations alone cannot be considered as evidence of active/ongoing denervation. However, in conjunction with chronic motor axon loss changes, they may have similar significance per the Awaji criteria.

Other caveats in the interpretation of needle electromyography include patient's tolerance for testing (intolerance usually manifested by suboptimal activation of MUAPs), and their ability to complete the full extensive protocol. Intolerance issues (e.g. from pain-related effects) could lead to incomplete estimation of MUAP recruitment, because of suboptimal MUAP activation. Additionally, incomplete muscle relaxation hampers reliable spontaneous activity assessment. This is commonly seen during craniobulbar muscle needle EMG, especially with impaired relaxation typically encountered when examining the tongue muscle.

Adequate discussion, including clarification of expectations should occur before requesting electrodiagnostic study to ensure that the patient understands the testing procedure, especially as the MND protocol is very extensive.

Some chronic muscle diseases can be very challenging to differentiate from a motor neuron disorder, particularly if there are superimposed chronic denervation-type changes (as can be commonly seen in inclusion body myositis). On

needle electromyography, they may exhibit chronic neurogenic changes with or without abundant spontaneous activity abnormalities (fibrillation potentials/positive wave potentials) which may be seen in both active/ongoing denervation and myopathy with inflammatory/necrotizing features. Therefore, these disorders can sometimes mimic a motor neuron process. As mentioned previously, the MUAP recruitment pattern can be used to differentiate between the two, as well as history and physical examination, and other laboratory testing (e.g. creatine kinase level). This is why electrodiagnostic testing alone cannot be used to diagnose a motor neuron disease, and can only be a component (albeit an important one) of the comprehensive evaluation. Amyotrophic lateral sclerosis remains a clinical diagnosis, supported by electrodiagnostic testing, neuroimaging, laboratory studies, and history/physical examination findings. On this basis, it may be prudent that the interpretation section of the EDX study does not claim that the pertinent results are "diagnostic" for MND/ALS, but rather are compatible/consistent with this diagnosis in the appropriate clinical context.

Case Study

A 68 year-old right-handed Caucasian woman, with a past medical history of hypertension, was referred for progressive left foot drop for about 4 months. The weakness started very distally at the toes, then slowly progressed proximally to involve the ankle. There was no lower back pain, limb numbness or paresthesia, symptoms of bowel/bladder dysfunction, or prior history of falls or trauma. She saw a neurosurgeon who advised her that there was no surgical intervention needed for the essentially unremarkable lumbar spine findings on MRI. There was no involvement of the right lower extremity, or the upper extremities. There were no symptoms of craniobulbar or respiratory muscle weakness. At another facility, she was recently diagnosed with a severe, subacute on chronic mixed axonal-demyelinating peripheral polyneuropathy, based on electrodiagnostic testing, and intravenous immunoglobulin therapy had been commenced. There is no family history of neurodegenerative diseases.

On initial neurological examination: mental status, cranial nerves, and spine/straight leg raise test were normal/negative. Both upper extremities and the right lower extremity were normal in motor and sensory examination. The left lower extremity had mild-to-moderate diffuse muscle atrophy, mostly distal to the knee with motor strength graded at 3- to 4−/5 (MRC scale), throughout the left L2-S1 myotomes. No fasciculations, no tongue atrophy, dystonic posturing, tremors, dysmetria or spasticity were noted. Reflexes were 2+ throughout, even in the context of the weakness noted in the left lower limb. Plantar responses were mute bilaterally, and there was no clonus. Sensory examination was normal to all modalities tested.

Since the history, neurological examination, and recent electrodiagnostic testing were rather contradicting, we decided to order additional testing. A lumbar puncture was performed showing normal: cell count, protein, glucose, albumin, IgG index/synthesis rate, myelin basic protein, culture, and smear. In addition, she tested negative for CSF Lyme antibodies, VDRL, and oligoclonal bands. On blood testing she had normal/negative: 24-hour urine heavy metal panel, comprehensive ganglioside panel, GAD antibody, vitamin B-12, comprehensive metabolic panel, Lyme IgG/IgM, CBC, ESR, and CRP. Neuroimaging showed multilevel degenerative changes in the cervical spine, and very minimal disc degeneration in the lumbar spine without evidence of significant central canal or neuroforaminal stenosis. There was evidence of widespread chronic ischemic white matter changes on the brain MRI, but no acute findings were seen.

On the follow-up appointment 6 months later, there was now more progressive leg weakness, involving the right lower extremity, and hands. She had subjective symptoms of mild swallowing dysfunction, without breathing difficulties. Sensory examination remained normal. Reflexes were now pathologically brisk, and mild spasticity was noted in the lower extremities. Considering normal testing, including CSF protein level, the patient agreed to have the electrodiagnostic testing repeated. Please refer to Table 9.3 for EDX study results.

Table 9.3 Case electrodiagnostic data

Sensory Nerve Conduction

Nerve	Stimulus	Recording	B-P Amp (μV)		LatNPk (ms)		CV (m/s)		Dist (mm)		Norm B-P Amp	Norm LatNPk	Norm CV	Temp (°C)	
			L	R	L	R	L	R	L	R				L	R
Sural	Lower Leg	Lat Malleolus	12.17		3.88		n/a		140		>3 uV	<4.6 ms	>40 m/s	31.9	
Superficial Per	Lower Leg	Ankle	6.25		3.64		n/a		100		>3 uV	<4.6 ms	>40 m/s	31.8	
Median	Wrist	Index	13.49		3.70		n/a		130		>10 uV	<3.8 ms	>50 m/s	32.8	
Ulnar	Wrist	5th Dig	16.02		2.80		n/a		110		>5 uV	<3.2 ms	>50 m/s	32.6	

Motor Nerve Conduction

Nerve	Recording	Stimulus	B-P Amp (μV)		LatOn (ms)		CV (m/s)		Dist (mm)		Norm B-P Amp	Norm Distal LatOn	Norm CV	Temp (°C)	
			L	R	L	R	L	R	L	R				L	R
Peroneal (fibular)/ EDB	EDB	Ankle	**2.40**		4.60		n/a		70		>2.5 mV	<6 ms	>40 m/s	32.3	
		Pop Foss - Knee	**2.00**		13.75		45.4		415					32.4	
Tibial/AH	AH	Ankle	4.01		4.05		n/a		80		>4 mV	<6 ms	>40 m/s	32.7	
		Pop Foss - Knee	**3.77**		13.20		44.8		410					32.8	
Peroneal (fibular)/ TA	TA	Below Fib Head	**2.67**		2.45		n/a				>3 mV	<4.5 ms	>40 m/s	33.1	
Median	APB	Wrist	5.32		3.90		n/a		50		>5 mV	<4 ms	>50 m/s	33.0	
		Elbow	**4.92**		9.10		57.7		300					33.0	
Ulnar/ADM	ADM	Wrist	9.26		2.96		n/a		50		>7 mV	<3.1 ms	>50 m/s	33.2	
		Below Elbow	8.68		6.90		58.2		230					32.9	
		Above Elbow	8.41		8.90		55.5		330					33.1	
Ulnar/1stDI	1stDI	Wrist	7.28		3.05		n/a				>7 mV	<4.5 ms	>50 m/s	33.3	

F-Wave Side-To-Side Comparison Table

Nerve	Stimulus	Recording	F-Waves Lat (ms)	
			L	R
Tibial/AH	Ankle	AH	56.70	
Ulnar/ADM	Wrist	ADM	29.00	

H-Reflex Summary Table				M-Wave		H-Wave	
Nerve	Stimulus	Recording	Side	Lat (ms)	Amp (mV)	Lat (ms)	Amp (mV)
	Pop Fossa	Soleus	Left	5.5ms	9.6mV	33.7ms	1.7

Needle EMG Summary																	
Side	Muscle	Ins Act	Fib	PW	Fasc	Other	Number	Recruit	Dur	Dur	Amp	Amp	Poly	Poly	Descript	Descript	Descript
L	1st Dorsal Inter	Norm	1+	1+	0+		2-	Rapid	Many	1+	Many	1+		Norm	NC	NC	NC
	Abduc.Pol.Brevis	Norm	1+	0	1+		3-	Rapid	All	1+	All	1+	Some	1+	ATR	NC	NC
	Abduc.Digiti.Minimi	Norm	0	0+	0		2-	Rapid	Many	1+	Some	1+		Norm	NC	NC	NC
	Flex.Pollicis Longus	Norm	0	0+	0		1-	Mod-R	Some	1+	Some	1+		Norm	NC	NC	NC
	Extn. Indicis Pro	Norm	0+	0	0+		1-	Rapid	Many	1+	Many	1+		Norm	NC	NC	NC
	Pronator Teres	Norm	0	0+	0+		1-	Mod-R	Few	1+	Few	1+		Norm	NC	NC	NC
	Biceps Brachii	Norm	0	0	0+		Norm	Full		Norm		Norm		Norm	NC	NC	NC
	Triceps-Lat	Norm	0	0	0		1-	Mod		Norm		Norm		Norm	NC	NC	NC
	Deltoid, Middle	Norm	1+	0	0+		1-	Mod-R	Few	1+		Norm	Few	1+	NC	NC	NC
	SCM	Norm	0	0+	0		1-	Mod-R	Few	1+	Few	1+		Norm	NC	NC	NC
	Cervical PSP (Low)	Norm	1+	0	1+			NE							NC	NC	NC
	Abductor Hallucis	Norm	0	0	0+	MTP	3-	Mod-R	Many	1+	Many	1+		Norm	NC	NC	NC
	Extn. Digitorum Brv	Norm	0+	0	0+		3-	Mod-V	Most	1+	Many	1+		Norm	NC	NC	NC
	Flex. Digitrum Longus						2-	Mod-R	Many	1+	Some	1+		Norm	NRLX	NC	NC
	Tibialis Anterior	Norm	2+	1+	1+		3-	Rapid	Most	1+	Many	1+	Some	1+	MMAV	NC	NC
	Gastroc. Medial H	Norm	0	1+	0+		2-	Mod-R	Many	1+	Some	1+	Few	1+	NC	NC	NC
	Rectus Famoris	Norm	0+	0	0		1-	Mod-R	Few	1+	Few	1+		Norm	NC	NC	NC
	Vastus Lateralis	Norm	1+	0	0		2-	Mod-R	Many	1+	Many	1+		Norm	NC	NC	NC
	Gluteus Medius	Norm	0	1+	0		2-	Mod-R	Many	1+	Many	1+	Few	1+	NC	NC	NC
	Lumbar PSP (Low)	Norm	0	0+	0			NE							NC	NC	NC
	Tongue	Norm	1+	0	1+		1-	Mod-R	Few	1+	Few	1+		Norm	NC	NC	NC
	Thoracic PSP (Mid)						2-	Mod-R	Many	1+	Few	1+	Some	1+	NRLX		
	Thoracic PSP (Low)	Norm	1+	0	1+		1-	Mod-R	Few	1+	Few	1+		Norms	NC	NC	NC

Abbreviations: *ATR* atrophy; *MMAV* moment-to-moment amplitude variation; *MTP* myotonic potential; *NE* recruitment pattern not examined (muscle examined at rest only) *NRLX* not relaxed; *SCM* sternocleidomastoid; *EDB* Extensor digitorum brevis; *AH* Abductor hallucis; *TA* Tibialis anterior; *APB* Abductor pollicis brevis; *ADM* Abductor digiti minimi; *1st DI* First dorsal interosseous; *PSP* Paraspinals

Considering the nerve conduction findings, especially the preserved SNAPs, we decided to perform a more extensive needle electromyography evaluation, conforming to the lab's MND protocol. Widespread chronic MUAP neurogenic changes (including increased duration and amplitude, with or without polyphasic units), with evidence of active/ongoing denervation (fibrillation and positive sharp wave potentials) in addition to scattered fasciculation potentials were seen in the muscles of the left upper and lower extremities, as well as the thoracic and craniobulbar regions. No myopathic units were seen. The findings spanned multiple nerve roots/myotomes (also implicating progression from the initial areas described as involved), correlating with the most recent worsening of clinical features disclosed at the follow-up office visit. Collectively, the results were consistent with a generalized active/ongoing on chronic motor axon loss process (conspicuously sparing sensory responses) compatible with an evolving widespread disorder of anterior horn cells/motor neurons.

These results cannot be explained by the neuroimaging, or laboratory/spinal tap results obtained. In this case, it became apparent that the diagnosis of MND/ALS was strongly supported by the latest EDX study, and that the initial study produced erroneous results and interpretation. Electrodiagnostic testing should be repeated for cases in which the clinical presentation is not consistent the EDX results provided. A repeat EDX study may also serve to more objectively demonstrate progression of disease. It is imperative to have the appropriate expertise when performing these studies. In this case, pertinent alternative etiologies were excluded by comprehensive testing.

ALS patients should ideally be further evaluated and managed at ALS multidisciplinary clinics, consistent with recommended best practice guidelines. Such specialized ALS clinics typically provide timely access to several services/resources including assistive devices/adaptive equipment, non-invasive ventilation, feeding tubes, and referral to other medical specialists (e.g. pulmonary, physical/occupational therapy, nutritionist), as well as referral to a medical social worker. Although the diagnosis of ALS may be initially difficult to elucidate, prompt diagnosis can allow the patient to have an opportunity to receive treatment/supportive care that could increase quality of life, even if the improvement in longevity is not very marked.

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