ALS and Other Motor Neuron Diseases

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ABSTRACT

Purpose of Review: This review describes the most common motor neuron disease, ALS. It discusses the diagnosis and evaluation of ALS and the current understanding of its pathophysiology, including new genetic underpinnings of the disease. This article also covers other motor neuron diseases, reviews how to distinguish them from ALS, and discusses their pathophysiology.

Recent Findings: In this article, the spectrum of cognitive involvement in ALS, new concepts about protein synthesis pathology in the etiology of ALS, and new genetic associations will be covered. This concept has changed over the past 3 to 4 years with the discovery of new genes and genetic processes that may trigger the disease. As of 2014, two-thirds of familial ALS and 10% of sporadic ALS can be explained by genetics. TAR DNA binding protein 43 kDa (TDP-43), for instance, has been shown to cause frontotemporal dementia as well as some cases of familial ALS, and is associated with frontotemporal dysfunction in ALS.

Summary: The anterior horn cells control all voluntary movement: motor activity, respiratory, speech, and swallowing functions are dependent upon signals from the anterior horn cells. Diseases that damage the anterior horn cells, therefore, have a profound impact. Symptoms of anterior horn cell loss (weakness, falling, choking) lead patients to seek medical attention. Neurologists are the most likely practitioners to recognize and diagnose damage or loss of anterior horn cells. ALS, the prototypical motor neuron disease, demonstrates the impact of this class of disorders. ALS and other motor neuron diseases can represent diagnostic challenges. Neurologists are often called upon to serve as a ''medical home'' for these patients: coordinating care, arranging for durable medical equipment, and leading discussions about end-of-life care with patients and caregivers. It is important for neurologists to be able to identify motor neuron diseases and to evaluate and treat patients affected by them.

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INTRODUCTION

The term motor neuron disease refers to various disease entities that result in progressive degeneration of motor neurons. The term motor neuron disease is also sometimes used interchangeably with amyotrophic lateral sclerosis (ALS), which is the most common disease in this category.

Motor neuron diseases can be hereditary or acquired and vary in underlying pathology and clinical presentation. ALS can affect both the lower motor neuron and the upper motor neuron, but most motor neuron diseases affect only the lower motor neuron.

The lower motor neurons are located in the spinal cord anterior horn and in the brainstem (motor nuclei of cranial nerves) and innervate the skeletal muscles. Since lower motor neurons of the spinal cord reside in the anterior horn, these diseases are also sometimes referred to as anterior horn cell diseases. The upper motor neurons are located in the motor cortex and give rise to the corticospinal and corticobulbar tracts.

KEY POINT

■ A motor unit is one motor neuron, its axon, and all the individual muscle fibers it innervates.

TABLE 1-1 Motor Neuron Diseases

- ALS
- Multifocal motor neuropathy
- Spinal muscular atrophy
- Spinal bulbar muscular atrophy/Kennedy disease
- Monomelic amyotrophy
- Poliomyelitis
- West Nile virus
- Paraneoplastic motor neuron disease[a]

ALS = amyotrophic lateral sclerosis.
[a] For more information on paraneoplastic motor neuron disease, please see the article "Paraneoplastic Neuropathies" by Srikanth Muppidi, MD, and Steven Vernino, MD, PhD, FAAN, in this issue of *Continuum*.

See **Table 1-1** for a list of the most common motor neuron diseases, which are discussed in this article. Of these, ALS is more common than all the others, so an adult presenting with motor neuron symptoms is most likely to have ALS.

The clinical hallmark of motor neuron disease is lower motor neuron dysfunction: atrophy, weakness, and fasciculations of affected motor units. A motor unit is one motor neuron, its axon, the neuromuscular junction, and all the individual muscle fibers it innervates (**Figure 1-1**[1]).

As the motor neuron undergoes apoptosis, the motor nerve axon degenerates, and the neuromuscular junction is destroyed. Muscle fibers innervated by that axon will be denervated and, subsequently, atrophy.

Electrically, the individual fiber will show fibrillations and positive waves, a marker of the instability of the denervated muscle membrane. When contracting as a group, the fibers of an affected motor unit will fasciculate, which can be seen clinically and electrically on EMG. Initially, with an acquired motor neuron disease, adjacent motor nerve axons will reinnervate the muscle

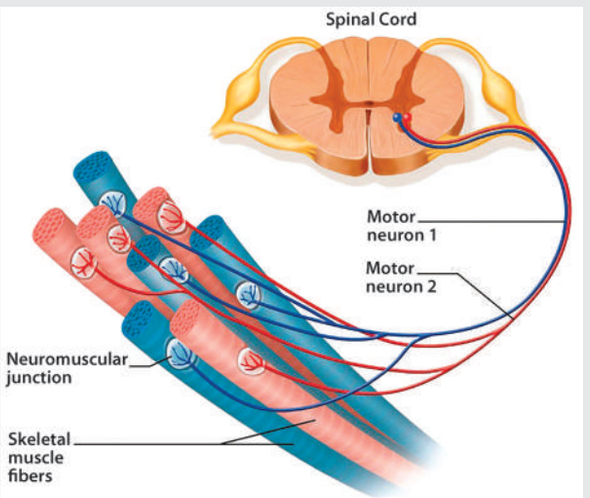

FIGURE 1-1 Motor unit. A motor unit consists of the anterior horn cell or lower motor neuron and all the skeletal muscle fibers it innervates. The number of muscle fibers in a motor unit may vary depending on the muscle. Depicted are two motor neurons that each innervate four fibers.

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fibers (causing a reinnervation pattern on EMG). However, as these motor neurons die too, eventually there are not enough motor neurons left for reinnervation and the predominating process that occurs is denervation.

Motor neurons of cranial nerve nuclei are variably affected, depending upon the disease and phenotype. Cranial nerves XI and XII are most often affected, especially with ALS and spinal bulbar muscular atrophy/Kennedy disease. Cranial nerves III, IV, and VI (extraocular muscle nuclei) are affected late, or never, in these diseases.

DIAGNOSIS

Motor neuron diseases are diagnosed clinically. Supportive testing, such as nerve conduction studies and EMG can confirm active denervation, which indicates loss of the motor neuron. For specific differential diagnoses, genetic testing or infectious disease titers can confirm the underlying pathology. These tests will be discussed in detail for each pertinent disease. Imaging does not play a role in the diagnosis of motor neuron disease, other than to exclude mimics.

Electrical Studies in Motor Neuron Disease

Nerve conduction studies and EMG can be very useful in the diagnosis of motor neuron disease. Electrodiagnostic studies reflect that sensory function is preserved while motor function is affected. Specifically, in the setting of advanced motor axon loss, nerve conduction studies may show low compound muscle action potential amplitudes with normal sensory nerve amplitudes. This may not apply to spinal bulbar muscular atrophy/Kennedy disease, which often has some sensory involvement on nerve conduction studies.

EMG in motor neuron disease will eventually show both active denervation and reinnervation in affected myotomes. A pattern of (1) low-amplitude compound muscle action potentials with preserved sensory responses on nerve conduction studies; (2) denervation changes (fibrillations, positive waves); and (3) and reinnervation changes (reduced numbers of large-amplitude, long-duration, polyphasic motor unit potentials) will be documented by the electromyographer. If a polyradicular pattern of denervation/reinnervation is seen (ie, more than one or two radicular levels), then the electromyographer must consider a motor neuron disease as the etiology of the pattern. EMG performed for suspected ALS must include at least three regions of the neuraxis to confirm a widespread pattern of denervation/reinnervation beyond regional damage from radiculopathies.

KEY POINT

- EMG performed for suspected ALS must include at least three regions of the neuraxis to confirm a widespread pattern beyond regional damage from radiculopathies.

CLINICAL DISEASES

ALS

ALS is the most common acquired motor neuron disease. ALS affects more than the motor neurons and is often associated with cognitive abnormalities (frontotemporal dysfunction) and pseudobulbar affect.

About 5000 people in the United States are diagnosed with ALS each year. The incidence worldwide is estimated to be 4 to 8 per 100,000 individuals. The mean age of onset is 56 years in individuals without a known family history and 46 years in individuals with familial ALS. The male to female ratio is 1.6 to 1. Average disease duration from onset of symptoms is about 3 years, but it can vary significantly. Patients usually die of respiratory failure.[2]

The primary feature of ALS is motor neuron dysfunction, which typically begins in one limb or one region of the spinal cord, but may also begin in cranial nerve nuclei, which is termed "bulbar" onset ("bulb" being an antiquated term for the brainstem). Limb onset occurs in 80% and bulbar onset in 20% of cases. Patients will often report gradual onset of

KEY POINTS

- It is not uncommon for fasciculations to go unrecognized by the patient and only be noticed by a family member or physician.
- Progression and spread of symptoms are hallmarks of ALS.
- ALS is often described as painless, but muscle cramps can be quite uncomfortable and, at times, painful.

weakness and may or may not recognize the muscle wasting and fasciculations (**Case 1-1**). It is not uncommon for the fasciculations to go unrecognized by the patient and only be noticed by a family member or physician.

The patient with ALS may then develop either spread of the weakness to the opposite limb or to another region of the brain or spinal cord; progression and spread of symptoms are hallmarks of ALS. The patient may also develop upper motor neuron signs and symptoms (eg, spasticity, weakness, hyperreflexia) in that limb or in another limb. Patients will often report the spasticity and weakness as stiffness but rarely as pain. Muscle cramps can occur in ALS and can be quite uncomfortable and, at times, painful.

Some patients have a predominantly upper motor neuron presentation of weakness and spasticity, while others have lower motor neuron predominant symptoms (**Figure 1-2**). Some patients have a combination of both in the same limb. No two patients will have the same presentation, although certain patterns are seen more often than others (**Table 1-2**).

Bulbar-onset ALS has a combination of upper motor neuron/lower motor neuron presentation that starts in bulbar muscles (pharyngeal, oral, and occasionally respiratory). These patients tend to have a shorter life span because of the critical nature of bulbar muscle function in eating, swallowing, and breathing. Primary lateral sclerosis is an upper motor neuron–only disease that has a slow progression and manifests with exclusive upper motor neuron symptoms. Primary muscular atrophy is a lower motor neuron–only disease and may have either a rapid progression or slow progression. A predominantly lower motor neuron form of ALS that starts in the upper extremities is called the brachial diplegia variant. It is more common in men, and patients will have severe arm/hand paralysis early with relatively preserved leg and bulbar function for a while.

Cognitive and behavioral abnormalities, in the form of frontotemporal dysfunction, occur in up to 50% of patients with ALS.[3] The cognitive and behavioral abnormalities may be present at the onset of the disease but may not be recognized initially and may require a dedicated neuropsychological assessment. Patients are often unaware of any cognitive and behavioral changes,

Case 1-1

A 64-year-old right-handed man presented to the neurology clinic with a chief concern of not being able to lift things. He had seen his primary care physician and an orthopedist for this problem. The patient stated that his symptoms had been present for 3 months, but his wife reported symptoms for at least 6 months.

On examination, with the patient in a gown, there was atrophy in the right arm. Fasciculations were noted in the right biceps brachii and left deltoid. The patient was not aware of these fasciculations. The patient had reduced strength in right arm muscles and subtle weakness in the left arm muscles. There was no sensory loss. Reflexes were brisk in both arms, and the patient had a prominent jaw jerk.

On EMG, the right deltoid, right biceps, and right first dorsal interosseous had increased insertional activity with fibrillations. In the right biceps, frequent fasciculations were recorded.

Comment. This case demonstrates several features of ALS. One, there is often an insidious onset, and a family member may notice symptoms before the patient. Second, patients will often be referred to other specialists due to the weakness. Next, patients with neuromuscular problems should always be examined while they are wearing a gown; proximal muscle atrophy and fasciculations may not be noticed otherwise. Finally, EMG findings are often patchy, especially early in the disease; several muscles may need to be examined for denervation and reinnervation changes.

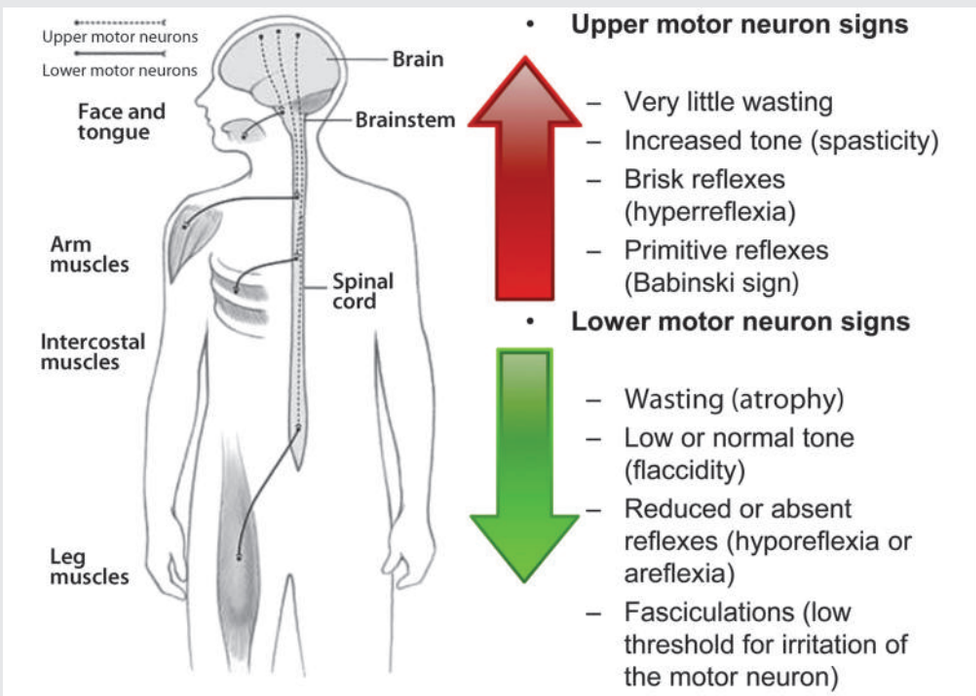

FIGURE 1-2 Upper motor neuron and lower motor neuron signs that are seen in addition to weakness.

and family members may mistake these changes for argumentativeness, fear, or stubbornness. The frontotemporal dysfunction may be significant enough to reach the more strict criteria of frontotemporal dementia in about 15% of patients. Frontotemporal dementia diagnosis requires neuropsychological assessment for diagnosis; patients with frontotemporal dementia have more significant and progressive dysfunction with semantic loss, behavioral disorders, and executive dysfunction abnormalities. Symptoms of frontotemporal dysfunction typically manifest as deficits in executive processes: difficulty with decisions, trouble prioritizing concerns, and inability to weigh consequences. Rarely are there memory abnormalities. Frontotemporal dysfunction has important clinical and financial implications for patients and their caregivers.

Pseudobulbar affect may be present in a portion of patients with ALS. Pseudobulbar affect is a condition of dysregulation of motor output of emotion. Patients will report excessive crying or laughing and the inability to control their

TABLE 1-2 Common Clinical Patterns of Amyotrophic Lateral Sclerosis

Pattern	Upper Motor Neuron Involvement Only	Lower Motor Neuron Involvement Only	Upper and Lower Motor Neuron Involvement
Limb onset	Primary lateral sclerosis	Progressive muscular atrophy	Classic ALS
Bulbar onset	Pseudobulbar palsy	Progressive bulbar palsy	Classic ALS

ALS = amyotrophic lateral sclerosis.

KEY POINTS

- Many neurodegenerative conditions are associated with pseudobulbar affect, which is not unique to ALS.
- The distinction of familial and sporadic ALS based on family history may become obsolete over time as new genes are discovered.

responses to emotions. Pseudobulbar affect is not to be confused with depression, which is a change in the patient's mood state. Many neurodegenerative conditions are associated with pseudobulbar affect; it is not unique to ALS.

Genetics and pathophysiology of ALS. ALS has traditionally been thought of as a sporadic disease. Even after the superoxide dismutase 1 (*SOD1*) gene mutation discovery, only about 10% of patients could definitively point to a family history of the disease. This concept has changed over the past 3 to 4 years with the discovery of new genes and genetic processes that may trigger the disease. As of 2014, two-thirds of familial ALS and 10% of sporadic ALS can be explained by genetics. Familial ALS can have great variability in age of onset and disease duration. This suggests that disease-modifying factors play a role. The distinction between familial and sporadic ALS based on family history may be artificial as new genes are discovered.

In 1993, *SOD1* was the first gene to be discovered for ALS.[4] It accounts for 20% of familial ALS. This gene defect has a predisposition for leading to cell death of the motor neuron, likely by protein accumulating in motor neurons and astrocytes, causing a toxic gain of function. Families with *SOD1* mutations have strong autosomal dominant penetrance, an earlier age of onset, and death or respiratory failure within 1 to 2 years of onset.

A major feature of ALS is the accumulation of a protein named transactive response (TAR) DNA binding protein 43 kDa (TDP-43).[5] This protein plays multiple roles in RNA processing.[6] The gene for this protein is known as *TARDBP*, and mutations of *TARDBP* account for 5% of familial ALS. *TARDBP*-related ALS is clinically not distinguishable from ALS due to other causes.

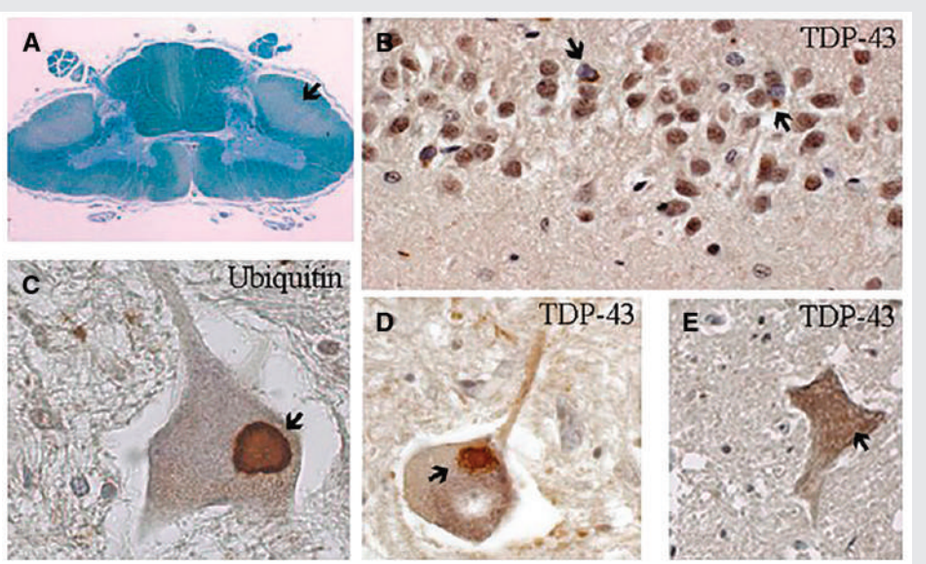

FIGURE 1-3 Neuropathology of ALS. *A*, Atrophic anterior horns and demyelinated corticospinal tracts (*arrow*); *B*, transactive response DNA binding protein 43 kDa (TDP-43) cytoplasmic inclusions (*arrows*) in dentate granules of hippocampus; *C*, ubiquitin-positive (*arrow*), and *D*, TDP-43-positive inclusions (*arrow*) in spinal cord motor neurons; and *E*, diffuse cytoplasmic TDP-43 deposition (*arrow*) in spinal cord motor neurons.

ALS = amyotrophic lateral sclerosis.

Reprinted with permission from Giordana MT, et al, Neurol Sci.[3] © 2010 *Springer-Verlag. link.springer.com/article/10.1007%2Fs10072-010-0439-6*.

TDP-43 aggregates can even be found in ALS patients without the mutated form of the gene, suggesting that this protein may play a role in sporadic ALS (**Figure 1-3**). TDP-43 pathology has also been linked to frontotemporal dementia (**Figure 1-4**). This, in addition to the clinical overlap of cognitive and behavioral changes, raises the question of whether ALS and frontotemporal dementia are different manifestations of a spectrum of TDP-43 deposition. A certain proportion of several other neurodegenerative diseases (eg, Alzheimer disease, hippocampal sclerosis, Pick disease, Parkinson disease, and Huntington disease) show TDP-43 immunoreactive histopathology, giving rise to the term TDP-43 proteinopathies (**Case 1-2**).[6]

Fused in sarcoma (FUS) is a protein with two RNA binding domains and a terminal nuclear localization signal. Normally a nuclear protein, it accumulates in the cytoplasm in ALS associated with FUS mutations.[7] This similarity to TDP-43 suggests the possibility of a common mechanism of disease.[8] FUS also appears to interact with histones and play a role in the repair of DNA damage. This role may be important for the integrity of the motor neuron. *FUS* mutations account for about 5% of familial ALS.

A hexanucleotide repeat expansion (GGGGCC) in the noncoding region

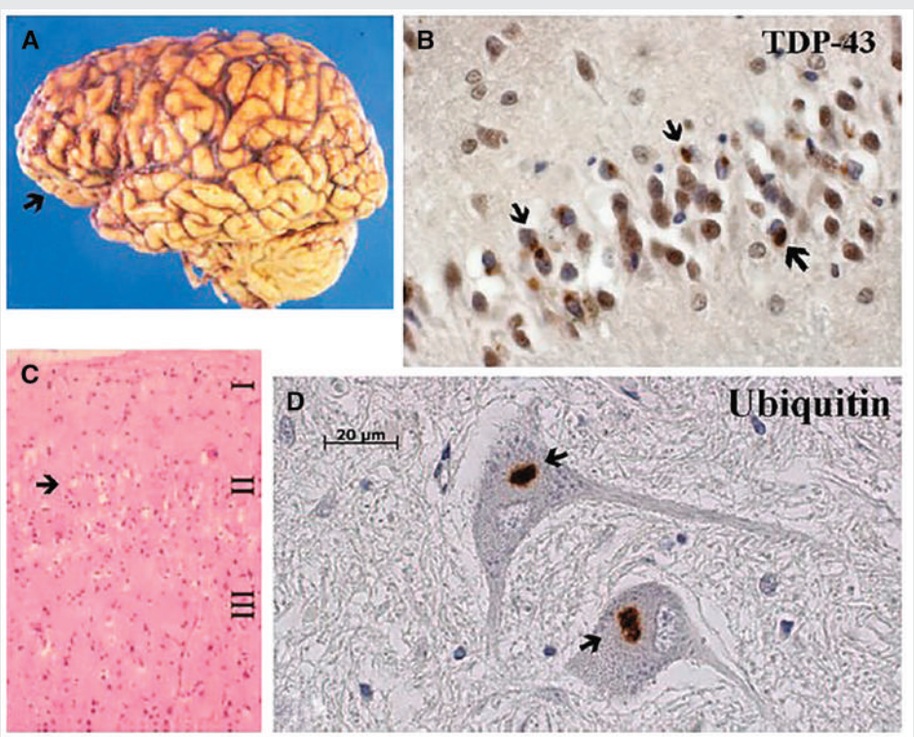

FIGURE 1-4 Neuropathology of frontotemporal dementia/ALS. *A*, Atrophy of the frontal lobes (*arrow*); *B*, transactive response DNA binding protein 43 kDa (TDP-43) cytoplasmic inclusions (*arrows*) in dentate granules of hippocampus; *C*, spongiosis involving layer I and II of the frontal cortex (*arrow*); and *D*, ubiquitinated inclusions (*arrows*) in spinal cord motor neurons.

ALS = amyotrophic lateral sclerosis.

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Case 1-2

A 69-year-old woman presented for a follow-up appointment regarding her ALS, diagnosed 6 months previously. She had lower motor neuron and upper motor neuron symptoms in three limbs. At this appointment, her daughter reported that the patient had fallen four times in 1 month and would not use her walker despite repeated reminders to do so. Further, the daughter had tried to discuss a living will and end-of-life issues, but the patient never was interested, often stating, ''oh, that.'' The patient was very impatient during the appointment, often standing up and asking to leave. When asked about her disease, the patient denied any symptoms, stating she could ''walk all day.'' She did not demonstrate capacity to make decisions because she could not verbally explain her condition. On examination, the patient did not exhibit depression, her mood was good, and when asked about her safety, she laughed and stated, ''I can still get around.''

Comment. This case illustrates the difficulties associated with frontotemporal dysfunction. The patient had difficulty understanding the seriousness of her symptoms and difficulty planning into the future. This had both immediate and long-term safety consequences. A patient without insight may continue to attempt physical activities when they lack the strength to safely do so, such as driving, climbing ladders, or walking unaided. A patient without insight or planning cannot adequately convey his or her wishes regarding end-of-life issues. Patients who do not have an advocate are at risk for both overuse and underuse of medical procedures. Family members need to be educated about frontotemporal dysfunction, and, if they have medical power of attorney, to be surrogate decision makers for the patient.

of chromosome 9 open reading frame 72 (*C9orf72*) can cause ALS and frontotemporal dementia and may account for the largest proportion of inherited ALS (**Figure 1-5**[9]).[10,11] When copies reach as few as 30, this expansion appears to be capable of producing disease. No protein aggregate is associated with this mutation, and much is still being discovered about this gene and protein product (**Figure 1-6**).

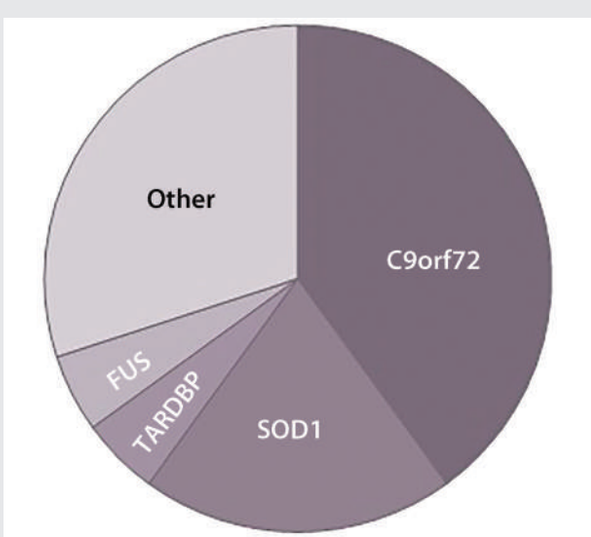

FIGURE 1-5 Genetics of familial ALS.

C9orf72 = chromosome 9 open reading frame; SOD1 = superoxide dismutase 1, soluble; TARDBP = transactive response DNA binding protein; FUS = fused in sarcoma RNA binding

Other genes that have been associated with familial ALS each account for a small proportion of cases. It is estimated that 60% of individuals with familial ALS have an identified genetic mutation. Given the rapid discovery of new mutations, please see *alsod.iop.kcl.ac.uk/* for an up-to-date resource.[12]

The genetics of ALS are of research interest because of the potential to help uncover the mechanism of cell death in ALS. Neuronal cytoplasmic protein aggregation and defective RNA metabolism appear to be common pathogenic mechanisms involved in ALS and possibly in other neurodegenerative disorders. Even though the research potential is significant, the clinical utility of genetic testing currently is limited. (**Case 1-3**).

Diagnosis of ALS. ALS remains a clinical diagnosis. Focal onset of weakness with muscle wasting and brisk reflexes that progresses and spreads

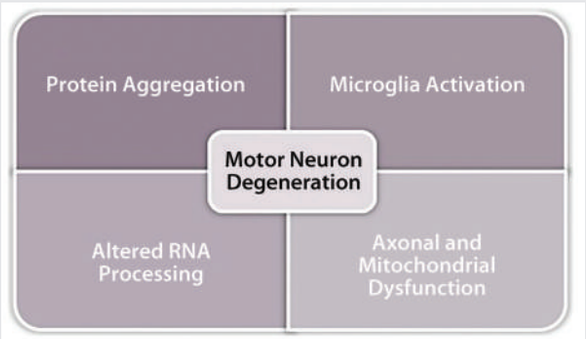

FIGURE 1-6 Pathophysiology of motor neuron degeneration.
RNA = ribonucleic acid.

over time prompts the consideration of ALS as the underlying cause. Despite best efforts, up to 10% of ALS patients are initially misdiagnosed.[13,14]

In 1994, the El Escorial criteria were published, summarizing a consensus statement of the World Federation of Neurology to facilitate accurate diagnosis of ALS.[15] The diagnosis by the El Escorial criteria requires the presence of upper motor neuron and lower motor neuron degeneration within the same region. There must be disease progression within a region with spread to other regions of the body (**Table 1-3**[16]). In addition, laboratory, electrophysiologic, or neuroimaging studies must exclude other conditions that may explain the signs of lower motor neuron and upper motor neuron degeneration.

When applying the criteria, the body is divided into four regions (bulbar, cervical, thoracic, lumbosacral) without consideration for right or left side. Each region is evaluated for either upper motor neuron or lower motor neuron findings. Preserved reflexes may indicate hyperreflexia in wasted muscles. A list of upper motor neuron and lower motor neuron signs in these various regions is provided in **Table 1-4**.

The El Escorial criteria have four levels of diagnostic certainty (definite, probable,

KEY POINTS

- Neuronal cytoplasmic protein aggregation and defective RNA metabolism appear to be common pathogenic mechanisms involved in ALS and possibly in other neurodegenerative disorders.
- Focal onset of weakness with muscle wasting and brisk reflexes that progresses and spreads over time prompts the consideration of ALS as the underlying cause.
- The diagnosis of ALS is suspected by the presence of upper motor neuron and lower motor neuron degeneration within the same region.
- Preserved reflexes may indicate hyperreflexia in wasted muscles.

Case 1-3

A 50-year-old woman came in for a second opinion with regard to her diagnosis of ALS. She had extensive lower motor neuron and upper motor neuron features in four regions of the brainstem and spinal cord. She wanted genetic testing performed. She reported that her sister died of ALS 5 years ago, and her mother died at an early age with cognitive abnormalities and choking.

Comment. This patient may have familial ALS. She presented at a young age and had at least one immediate family member who was diagnosed with the disease. Before testing is performed in a patient with a similar history, the patient should, ideally, meet with a genetic counselor to discuss the ethical and emotional issues surrounding the uncovering of a genetic trait. Once the patient is able to give full, informed consent, testing may be considered. For this patient, with a family member with possible frontotemporal dysfunction, testing for *C9orf72* or *TARDBP* was reasonable. An *FUS* mutation is less likely due to its rarity, and *SOD1* mutations are not associated with dementia. Genetic testing is changing: Whole genome sequencing will look for notable deviations in the entire genome (array of genes) rather than the sequential, step-by-step method currently being used. This may allow patients to be evaluated quickly for a broad array of genetic traits.

KEY POINT

■ According to El Escorial criteria, upper motor neuron and lower motor neuron involvement in three regions constitutes definite ALS.

TABLE 1-3 Summary of Revised El Escorial Criteria[a]

▶ **Presence**

Signs of lower motor neuron degeneration by clinical, electrophysiologic, or neuropathologic examination

Signs of upper motor neuron degeneration by clinical examination

And

Progressive spread of signs within a region or to other regions

▶ **Absence**

Electrophysiologic evidence of other disease processes that might explain the signs of lower motor neuron and/or upper motor neuron degeneration

Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs

[a] Data from Brooks BR, et al, Amyotroph Lateral Scler Other Motor Neuron Disord.[16] *informahealthcare.com/doi/abs/10.1080/14660820030079536?journalCode=aml.*

possible, and suspected) (**Table 1-5**[17]). The certainty of the diagnosis depends on the number of regions that are involved. The diagnosis of definite ALS requires upper motor neuron and lower motor neuron involvement of three out of four regions. Probable ALS shows involvement of two regions. A single region with a combination of upper motor neuron and lower motor neuron findings is considered possible ALS. If only upper motor neuron or lower motor neuron findings are present, only a suspicion for ALS is raised.

The revised El Escorial criteria introduced the category of laboratory-supported probable ALS in which the involvement of two regions is demonstrated by EMG findings rather than clinically.[16] The revised El Escorial

TABLE 1-4 Clinical Findings in Motor Neuron Disease by Region of Involvement

Motor Neuron Signs	Bulbar	Cervical	Thoracic	Lumbosacral
Lower motor neuron signs (eg, reduced tone, muscle atrophy, fasciculations, reduced muscle stretch reflexes)	Tongue fasciculations and atrophy	Wasting of intrinsic hand muscles (in particular, first dorsal interosseous muscle), thenar and hypothenar	Fasciculations in back and abdominal area	Wasting Foot drop
Upper motor neuron signs (eg, spasticity, clonus, brisk and spreading muscle stretch reflexes, pathologic reflexes)	Slowness of tongue movement Brisk jaw jerk Exaggerated gag and yawning Pseudobulbar affect Prominent snout, glabellar, and palmomental reflex	Hoffman reflex Grasp reflex Brisk pectoralis reflex	Loss of superficial abdominal reflexes	Increased tone Babinski sign Ankle clonus Crossed adductors

TABLE 1-5 Diagnostic Certainty Based on Revised El Escorial Criteria[a,b,c]

Level of Certainty	Degree of Involvement
Suspected ALS	UMN signs only in one or more regions, or LMN signs only in one or more regions
Possible ALS	UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions without UMN signs rostral to the LMN signs
Probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Laboratory-supported probable ALS	UMN signs in one or more regions with LMN involvement by EMG in at least two regions
Definite ALS	UMN and LMN signs in three regions
Laboratory-supported familial ALS	UMN and LMN signs in one region and confirmatory genetic testing

ALS = amyotrophic lateral sclerosis; UMN = upper motor neuron; LMN = lower motor neuron; EMG = electromyography.
[a] Data from Caravalho M, et al, Clin Neurophysiol.[17] *www.clinph-journal.com/article/S1388-2457(07)00643-8/abstract.*
[b] Cervical and lumbar region requires involvement of two muscles innervated by different nerve roots.
[c] Bulbar and thoracic region requires involvement of only one muscle per region.

criteria are considered a gold standard and allow for a very accurate diagnosis of ALS with nearly 100% specificity. However, the sensitivity may be as low as 57% at the time of diagnosis[18] because patients often present with only lower motor neuron or upper motor neuron features or present with symptoms only in one region at onset.

In 2008, the Awaji criteria were introduced to facilitate more accurate early diagnosis and earlier entry into clinical trials.[19] According to these criteria, the presence of fasciculations in a muscle with chronic reinnervation changes is sufficient evidence for lower motor neuron involvement, in particular in bulbar muscles (**Table 1-6**[20]). The Awaji criteria have been shown to increase diagnostic sensitivity from 62.2% to 81.1% without changing specificity.[20]

Testing for ALS and its mimics. Nearly every patient with ALS asks: "Is there anything else it could be?" While ALS is a

TABLE 1-6 Criteria for Detection of Neurogenic Changes on Needle Electromyography[a]

	Revised El Escorial Criteria	Awaji Criteria
Evidence of lower motor neuron loss	Rapid firing of a reduced number of motor units	Same
Evidence of reinnervation	Large amplitude, long duration, polyphasic motor unit potentials	Same
Evidence for ongoing denervation	Fibrillations and positive waves	Fibrillations and positive waves or fasciculations in the presence of chronic neurogenic changes

[a] Data from Costa J, Arch Neurol.[18]

KEY POINTS

- Any patient with bulbar involvement, by definition, has symptoms above the cervical level and is, therefore, not likely to have a cervical myelopathy.
- The El Escorial criteria help in ruling out mimics of ALS. If there are atypical features or lack of symptom progression that spreads into other anatomic regions, then reassessment of the diagnosis is recommended.

clinical diagnosis, testing is helpful to exclude mimics and assess for other causes of motor neuron involvement.

Nerve conduction studies and EMG can exclude mimics such as polyradiculopathy, multifocal motor neuropathy, and mononeuritis multiplex.

MRI of the brain and spinal cord are helpful to exclude alternative explanations of symptoms. Cervical stenosis with cervical myelopathy can produce lower motor neuron symptoms at the level of cord compression and upper motor neuron symptoms below the level. Any patient with this presentation (lower motor neuron symptoms in regions above regions with upper motor neuron symptoms) should have neuroimaging to exclude a compressive cervical myelopathy. Any patient with bulbar involvement, by definition, has symptoms above the cervical level and is, therefore, not likely to have a cervical myelopathy.

Conventional neuroimaging techniques do not demonstrate gross structural nervous system changes in ALS.[21] Advanced imaging techniques, such as diffusion tensor imaging and proton magnetic resonance spectroscopy, show promise, but are not currently of clinical utility.

Other mimics of ALS are exceedingly rare. **Table 1-7** lists laboratory tests used to exclude conditions mimicking ALS. Unfortunately, in a patient with a classic presentation, it is more likely to be ALS than a mimic.

The El Escorial criteria help in ruling out mimics. If there are atypical features or lack of symptom progression that spreads into other anatomic regions, then reassessment of the diagnosis is recommended (**Figure 1-7**[22]).

Management of ALS. Patients with ALS go through various emotional and clinical stages (**Table 1-8**[23]). Patients must come to terms with the diagnosis, cope with functional decline and disability, and

TABLE 1-7 Laboratory Testing for Motor Neuron Disease

Clinical Presentation	Disease	Testing
Upper motor neuron predominant	Tropical spastic paraparesis	Human T-cell lymphotropic virus 1 serology
	Copper or vitamin B_{12} deficiency myelopathy	Copper and zinc, vitamin B_{12} levels
Lower motor neuron predominant	Multifocal motor neuropathy	GM1 antibodies
	Spinal muscular atrophy	Genetic testing, muscle biopsy
	West Nile virus	Serology (serum, CSF)
	Polio	Serology (serum, CSF), stool antigen
	Hypothyroidism	Thyroid-stimulating hormone, free T4
	Hyperparathyroidism	Ionized calcium, intact parathyroid hormone
	Lyme disease	Serology (serum, CSF)
	Paraneoplastic	Antibody panel (serum, CSF)

CSF = cerebrospinal fluid.

make end-of-life plans, including for hospice care and death. These phases of the disease require a close collaboration between the patient, his or her caregivers, the physician, and the ALS care team, if present. The patient and caregivers may go through these phases differently and have differing needs. Cognitive impairment may decrease acceptance of care interventions and impair decision making.

The complexity and progressive nature of ALS often necessitates multidisciplinary care, which leads to better outcomes and less utilization of emergency care. Prolonged survival and improved quality of life are important benefits of such team-based ALS treatment.[24–26]

Neurologists have the important task of making the diagnosis and delivering the news. While ALS is not curable, every symptom requires treatment, and neurologists play a key role in symptom management. Respiratory and nutritional management are important for quality of life and can alter the disease course. Disease-specific advanced directives that focus on the expected problems in ALS are available[27] and should be regularly revisited and revised. Neurologists also play a crucial role in sharing information about ongoing research and carrying out clinical trials. All ALS patients should be encouraged to participate in the National ALS Registry at *www.cdc.gov/als/*.

Disease-modifying drug treatment. The only US Food and Drug Administration–approved drug for the treatment of ALS is riluzole, which blocks the release of glutamate and has been available to patients since 1996. The drug should be discussed with patients and may be offered early in the course; benefits are not clear in advanced stages of the disease.[28,29] A survival advantage of 2 to 3 months has been shown.[30–32] Riluzole is generally well tolerated, but gastrointestinal side effects or fatigue may require discontinuation. Monitoring of liver function tests 1 month after initiation and at 3-month intervals thereafter is recommended; treatment should be discontinued if the

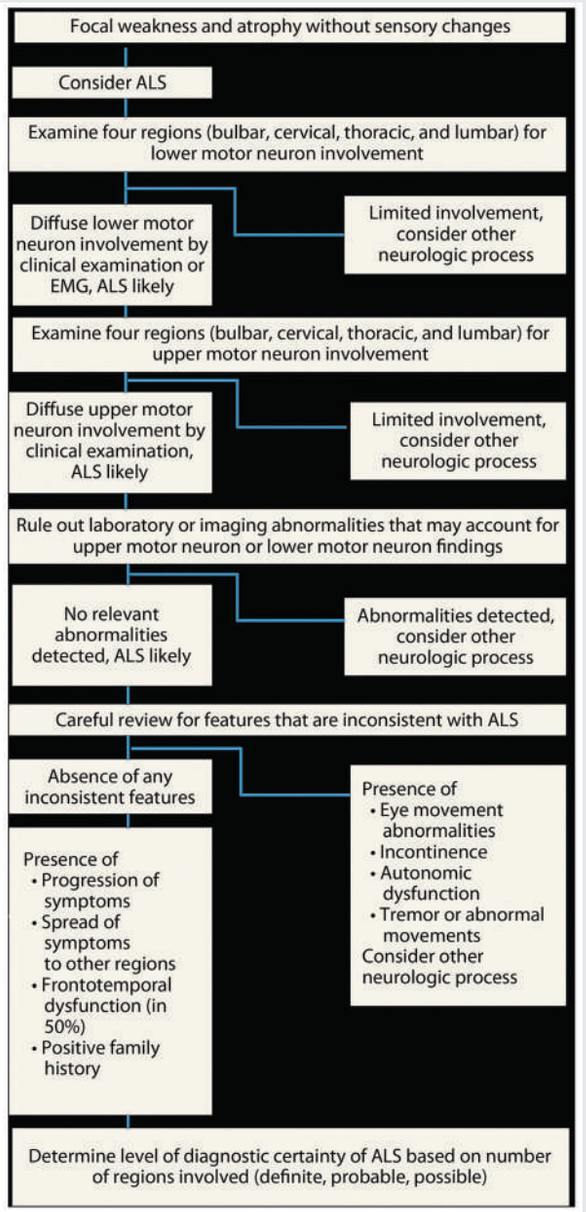

FIGURE 1-7 Algorithm of diagnosis of ALS.

ALS = amyotrophic lateral sclerosis; LMN = lower motor neuron; EMG = electromyography; UMN = upper motor neuron.

Adapted with permission from Bromberg M, Neurologist.[22] © 1999 Lippincott Williams & Wilkins. journals. *lww.com/theneurologist/toc/1999/03000.*

KEY POINTS

- Cognitive impairment may decrease acceptance of care interventions and impair decision-making.
- All ALS patients should be encouraged to participate in the National ALS Registry at *wwwn.cdc.gov/als/*.

TABLE 1-8 Staging of Amyotrophic Lateral Sclerosis[a]

Stage	Clinical Involvement
Stage 1	Symptom onset (involvement of first region)
Stage 2A	Diagnosis
Stage 2B	Involvement of a second region
Stage 3	Involvement of a third region
Stage 4A	Need for gastrostomy
Stage 4B	Need for respiratory support (noninvasive ventilation)

[a] Adapted with permission from Roche JC, et al, Brain,[23] with a proposed staging system based on clinical progression. © 2012 The Author. *brain.oxfordjournals.org/content/135/3/847.full*.

alanine aminotransferase level is five times the upper limit of normal. A rare complication is hypersensitivity pneumonitis.[33] Despite many attempts at identifying additional drugs, and an exponential increase in clinical research studies, no further agents have risen to the level of significance thus far.

Symptomatic treatment. The symptoms of ALS relate to the decline in strength of muscles of the limbs, swallowing, speaking, and breathing. In addition, pseudobulbar affect and cognitive changes are common. **Table 1-9** provides a summary of interventions that can be used to treat the symptoms of ALS. The following interventions have been shown to have benefit: care in a multidisciplinary setting, the use of riluzole, noninvasive ventilation, treatment of pseudobulbar affect with dextromethorphan/quinidine, and nutritional support. Other interventions

TABLE 1-9 Summary of Interventions in Amyotrophic Lateral Sclerosis

Symptom	Nonpharmacologic Intervention	Pharmacologic Intervention[a]	Practice Tips
Air hunger	Meditation, mindfulness-based breathing exercises	Lorazepam 1–3 mg 3 times/d Morphine sulfate tablets or elixir (20 mg/mL) 5–10 mg every 8 hours as needed or morphine subcutaneous pump at 1–5 mg/hour	Consider using a fan Keep room temperature low Elevate head of bed
Anxiety	Psychological support, counseling	Selective serotonin reuptake inhibitors (SSRIs) (see SSRI dosing listed in depression section) Lorazepam 0.5–1 mg 3 times/d as needed	
Cramps and fasciculations	Positioning, stretching, massage, pool therapy	Magnesium oxide 400–600 mg/d Vitamin E 400 IU 2–3 times/d Carbamazepine 200 mg 2 times/d Phenytoin 100 mg 3–4 times/d	Quinine sulfate is no longer approved for leg cramps in the United States; other medications are under investigation (mexiletine and levetiracetam)

Continued on next page

TABLE 1-9 Summary of Interventions in Amyotrophic Lateral Sclerosis *(Continued)*

Symptom	Nonpharmacologic Intervention	Pharmacologic Intervention[a]	Practice Tips
Constipation	Review fluid and fiber intake	Begin with: Polyethylene glycol 8.5–17 g/d or every other day as needed Sennosides 15 mg, start 1 tab 2 times/d and increase to 3–4 tabs 2 times/d as needed Bulk fiber laxative 1–2 Tbsp/d as needed (take with 8–10 oz of water) Progress to: Bisacodyl suppository 10 mg/d per rectum as needed (if good stool consistency but unable to have a bowel movement) Magnesium citrate 1.745 g/30 mL, 150–300 mL/d	Adjust tube feeding formula if applicable
Depression	Psychological support, counseling	SSRIs Sertraline 50–200 mg/d Paroxetine immediate release tablets 10–50 mg/d Paroxetine controlled release tablets 12.5–62.5 mg/d Citalopram 20–40 mg/d Escitalopram 10–20 mg/d Fluoxetine 10–80 mg/d Serotonin norepinephrine reuptake inhibitor Venlafaxine extended release tablets 37.5–225 mg/d Norepinephrine dopamine reuptake inhibitor Bupropion hydrochloride sustained release tablets 300–400 mg/d in 2 divided doses Bupropion hydrochloride extended release tablets 300–450 mg/d Norepinephrine serotonin modulator Mirtazapine 15–45 mg/d at bedtime	Select appropriate antidepressant depending on side effect profile
Dry mouth and thick secretions/ phlegm	Assisted cough insufflator-exsufflator and chest wall oscillation, reduced intake of dairy	Guaifenesin tablets, capsules, oral solution 200–400 mg every 4 hours as needed Guaifenesin extended release capsules 600–1200 mg every 12 hours with maximum of 2400 mg/d Carbocisteine[b] 750 mg 3 times/d and reduce to 750 mg 2 times/d when satisfactory response is obtained	Review fluid intake Consider humidifier

Continued on next page

TABLE 1-9 **Summary of Interventions in Amyotrophic Lateral Sclerosis** *(Continued)*

Symptom	Nonpharmacologic Intervention	Pharmacologic Intervention[a]	Practice Tips
Early satiety		Metoclopramide 5–10 mg 30 min before meals and at bedtime	Encourage frequent, smaller meals
Excessive yawning		Baclofen 10–20 mg 3–4 times/d	
Fatigue	Energy conservation techniques	Amantadine 100 mg 2 times/d Methylphenidate 5–10 mg 2 times/d Amphetamine and dextroamphetamine combination tablet 5–10 mg every 4–5 hours Pyridostigmine 60 mg 3 times/d	Carefully screen for nocturnal hypoventilation
Insomnia	Sleep hygiene	Amitriptyline 10–75 mg at bedtime Trazodone 50 mg at bedtime Chloral hydrate 500 mg at bedtime Diphenhydramine 25–50 mg at bedtime Lorazepam 0.5–2.5 mg at bedtime	Carefully screen for respiratory failure and pain Rule out advanced or delayed sleep phase syndromes
Jaw quivering or clenching	Stretching	Clonazepam 0.5 mg 3 times/d as needed Lorazepam 0.5 mg 3–4 times/d as needed Diazepam 2.5–5 mg 3 times/d as needed Botulinum toxin injection	
Laryngospasm		Lorazepam (if frequent) 0.5–2 mg 2–3 times/d as needed Proton pump inhibitor Omeprazole 40 mg/d	Educate on self-limiting nature and identify triggers Teach breathing out against the vocal folds
Nasal congestion/ postnasal drip		Pseudoephedrine 30–60 mg 3 times/d Diphenhydramine 25–50 mg 2 times/d Budesonide nasal spray 2 sprays 2 times/d Ipratropium bromide nasal spray 0.03–0.06% solution, 2 sprays in each nostril 3 times/d	Rule out allergies
Pain	Positioning, stretching, pool therapy, massage, acupuncture, meditation	Acetaminophen 325–650 mg 4 times/d Nonsteroidal anti-inflammatory drugs Morphine sulfate 5–10 mg 2 times/d Other narcotics	Initiate bowel regimen with use of narcotics
Pseudobulbar affect		Dextromethorphan 20 mg/quinidine 10 mg 2 times/d SSRI Paroxetine 40 mg/d (or other SSRI as documented in depression section)[c]	Consider using SSRI if patient has concomitant depression; consider using amitriptyline if patient has concomitant sialorrhea or insomnia

Continued on next page

TABLE 1-9 Summary of Interventions in Amyotrophic Lateral Sclerosis *(Continued)*

Symptom	Nonpharmacologic Intervention	Pharmacologic Intervention[a]	Practice Tips
Sialorrhea	Home suction device	Atropine sulfate ophthalmic drops (1–2 drops sublingual every 4–6 hours) or tablets (1–2 mg orally every 6 hours) Glycopyrrolate 0.1–0.2 mg 3 times/d Scopolamine transdermal patch 1–2 patches every 72 hours Amitriptyline 10–150 mg at bedtime Hyoscyamine 0.125–0.25 mg every 4 hours Botulinum toxin injection Radiotherapy per radiation oncology assessment	
Spasticity	Stretching, positioning, pool therapy, massage	Baclofen 40–80 mg/d in 3–4 divided doses Tizanidine 6–24 mg/d in 3 divided doses Benzodiazepines Diazepam 2–10 mg 3–4 times/d Clonazepam 1–2 mg 2–3 times/d Dantrolene 100 mg 2–3 times/d (carefully monitor liver enzymes if also on riluzole) Botulinum toxin injection	
Urinary urgency and frequency	Toileting schedule	Oxybutynin extended release tablets 5–10 mg/d up to 30 mg/d	Rule out urinary tract infection

[a] All medications are taken orally unless otherwise indicated.
[b] Medication not available in the United States.
[c] Tricyclic antidepressants and SSRIs can be used off-label to manage pseudobulbar affect; dextromethorphan/quinidine is the only US Food and Drug Administration–approved treatment.

are based on expert opinion and have few data to support their use. Refer to the AAN guidelines regarding best evidence for management.[34–36] Please also refer to the February 2009 article "ALS Update: Signs of Progress, Reasons for Hope" in the CONTINUUM issue on Myasthenic Disorders and ALS for a full overview of ALS symptomatic management.

Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is arguably one of the most important entities to exclude when diagnosing a patient with symptoms consistent with ALS. MMN is a lower motor neuron disease that affects one limb before progressing to other limbs. Patients have severe focal weakness, atrophy, and fasciculations. Weakness in MMN is out of proportion to the degree of atrophy. However, an important exclusion fact is that patients with MMN do not have upper motor neuron symptoms. MMN is a demyelinating disease of the motor nerve, in which there is a focal conduction block of the motor axon. This disease is excluded by nerve conduction studies in which motor nerves are carefully assessed for demyelination and proximal conduction block.[37] Laboratory testing for GM-1 antibodies are helpful, but the sensitivity of this antibody is not high (30% of patients with MMN). For

KEY POINT

- Weakness in multifocal motor neuropathy is out of proportion to the degree of atrophy.

further discussion of multifocal motor neuropathy, refer to the article "Acquired Immune Demyelinating Neuropathies" by Mazen M. Dimachkie, MD, FAAN, FANA, and David S. Saperstein, MD, in this issue of CONTINUUM.

OTHER MOTOR NEURON DISEASES

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a genetic disease in which there is autosomal recessive loss of the *SMN1* gene on chromosome 5q13.2. In the United States, the carrier frequency is 1/50.[2,38]

The classic phenotypes of SMA are type I (Werdnig-Hoffman disease), type II, and type III (Kugelberg-Welander disease). Type IV is known as adult-onset SMA. The shorthand description of this disease is: "Type I, never sit; type II, never walk; type III, never run." Although ignoring the full spectrum of patient presentations, this may be a useful way to categorize disease severity. Type IV patients have variable presentations and may even be able to play sports into their teenage years before weakness manifests and limits function.

Type I patients typically manifest immediately after birth or in the neonatal period. Infants will have respiratory distress and poor feeding; however, they are noted to be alert with intact extraocular movements. In the past, EMG or muscle biopsy was the initial workup; currently, the appropriate first step is genetic testing for the *SMN1* gene deletion. Given the profound loss of motor neurons with severe paralysis, these patients tend to have early mortality.

The muscle biopsy of SMA is worth recognizing because it is the classic example of grouped atrophy. There is dropout of axons before birth and the remaining motor axons then innervate adjacent muscle fibers, causing fiber-type grouping (**Figure 1-8**[39]).

Table 1-10[40] presents the spectrum of phenotypic manifestations in spinal muscular atrophy. Type II patients sit but never walk and the disease manifests within the first 18 months of life. Again, when the disease is suspected, genetic testing is the appropriate first step. These patients will be wheelchair dependent. The majority of patients live into young adulthood, but respiratory complications of restrictive lung disease are a major cause of early morbidity and mortality. Restrictive lung disease is due to a combination of diaphragmatic and accessory muscle weakness and scoliosis (which limits lung capacity).

Type III patients walk; their weakness is typically proximal more than distal, and hip and shoulder girdles are prominently affected. Rising from a chair may be very difficult. Type IV patients do not present until adulthood.

The *SMN1* protein product is important in the formation of spliceosomes. Spliceosomes are important agents in the processing of pre-mRNA into mRNA.

Homozygous recessive gene deletions are lethal to motor neurons.[41] It is uncertain why the motor neuron is so specifically vulnerable to this gene defect,

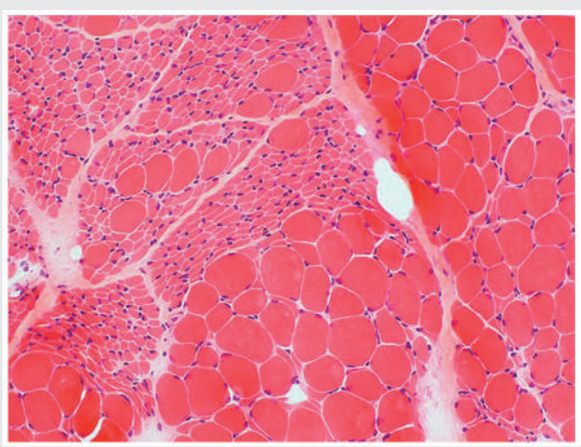

FIGURE 1-8 Spinal muscular atrophy muscle biopsy with grouped atrophy.

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TABLE 1-10 Spectrum of Phenotypic Manifestations in Proximal Spinal Muscular Atrophy[a]

Spinal Muscular Atrophy (SMA) Type	Typical Age of Onset	Typical Life Span	Also Called	Clinical Characteristics and Maximum Milestones Achieved
0	Prenatal	<6 months	SMA-arthrogryposis multiplex congenita type	Congenital hypotonia, weakness, respiratory failure, and proximal joint contractures Unable to breathe unsupported
I	Birth to 6 months	About 32% survival probability >2 years	Werdnig-Hoffmann disease	Infantile onset of generalized hypotonia, weakness, impaired bulbar function, and respiratory insufficiency Unable to sit unsupported
II	6 to 12 months	About 70% survival to adulthood	SMA, Dubowitz type	Onset of limb weakness as infants or toddlers Progressive weakness, respiratory insufficiency, scoliosis, and joint contractures in childhood Able to sit independently
IIIa	After 12 months	Normal	Kugelberg-Welander disease	Onset of proximal muscle weakness in childhood
IIIb	After 3 years			Able to walk independently, although 50% of patients with type IIIa lose independent ambulation by 12 years of age
IV	Adulthood	Normal		Onset of proximal leg weakness in adulthood Able to walk independently

[a] Reprinted with permission from Jones HR, et al, eds, Elsevier.[40] © 2013 Elsevier.

because this gene and protein product are ubiquitous in all cells. The phenotype is predicated by the presence of a second gene, *SMN2*, also located on chromosome 5. More copies of *SMN2* modify the clinical presentation of SMA. Humans have variable numbers of *SMN2* genes: some patients have no *SMN2* genes, some have as many as four. *SMN2* makes a less robust protein product, but it is enough to have a favorable impact on motor neuron survival and function.

SMN is a candidate for gene therapy: alternative gene splicing can remove the most commonly affected region in the *SMN1* gene (exon 7), which leads to a less robust, but functional, protein product. This is being evaluated to try to aid patients with SMA.

Spinal Bulbar Muscular Atrophy (Kennedy Disease)

Spinal bulbar muscular atrophy, or Kennedy disease, is an adult-onset hereditary X-linked motor neuron disease. Males are always affected, while female carriers can manifest with less severe symptoms. Spinal bulbar muscular atrophy manifests in the fourth to seventh decades for most patients. The disease is caused by an unstable trinucleotide

KEY POINT

■ Spinal bulbar muscular atrophy patients have prominent tongue and perioral fasciculations.

CAG repeat on the X chromosome in the androgen-receptor gene. Patients with repeat numbers greater than 40 are affected. The affected protein product, the androgen receptor, can lead to degeneration of motor neurons. In addition, there are endocrinologic changes due to androgen insensitivity that manifest as enlargement of male breasts (gynecomastia), low sperm count, impotence, or infertility.

In spinal bulbar muscular atrophy, bulbar onset is most common; perioral and tongue fasciculations are typical initial symptoms. Male patients then develop proximal weakness, fasciculations, and atrophy in proximal muscle groups. Many patients eventually use wheelchairs due to hip girdle weakness (**Case 1-4**).[42]

In spinal bulbar muscular atrophy, the endocrine system is affected and patients are more likely to develop diabetes mellitus.

The evaluation of a patient with suspected spinal bulbar muscular atrophy includes laboratory, EMG, and genetic testing. The creatine kinase (CK) will be elevated, occasionally significantly. Nerve conduction studies will show both motor and sensory nerve conduction abnormalities (despite minimal sensory findings on patient examination). EMG will show acute and chronic denervation. Genetic testing is done to evaluate for a CAG expansion on the X chromosome; this is confirmatory. Despite our understanding of the genetic basis for spinal bulbar muscular atrophy, there are no known treatments at this time. Testosterone has been tried without success.[42]

Spinal bulbar muscular atrophy has many features in common with ALS. However, the temporal progression of spinal bulbar muscular atrophy is over many years and with a lesser degree of disability. There may be a family history of an X-linked lower motor neuron illness. Clinically, in spinal bulbar muscular atrophy, tongue and perioral fasciculations occur early and are prominent, but the dysphagia is proportionally less severe. Gynecomastia is only seen in spinal bulbar muscular atrophy, and not ALS. Genetic testing for the trinucleotide repeat is conclusive.

Case 1-4

A 55-year-old man presented for a neurologic consultation for an evaluation of difficulty swallowing. For several years, he had noticed choking on liquids and now noticed choking on solid foods. During the history, he reported that he fell occasionally. Examination showed tongue atrophy with fasciculations and mild perioral facial weakness. Motor examination showed mild (4+/5) weakness in his proximal hip flexors and ankle dorsiflexors bilaterally. Reflexes were decreased diffusely. Fasciculations were noted in proximal muscles of the shoulder and hip girdle. Gynecomastia was noted on chest wall examination. EMG showed rare fasciculations with insertional activity and large–duration polyphasic motor units with decreased recruitment (a chronic neurogenic pattern).

A more detailed family history was obtained. The patient recalled that his mother's brother had difficulty with gait and eventually used a wheelchair for mobility. With this information, genetic testing was performed for the CAG repeat expansion on the X chromosome associated with the androgen-receptor gene.

Comment. This case illustrates the difficulties in distinguishing motor neuron diseases. Many of this patient's clinical characteristics (eg, age, choking, falling, fasciculations) were suggestive of ALS. However, the patient reported several years of symptoms, which is atypical for ALS. His EMG showed only mild denervation and reinnervation. Spinal bulbar muscular atrophy (Kennedy disease) is rare, but should be considered in any male patient who reports years of lower motor neuron symptoms.

Monomelic Amyotrophy (Benign Focal Amyotrophy)

Monomelic amyotrophy is, as the name implies, a focal loss of motor neurons that does not spread to other regions. This syndrome has other names, including benign focal amyotrophy, juvenile segmental muscular atrophy, and Hirayama disease.

This disease is rare and most often involves a unilateral cervical spine region, but it may occur bilaterally. Typically, the onset is in the teenage years: patients may notice several years of slow progression and then stability. Males are more often affected.

Nerve conduction studies and EMG will reveal a lower motor neuron picture in the affected upper limbs only. Other limbs should be normal for this diagnosis. Some authors have implicated focal intermittent compression of the spinal cord during late adolescent growth as the etiology.[43–45]

There are no specific tests for monomelic amyotrophy; therefore, initially, this disease may be difficult to distinguish from early ALS. Flexion/extension MRI may show anterior cord displacement and atrophy in the cervical region. Over time, monomelic amyotrophy will not progress and no upper motor neuron features manifest. The presence of conduction block should initiate an evaluation for MMN rather than monomelic amyotrophy.

Poliomyelitis

Poliomyelitis is infection of the spinal cord (myelitis) by the polio virus. The polio virus is in the genus *Enterovirus* and is an RNA virus transmitted by oral-fecal contamination.[46] This virus has strong, trophic predilection for the spinal cord, specifically the anterior horn cells. In the prevaccine era, polio virus was endemic worldwide, and infections spiked in the summer months. Most cases were asymptomatic or mild, but a significant percentage of affected patients, often children, developed acute flaccid paralysis due to myelitis. The polio vaccine was developed in 1955, leading to the end of this illness in the United States.

The myelitis and subsequent anterior horn cell death could be regional (unilateral or bilateral limbs), or extensive, involving even the upper cervical cord and respiratory functioning. After the initial infection and paralysis, those patients who survived experienced a slow improvement in strength, due to reinnervation of motor units from remaining motor neurons. However, over their lifetime, these patients may experience a slow, subacute return of weakness, likely due to premature aging of the remaining motor neurons. This has often been called the "post-polio syndrome."[47]

West Nile Virus

West Nile virus is an infectious virus of the Flavivirus family, transmitted by a mosquito vector. Most patients infected with this virus have a self-limited viral illness with fever, chills, and respiratory symptoms.[46] However, the virus does exhibit neurotrophic properties with a predilection for the motor neuron.[48] A small percentage of those infected with West Nile virus (5% or so) will have involvement of the motor neurons.[48] These patients develop an acute, regional, flaccid paralysis; occasionally, there is concurrent sensory involvement. The virus may also infect the cerebrum, causing an encephalopathy. EMG will not demonstrate denervation changes for 3 to 4 weeks.

Treatment is supportive: intensive care unit monitoring, fluids, and fever management are performed, but will not stop the destruction of the motor neurons if they are infected. For more information, refer to the article "Infectious Neuropathies" by Michael K. Hehir II, MD, and Eric L. Logigian, MD, FAAN, in this issue of CONTINUUM.

KEY POINT

- There are no specific tests for monomelic amyotrophy; therefore, initially, this disease may be difficult to distinguish from focal ALS. Over time monomelic amyotrophy will not progress and no upper motor neuron features manifest.

CONCLUSION

Motor neuron diseases are a heterogeneous group of disorders which include hereditary, idiopathic, or acquired causes. Damage to the lower motor neuron produces weakness, hypotonia, muscle atrophy, and fasciculations.

Treatment is dependent upon the etiology, but motor neurons cannot be repaired and management is often supportive. ALS, the most common motor neuron disease, is best approached with multidisciplinary care: treating specific symptoms and focusing on quality of life.

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