

Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

REVIEW ARTICLE



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ABSTRACT

PURPOSE OF REVIEW: This article reviews the clinical features, diagnostic approach, and treatments available for amyotrophic lateral sclerosis (ALS) and other motor neuron diseases. The article also provides an update on the genetics and pathophysiology of ALS.

RECENT FINDINGS: ALS remains a clinical diagnosis without a unique biomarker. The areas of greatest progress include a large expansion in the number of genes associated with familial and sporadic ALS. The discovery of these genes, along with other work, has provided a deeper understanding of the mechanisms of motor neuron failure in ALS. Areas of particular interest include the role of transactive response DNA-binding protein 43 and other RNA-processing proteins in the development of disease.

SUMMARY: ALS remains a relentlessly progressive disorder with an elusive core pathophysiology. The current mainstay of treatment remains symptom management and palliation, particularly in the setting of a multidisciplinary clinic. The future holds potential for targeted therapies based on an ever-evolving understanding of the pathophysiology of both familial and sporadic ALS.

INTRODUCTION

Motor neuron diseases include a variety of acquired and inherited neurodegenerative conditions that entirely or predominantly injure motor neurons. Amyotrophic lateral sclerosis (ALS) is the most common of these diseases and will be the focus of much of this discussion.

The motor neuron system is composed of upper and lower motor neurons. Upper motor neurons reside in the primary motor cortex of the brain, and their axons comprise the corticobulbar tract (connecting to the brainstem) and the corticospinal tract (connecting to the spinal cord). Lower motor neurons, also referred to as alpha motor neurons or anterior horn cells, are located in motor nuclei in the brainstem or the anterior gray matter of the spinal cord. Their axons connect to muscles of the bulbar region or limbs. Injury to the motor neuron system results in loss of voluntary muscle function that may affect limb, bulbar, and/or respiratory function, with the specific symptoms depending on which part of the motor pathway is affected.

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RELATIONSHIP DISCLOSURE:

Dr Quinn serves on advisory boards for Acceleron Pharma, Inc, and Amylyx Pharmaceuticals and as a consultant for Amicus Therapeutics, Inc. Dr Quinn receives research/grant support from Acceleron Pharma, Inc; Amicus Therapeutics, Inc; and Amylyx Pharmaceuticals. Dr Elman serves on advisory boards for Biogen and Genentech, Inc, and receives publishing royalties from UpToDate, Inc.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Drs Quinn and Elman discuss the unlabeled/investigational use of anticholinergics, clonazepam, levetiracetam, mexiletine, mirtazapine, phenytoin, selective serotonin reuptake inhibitors, steroids, and tricyclic antidepressants for the treatment of amyotrophic lateral sclerosis and other motor neuron diseases.

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Since the earliest descriptions of the clinical and pathologic features of ALS by Jean-Martin Charcot in the 1870s, our understanding of the underlying pathophysiology of the disease has expanded enormously. Still, a unifying causal theory remains elusive. This article describes the clinical features of ALS; outlines an approach to diagnostic evaluation; reviews the latest understanding of the genetics, pathology, and pathophysiology of the disease; and discusses current management approaches. It also reviews variants of ALS and some motor neuron disorders that can mimic features of ALS. Specific cases are used to highlight relevant discussion points.

EPIDEMIOLOGY

The global incidence of ALS is 2 per 100,000 to 3 per 100,000, which leads to a prevalence of 4 per 100,000 to 5 per 100,000.^{1,2} Historically, certain areas have seen a higher disease concentration, including the island of Guam, the Kii Peninsula of Japan, and others.³ People of non-European descent are thought to possibly have a lower relative risk of the disease.³ The lifetime risk of ALS in the United States and Europe is 1 in 350 for men and 1 in 400 for women,³ demonstrating the male predominance of this disease, which is generally higher at younger ages of onset.⁴ Risk of ALS increases with age until the eighth decade, with an average age of onset in the late fifties and early sixties.^{2,5} Familial ALS, defined as ALS in which there are multiple affected family members, accounts for approximately 10% of cases; the remaining 90% are sporadic. Even in sporadic cases, the overall disease risk attributable to genetics approaches 60%, with the remaining 40% of risk related to environmental factors.⁶ Uncovering the identity of individual environmental risk factors has been extraordinarily challenging. Epidemiologic evidence suggests high levels of physical fitness/athleticism^{7,8} and slimness^{7,9,10} increase ALS risk. Since Lou Gehrig was diagnosed with ALS, professional athletics and ALS have been associated. More recently, focus has been on increased risk in players of soccer¹¹ and American football,¹² raising the question of whether this is because of the sport activity, the genetic ability to participate in the sport, head or other trauma experienced during play, or other factors such as pesticides on the field. Although this question still remains unresolved, emerging data suggest that professional sports with concussive risk (eg, American football and soccer) carry the highest relative risk of ALS compared to professional sports without concussive risk and nonprofessional sports with and without concussive risk.¹³ An association also exists between having served in the US military and developing ALS.^{14,15} In addition to athletes and military personnel, other occupations with risks associated with ALS include veterinarian, hairdresser, and power-production plant operator.¹⁶ Some evidence exists that exposure to certain organic solvents and pesticides may pose a slightly increased risk of ALS.¹⁷ The contribution of smoking to the risk of ALS is quite unclear, as some studies have indicated a risk whereas others have not,^{18–21} and a clear dose-response has not been demonstrated.²² Other suggested environmental risk factors for ALS, including exposure to heavy metals,¹⁷ cyanotoxins,²³ and electric shock,²⁴ have not held up under statistical scrutiny. Evidence of spatial clustering is limited. Most reports are anecdotal and likely better explained by chance. A large Finnish study examined spatial relationships at birth and death and found two clusters of disease, although the underlying etiology of these clusters was not clear.²⁵

CLINICAL FEATURES

ALS is a heterogeneous disease with a variety of potential clinical phenotypes; however, all presentations have at their core a progressive decline in physical function due to weakness or spasticity without equivalent sensory loss or pain. Some patients also experience changes to emotional expression or cognitive abnormalities.

Motor Features

Approximately 70% of patients with ALS present with weakness of the limbs, which is typically asymmetric and distal at onset. Twenty-five percent of patients present with bulbar symptoms, which manifest as difficulty speaking, chewing, or swallowing (CASE 9-1). A small minority of patients have respiratory onset, and less than 1% present with diffuse fasciculations and a wasting syndrome. Extraocular movements are spared until late-stage disease. The progressive nature of symptoms is a critical component to diagnosis. Symptoms begin insidiously in an affected region and progress in that region as spread to other regions also occurs. Of note, some patients with ALS will describe “sudden” onset or stepwise symptoms, but careful review of their history will typically reveal progressive symptoms before the loss of a particular functional ability.

The symptoms and signs of ALS can be broadly classified as upper motor neuron or lower motor neuron and can also be classified by the segment of the body in which they occur. Upper motor neuron weakness is caused by loss of downgoing inhibition in the corticobulbar and corticospinal tracts and leads to increased tone and spasticity, slowness of movement, increased tendon reflexes, and the presence of pathologic reflexes. Lower motor neuron weakness is caused by damage to the anterior horn cell or its axon and results in pure motor weakness, reduced reflexes, muscle atrophy, fasciculations, and cramps. The electrophysiologic features of lower motor neuron injury are discussed in the diagnostic evaluation section below. In the bulbar segment, these symptoms and signs can manifest as dysarthria and dysphagia, along with facial weakness. Upper motor neuron, or spastic, dysarthria is characterized by slow and strained speech, often with spastic dysphonia. Lower motor neuron, or flaccid, dysarthria is characterized by weakness of lingual, facial, and palatal muscles causing imprecise, breathy, and hypernasal speech. Laryngospasm and involuntary cheek or tongue biting are additional bulbar upper motor neuron symptoms. Facial weakness and dysphagia often lead to sialorrhea and difficulty managing secretions. Brisk and pathologic reflexes that may be found in the bulbar segment include the jaw jerk, palmomental signs, and facial reflexes. The presence of a mixed spastic and flaccid dysarthria is almost always indicative of ALS. Upper motor neuron and lower motor neuron signs in the limbs are described above and may particularly cause imbalanced gait when present in the legs. Cramps may frequently occur in the limbs, thoracic region, and neck and are often brought about by activity that causes contraction and shortening of the involved muscle. Respiratory insufficiency is typically thought to be caused preferentially by lower motor neuron dysfunction of the diaphragm and accessory muscles of respiration²⁶ resulting in shortness of breath, orthopnea, sleep-disordered breathing, paradoxical breathing,²⁷ and reduced vocal volume.

KEY POINTS

- The incidence of amyotrophic lateral sclerosis (ALS) has remained constant at around 2 per 100,000 per year to 3 per 100,000 per year and is slightly higher in men than in women.
- Of patients with ALS, 90% have sporadic disease and 10% have familial ALS, which follows an autosomal dominant pattern of inheritance.
- Patients with ALS typically have a combination of upper motor neuron and lower motor neuron signs that affect multiple segments of the body.

Pseudobulbar Affect

Pseudobulbar affect is a disorder of emotional expression that is caused by disruption of corticopontocerebellar pathways.^{28,29} Patients describe laughing or crying that is not under voluntary control and is out of proportion to their internal emotional state; excessive yawning may also be a feature of this syndrome. Pseudobulbar affect is not specific to ALS but, when present in the setting of progressive weakness, can point to a neurogenic cause for the weakness, thus distinguishing it from other neuromuscular disorders.

Cognitive Features

Cognitive abnormalities have been described in ALS for more than a century.³⁰ In the past 30 years, multiple observational studies have suggested that up to one-half of patients with ALS have neuropsychological abnormalities, most commonly manifesting as executive dysfunction.^{31–33} A smaller population of patients with ALS (5% to 15%) have frank frontotemporal dementia (ALS-FTD).³⁴

CASE 9-1

A 67-year-old man presented with an 8-month history of progressive slurring of speech. Over the same period of time, he had noted weakness of his left hand but denied numbness. He had also experienced muscle cramping in his hands and legs. When asked, he said that he had been crying spontaneously, which was unusual for him.

Neurologic examination revealed mixed spastic and flaccid dysarthria and frequent yawning. He had fasciculations of the tongue, upper arms, and thighs and atrophy of the tongue and left hand (**FIGURE 9-1**) but no clear atrophy elsewhere. Proximal arm and lower extremity strength were normal, but he had weakness of the left greater than right finger extensors and intrinsic hand muscles. A jaw jerk was present, and arm and leg reflexes were brisk (3+). Hoffman sign was present on the right. Plantar responses were extensor. Sensation was preserved.

MRI of the brain and cervical and thoracic spine was unremarkable. Sensory and motor nerve conduction studies in the right arm and leg were normal. Needle EMG revealed fasciculation potentials in multiple arm and leg muscles. Fibrillation potentials and positive sharp waves were seen in the right and left triceps and intrinsic hand muscles, left distal leg muscles, and left thoracic paraspinals. Large motor units with reduced recruitment were seen in the left hand and multiple left leg muscles.

Most patients with ALS-FTD present with the behavioral variant of FTD, demonstrating disinhibition, lack of empathy, poor initiation, and impaired executive functioning (**CASE 9-2**), although disorders of language production manifesting as the nonfluent/agrammatic variant of primary progressive aphasia have also been reported.^{34,35} Conversely, approximately 15% of patients who present with FTD will develop ALS.^{36,37} Common tools for evaluation include the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) and the ALS Cognitive Behavioral Screen (ALS-CBS).^{38,39}

DIAGNOSTIC EVALUATION AND DIFFERENTIAL DIAGNOSIS

To date, no single diagnostic test is available for ALS. Diagnosis is based on the combination of historical features, examination findings, and electrophysiologic features and the exclusion of other potential causes for these findings. The symptoms described by patients with ALS are detailed above. On examination, a combination of upper motor neuron and lower motor neuron signs is expected,



FIGURE 9-1

Photographs of the patient in **CASE 9-1** with amyotrophic lateral sclerosis. **A**, Atrophy of the tongue. Atrophy of the hand is worst in the lateral ulnar (**B**, first dorsal interosseous) and median (**C**, abductor pollicis brevis) innervated muscles, commonly referred to as split hand syndrome.

This patient had bulbar-onset amyotrophic lateral sclerosis (ALS). The examination and EMG showed signs of lower motor neuron involvement in the bulbar, cervical, thoracic, and lumbosacral body segments. Additionally, the examination showed signs of upper motor neuron involvement affecting the bulbar, cervical, and lumbosacral regions. No signs of a structural cause for upper motor neuron pathology were seen on MRI. In the absence of any alternative explanation for these findings, the criteria for a diagnosis of ALS was met (Revised El Escorial: clinically definite).

COMMENT

although, in the authors' experience, approximately 15% of patients present with isolated lower motor neuron findings and a significantly smaller portion (4%) present with isolated upper motor neuron findings (unpublished data from the Penn Integrated Neurodegenerative Diseases Database 2007–2020, data reviewed May 8, 2020).

The revised El Escorial⁴⁰ and Awaji⁴¹ criteria are common diagnostic criteria used for the clinical diagnosis of ALS (**FIGURE 9-2**). It is important to note that these are classification criteria and not a measure of disease severity. Although a classification of clinically definite ALS does, on average, carry a worse prognosis than clinically possible ALS, one patient may be minimally disabled with clinically definite ALS and another may die, never having moved beyond a classification of clinically possible ALS. Staging systems that aim to inform disease progression and prognosis have also been proposed and are starting to gain ground and acceptance. The King's staging system classifies ALS into stage 1, symptom onset (involvement of first region); stage 2A, diagnosis; stage 2B, involvement of second region; stage 3, involvement of third region; stage 4A,

CASE 9-2

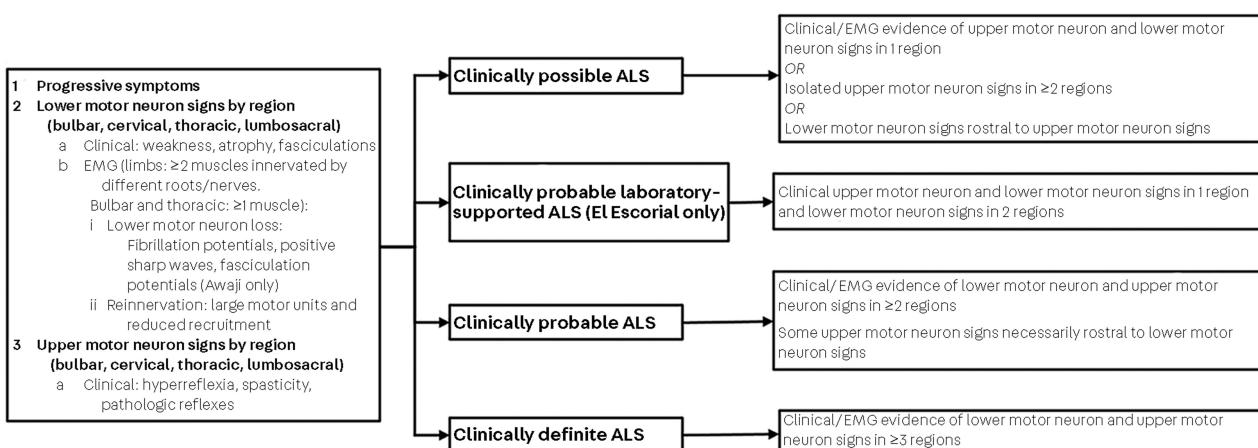
A 58-year-old woman was brought into clinic by her daughter, who described her mother as having had 1 year of progressive difficulty walking and behavioral changes. She noted that her mother had always been kind and interested in her daily life, but over the past year she had stopped asking about her grandchildren. Her eating habits had changed, and she had gained 15 pounds because of excessive daily consumption of butter pecan ice cream. The patient became angry when asked about these changes, which was unusual for her. The patient's father had died of symptoms consistent with amyotrophic lateral sclerosis (ALS), and her paternal grandmother struggled with dementia before her death.

On examination, the patient was pleasant but disinhibited. She repeatedly asked about the examiner's marital status. She was oriented to time and place. Her motor examination revealed atrophy of the distal right greater than left leg. Rare fasciculations were seen in her legs. Gait demonstrated right greater than left footdrop. Reflexes were 3+ at the knees with crossed adductors and absent at the ankles. Palmonatal signs were present bilaterally.

MRI of the brain was unremarkable. EMG revealed diffuse active denervation and chronic reinnervation in the legs. An ALS gene panel revealed a chromosome 9 open reading frame (**C9orf72**) gene repeat expansion.

COMMENT

This patient has familial ALS frontotemporal dementia (ALS-FTD) in the setting of a **C9orf72** repeat expansion. She has abnormalities on examination and EMG consistent with ALS. Her behavioral changes are consistent with impaired executive function and disinhibition and strongly suggest a behavioral variant of FTD. Her family history indicates a dominantly inherited disorder causing dementia or ALS, or both. Mutations in **C9orf72** are the most common cause of familial ALS and ALS-FTD.



need for gastrostomy; and stage 4B, need for noninvasive ventilation.⁴² The ALS Milano-Torino staging system starts at stage 0 with symptoms but no loss of independence and includes stages 1 through 4 for loss of independence in a number of domains derived from the ALS Functional Rating Scale-Revised (ALSFRS-R) (swallowing, walking/self-care, communicating, and breathing); stage 5 represents death.⁴³ The two staging systems are considered to be complementary and are now included in some clinical trials.⁴⁴

For patients with a history of progressive weakness and an examination revealing diffuse upper motor neuron and lower motor neuron findings, the diagnostic evaluation can be focused. Nerve conduction studies and EMG should be performed. Nerve conduction studies typically demonstrate preservation of sensory responses with normal or reduced motor amplitudes. As comorbid sensory polyneuropathy may occur, abnormal sensory responses should not exclude the diagnosis of ALS and should be considered in proportion to the motor findings. Motor responses are often preserved in early or slowly progressive ALS because of collateral sprouting of the remaining motor neurons. Needle EMG should demonstrate signs of active denervation (fibrillation potentials and positive sharp waves) along with chronic denervation in multiple myotomes. Limited electromyographic abnormalities with upper motor neuron examination findings may be seen in early or upper motor neuron–predominant disease; however, this should prompt consideration of an alternative etiology of upper motor neuron involvement with a coexistent lower motor neuron injury (eg, cervical radiculomyopathy). The authors recommend MRI of the neuraxis at and rostral to the lowest level of upper motor neuron findings. For example, a patient with brisk upper and lower extremity reflexes would require imaging of the brain and cervical and thoracic spine to exclude an alternative explanation for these findings.

In addition to electrodiagnostic evaluation and neuroimaging, limited further testing may be required to exclude particular diagnoses in certain clinical scenarios (TABLE 9-1). In patients with isolated findings of diffuse weakness, a broad differential should be considered, including myopathy, a defect

in neuromuscular junction transmission, polyradiculopathy, or a motor-predominant polyneuropathy. A myopathy is typically excluded by the presence of fasciculations, the pattern of weakness (distal and asymmetric), the degree of creatine kinase elevation (typically <1000 U/L in ALS), and the lack of myopathic findings on needle EMG. At times, myopathic processes, such as fascioscapulohumeral muscular dystrophy and inclusion body myositis, may be asymmetric, but in these instances the overall pattern of weakness typically suggests the underlying diagnosis. Some myopathies have modest creatine kinase elevations or have a “neurogenic appearance” on needle EMG (both are common with inclusion body myositis). Rarely, it may be necessary to resort to muscle biopsy to confirm a neurogenic process.

TABLE 9-1**Amyotrophic Lateral Sclerosis Mimics^a**

Diagnosis	Diagnostic Clue	Confirmatory Testing
Lower motor neuron predominant/weakness		
Benign fasciculations	Acute onset, widespread, no weakness	EMG does not demonstrate denervation or chronic reinnervation (and often does not show fasciculations)
Inclusion body myopathy	Weakness of deep finger flexors and quadriceps	Myopathic EMG, plus NT5C1A antibody (helpful when present), muscle biopsy findings
Multifocal motor neuropathy (MMN) with conduction block	Nerve (rather than myotome) pattern with asymmetric upper extremity predominance	Partial motor conduction block on nerve conduction studies, positive anti-GM1 antibodies
Neuralgic amyotrophy	Pain at onset, involvement of named nerves, self-limited course	Nerve conduction studies and EMG findings, MRI with and without contrast of the involved plexus
Monomelic amyotrophy (Hirayama disease)	Young male with asymmetric hand and distal forearm weakness and atrophy, self-limited course	MRI findings
Spinal bulbar muscular atrophy (Kennedy disease)	Slow progression, facial twitching, tremor, sensory neuropathy, evidence of androgen insensitivity (eg, gynecomastia, testicular atrophy)	Absent sural sensory responses, CAG repeat expansion in the androgen receptor gene
Motor-predominant Charcot-Marie-Tooth disease (CMT)/distal spinal muscular atrophy	Symmetric and distal onset, young age of onset, slow progression	Nerve conduction studies demonstrating abnormal sensory nerve action potential (SNAP) amplitudes and (in CMT type 1) evidence of demyelination; positive genetic testing for CMT
Post-severe denervation (postpolio syndrome)	History of distant polio or other severe nerve injury with recovery followed by slow progression of weakness in the distribution of prior polio symptoms; muscle pain is common	Giant motor unit action potentials on EMG

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Nerve conduction studies should demonstrate sparing of sensory nerves/neurons. Sensory involvement that maps to the regions of weakness should suggest an acquired (eg, vasculitis) or inherited (eg, familial amyloid) polyneuropathy. Careful assessment of motor responses should be performed to assess for demyelinating features (distal latencies >30% prolonged, conduction velocity <70% normal, or conduction block), which, if present, suggest an acquired demyelinating neuropathy such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or multifocal motor neuropathy (MMN). For more information on CIDP and MMN, refer to the article “Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Its Variants” by Kelly Gwathmey, MD,⁴⁵ in this issue of *Continuum*. If MMN is suspected on the basis of

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Diagnosis	Diagnostic Clue	Confirmatory Testing
Upper motor neuron predominant		
Nutritional myeloneuropathies	Sensory (predominantly dorsal column) deficits, sensory neuropathy	Abnormal sensory nerve conduction studies, vitamin B ₁₂ or copper deficiency, dorsal column abnormalities on MRI
Hereditary spastic paraparesis	Young onset, family history, slow progression, predominantly leg involvement	Positive hereditary spastic paresis genetic screen
Adrenomyeloneuropathy	Sensory neuropathy, with or without adrenal insufficiency, X-linked (females may still be affected)	Abnormal sensory nerve conduction studies, ABCD1 mutation
Late-onset Tay-Sachs disease	Cerebellar ataxia/atrophy, psychiatric features, Ashkenazi descent (recessive)	HEXA mutations
Polyglucosan body disease	Distal sensory loss, neurogenic bladder, cerebellar ataxia, cognitive deficits	White matter changes on MRI, GBE1 mutations
Human immunodeficiency virus (HIV) myelopathy	Extended history of HIV; MRI may be unremarkable	HIV positive
Multiple sclerosis	Sensory and sphincter involvement, relapsing-remitting course (some)	MRI findings, CSF findings
Mixed lower motor neuron/upper motor neuron		
Cervical radiculomyelopathy	Sphincter involvement, pain, sensory symptoms/level	Foraminal and canal stenosis on MRI (should be rostral to highest upper motor neuron examination findings)

CSF = cerebrospinal fluid; EMG = electromyography; MRI = magnetic resonance imaging.

^a The diagnoses in this table largely assume the presence of significant amyotrophic lateral sclerosis features that may confuse clinicians. Many of these diagnoses are quite rare and do not warrant individual investigation unless additional features as described in the Confirmatory Testing column are present. More common disorders considered when examining a patient with painless weakness are discussed in the article text and not addressed in this table.

electrodiagnostic testing or by the involvement of specific named nerves, anti-GM1 antibodies should be checked, although the sensitivity of this test is about 50%.⁴⁶ In the setting of preserved sensory responses with diffuse EMG abnormalities and no upper motor neuron findings, an immune (eg, CIDP, sarcoid), infectious (eg, varicella-zoster virus, cytomegalovirus, West Nile virus, Lyme disease), or neoplastic (eg, lymphomatous or carcinomatous) subarachnoid process should be sought by collecting CSF. Men with a lower motor neuron syndrome with abnormal sensory responses on nerve conduction studies should be tested for spinal bulbar muscular atrophy (Kennedy disease) with testing for a CAG repeat expansion in the androgen receptor gene, especially in the setting of slowly progressive disease, infertility, and gynecomastia. If prominent cerebellar or psychiatric symptoms are present, *HEXA* gene testing is appropriate to exclude adult-onset Tay-Sachs disease. Human immunodeficiency virus (HIV) may rarely be associated with an ALS-like syndrome (known as HIV-associated motor neuron disease). Because reports exist of patients with this syndrome having a response to antiretroviral therapy,⁴⁷ HIV testing should be part of the diagnostic evaluation in patients who are at risk.

Isolated upper motor neuron examination findings should prompt careful examination of the neuraxis, with MRI performed to exclude structural causes of upper motor neuron injury. Nutritional causes of myelopathy, including vitamin B₁₂ and copper deficiency, should be excluded. Infectious causes of chronic myelopathy include human T-cell lymphotropic virus types 1 and 2 (HTLV-1/HTLV-2) and HIV vacuolar myelopathy; these should be sought in the appropriate setting. Stiff person syndrome can present as an upper motor neuron phenotype and can be investigated with anti-glutamic acid decarboxylase (GAD) antibodies. In patients with slowly progressive symptoms predominantly in the legs, genetic evaluation for hereditary spastic paraparesis (HSP) should be performed whether or not the patient has a family history of similar issues. In patients with isolated clinical upper motor neuron signs, nerve conduction studies and EMG are useful tools to confirm the absence of sensory involvement and to look for subclinical lower motor neuron abnormalities on the needle study. In patients with predominant upper motor neuron clinical findings but sensory involvement on nerve conduction studies, testing of the *ABCD1* gene should be performed to exclude adrenomyeloneuropathy.

Once the diagnosis of ALS is established, careful reassessment should be routinely performed in follow-up visits to ensure that any new symptoms or signs remain consistent with the diagnosis of ALS and do not suggest an alternative diagnosis.

AMYOTROPHIC LATERAL SCLEROSIS BIOMARKERS

Currently, no nonclinical biomarkers are used in standard practice for diagnosis (beyond exclusion of other etiologies) or tracking of disease progression, although several have demonstrated some promise, particularly in predicting prognosis and disease progression. These include body fluid markers (eg, neurofilament light chain and phosphorylated neurofilament heavy chain, cystatin C, transthyretin, p75 neurotrophin receptor extracellular domain, miR-451, monocyte chemoattractant protein-1),⁴⁸ electrophysiologic measures (eg, electrical impedance myography, motor unit

number estimation), and imaging techniques (eg, MRI, positron emission tomography [PET]). Specific biomarkers have been developed for certain forms of familial ALS, including CSF superoxide dismutase 1 (SOD1) levels in familial ALS due to *SOD1* mutations. Development of biomarkers is critical for drug development, particularly given the heterogeneity of the clinical features of ALS.^{49,50}

PATHEOLOGY

The name amyotrophic lateral sclerosis is reflective of the original pathologic features described by Charcot. Along with muscle atrophy (amyotrophy) due to denervation, he noted scarring and hardening (sclerosis) of the lateral portions of the spinal cord, the location of the corticospinal tracts. Microscopic evaluation of the motor cortex and anterior horns of the spinal cord reveals loss of motor neuron cell bodies (**FIGURE 9-3**) and signs of neuroinflammation. Classic pathologic features of ALS also include Bunina bodies, small eosinophilic cytoplasmic inclusions found in the cytoplasm of surviving motor neurons in nearly all types of ALS; however, their significance has not yet been explained.⁵¹ Potentially more mechanistically relevant are the ubiquitinated cytoplasmic inclusions that contain transactive response DNA-binding protein 43 (TDP-43), which are present in nearly all patients with ALS (**FIGURE 9-4**).⁵² First described in a landmark article in 2006, TDP-43 intracytoplasmic inclusions represent the pathologic link between the

KEY POINTS

- Frontotemporal dementia occurs in 5% to 15% of patients with ALS, and a larger proportion of patients will have subtle findings of personality change or executive dysfunction.
- The diagnostic evaluation of ALS does not need to be extensive in the setting of the appropriate clinical history and physical examination, although it is imperative to exclude all treatable conditions.
- MRI should be performed at the lowest level of upper motor neuron findings and above in patients with suspected ALS.
- Isolated upper motor neuron examination findings should prompt careful examination of the neuraxis, with MRI performed to exclude lesional causes of upper motor neuron injury.

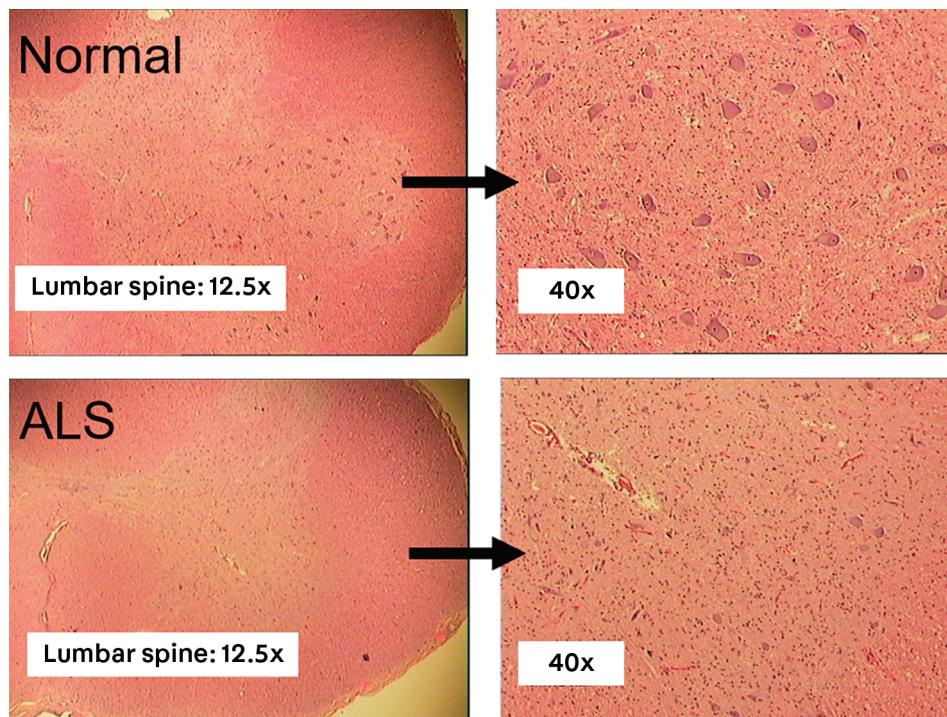
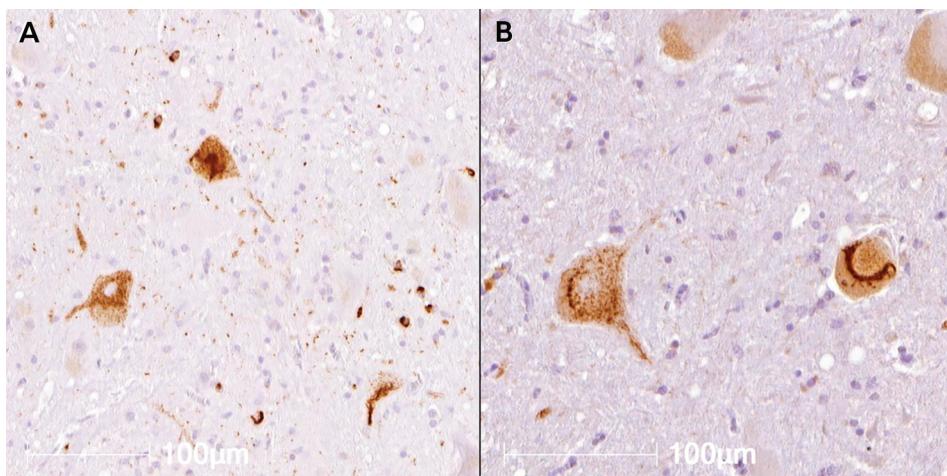


FIGURE 9-3

Hematoxylin and eosin (H&E) stains of the lumbar spinal cord in a healthy individual and in a patient with amyotrophic lateral sclerosis. In the spinal cord of a healthy individual, numerous motor neurons are visible at low-power and high-power magnification. In a patient with amyotrophic lateral sclerosis, a paucity of motor neuron cell bodies is seen at the same magnifications.

**FIGURE 9-4**

Transactive response DNA-binding protein 43 (TDP-43) immunohistochemistry of the lumbar spinal cord in a patient with amyotrophic lateral sclerosis. Sections were stained using an antibody that recognizes phosphorylated TDP-43 and counterstained with hematoxylin for nuclei (blue). The immunostain demonstrates cytoplasmic and neuritic TDP-43 inclusions affecting motor neurons (brown). **Panel A** is at slightly lower magnification and shows neuronal cell body TDP-43 pathology and neuritic pathology; **panel B** emphasizes cell body inclusions. Figure courtesy of John L. Robinson, MS.

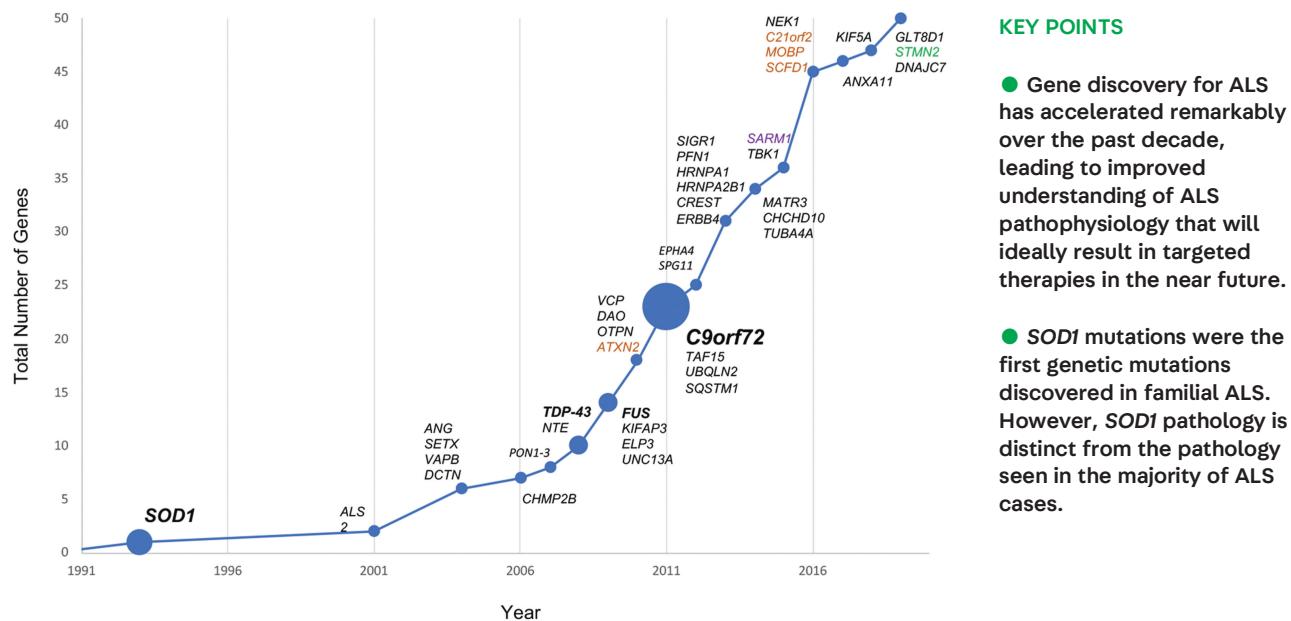
phenotypes of ALS and FTD; their discovery heralded the genetic link that was discovered shortly thereafter.

GENETICS

ALS is most commonly a sporadic disease, with no family history in 90% of patients. Approximately 10% of patients have a family history (familial ALS), which is typically dominant; over the past 30 years, this population has been extensively explored, with a goal of explaining the genetic underpinnings of their disease and leveraging this knowledge to a greater understanding of the underlying mechanisms of cell death in all forms of ALS.

In 1993, *SOD1* mutations were the first genetic cause of familial ALS to be described. *SOD1* mutations account for approximately 20% of familial ALS. Whereas the mutation was initially thought to cause oxidative damage in the setting of haploinsufficiency, further study demonstrated a dominant negative effect of the most common *SOD1* mutations.⁵³ As no other familial ALS mutations were discovered for 15 years after *SOD1*, this gene became the primary model for ALS genetics through the mid-2010s; however, concerns have been raised that *SOD1* pathophysiology may be distinct because of some unique features of *SOD1*-mediated ALS pathology (discussed later in this article).

In 2008, after a prolonged period without major gene discoveries in ALS, a family with dominant ALS was identified with a common mutation in the *TARDBP* gene. Although an uncommon cause of familial ALS (approximately 4%), the discovery of the *TARDBP* mutation was an important turning point because it linked a gene mutation to the most common pathologic feature seen in ALS (TDP-43 inclusions), and it marked the beginning of a decade of discovery of new genes associated with familial ALS (FIGURE 9-5). TDP-43 plays a critical role in RNA processing, and this pathway has become a central focus in the pathogenesis of ALS (refer to the pathophysiology section below).



KEY POINTS

- Gene discovery for ALS has accelerated remarkably over the past decade, leading to improved understanding of ALS pathophysiology that will ideally result in targeted therapies in the near future.

- SOD1 mutations were the first genetic mutations discovered in familial ALS. However, SOD1 pathology is distinct from the pathology seen in the majority of ALS cases.

FIGURE 9-5

Timeline of amyotrophic lateral sclerosis (ALS) gene discovery. The discovery of genes associated with familial and sporadic ALS has rapidly increased over the past 20 years. Most of the genes identified are associated with familial ALS, with *C9orf72* representing the largest proportion, followed by *SOD1* and then *TDP-43* and *FUS*. Some genes listed are ALS risk factors (*ATXN2*, *C21orf2*, *MOBP*, and *SCFD1*) or possible disease modifiers (*SARM1*). *STMN2* mutations have not been found in familial ALS, but missplicing of *STMN2* RNA appears to be important in ALS pathophysiology. The size of the circles is proportionate to the contribution of each gene to the overall population of familial ALS.

Data courtesy of Robert H. Brown Jr, DPhil, MD.

Soon after the discovery of the *TARDBP* mutation, another gene involved in RNA processing was found to be a cause of familial ALS. Mutations in the fused in sarcoma (*FUS*) gene are an uncommon cause of familial ALS (<5%) but are important because of the similarity between *FUS* and *TARDBP* function, although, interestingly, *FUS*-related familial ALS lacks TDP-43 pathology.^{54,55} Additionally, *FUS* mutations are more commonly seen in patients with early-onset ALS and should be considered in any patient presenting with ALS in the second or third decade of life.⁵⁴

The most significant discovery in ALS genetics of the past decade is the location of a mutation on *C9orf72*. An important locus on chromosome 9 was initially identified by a genome-wide association study performed in Finland,⁵⁶ which is an ideal geographic region for study because of a high incidence of ALS and relative genetic homogeneity. Later work revealed a hexanucleotide repeat expansion (GGGGCC) in the noncoding region of *C9orf72*, causing an autosomal dominant form of familial ALS.^{57,58} Expansions of at least 30 repeats are associated with ALS, FTD, or ALS-FTD. Expansions in *C9orf72* explain 40% of familial ALS in a European ALS population and nearly 10% of sporadic ALS.⁵⁹ Of note, the contribution of *C9orf72* expansions in non-European populations may be different. For example, a study of 59 Japanese patients with familial ALS revealed *C9orf72* expansion in less than 4% of families.⁶⁰ The penetrance of the mutation nears 100%. Patients who are going to develop ALS do so at a younger age than those who develop FTD. Spinal onset tends to occur at a younger age than bulbar onset, and males also tend to have a younger onset; this pattern holds

true whether the mutation is inherited or sporadic.⁶¹ Approximately 50% of people with *C9orf72* expansions will develop *C9orf72*-associated disease by age 60, and nearly 100% are symptomatic by 80 years of age.⁵⁹

PATHOPHYSIOLOGY

A unifying theory of ALS pathophysiology remains elusive and may ultimately prove unobtainable. The multiple potential pathways that may play a role in ALS pathophysiology are reviewed below. These pathways likely interact and may vary in importance in individual patients with ALS.

***C9orf72* Mutations**

As the most common cause of familial ALS, mutations in *C9orf72* are of significant interest as they promise to inform our understanding of ALS pathophysiology. Both loss-of-function and toxic gain-of-function mechanisms have been proposed. Although *C9orf72* protein function is not entirely elucidated, it appears to be related to membrane trafficking. Patients with expansions in the hexanucleotide repeat region of *C9orf72* produce less mRNA and *C9orf72* protein than patients with a standard number of repeats (<30), which suggests haploinsufficiency. Through repeat-associated non-AUG (RAN) translation, the expanded hexanucleotide repeat region can produce multiple dipeptide repeat proteins that form cytosolic aggregations. The functional significance of the pre-mRNA and dipeptide repeat proteins generated by the repeats is not clear, although concern exists that pre-mRNA may occupy nuclear binding proteins required for proper splicing of other mRNAs.^{62,63}

Impaired Protein Processing

Cytosolic aggregation of misfolded proteins and impaired protein degradation processes are features of nearly all neurodegenerative conditions. Similarly, multiple mutant proteins associated with the development of ALS form potentially pathogenic intracellular aggregations. *SOD1*, the first gene associated with ALS, has a dominant negative effect likely due to the accumulation of misfolded mutant proteins with direct toxic effect on cellular function and indirect effects through impairment of cellular degradation of proteins in proteasomes and autophagolysosomes. Aggregations of wild-type *SOD1* protein have also been noted in patients with sporadic ALS. Other protein mutations seen in rare cases of familial ALS, including ubiquilin 2, valosin-containing protein, and optineurin, are associated with impaired protein degradation.

Impaired RNA Processing

With the discovery of cytoplasmic TDP-43 inclusions in ALS, RNA processing became a major area of focus in ALS pathogenesis. TDP-43 is a DNA/RNA-binding protein involved in transcription, RNA splicing, and transport and is usually exclusively located in the nucleus. The discovery of displaced cytoplasmic TDP-43 raised concern for either a loss of nuclear TDP-43 function in RNA processing or a toxic effect of TDP-43 cytoplasmic aggregates, or a combination of the two. More recent evidence has suggested that altered nuclear RNA splicing may impact critical proteins involved in axonal function. Specifically, altered stathmin-2 splicing may result in early truncation and loss of full-length protein, which is essential for axon stability and regeneration.⁶⁴ FUS is another

RNA-binding protein associated with ALS, further supporting the notion of RNA processing as an important pathway in ALS neurodegeneration.⁵⁵

Cellular Abnormalities and Failure

Numerous signs of cellular abnormalities in ALS are difficult to categorize as either primary issues or downstream consequences of neurodegeneration from one of the mechanisms discussed above. These include neuronal hyperexcitability, endoplasmic reticulum stress, mitochondrial failure, cytoskeletal abnormalities, impaired axonal transport, axonal retraction, and synaptic failure.⁵³

Immune Dysregulation/Inflammation

The role of the immune system and immunomodulatory therapy in ALS has long been debated. Clear evidence exists of immune activation in ALS and a relationship between proinflammatory states and faster disease progression.

Activated microglia and macrophages are found in the motor cortex and spinal cords of patients with ALS and are typically absent in controls.⁶⁵ Microglia are the resident immune cells of the central nervous system and may have a proinflammatory (M_1) or anti-inflammatory (M_2) influence on the immune response.⁶⁶ Proinflammatory cytokines (eg, IL-6)⁶⁷ and lower numbers of regulatory (compared to cytotoxic) T cells are associated with faster disease progression.⁶⁸ Despite these findings, multiple trials of immunosuppression, including corticosteroids with azathioprine,⁶⁹ cyclophosphamide with IV immunoglobulin (IVIg),⁷⁰ and a posttransplant regimen of immunosuppression (basiliximab, tacrolimus, mycophenolate mofetil, and prednisone)⁷¹ have failed to show a significant effect on ALS disease progression in humans.

Nonetheless, current approaches to reduce the proinflammatory state (eg, masitinib,⁷² tocilizumab⁷³) or encourage an anti-inflammatory/proregulatory state (eg, rapamycin,⁷⁴ T-regulatory cell infusions plus IL-2⁷⁵) are in active or planned human trials. Mesenchymal stem cells, which may have a variety of trophic effects on motor neurons, also appear to have an impact on inflammatory markers, which may predict response to this therapy.⁷⁶

MANAGEMENT

Currently, ALS has no cure. A few disease-modifying options with limited efficacy are available. Much of the focus of ALS care centers on multidisciplinary management of symptoms.

Disease-Modifying Therapies

Despite decades of clinical trials involving numerous agents with varying mechanisms of action, only two disease-modifying agents are currently available, both of which have modest effects on disease outcomes. Riluzole, an inhibitor of neuronal glutamatergic transmission, was first approved in 1995 after demonstrating a 12% increase in 1-year survival in subjects treated with 50 mg 2 times a day compared to subjects treated with placebo.⁷⁷ Repeated studies of riluzole have consistently demonstrated a modest survival benefit averaging 3 months.⁷⁸ Edaravone, which is an intravenously administered free radical scavenger that reduces oxidative stress in the setting of cellular injury, was approved in 2017 based on a small study of Japanese patients with early, diffuse, and rapidly progressive ALS. In this population, a 33% reduction in the decline of the ALS Functional Rating Scale-Revised (ALSFRS-R) was seen over the course

KEY POINTS

- Hexanucleotide repeat expansions in *C9orf72* are the most common cause of familial ALS.
- No single cause of ALS has been determined, although multiple critical pathways in motor neuron degeneration have been identified. Of particular current interest are abnormalities in RNA processing.
- Cytoplasmic transactive response DNA-binding protein 43 (TDP-43) inclusions are a hallmark of ALS pathology in the vast majority of patients.
- No curative therapy has been identified for ALS. The mainstay of treatment is multidisciplinary care and palliative symptom management.
- The oral drug riluzole is the most widely used disease-modifying agent in ALS and has a well-established, albeit modest, effect on survival.
- Edaravone is an IV disease-modifying agent that slowed the rate of functional decline in a small number of select ALS patients with early, diffuse, and rapidly progressing disease. However, a prior trial in a broader population was negative and questions remain regarding its long-term effectiveness in the general ALS population.

of 6 months.⁷⁹ A prior trial in a broader ALS population failed to demonstrate this effect. A number of questions remain about edaravone's efficacy, including whether it is effective in the general ALS population, whether it provides benefit beyond 6 months, and whether its efficacy is long lasting.⁸⁰ A post hoc analysis of an extension trial in which some patients had delayed initiation of edaravone (24 weeks after the start of the trial) found that no benefit was seen with delayed edaravone even in the group that was expected to benefit the most from the drug (clinically definite ALS, forced vital capacity >80% predicted, score ≥2 on all ALSFRS-R items).⁸¹

Care of the Patient With Amyotrophic Lateral Sclerosis

Nonpharmaceutical interventions have also demonstrated benefit in ALS. Specifically, patients receiving multidisciplinary care report better quality of life and longer survival,^{82,83} and patients receiving early noninvasive ventilation have slower decline in respiratory weakness and prolonged survival compared to untreated cohorts.^{84–86} Optimal outpatient care involves having patients with ALS attend a multidisciplinary clinic every 3 months, in which body mass index and forced vital capacity are carefully tracked. Recommendations regarding

TABLE 9-2

Symptom Management in Amyotrophic Lateral Sclerosis

Symptom	Nonpharmacologic Management	Pharmacologic Management
Bulbar segment		
Dysarthria	Early voice banking, augmentative communication devices	None
Dysphagia/weight loss	Alteration of food consistencies, behavioral strategies for eating (small bites, chin tuck), offer feeding tube placement	None
Weak cough	Insufflator-exsufflator, aggressive secretion management	None
Sialorrhea	Suction device, radiation therapy	Tricyclic antidepressants, anticholinergics, botulinum toxin injection to the salivary glands
Thickened secretions	Ensure adequate hydration	Guaifenesin, nebulized medications (saline bullets, albuterol with acetylcysteine)
Laryngospasm	Botulinum toxin to laryngeal adductor muscles, tracheostomy	Clonazepam
Jaw clenching/biting	Bite guard	Clonazepam, baclofen, botulinum toxin injection to specific muscles
Pseudobulbar affect	None	Dextromethorphan HBr/quinidine sulfate, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants
Limb-related		
Weakness	Energy conservation, bracing and adaptive equipment	None

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nutrition, use of equipment and mobility devices, and respiratory interventions should be discussed and support offered to patients and caregivers.^{87,88} ALS is associated with substantial morbidity, and treatment of the symptoms of ALS is a critical focus of multidisciplinary care (TABLE 9-2).

AMYOTROPHIC LATERAL SCLEROSIS VARIANTS

The classic definition of ALS is a combination of upper motor neuron and lower motor neuron dysfunction affecting multiple segments of the body, which is reflected in the Revised El Escorial and Awaji criteria. If the disease is limited by body segment or limited to either upper motor neuron or lower motor neuron disease, a variant should be considered.

Progressive bulbar palsy is a rare syndrome in which disease is limited to the bulbar segment. It most often presents in older women, and the prognosis can be quite good if early intervention with feeding tube placement and secretion management is implemented.⁸⁹ Flail arm, also known as brachial amyotrophic diplegia, involves slowly progressive loss of arm function, which is often initially asymmetric and proximal. Flail leg, also known as leg amyotrophic diplegia, is also slowly progressive and asymmetric but may be proximal or distal at onset.

CONTINUED FROM PAGE 1338

Symptom	Nonpharmacologic Management	Pharmacologic Management
Spasticity	Stretching regimen	Oral centrally acting muscle relaxants (baclofen, tizanidine), benzodiazepines, gabapentin, intrathecal baclofen via pump, botulinum toxin injection to specific muscles
Cramps	Stretching/position change	Mexiletine, phenytoin, levetiracetam
Contractures	Splints in neutral for wrists/fingers and ankles	None
Respiratory		
Respiratory insufficiency	Noninvasive positive pressure ventilation, invasive ventilation	Morphine for air hunger
Other		
Cognitive-behavioral impairment	Caregiver education regarding presence of cognitive-behavioral issues	Low-dose SSRIs, low-dose trazodone, low-dose atypical antipsychotics (olanzapine, quetiapine, aripiprazole) ^a
Depression	Counseling	Antidepressant medications
Anxiety	Meditation, biofeedback	Buspirone, antidepressants with anxiolytic indication (SSRIs, serotonin norepinephrine reuptake inhibitors [SNRIs]), benzodiazepines
Insomnia	Sleep hygiene	Melatonin, sedative hypnotics, trazodone, mirtazapine
Anorexia	Offer feeding tube placement	Megestrol, dronabinol, mirtazapine, steroids

^a Atypical antipsychotics carry a US Food and Drug Administration (FDA) black box warning for increased mortality in older individuals with dementia.

Both flail arm and flail leg are considered regional variants of ALS and portend a better prognosis than “classic” ALS. Over time, a certain proportion of patients with flail arm or flail leg will progress to more widespread disease, but the factors that predict progression and the exact proportion of patients that convert to widespread disease remain somewhat unclear.⁹⁰

Progressive muscular atrophy occurs when clinical disease is limited to the lower motor neuron, at least for an extended period of time at disease onset. One series showed that patients with progressive muscular atrophy are more likely to be male and older at disease onset and survive longer⁹¹; however, in another series, no difference between males and females was seen and progressive muscular atrophy life expectancy was shorter than in ALS.⁹² By approximately 5 years after onset, 22% of patients will have upper motor neuron features of disease, and the disease is then considered ALS with lower motor neuron onset. Neuropathologic studies indicate that at least a significant portion of patients diagnosed in life as having progressive muscular atrophy have upper motor neuron pathology.^{92–94} The majority of patients with progressive muscular atrophy have TDP-43 pathology, although a significant minority demonstrate FUS pathology.⁹⁴

Primary lateral sclerosis is a slowly progressive disorder with prolonged survival that remains isolated to the upper motor neuron for at least 4 years from onset. Primary lateral sclerosis typically has onset around age 50, most often begins in the legs, and frequently involves the bulbar region. Recent consensus

CASE 9-3

A 20-year old man presented to a neuromuscular clinic with 24 months of progressive asymmetric hand weakness and atrophy. He denied preceding trauma, pain, or sensory loss. His medical history was unremarkable. He stated that his symptoms had started in the right hand and progressed to involve his left hand within several months.

Examination revealed atrophy in the right thenar and hypothenar eminences and asymmetric weakness in muscles of the C8-T1 myotomes (wrist extensors, finger flexors, finger abductors, and thumb abductors all grade 3 on the right and 4 on the left). The rest of the neurologic examination was normal.

Nerve conduction studies revealed reduced motor amplitudes in the right ulnar and median nerves with normal sensory responses. Needle EMG demonstrated severe chronic denervation in muscles innervated by the C8/T1 nerve roots and mild to moderate chronic denervation in the triceps bilaterally, worse on the right; the legs and thoracic paraspinal muscles were normal. MRI of the cervical spine in the neutral position revealed the loss of normal cervical lordosis but no disk herniation or cord signal change. MRI with flexion of the neck showed slight enlargement and diffuse enhancement within the posterior epidural space from C5 through C7-T1, with small flow voids seen on the T2-weighted sequences (FIGURE 9-6).

COMMENT

This patient has monomelic amyotrophy (Hirayama disease). His weakness can be expected to stop progressing and not spread beyond its current extent. He was advised to avoid prolonged neck flexion.

diagnostic criteria include categories of diagnostic certainty based on duration of isolated upper motor neuron signs as well as the requirement of the absence of lower motor neuron signs and alternative explanations.⁹⁵ Clinical cases of both primary lateral sclerosis and progressive muscular atrophy with the genetic mutations seen in ALS have been diagnosed.

AMYOTROPHIC LATERAL SCLEROSIS MIMICS

A number of disorders that phenotypically may resemble ALS are reviewed in the section on differential diagnosis. Diagnostic differentiation can be difficult because of the lack of definitive testing available for ALS. The most commonly encountered mimics and their differentiating features are presented in TABLE 9-1. Two disorders that have classically (although perhaps not completely correctly) been considered motor neuron disorders, monomelic amyotrophy and spinal bulbar muscular atrophy, are discussed in more detail here.

Monomelic Amyotrophy

Originally described in the Japanese population and also called Hirayama disease, monomelic amyotrophy most commonly presents with asymmetric arm weakness in young men around the age of 20. It typically involves the C8/T1 musculature, although some involvement of C7-innervated muscles may be seen; progression occurs over the course of 2 to 5 years (CASE 9-3). The diagnosis is

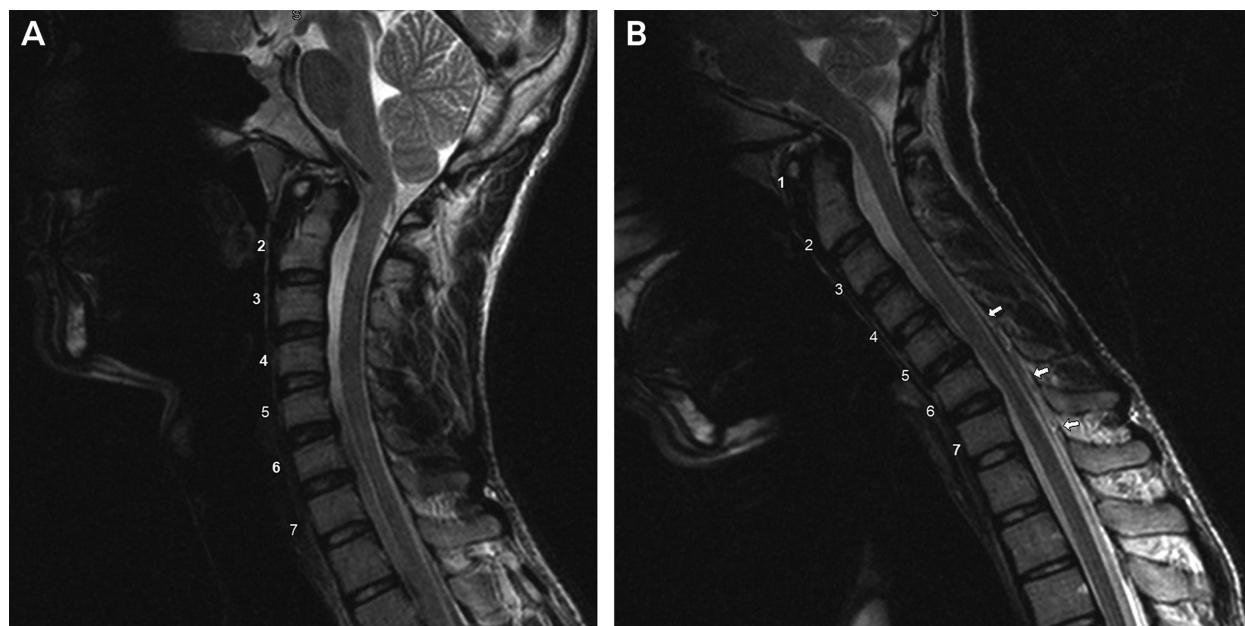


FIGURE 9-6

Imaging of the patient in CASE 9-3 with monomelic amyotrophy (Hirayama disease). A, Sagittal T2-weighted MRI of the cervical spine in a neutral position is fairly unremarkable. B, Sagittal T2-weighted MRI with neck flexion shows enlargement of the posterior epidural space from C5 to T1 (arrows).

KEY POINTS

- The presence of isolated lower motor neuron or upper motor neuron abnormalities should broaden the differential diagnosis but does not preclude an ALS diagnosis.
- Monomelic amyotrophy presents in young men with atrophy of one or both arms, typically in the lower cervical myotomes. The diagnosis is typically confirmed by findings on cervical MRI, including dynamic flexion demonstrating forward displacement of the dura. Although the cause of injury is not certain, the most common theory is microvascular disturbance due to compression with resultant ischemia of the anterior horn cells at C8 and T1.
- Spinal bulbar muscular atrophy is a rare cause of motor neuropathy but should be considered in men with lower motor neuron disease, sensory neuropathy on nerve conduction studies, predominant bulbar symptoms, and facial twitching. It is caused by an X-linked trinucleotide repeat disorder in the androgen receptor gene. Neurodegeneration is due to a toxic gain of function that occurs in the setting of ligand (testosterone and dihydrotestosterone) binding to the mutant receptor.^{103,104}

made on the basis of history, the classic clinical findings, and findings on cervical MRI, including dynamic flexion. Imaging findings include mild to moderate atrophy of the lower cervical cord, loss of posterior dural attachment on neutral images, forward displacement of the posterior dural sac and flattening of the cord with flexion, and prominent posterior epidural venous plexus.^{96–98} These MRI findings are supportive of the proposed pathophysiologic mechanism of forward displacement of the dura with flexion leading to compression of the spinal cord with resultant ischemia of the anterior horn cells at C8 and T1.⁹⁸ This may stem from insufficient growth of the dura relative to the vertebral column during puberty,⁹⁸ which would explain the age of onset; this phenomenon is more prevalent in young men, which explains the male preponderance of monomelic amyotrophy. Additionally, this points to an ischemic mechanism of anterior horn cell loss, which is borne out by the few pathologic samples available.⁹⁹ Thus, although the disease was originally believed to be a self-limited degenerative motor neuron disease, it is probably best thought of as an ischemic poliomyopathy. Management of monomelic amyotrophy is typically conservative. Cervical collar therapy and avoidance of prolonged forward neck flexion has been recommended during the early or rapidly progressive phase of disease.¹⁰⁰ Surgical intervention may rarely be indicated.^{101,102}

Spinal Bulbar Muscular Atrophy

Also called Kennedy disease, spinal bulbar muscular atrophy is an X-linked CAG trinucleotide repeat disorder caused by a mutation in the androgen receptor gene. Neurodegeneration is caused by a toxic gain of function that occurs in the setting of ligand (testosterone and dihydrotestosterone) binding to the mutant receptor.^{103,104} Men with disease usually present as adults with fasciculations, cramps, tremor, elevated creatine kinase (less than 1000 U/L), and weakness. Onset of weakness most commonly occurs in the bulbar region, followed by the lumbosacral region and then the cervical region.¹⁰⁵ Dysphagia with poor nutritional status may become an important medical concern; neuromuscular respiratory failure is rare in spinal bulbar muscular atrophy but can occur. Symptoms of androgen insensitivity, including infertility and gynecomastia, are common. Measurement of hormone levels shows elevations in testosterone, free testosterone, dihydrotestosterone, and estradiol and decreased androstenedione.¹⁰⁵ Decreased sensation, often modest and subclinical, and abnormal sensory nerve conduction studies are found in the majority of those affected. As in other trinucleotide repeat diseases, repeat length inversely correlates with age of onset¹⁰⁶; repeat length also predicts results of sensory and motor nerve conduction studies.¹⁰⁷ Attempts to treat spinal bulbar muscular atrophy with antiandrogens have not yet been a clear success.^{108,109} Because of known low concentrations of insulinlike growth factor 1 (IGF-1) in patients with spinal bulbar muscular atrophy, studies of IGF-1 mimetics remain under way.¹¹⁰

CONCLUSION

Motor neuron diseases, particularly ALS, remain devastating disorders without substantial disease-modifying treatments. ALS diagnosis remains clinical based on upper motor neuron and lower motor neuron symptoms and signs. Encouraging biomarker development has occurred in the past decade, although

this is largely focused on prognosis and progression rather than diagnosis. Gene discovery in familial ALS has expanded our understanding of the affected pathways resulting in cellular degeneration. Still, a unifying theory of motor neuron degeneration or a distinct categorization of different disease types by pathophysiology remains elusive. The next decade should bring further advances in our understanding of ALS pathophysiology along with treatments that take advantage of new drug delivery mechanisms and target both specific familial subtypes and common pathways in sporadic disease.

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