AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES
Eva L. Feldman
**Definition**

*Motor neuron diseases* are a heterogeneous group of disorders that selectively affect upper or lower motor neurons, or both (Table 1). Upper motor neurons are large cerebral and bulbar motor neurons whose dysfunction leads to decreased strength, spasticity, and hyperreflexia. Lower motor neurons are located in the ventral spinal cord; lesions result in decreased strength, tone, and reflexes accompanied by fasciculations and atrophy. Pure upper motor neuron disorders are most commonly acquired, whereas pure lower motor neuron disorders are frequently inherited. The most common acquired motor neuron disease, amyotrophic lateral sclerosis (ALS), usually includes dysfunction of both upper and lower motor neurons. Recent advances in the molecular genetics of hereditary motor neuron diseases have improved their classification and have led to advances in defining potential underlying causes of acquired motor neuron disorders.

**Table 1 - MAJOR MOTOR NEURON DISEASES**

<table>
<thead>
<tr>
<th>HEREDITARY</th>
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| Autosomal dominant
| Familial ALS
| Autosomal recessive
| Spinal muscular atrophy
| Type I: acute, infantile (Werdnig-Hoffmann disease)
| Type II: late infantile
| Type III: juvenile and adult types (Kugelberg-Welander disease)
| X-Linked
| Bulbospinal muscular atrophy (Kennedy's syndrome)

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| Acute
| Anterior poliomyelitis
| Chronic
| Sporadic ALS
| Postpoliomyelitis syndrome, motor neuron loss associated with spinocerebellar degeneration, multisystem atrophy, Creutzfeldt-Jakob disease
| ALS-like syndromes
| Motor neuron disease with gammopathy or paraproteinemia, heavy metal intoxication, hexosaminidase A deficiency, paraneoplastic motor neuronopathy
| Primary lateral sclerosis

ALS = amyotrophic lateral sclerosis.
AMYOTROPHIC LATERAL SCLEROSIS

Definition and Epidemiology
Sporadic ALS accounts for approximately 80% of all cases of acquired motor neuron disease, whereas the remaining 20% of patients have either only lower motor neuron signs or a familial form of ALS (FALS). The 80% of patients who have sporadic ALS present with spasticity, hyperreflexia, and Babinski's sign (upper motor neuron signs) in the setting of progressive muscle wasting and weakness (lower motor neuron signs). ALS has an estimated annual incidence of 2 per 100,000 with a worldwide prevalence of 4 to 6 per 100,000.

Pathobiology
Autosomal dominant familial ALS is an adult-onset disease that is clinically and pathologically indistinguishable from sporadic ALS. The protein cytosolic copper-zinc superoxide dismutase (SOD1) is mutated in several families affected by familial ALS, and more than 90 mutations in SOD1 (mostly missense) occur in patients with familial ALS. However, SOD1 mutations account for only approximately 20% of cases of familial ALS. Another gene implicated in familial ALS is alsin (also known as ALS2), which is a guanine-nucleotide-exchange factor that is essential for normal cytoskeletal dynamics. A mutant gene product of ALS2 is present in a slowly progressive, early-onset form of familial ALS. Linkage to chromosomes 16, 18, and 20 has also been reported in separate families with familial ALS, thereby implicating additional undiscovered genes.

The importance of the work on familial ALS lies in the finding that affected patients are clinically identical to patients with sporadic ALS, a feature suggesting a common mechanism of disease. Sporadic ALS may represent an acquired age-associated change in SOD1 function with resultant oxidative injury to the nervous system. Other potential causes of sporadic ALS include altered protein trafficking, glutamate excitotoxicity or neurotoxicity, abnormal accumulations of neurofilaments, and altered neurotropism.

Pathology
At autopsy, patients with ALS have brain stem and spinal cord atrophy with loss of motor neurons and associated extensive gliosis. In the cortex, large pyramidal cell loss leads to degeneration of the corticospinal tracts and gliosis of the lateral spinal cord columns. As with other denervating disorders, patients have loss of ventral nerve roots, with histologic evidence of denervation and reinnervation in affected muscle groups.

Clinical Manifestations
ALS is a disorder of upper and lower motor neurons. This combination results in a complex clinical syndrome. Painless, progressive weakness is the usual presenting sign and symptom of ALS. Usually focal in onset, weakness then spreads to contiguous muscle groups. Weakness is accompanied by muscle atrophy (Fig.1). Head “ptosis” resulting from weakness of neck extensor muscles with head droop is often present. Individuals frequently experience muscle cramps. Spasticity is common, and patients may complain of spontaneous clonus. With more long-standing disease, foot and hand deformities are seen as a result of tendon imbalance and secondary joint contractures.
ALS can manifest initially with bulbar dysfunction, although more commonly bulbar signs and symptoms are seen in the presence of extremity and truncal weakness. Individuals experience dysarthria, or impaired speech, which may be flaccid or spastic or of a mixed flaccid-spastic quality. Dysphagia with choking is common and places patients at a high risk of aspiration. The absence of spontaneous swallowing results in sialorrhea, or drooling.

Weakness of respiratory muscles is common and is the presenting symptom in rare cases in ALS. Early in ALS, individuals complain of dyspnea with exertion and frequently sigh at rest. With disease progression, dyspnea at rest, inability to sleep in a supine position (orthopnea), sleep apnea, and morning headaches are present. Constitutional symptoms reflect loss of muscle mass and difficulties with swallowing and breathing. Individuals experience weight loss and frequently complain of fatigue.

Several aspects of neurologic function are usually spared in ALS, including mentation, extraocular movements, bowel and bladder function, and sensation. However, approximately 1 to 2% of patients with ALS have dementia and ophthalmoplegia, usually reflecting ocular apraxia. Although bladder function is usually reported as normal, detailed study of bladder function reveals that nearly one third of patients with ALS experience urgency and obstructive micturition.

Debate continues about whether a disorder termed primary lateral sclerosis is a subtype of upper motor neuron ALS or is a separate entity. In this rare condition, individuals present with slowly progressive spastic paraparesis or quadriparesis, with no evidence of lower motor neuron involvement, either by clinical examination or diagnostic testing. Individuals with these presenting signs and symptoms should undergo the same diagnostic procedures...
and require similar treatment strategies as patients with sporadic ALS. Some patients with primary lateral sclerosis have an autosomal recessive form of hereditary spastic paraplegia.

Diagnosis

The El Escorial World Federation of Neurology criteria provide a set of guidelines for the diagnosis of ALS. In these criteria, the body is divided into four regions: (1) bulbar (jaw, face, palate, larynx, and tongue), (2) cervical (neck, arm, hand, and diaphragm), (3) thoracic (back and abdomen), and (4) lumbosacral (back, abdomen, leg, and foot). The diagnosis of definite ALS is made when upper and lower motor neuron signs are present in the bulbar region and two other spinal regions or in three spinal regions. Individuals with upper and lower motor neuron signs in two spinal regions alone are classified as having probable ALS; possible ALS is diagnosed when dysfunction is present in only one region or when an individual presents with only upper motor neuron signs in two regions or lower motor neuron signs are rostral to upper motor neuron signs.

When the clinical findings suggest a diagnosis of ALS, nerve conduction studies with repetitive stimulation and electromyography (EMG) confirm lower motor neuron degeneration and exclude disorders of the neuromuscular junction, such as myasthenia gravis, and of peripheral nerve and muscle. Neuroimaging of the brain and spinal cord is often needed to confirm the expected normal anatomy present in ALS and to exclude structural pathologic processes. Routine clinical laboratory tests are necessary to exclude ALS-related syndromes. These tests include complete blood cell count and routine chemical analyses, thyroid studies, serum protein electrophoresis, serum immunoelectrophoresis with immunofixation, and measurements of serum VDRL (Venereal Disease Research Laboratory) parameters, creatine kinase, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and, when clinically indicated, hexosaminidase A, parathyroid hormone, and paraneoplastic antibodies. Additional tests may be warranted on the basis of the patient’s clinical presentation. The EMG, neuroimaging, and clinical laboratory tests exclude the most common ALS-related disorders (Table 2): polyradiculopathy with myelopathy, postpolio syndrome, multifocal motor neuropathy, motor neuron disease with paraproteinemia, heavy metal intoxication, hexosaminidase A deficiency, paraneoplastic motor neuronopathy, and syringomyelia and syringobulbia.
<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Possible Disorder</th>
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<tbody>
<tr>
<td>Muscle</td>
<td>Idiopathic inflammatory myopathy (especially IBM), distal myopathy, nemaline myopathy, isolated neck extensor myopathy, metabolic myopathy, oculopharyngeal dystrophy</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>MG, Lambert-Eaton myasthenic syndrome</td>
</tr>
<tr>
<td>Roots, plexus, nerve</td>
<td>Radiculopathy, diabetic polyradiculoneuropathy, infectious polyradiculopathy, plexopathies, mononeuropathies, motor neuropathies</td>
</tr>
<tr>
<td>Anterior horn cells</td>
<td>Spinal muscular atrophy, BSMA, monomelic amyotrophy, paraneoplastic motor neuropathy, progressive postpolio muscular atrophy, hexosaminidase deficiency</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Spondylotic myelopathy, syringomyelia, MS, adrenomyeloneuropathy, vitamin B₁₂ deficiency, familial spastic paraparesis, HTLV-1 myelopathy</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Parkinson's disease, Creutzfeldt-Jakob disease, multisystem atrophy, Huntington's disease, brain stem stroke, brain stem glioma, foramen magnum tumors</td>
</tr>
<tr>
<td>Systemic disorders</td>
<td>Hyperthyroidism, hyperparathyroidism</td>
</tr>
</tbody>
</table>

BSMA = bulbospinal muscular atrophy, HTLV-1 = human T-lymphotropic virus type 1, IBM = inclusion body myositis, MG = myasthenia gravis, MS = multiple sclerosis.
Treatment and Prognosis

For direct disease treatment, the only drug currently available is riluzole (2-amino-6-trifluoromethoxy benzothiazole). Riluzole blocks release of glutamic acid and may slow the progression of disease by disrupting glutamate-mediated neurotoxicity. Administered at 50 mg twice a day, riluzole is generally well tolerated, although some patients experience nausea and general asthenia. Over the past decade, double-blind, placebo controlled trials of antiepileptic agents, antibiotics, antioxidants, protease inhibitors, platelet inhibitors, and growth factors have shown no benefit for the treatment of ALS.

Combining the results of several clinical epidemiology studies, the mean duration between the onset of symptoms and death in sporadic ALS ranges from 27 to 43 months, and the median duration is from 23 to 52 months. The average 5-year survival is 25%. The mean disease duration of primary lateral sclerosis is much longer, with an average of 224 months between symptoms and death. The relentless progression and poor prognosis of ALS require that patients receive attentive, supportive care.

A multidisciplinary approach is essential and is best coordinated by a dedicated ALS nurse or other health care professional. Symptomatic treatment is frequently required for sialorrhea, pseudobulbar symptoms, cramps, and spasticity. A social worker should help the patient cope with a sense of general fear, anxiety, and depression. A physical therapist should provide the patient with exercises for stretching and flexibility and should recommend needed bracing and adaptive walking devices. An occupational therapist should arrange adaptive devices to improve functional independence. As swallowing function decreases and speech becomes more difficult, a speech pathologist is helpful to oversee barium swallow tests and to obtain augmentative communication devices. For patients who undergo percutaneous endoscopic gastrostomy, a dietitian assists in selection of proper feedings. Pulmonary specialists are often helpful in determining when noninvasive ventilation techniques, such as bilevel positive airway pressure, will be helpful for pulmonary symptoms and in assisting in the long-term care of patients who choose to become ventilator dependent.
SPINAL MUSCULAR ATROPHIES

Definition
The spinal muscular atrophies (SMAs) are hereditary, progressive motor neuron disorders that can begin in utero, during infancy, in childhood, or in adulthood. SMA types 1 to 3 and bulbospinal muscular atrophy (BSMA), also known as Kennedy's syndrome, are more readily diagnosed than other SMAs because their genetic characteristics are defined. Other disorders include distal hereditary motor neuropathy types I and II, upper limb–predominant hereditary motor neuropathy (type V), proximal SMA, and scapuloperoneal syndromes resulting from SMAs (see Table 1).

Epidemiology
The estimated carrier frequency of a survival motor neuron mutation is 1 in 50. SMA 1 (Werdnig-Hoffmann disease) has a cumulative incidence of disease of 1 in 8000 births.

Pathobiology
SMAs 1 to 3 represent the first class of neurologic disorders in which a developmental defect in neuronal apoptosis is the most likely cause. Linkage to chromosome 5q13 led to the identification of the survival motor neuron (SMN) genes, two copies of which exist on 5q13. The form of SMA with the earliest onset and most severe disease, SMA 1 (Werdnig-Hoffmann disease), is caused by homozygous deletions in exons 7 and 8 of the telomeric gene copy (SMNt). Mutations that convert SMNt to the centromeric copy result in a milder disease phenotype, SMA 2 (late infantile) and SMA 3 (Kugelberg-Welander disease). The SMN gene is highly expressed in spinal neurons and is involved in RNA splicing. Deletions of exons 5 and 6 or complete absence of another gene on 5q13, the neuronal apoptosis inhibitor (NAIP), occur in 45 to 65% of patients with SMA 1 and in 20 to 40% of individuals with SMA 2 and 3. NAIP mutations may modify the severity of SMA.

Pathology
At autopsy, patients with SMA have atrophic spinal cords with loss of α-motor neurons and evidence of motor neuron degeneration and gliosis. Ventral roots are atrophic, and muscle groups supplied by these motor neurons and roots are atrophied and show microscopic evidence of denervation and reinnervation.

Clinical Manifestations
The onset of SMA 1 (Werdnig-Hoffmann disease), by definition, occurs either in utero or within the first 3 months of life. Infants present with severe diffuse weakness, hypotonia, reduced or absent reflexes, and tongue fasciculations. The usual cause of death is respiratory failure; 50% of infants die by age 7 months and 95% by 17 months.

Individuals with SMA 2 (late infantile form) and SMA 3 (Kugelberg-Welander disease) are less severely affected than those with SMA 1. SMA 2 is considered an intermediate phenotype. The onset occurs in children younger than 18 to 24 months. These children may never stand or walk, develop early scoliosis and respiratory insufficiency, and have a shortened lifespan. SMA 3 is the mildest phenotype, with onset frequently in later childhood or even in the teen years. These individuals have proximal, symmetrical weakness but stand and walk independently. With time, slow and mild loss of function usually takes place. Death occurs in adulthood, and whether SMA 3 shortens an individual's lifespan remains uncertain.
Diagnosis
The diagnosis of SMAs 1 to 3 is made by genetic testing in a patient with appropriate clinical signs and symptoms. Ninety-five percent of affected individuals have SMN deletions. Currently, carrier testing can be performed only by linkage analysis. Prenatal diagnosis is available. EMG and muscle biopsy, which are often performed before the diagnosis has been considered, reveal evidence of denervation but are unnecessary if a molecular diagnosis is established. Cerebrospinal fluid analysis is normal, and serum creatine kinase levels are elevated only in SMA 3.

It is important to distinguish SMA 1 from infantile botulism, which can have a similar initial clinical picture. EMG with high-frequency repetitive nerve stimulation shows a decrement in botulism but not in SMA. Examination of the stool for botulinum can confirm the diagnosis of infantile botulism. SMA 2 and SMA 3 can be distinguished from chronic inflammatory demyelinating polyneuropathy by the presence of normal cerebrospinal fluid protein and normal nerve conduction studies in SMA. SMA 3 and the hereditary motor sensory neuropathies (Charcot-Marie-Tooth disease) can be clinically similar. In addition to genetic testing, key diagnostic differences lie in normal nerve conduction studies in individuals with SMA 3 compared with abnormal studies in individuals with hereditary motor sensory neuropathies.

Treatment and Prognosis

No treatment is currently available, although trials with ciliary neurotrophic factor, brain-derived neurotrophic factor, gabapentin, and riluzole are under way. In SMA 2 and SMA 3, children benefit from passive and active physical therapy, lightweight braces, and, if necessary, surgery to correct scoliosis.
**BULBOSPINAL MUSCULAR ATROPHY**

**Definition and Etiology**

BSMA was first described by Kennedy and colleagues; consequently, it is also called Kennedy's syndrome. It is an X-linked recessive disorder. Incidence and prevalence have not been defined, but it is commonly held that BSMA is the most common form of adult-onset SMA.

**Pathobiology**

BSMA is a trinucleotide-repeat disorder with a CAG expansion encoding for a polyglutamine tract in the first exon of the androgen receptor gene on chromosome Xq11-12. Nuclear inclusions, aggregates, and aberrant proteolytic processing of the mutant androgen receptor are observed in bulbar and spinal motor neurons, which may lead to the pathologic features. It is not known why this mutation causes motor neuron disease instead of the testicular feminization caused by other androgen receptor mutations.

**Pathology**

At autopsy, patients with BSMA have findings similar to those of SMA 3. Mild brain stem and spinal cord atrophy with loss of α-motor neurons are seen, as are evidence of motor neuron degeneration and gliosis. Muscle biopsy reveals denervation and reinnervation in affected muscle groups.

**Clinical Manifestations**

The mean onset of BSMA is 30 years, with a range of 15 to 60 years. Gynecomastia occurs in 50% of affected individuals. Patients present with facial, tongue, and proximal weakness. Dysphagia, dysarthria, and masseter muscle weakness are common. Weakness is symmetrical and slowly progressive over decades; patients generally become dependent on canes or walkers in the fifth or sixth decades of life. Fasciculations are present largely in the face, and tendon reflexes are reduced or absent. Individuals frequently experience a mild postural tremor and a mild loss of vibratory sensation. No upper motor neuron signs are present.

**Diagnosis**

The diagnosis of BSMA is made when a patient with appropriate clinical signs and symptoms has positive genetic test results. Individuals affected at a younger age and more severely have more CAG expansion and longer polyglutamine tracts. The absence of upper motor neuron signs distinguishes BSMA from ALS. EMG and a muscle biopsy, which are often performed because creatine kinase levels are frequently elevated (up to 10-fold), reveal evidence of chronic denervation, which differentiates BSMA from muscular dystrophy and other myopathies.

**Treatment and Prognosis**

No specific treatment is available. Lifespan is usually unaffected, and therapy consists of supportive care, such as ambulatory aids.