Neurodegenerative Disorders:
Amyotrophic Lateral Sclerosis and Inclusion Body Myositis

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Table of Contents

Introduction ........................................ 2
Amyotrophic Lateral Sclerosis ................. 4
Inclusion Body Myositis ....................... 11
Summary Points .................................. 15
References ...................................... 15

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Neurodegenerative Disorders: Amyotrophic Lateral Sclerosis and Inclusion Body Myositis

Andrew J. Waclawik, MD

INTRODUCTION

Volume 8 of the Hospital Physician Neurology Board Review Manual focuses on sporadic degenerative conditions that affect the nervous system. This review addresses 2 conditions: amyotrophic lateral sclerosis (ALS) and inclusion body myositis (IBM).

ALS is a neurodegenerative condition affecting the motor neurons of the motor cortex, brainstem, and spinal cord (Figure 1). It is a fatal and relentlessly progressive disorder with eventual severe paresis of all limbs and bulbar muscles in most patients. Average disease duration from onset to death is approximately 3 to 4 years, with approximately 10% of patients surviving more than 10 years. Older age at onset and bulbar or severe respiratory involvement at onset are typically associated with poor prognosis. ALS is relatively easy to diagnose in advanced stages, when the typical combination of clinical signs develops. Clinical presentation in the early stages of the disease, however, may be non-specific and the diagnosis of ALS may be difficult.

IBM has traditionally been classified as an inflammatory myopathy and in many textbooks and review articles is discussed together with polymyositis and dermatomyositis. Although the cause of IBM remains unknown, IBM has been recognized as clinically and pathologically distinct from polymyositis and dermatomyositis. IBM has features consistent with a degenerative process affecting the skeletal muscle, and the inflammatory reaction in IBM may be an epiphenomenon of the myodegenerative process. As is the case with many degenerative conditions, there is no effective treatment for IBM.

The purpose of discussing ALS and IBM in a single review is that IBM may be misdiagnosed as ALS. There are several reasons for this:

- Both ALS and IBM are most prevalent in the elderly population.
- ALS and IBM share many clinical similarities, with muscle weakness, atrophy, and dysphagia common in both conditions (caused in ALS by motor neuron degeneration and in IBM by muscle degeneration).
- Creatine kinase (CK) may be normal or mildly elevated in both ALS and IBM.
- The pattern of electromyographic abnormalities in IBM may be misinterpreted for a primary neurogenic condition such as ALS.
- Patients with IBM may exhibit incidental upper motor neuron (UMN) signs (eg, signs of corticospinal tract involvement caused by cervical spinal stenosis, or ischemic brain changes in elderly patients), which increase the risk of misdiagnosis of ALS.

TERMINOLOGY

The term amyotrophic lateral sclerosis was coined in 1874 by Charcot to emphasize the lateral corticospinal tract involvement in this disease. Many clinicians also use the term motor neuron disease, which is essentially synonymous with ALS. The term motor neuron disease was introduced into the neurologic literature by Brain in 1933 to indicate the spectrum of clinical presentations of patients with degeneration of UMN's and lower motor neurons (LMNs). This spectrum includes purely LMN involvement (progressive muscular atrophy), typical ALS (“Charcot” ALS), purely UMN dysfunction (primary lateral sclerosis), and purely bulbar involvement (progressive bulbar palsy). In the United States, the term amyotrophic lateral sclerosis traditionally has been used to refer to the entire spectrum of patients (those who have ALS, progressive muscular atrophy, primary lateral sclerosis, or progressive bulbar palsy), whereas the term motor neuron disease is used commonly in the British neurologic nomenclature. However, many physicians in the United States also may use the term motor neuron disease.

An important distinction in terminology must be made between the terms motor neuron disease and motor neuron diseases. The term motor neuron diseases is used frequently as an all-encompassing term to apply to a broad category of conditions of various etiologies.
(genetic and acquired) affecting anterior horn cells of the spine, bulbar motor neurons, and motor neurons of cerebral cortex and corticospinal tracts. Genetically determined conditions, such as spinal muscular atrophy, and infectious conditions, such as poliomyelitis, are examples of motor neuron diseases.

The term ALS-related syndromes refers to a group of conditions that may be associated with secondary motor neuron dysfunction and may mimic classic ALS. In ALS-related syndromes, there is some clinical, epidemiologic, or laboratory evidence of a possible cause for motor neuron degeneration. However, the association of the laboratory abnormality with the ALS phenotype is frequently incidental, and if correction of the laboratory-defined feature does not result in correction of the ALS phenotype, the patient with the ALS-related syndrome will experience a clinical course equivalent to that of sporadic ALS. Examples of conditions that may be associated with ALS-related syndromes include endocrinopathies (especially hyperthyroidism or hyperparathyroidism), infections (HIV, human T lymphotrophic virus 1 [HTLV-1]), exogenous toxins (mercury, lead), radiation or electric shock induced injuries, paraneoplastic processes in association with lymphoma (Hodgkin’s, non-Hodgkin’s) or cancer, and monoclonal gammapathies or disimmune motor system degenerations (e.g., associated with high titers of antiganglioside GM₁ [anti-GM₁] antibodies).

Figure 1. Neuroanatomic pathways involved in amyotrophic lateral sclerosis (ALS). ALS affects the upper motor neurons, the lower motor neurons, and the skeletal muscles (bulbar, limb) innervated by the lower motor neurons. (Adapted with permission from Belsh JM. Definition of terms, classification, and diagnostic criteria of ALS. In: Belsh JM, Schifffman PL, editors. Amyotrophic lateral sclerosis: diagnosis and management for the clinician. Armonk (NY): Futura Publishing Company; 1996:27.)
AMYOTROPHIC LATERAL SCLEROSIS

EPIDEMIOLOGY
The incidence of sporadic ALS varies from 0.6 to 2.4 per 100,000 population; the prevalence rates are 2.7-fold to 4.3-fold higher.13 The peak age of onset is between 65 and 75 years,2 with a mean age of onset of approximately 58 years.1 Very rarely, ALS may be diagnosed in individuals younger than age 20 years. Men are affected more often than women (male:female ratio of 1.5 to 2.1:1); the exception is bulbar-onset ALS, which is reported more commonly in women.1

ETIOLOGY AND PATHOGENESIS
The etiology of sporadic ALS is unknown. It is possible that ALS is a neurodegenerative condition with multiple causes. Approximately 10% of cases are familial, with an autosomal dominant inheritance pattern in most families. Of those cases, approximately 20% are associated with a mutation in the copper/zinc superoxide dismutase 1 (SOD1) gene.9,14 Statistical and genetic evidence suggests that some sporadic cases of ALS may in fact be familial cases in pedigrees with very low disease penetrance.14 Mutations in the SOD1 gene may cause impaired antioxidant activity of the enzyme and lead to toxic accumulation of the superoxide and oxidative injury by free radicals. However, this hypothesized “loss of function” of enzyme activity has not been proven; further, current experimental data indicate that the toxic “gain of function” of the mutant enzyme may cause motor neuron degeneration.9,10,15

Familial and sporadic ALS cases share many clinical and pathologic similarities, suggesting similar underlying mechanisms. Although most cases of ALS are not hereditary, patients with sporadic ALS may have some genetic risk factors that predispose them to develop ALS in certain circumstances.

Glutamate excitotoxicity has been postulated as the mechanism of neuron demise in ALS because high glutamate levels can induce calcium-mediated cell death.15 Increased glutamate levels have been found in the cerebrospinal fluid (CSF) of patients with sporadic ALS.9 Neurofilament dysfunction also may be a factor in the pathogenesis of ALS. Accumulations of neurofilament in motor neurons have been reported in ALS, and gene mutations in the heavy neurofilament subunit gene have been identified in a few patients with sporadic ALS.10 Transgenic mice overexpressing either a mutant or a wild type of neurofilament subunit develop motor neuron degeneration.16

Recently, significant interest has been generated by the possibility that a mechanism of programmed cell death, termed apoptosis, may be responsible for the motor neuron degeneration in ALS.17 Autoimmunity may play a role in ALS; however, conclusive evidence is lacking and treatments typically used for autoimmune conditions have been ineffective.10

For many years, exogenous toxins have been postulated to play a role in the pathogenesis of ALS. Although lead or mercury toxicity may cause motor polyneuropathy or myelopathy, it has not been convincingly demonstrated that heavy metal toxicity is responsible for sporadic ALS.9

Finally, although some viruses (eg, HIV, HTLV-1) can cause ALS-like syndromes, there is no evidence to date that a viral infection may trigger degeneration of motor neurons leading to typical ALS.2

PATHOLOGY
Autopsy may show gross atrophy of the motor cortex areas and atrophy of the ventral spinal nerve roots. Microscopic examination in advanced cases typically shows evidence of loss and degeneration of motor neurons in the anterior horns of the spinal cord and brainstem nuclei, loss of pyramidal cells in the motor cortex, and degeneration of axons in the corticospinal tracts (Figure 2). A consistent finding in ALS is pathologic sparing of the Onuf’s nucleus in the anterior horn of the sacral cord, which correlates with preservation of sphincter function, even in the advanced stages of ALS.1 Other typical histopathologic features of ALS include spheroid bodies, Bunina bodies, and Lewy body–like inclusions.9

CLINICAL FEATURES
Case Patient 1: Presentation
A 75-year-old woman is referred to a neurologist for evaluation. For several months, the patient has had difficulty swallowing and slurred speech as well as difficulty holding her head up. She also has complained of fatigue, cramping in her legs, and muscle twitching in her arms for the last year. She denies any double vision or headaches, pain or numbness in any body region, and bowel or bladder problems.

Neurologic examination reveals normal mental status. The patient’s speech is significantly dysarthric, with marked hypernasality. Cranial nerve examination is significant for atrophy and fasciculations of the tongue. Motor examination reveals atrophy of the intrinsic muscles of both hands. Muscle tone is markedly increased (spastic catches in both upper and lower extremities). Fasciculations are observed in all 4 extremities as well as...
in the pectoralis muscles. Diffuse weakness (grade 4 on the Medical Research Council Scale) is noted in multiple muscle groups in the upper and lower extremities. Severe weakness of neck extensors (grade 3) also is noted. No sensory deficits are detected. Muscle stretch reflexes are pathologically brisk in all 4 extremities, jaw jerk also is pathologically brisk. Babinski’s sign is present bilaterally. The patient has diminished fine motor skills in her upper extremities, and her coordination is mildly compromised because of weakness. Gait examination is characterized by bilaterally diminished arm swing.

- What is the neuroanatomic localization and the differential diagnosis of the neurologic deficit in this patient?
- What examination findings suggest a diagnosis of ALS in this patient?

This patient’s clinical presentation and pattern of neurologic findings (ie, diffuse UMN and LMN signs in all extremities and the bulbar region, with no sensory, autonomic, or other systems involved) indicate pure motor neuron involvement and suggest a diagnosis of ALS. A series of tests should be recommended to help in making a more conclusive diagnosis.

Typical Signs and Symptoms of ALS

Initial symptoms of ALS may be very nonspecific. Patients may complain of fatigue, weakness, cramps, muscle twitching, poor coordination, loss of dexterity, shortness of breath, or difficulty with speech or swallowing. The distribution of abnormal neurologic findings depends on the pattern of LMN and UMN involvement in different areas of the neuraxis in individual patients. The typical signs associated with LMN degeneration include atrophy, hypotonia, fasciculation, hyporeflexia, and shortness of breath. UMN signs include spasticity and pathologic hyperreflexia, extensor plantar reflexes (Babinski’s sign), and Hoffmann’s sign. Atrophy is milder and appears later with UMN involvement than with LMN involvement. Weakness, dysarthria, dysphagia, and decreased dexterity and coordination may be caused by both UMN and LMN dysfunction.

Rarely, patients may present with only UMN signs and never develop any significant clinical LMN signs; these patients are classified as having primary lateral sclerosis. Patients who present with only LMN signs and never develop UMN signs are classified as having progressive muscular atrophy.18 However, most patients who initially present with only LMN or UMN signs eventually exhibit both UMN and LMN signs and then meet the criteria for clinically definite ALS.

In approximately 60% to 85% of patients, ALS begins in the limbs, typically asymmetrically in the distal muscles. Upper extremity onset clinically manifests as deterioration of dexterity, difficulty with fine motor skills, difficulty holding objects, or poor penmanship. Patients with upper extremity onset are frequently misdiagnosed with either cervical radiculopathy or ulnar neuropathy before the condition becomes more diffuse and spreads to other regions. Patients with lower extremity onset may complain of tripping, difficulty walking, or falling. Patients who develop foot drop may be initially misdiagnosed as having either peroneal neuropathy or L5 radiculopathy.

Bulbar onset ALS, which manifests as slurred speech and difficulty swallowing, occurs in 20% to 30% of patients1 and is common in older women with ALS, more than 50% of whom present with bulbar symptoms.19 Examination typically reveals dysarthria associated with tongue atrophy and fasciculations.

Other Signs and Symptoms

In rare cases, patients may initially present with isolated respiratory difficulty without significant limb or bulbar muscle involvement. In addition to resting or exertional dyspnea, symptoms indicative of respiratory muscle involvement may include excessive daytime sleepiness or headaches, which are typically related to carbon dioxide retention. Because the respiratory insufficiency progresses relatively slowly, many patients may adapt well to progressive hypoxia and hypercapnia and may not complain until functional vital capacity drops to 60% or less.1

Extraocular muscles typically are spared. Clinically significant sensory or autonomic involvement is not
observed, although a small subset of patients may have evidence of mild sensory or autonomic system involvement on advanced electrophysiologic testing. Cognitve function is typically preserved, with less than 5% of patients exhibiting signs of dementia. Some patients may develop emotional lability with pathologic outbursts of crying or laughing, termed pseudobulbar affect, a condition thought to be related to degeneration of the corticobulbar tracts.

Variant Presentations

In addition to having prominent motor neuron degeneration, patients with ALS variants show features of other system involvement, such as parkinsonism, dementia, or cerebellar dysfunction. Representative conditions include ALS-parkinsonism-dementia complex of Guam or ALS-multiple system atrophy variants. A hemiplegic (Mill’s variant) presentation of ALS is well recognized, with UMN and LMN signs isolated to one side. Up to 10% of ALS patients may present with a flail-arm syndrome, with severe, symmetric, proximal and distal upper extremity atrophy and weakness and coexisting bilateral corticospinal signs in the lower extremities.

• What conditions should be in the differential diagnosis of a patient presenting with a “dropped head” sign?

Typical conditions that may present with severe weakness of neck extensors include motor neuron disease, polymyositis, myasthenia gravis, and isolated neck extensor myopathy. These conditions usually can be ruled out in a patient with suspected ALS by careful clinical assessment, electrodiagnostic studies, and laboratory or pharmacologic testing (eg, edrophonium test in suspected myasthenia gravis).

• How is the diagnosis of ALS made?

• What diagnostic studies are considered most helpful?

DIAGNOSIS

The diagnosis of ALS can be difficult to make at the time of initial evaluation because of the variability of neurologic findings early in the course of disease and the lack of any specific laboratory diagnostic markers. Up to 43% of patients with ALS may be misdiagnosed early in the diagnostic evaluation.

Diagnostic Criteria

In 1994, the World Federation of Neurology proposed clinical criteria for the diagnosis of ALS, known as the El Escorial criteria, which were revised in 1998 (Figure 3). Although initially developed to ensure the uniformity of patient cohorts enrolled in clinical trials of potential therapies for ALS, these diagnostic criteria also provide useful guidelines for neurologic practice. The revised El Escorial criteria for clinically defined ALS have demonstrated high sensitivity and accuracy in a clinicopathologic study of autopsy-proven cases of ALS.

Based on the revised El Escorial criteria, the diagnosis of ALS requires all of the following:

• The presence of: (1) evidence of LMN degeneration by clinical, electrophysiologic or neuropathologic examination (muscle biopsy); (2) evidence of UMN degeneration by clinical examination; and (3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.

• The absence of: (1) electrophysiologic and pathologic evidence of other disease processes that might explain the signs of LMN or UMN degeneration; and (2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs.

Based on the distribution of UMN and LMN signs in different body regions (bulbar/brainstem, cervical, thoracic, and lumbosacral regions) and electromyographic findings, patients with ALS can be classified as having clinically definite ALS, probable ALS, possible ALS, suspected ALS, or probable laboratory-supported ALS.

Electrodiagnostic Studies

All patients with suspected ALS should undergo electrodiagnostic studies (ie, nerve conduction studies and needle electromyography [EMG]) to: (1) confirm LMN involvement in clinically affected regions; (2) detect possible LMN disease in regions that are not clinically involved; and (3) exclude other neurologic conditions affecting peripheral nerves, neuromuscular junctions, or muscles that may mimic or confound the diagnosis of ALS. Examples of such conditions include multifocal motor neuropathy with conduction blocks, chronic inflammatory demyelinating polyneuropathy, conditions affecting neuromuscular transmission (myasthenia gravis, Lambert-Eaton myasthenic syndrome), focal neuropathies, plexopathies, radiculopathies, and myopathies.

In patients with a benign fasciculation syndrome, fasciculations are the only abnormality observed on needle EMG; neither fibrillation potentials nor neurogenic (high-amplitude, long-duration) motor unit potentials are present. Multifocal motor neuropathy may mimic ALS because of frequently asymmetric presentation,
with the involvement of distal muscles more often than proximal muscles and the lack of sensory abnormalities. A characteristic electrophysiologic feature of multifocal motor neuropathy is presence of conduction blocks on nerve conduction studies. Many cases of multifocal motor neuropathy are associated with presence of anti-GM₁ antibodies. Some patients develop a clinical syndrome identical to multifocal motor neuropathy in association with anti-GM₁ antibodies but without evidence of conduction blocks on nerve conduction studies.

Patients with ALS typically have electrophysiologic evidence of active denervation changes (eg, fibrillation potentials, positive sharp waves) as well as chronic denervation changes (eg, large-amplitude, long-duration motor unit potentials). Based on the revised El Escorial criteria, EMG findings typical of LMN dysfunction required to support the diagnosis of ALS must be found in at least 2 of 4 nervous system regions (bulbar, cervical, thoracic, and lumbosacral). In the cervical and lumbosacral regions, at least 2 muscles innervated by different nerve roots and peripheral nerves must show EMG abnormalities. In the thoracic region, it is necessary to demonstrate neurogenic changes in the paraspinal muscles at or below the T6 level or in the abdominal muscles. EMG signs of denervation in one muscle supplied by the brainstem motor nuclei (tongue, facial, or jaw muscles) are sufficient to confirm bulbar involvement in patients with suspected ALS. Detailed guidelines regarding electrophysiologic evaluation of patients with suspected ALS are published at the World


Neuroimaging Studies

Magnetic resonance imaging (MRI) of the brain and/or spinal cord may be necessary to exclude structural lesions and other alternative diagnoses in a patient with suspected ALS. In patients presenting with bulbar signs (eg, slurred speech in the case patient), an MRI of the brain should be obtained. MRI of the corresponding region of the spine should be performed in patients with limb involvement at disease onset and only LMN signs on initial presentation. In patients with limb involvement at disease onset who exhibit UMN signs, MRI of both the spinal cord and brain may be necessary, depending on the pattern of neurologic findings on clinical evaluation.

Laboratory and Other Imaging Studies

There is no specific test to diagnose sporadic ALS. The diagnosis remains predominantly a clinical one. Laboratory studies of blood, urine, and CSF are focused on exclusion of conditions that may mimic ALS (Table). The selection of different tests should depend on the clinical presentation of individual patients. Laboratory screening tests may include the following: complete blood count (CBC); fasting glucose concentration; liver and renal function tests; CK level; serum electrolyte panel; magnesium, calcium, and phosphate levels; thyroid-stimulating hormone (TSH) level; erythrocyte sedimentation rate (ESR); serum and urine protein immunoelectrophoresis. All results are normal. Pulmonary function tests show a functional vital capacity at 75% of predicted. Swallow study shows decreased number of motor unit potentials (muscle denervation) may be considered because these conditions present as LMN syndromes. In patients with a positive family history for ALS, testing for SOD1 gene mutation may help to confirm the diagnosis. Screening chest radiography may be obtained in elderly patients or in patients with a history of tobacco abuse. More extensive imaging studies, including computed tomography of the chest, abdomen, and pelvis, may be necessary if a paraneoplastic syndrome is suspected.

Muscle Biopsy

In some patients with atypical presentations, especially without convincing UMN signs, muscle biopsy should be considered to rule out myopathy. One of the frequently misdiagnosed conditions mimicking ALS is IBM. Case Patient 1: Diagnostic Evaluation

The patient undergoes electrodiagnostics studies. Nerve conduction studies reveal decreased amplitudes of the compound muscle action potentials (CMAPs) in the upper and lower extremities, with normal sensory responses. Repetitive nerve stimulation (2 Hz) shows no CMAP decrement. An EMG shows evidence of diffuse spontaneous activity (fibrillating potentials, positive sharp waves and fasciculation potentials) and chronic neurogenic changes, with large-amplitude, long-duration polyphasic motor unit potentials and decreased recruitment (high-firing frequency with a decreased number of motor unit potentials) in all 4 extremities, the tongue, and diffusely in the paraspinal muscles. The patient’s pattern of electrodiagnostic findings is seen as strongly supportive of a diagnosis of ALS/motor neuron disease.

Due to the patient’s significant dysarthria, MRI of the brain also is performed, but no significant abnormalities are noted. Cervical spine MRI shows mild degenerative joint disease but no evidence of spinal cord or nerve root compromise. Chest radiography is normal. Pulmonary function tests show a functional vital capacity at 75% of predicted. Swallow study shows severe weakness and discoordination of the pharyngeal muscles with evidence of mild, silent aspiration.

Several laboratory studies are also performed (CBC, fasting glucose, serum electrolyte panel, liver and renal function tests, CK level, ESR, TSH level, rapid plasma reagin test, vitamin B₁₂ level, and serum and urine protein immunoelectrophoresis). All results are normal with the exception of the CK level, which is mildly elevated at 450 U/L (normal, 0 to 250 U/L).

• Does this patient have ALS?

The pattern of neurologic signs in this patient strongly suggested the diagnosis of ALS, and the clinical diagnosis was supported by EMG showing diffuse active and chronic denervation changes, indicating widespread anterior horn cell and brainstem motor neuron involvement. Compressive lesions were excluded by the normal MRI of the brain and cervical spine. Laboratory tests did not reveal any underlying systemic diseases.

8 Hospital Physician Board Review Manual
# Table. Differential Diagnosis of Amyotrophic Lateral Sclerosis

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>Disorder</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td>Parkinon’s disease</td>
<td>Levodopa trial</td>
</tr>
<tr>
<td></td>
<td>Huntington’s disease</td>
<td>MRI, CAG repeat</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
<td>MRI brain</td>
</tr>
<tr>
<td></td>
<td>Prion disease, HIV</td>
<td>EEG, CSF, biopsy</td>
</tr>
<tr>
<td></td>
<td>Multiple system atrophy</td>
<td>Autonomic testing</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar atrophy</td>
<td>Genetic testing</td>
</tr>
<tr>
<td><strong>Brainstem and spinal cord</strong></td>
<td>Brainstem glioma, plaque, infarct</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>Foramen magnum mass</td>
<td>MRI</td>
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<tr>
<td></td>
<td>Syringobulbia</td>
<td>MRI</td>
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<tr>
<td></td>
<td>Kennedy’s disease</td>
<td>CAG repeat</td>
</tr>
<tr>
<td></td>
<td>Spondylosis, syringomyelia, MS, SCDC, HTLV-1,</td>
<td>MRI, EMG, CSF</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td></td>
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<tr>
<td></td>
<td>Adrenomyeloneuropathy</td>
<td>VLCFAs</td>
</tr>
<tr>
<td></td>
<td>Hereditary spastic paraparesis</td>
<td>DNA testing (some patients)</td>
</tr>
<tr>
<td><strong>Anterior horn cell</strong></td>
<td>Spinal muscular atrophy</td>
<td>SMN gene testing</td>
</tr>
<tr>
<td></td>
<td>Kennedy’s disease</td>
<td>CAG repeat, EMG</td>
</tr>
<tr>
<td></td>
<td>Monomelic amyotrophy</td>
<td>EMG</td>
</tr>
<tr>
<td></td>
<td>Hexosaminidase A deficiency</td>
<td>Hexosaminidase A assay</td>
</tr>
<tr>
<td></td>
<td>Postpoliomyelitis syndrome</td>
<td>EMG</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic syndrome</td>
<td>Anti-Hu AB</td>
</tr>
<tr>
<td><strong>Root, plexus, and nerve</strong></td>
<td>Radiculopathy</td>
<td>EMG, MRI</td>
</tr>
<tr>
<td></td>
<td>Diabetic polyradiculoneuropathy</td>
<td>EMG, glucose</td>
</tr>
<tr>
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<td>Polyradiculoneuropathy (CIDP, GBS, porphyria,</td>
<td>EMS, laboratory and serologic studies, CSF</td>
</tr>
<tr>
<td></td>
<td>HIV, CMV, Lyme disease, syphilitic, post radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuralgic amyotrophy</td>
<td>EMG</td>
</tr>
<tr>
<td></td>
<td>POEMS, MMNCB, mononeuropathies</td>
<td>EMG, SPI, anti-GM, AB</td>
</tr>
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<td><strong>Neuromuscular junction</strong></td>
<td>Lambert-Eaton syndrome</td>
<td>Repetitive stimulation</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>Repetitive stimulation, SFEMG, AchR AB assay</td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td>Inclusion body myositis</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Oculopharyngeal dystrophy</td>
<td>GCG repeat, biopsy</td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy</td>
<td>CTG repeat</td>
</tr>
<tr>
<td></td>
<td>Isolated neck extensor myopathy</td>
<td>EMG, biopsy</td>
</tr>
<tr>
<td></td>
<td>Metabolic and congenital myopathies</td>
<td>EMG, biopsy</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>Hyperthyroidism</td>
<td>TSH, T₄</td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism</td>
<td>Ca²⁺, PTH assay</td>
</tr>
<tr>
<td></td>
<td>Benign fasciculations</td>
<td>EMG</td>
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<tr>
<td></td>
<td>Cramp-fasciculation syndrome</td>
<td>EMG</td>
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AB = antibody; AchR = acetylcholine receptor; anti-GM₁ = anti-ganglioside GM₁; Ca²⁺ = calcium; CAG = cytosine-adenine-guanine; CIDP = chronic inflammatory demyelinating polyneuropathy; CMV = cytomegalovirus; CSF = cerebrospinal fluid; CTG = cytosine-thymine-guanine; EEG = electroencephalography; EMG = electromyography; GBS = Guillain Barré syndrome; GCG = guanine-cytosine-guanine; HTLV-1 = human T lymphotropic virus 1; MMNCB = multifactorial motor neuropathy with conduction block; MRI = magnetic resonance imaging; MS = multiple sclerosis; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; PTH = parathyroid hormone; SCDC = subacute combined degeneration of the cord; SMN = survival motor neuron; SFEMG = single fiber electromyography; SPI = serum protein immunofixation; T₄ = thyroxine; TSH = thyroid-stimulating hormone; VLCFA = very long chain fatty acids. (Adapted from Murray B, Misumoto H. Amyotrophic lateral sclerosis. In: Katirji B, Kaminski HJ, Preston DC, et al, editors. Neuromuscular disorders in clinical practice. Boston: Butterworth Heinemann; 2002:430, with permission from Elsevier.)
• What treatments should be considered in a patient with ALS?

TREATMENT AND PROGNOSIS

Given the gravity of the diagnosis of ALS, it is critical that physicians present news about the diagnosis to patients in the most careful, considerate, and thoughtful way possible. It is most important to allow enough time to discuss the diagnosis and treatment options with the patient and the patient’s family or caregivers and to answer all questions. The diagnosis and prognosis should be discussed truthfully and with empathy. A second opinion may be offered. Patients and families should be provided with sources of additional information (eg, Muscular Dystrophy Association publications) and contacts to local support groups.

There is no effective treatment for ALS. The only medication approved for use in ALS, riluzole (a glutamate antagonist), has only a modest impact on the course of the disease but may prolong survival by 3 to 6 months. The essence of treatment for ALS is diligent symptomatic and palliative care to minimize secondary complications. Management involves a multidisciplinary team of health care professionals based in both the hospital and the community. Important team members include a neurologist, a nurse experienced in care of patients with neurologic disabilities, physical and occupational therapists, a respiratory therapist, a speech pathologist, a dietitian, social workers, and possibly a psychologist.

Management of Symptoms

Spasticity can be managed with baclofen, tizanidine, benzodiazepines, or dantrolene. Cramps may respond to quinine sulfate or to anticonvulsants (eg, carbamazepine, gabapentin, dilantin). Excessive salivation may be managed by tricyclic antidepressants (eg, amitriptyline, nortriptyline) or anticholinergic agents (eg, glycopyrrolate, scopolamine patch). A portable suction device may be indicated. Adequate fiber and fluid intake is important to prevent constipation. Stool softeners may be prescribed. Antidepressants and antianxiety agents should be started early in the course of the disease, if indicated. The importance of adequate pain control cannot be overstated.

Patients frequently take supplements, such as creatine monohydrate or vitamin E, although there is no convincing evidence for their efficacy to slow ALS progression. Vitamin E has unproven benefit in ALS but is frequently used, secondary to experimental studies supporting its role in neuroprotection. Nutritional status should be monitored carefully, and close follow-up by a dysphagia specialist is necessary. If progressive dysphagia compromises the caloric intake or puts the patient at significant risk for aspiration, percutaneous gastrostomy placement should be discussed with the patient. Speech therapy interventions may help preserve communication; when the patient’s speech becomes unintelligible, communication aids (eg, communication board, portable personal computer, portable speech synthesizer) may be prescribed.

Good pulmonary care is essential because respiratory failure is the main cause of death in patients with ALS. Options for noninvasive ventilatory support include bilevel positive airway pressure and continuous positive airway pressure systems. Advanced discussions should be held with patients to determine whether they want to proceed with tracheostomy and full ventilatory support, which is not preferred in most cases.

Occupational and physical therapy interventions may help preserve hand function and mobility as long as possible. Patients may need to be provided with orthotic devices (eg, ankle foot orthosis if foot drop develops). Use of a cane or walker should be encouraged to improve safety of ambulation. Use of a motorized wheelchair with a neck support and tilt mechanism should be prescribed with progression of weakness. A transfer board or hydraulic patient lift may assist with transfers. Patients typically benefit from such devices as a tub rail, grab bars, a raised toilet seat, a rolling bedside commode, and a shower chair. Neck orthosis helps prevent head drop if severe neck extensor weakness develops.

End-of-Life Care

Early enrollment in hospice programs may be most beneficial for both the patient and family. It is of paramount importance to reassure the patient and family that the patient will not suffer. In the terminal stages of ALS, patients typically develop progressive drowsiness, sleepiness, and eventually coma secondary to increasing hypercapnia. If signs of respiratory distress develop, morphine is frequently administered in combination with anxiolytic medications, if necessary.

Case Patient 1: Treatment

The patient is started on riluzole (50 mg, twice daily). Her depression and anxiety are treated with antidepressant and antianxiety medications, and her drooling markedly improves with nortriptyline (10 mg at bedtime). She also takes quinine (260 mg at bedtime) for cramps. Spasticity improves with baclofen (10 mg, 3 times daily).

Approximately 3 months later, the patient is started on nocturnal bilevel positive airway pressure treatment.
because of progressive respiratory failure. At about the same time, progressive dysphagia leads to the need for percutaneous gastrostomy for placement of a feeding tube. The use of a motorized wheelchair with neck support and tilt mechanism, hydraulic patient lift, and fully electric hospital bed also are prescribed.

INCLUSION BODY MYOSITIS

EPIDEMIOLOGY

IBM is the most common acquired muscle disease in patients older than age 50 years. The prevalence is approximately 2 to 5 per 100,000 population, with 3:1 male preponderance. The mean onset of symptoms is in the sixth decade of life, with patients younger than age 30 years being uncommon.

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of IBM are unclear. Cases of hereditary myopathies with clinical and pathologic features resembling sporadic IBM have been reported. In contrast to patients with sporadic IBM, patients with familial IBM typically do not have significant inflammatory reaction. These conditions are referred to as hereditary inclusion body myopathies. Although different pathogenetic mechanisms may be responsible, there may be a similar pathway for both the sporadic and familial forms of IBM.

Both immune and degenerative mechanisms appear to be involved in the pathogenesis of sporadic IBM. In contrast to other inflammatory myopathies such as polymyositis or dermatomyositis, IBM does not respond to treatment with corticosteroids or other forms of immunotherapy. The decrease in inflammatory reaction shown on muscle biopsies in the course of steroid treatment is not associated with clinical improvement. Despite treatment with prednisone, there is evidence of progressive muscle degeneration with an increase of vacuolated fibers as well as fibers containing amyloid deposits. Some studies have shown increased transcription and accumulation of amyloid-beta precursor protein and accumulation of its proteolytic fragment, amyloid-beta. One hypothesis postulates that the abundant vacuoles and filamentous inclusions may be secondary to the degeneration of the elements of the myonuclear matrix. These clinical and pathologic observations support the notion that IBM is primarily a myodegenerative condition and that inflammatory reaction in IBM may represent a secondary change.

PATHOLOGY

IBM has characteristic pathologic findings. Muscle biopsy on light microscopic evaluation typically shows predominantly endomysial inflammatory changes, often with focal invasion of non-necrotic fibers; however, inflammatory changes are sparse in some cases of sporadic IBM. Similar to polymyositis, cytotoxic CD8+ T cells and macrophages focally surround and invade non-necrotic fibers. A highly characteristic although nonspecific finding is the presence of vacuoles rimmed by basophilic material. These vacuoles have autophagic character. Eosinophilic inclusions (in a minority of biopsies) and groups of atrophic...
fibers are other typical features of IBM. Congophilic material can be found in some fibers, typically in the vicinity of rimmed vacuoles. Ragged red fibers and cytochrome-\(c\) oxidase–negative fibers are relatively common findings in IBM, indicating mitochondrial disturbance.

Electron microscopy typically demonstrates filamentous inclusions, approximately 15 to 20 nm in diameter (Figure 6). The inclusions may be located in the muscle nuclei or in the sarcoplasm, frequently in the vicinity of autophagic vacuoles. The nature of the inclusions is uncertain—they do not represent viral particles as initially suspected. Possibly, the inclusions consist of altered myonuclear matrix material. The autophagic vacuoles observed by electron microscopy typically contain degenerating membranous material and debris. The inclusions are immunoreactive with a number of antibodies, including antibodies against ubiquitin and phosphorylated tau protein.

**CLINICAL PRESENTATION**

**Case Patient 2: Presentation**

A 79-year-old woman is referred to a neurologist for evaluation of dysphagia and diffuse weakness. The patient has experienced progressive difficulty swallowing over the past 10 years. She also has had progressive weakness of both hands, with gradually weakening grip, as well as weakness of both lower extremities for the last 4 to 5 years, manifesting as difficulty walking and climbing stairs.

Neurologic examination shows normal mental status and speech. Cranial nerve examination is unremarkable; there is no facial weakness and no atrophy or weakness of the tongue. There is mild weakness of neck extension. Significant atrophy of the volar aspect of both forearms and severe atrophy of both quadriceps muscles are noted. The long finger flexors are weak (grade 4). On examination of the lower extremities, knee extension and ankle dorsiflexion are weak bilaterally (grade 4−). The other muscle groups in both the upper and lower extremities are grade 4+. Muscle stretch reflexes are normal except for absent knee reflexes. Sensory examination is normal. The patient has a wide-based gait and is unable to walk on her tiptoes.

- **What is the neuroanatomic localization and the differential diagnosis of the neurologic deficit in this patient?**
- **Is this patient’s clinical presentation and pattern of neurologic findings consistent with a diagnosis of ALS?**

The pattern of diffuse muscle weakness and atrophy, dysphagia, and diminished muscle stretch reflexes in this patient is consistent with a motor unit disorder, most likely a myopathic process or a disorder affecting anterior horn cells of the spinal cord or motor neurons in the brainstem. Although many patients with ALS may have a slowly progressive course and some patients with ALS may never acquire UMN signs, the diagnosis of ALS would be unusual in this case. The age of this patient, the slow progression of difficulty swallowing over 10 years, and the pattern of muscle weakness suggest that the diagnosis of IBM should be suspected. Other neuromuscular conditions that should be considered in the differential diagnosis of dysphagia include myasthenia gravis, many forms of muscular dystrophy (eg, oculopharyngeal muscular dystrophy, myotonic dystrophy), and inflammatory myopathies (eg, polymyositis).

**Typical Clinical Features of IBM**

Both proximal and distal muscle weakness may be apparent, even early in the course of IBM, and significant distal muscle weakness is present in at least 50% of patients. One of the characteristic features of IBM is atrophy and weakness of volar forearm muscles, frequently leading to disabling weakness of finger and wrist flexors (Figure 7). Distal lower extremity weakness may lead to foot drop. Severe atrophy of the quadriceps muscles (Figure 8) and depression or loss of knee reflexes are other characteristic features.

Clinically significant facial weakness is unusual, but dysphagia may develop in approximately 30% of patients. Dysphagia is rarely severe enough to require gastrostomy. Dysphagia is caused either by decreased...
upper esophageal motility or by cricopharyngeal achalasia. Convincing evidence of heart muscle involvement has not been reported.

- What diagnostic studies would be most helpful in this patient?

**DIAGNOSTIC STUDIES**

**Electrodiagnostic Studies**

Nerve conduction studies and needle EMG should be performed to confirm the myopathic process and to rule out alternative diagnoses. Nerve conduction studies and needle EMG demonstrate a myopathic pattern with short-duration, low-amplitude, polyphasic motor unit potentials; however, in many patients, long-duration, large-amplitude (“neurogenic”) motor unit potentials also are observed. Spontaneous activity in the form of abundant fibrillation potential is common. The mixed myopathic and neurogenic EMG pattern is suggestive of IBM but is not specific. Presence of fibrillation potentials and neurogenic motor unit potentials on EMG may lead to the erroneous diagnosis of motor neuron disease.

**Muscle Biopsy**

The clinical features and electrodiagnostic findings, although in some patients most suggestive of IBM, are nonspecific. Therefore, muscle biopsy is necessary to make a diagnosis of IBM and to rule out alternative diagnoses that are potentially treatable (eg, polymyositis).

**Neuroimaging**

MRI of the brain may be helpful in patients who present with severe swallowing dysfunction, to rule out any abnormalities of the brainstem or cranial nerves that also cause dysphagia. MRI of the lumbar and cervical spine frequently is obtained to rule out compressive lesions.

**Laboratory and Other Imaging Studies**

Typical laboratory studies include CBC, serum chemistry and electrolyte panel, liver and renal function tests, CK level, ESR, TSH level, acetylcholine receptor antibody testing (in some cases), and serum protein electrophoresis. CK is mildly elevated (up to 5 to 7 times normal) in approximately two thirds of patients, but a normal CK level is not uncommon in patients with IBM. It is important to remember that mild elevation of CK may be observed in both myopathic and neuropathic conditions. Chest radiography should be performed in older patients to rule out malignancy.

**Case Patient 2: Diagnostic Evaluation**

The patient undergoes nerve conduction studies, EMG, brain MRI, and laboratory testing. The results of nerve conduction studies are unremarkable. EMG shows spontaneous activity (fibrillation potentials and positive waves) in many muscles of the lower and upper extremities. Analysis of motor unit potentials reveals predominance of short-duration, small-amplitude...
motor unit potentials as well as some long-duration, large-amplitude motor unit potentials in most of the muscles tested in the upper and lower extremities. MRI of the brain is normal. The CK value is 56 U/L.

Muscle biopsy shows scattered necrotic and regenerating fibers, small groups of atrophic fibers, inflammatory changes in endomysium, and focal invasion of non-necrotic fibers. Numerous fibers contain autophagic vacuoles rimmed by basophilic material. Electron microscopy demonstrates filamentous inclusions in some fibers. These findings confirm the diagnosis of IBM.

Swallow study reveals cricopharyngeal achalasia, with severe hypertrophy of the cricopharyngeal muscle.

- **What are the possible diagnostic pitfalls with regard to interpretation of electrodiagnostic and pathologic findings in IBM?**

**Diagnostic Pitfalls**

Many elderly patients have “incidental" UMN signs on clinical examination that in combination with EMG findings (frequently showing a mixed myopathic and neurogenic pattern) can lead to initial suspicion of ALS. Clinicians should have a very low threshold for muscle biopsy if IBM is considered in the differential diagnosis.

Patients with IBM also may be misdiagnosed with polymyositis.31 The rimmed vacuoles characteristic in IBM may be sparse in some patients with the disease, and the pattern of inflammatory changes in IBM is indistinguishable from the pattern in typical polymyositis, although these changes usually are less prominent in IBM. Frequently, in a patient who is not responding to immunotherapy, repeat biopsy may reveal changes characteristic of IBM.31 In most patients with IBM, the distinctive pattern of weakness and muscle atrophy, coupled with characteristic findings on muscle biopsy, allows the clinician to make a diagnosis with a high degree of confidence.

The diagnostic criteria for IBM proposed by Griggs et al34 strongly emphasize the importance of characteristic light and electron microscopic features. Muscle biopsy may not reveal characteristic changes; however, this may be a result of a sampling error. Some expert clinicians believe that the diagnosis of IBM should not be rejected if the patient presents with characteristic clinical findings but the pathologic studies do not show typical abnormalities.33 Other conditions—including lumbosacral spinal stenosis, predominantly motor polyneuropathies, and myasthenia gravis—usually can be differentiated from IBM on the basis of typical clinical, neuroimaging, electrodiagnostic, and laboratory findings.

- **What treatments should be considered in a patient with IBM?**

**TREATMENT**

There is no effective treatment of IBM.4,38 In contrast to patients with polymyositis or dermatomyositis, patients with IBM typically do not respond to corticosteroids or other forms of immunosuppressive therapy. Transient improvement may be observed in some patients treated with corticosteroids, various immunosuppressive agents, or high-dose intravenous immunoglobulins,39 but the course of IBM is slowly progressive. Also, steroids and other immunosuppressive agents may cause significant iatrogenic side effects. One of the values of confirming the diagnosis of IBM by muscle biopsy is to avoid unnecessary, potentially toxic therapies.

Tendon transfer treatment may be considered for some patients with disabling finger flexion weakness.40 Dysphagia must be monitored periodically to avoid weight loss and the risk of aspiration. Nutritional supplements may be necessary. Cricopharyngeal achalasia is prominent in a subset of patients with IBM. The food may remain in the hypopharynx because the cricopharyngeal muscle does not contract normally. This complication of IBM is important to recognize because it may be effectively corrected with surgery.41

Many patients with IBM may become severely disabled with disease progression. Severe weakness of the lower extremity muscles increases the risk of falls, with secondary complications. Some patients may benefit from ankle-foot or knee orthoses. Physical therapy evaluation to determine the patient’s safety of ambulation may be beneficial. Patients should be encouraged to use a cane or a walker, if necessary. Most patients with IBM remain ambulatory even after many years of illness, but some patients may benefit from the use of a motorized wheelchair or scooter. Despite progressive disability, longevity in most IBM patients does not appear to be significantly affected. Progression is faster in patients who experience the onset of disease later in life. Patients with disease onset in their sixties usually require assistive devices many years later compared with patients whose symptoms begin in their seventies, presumably because of lesser muscle reserves in older patients.39
Case Patient 2: Treatment and Outcome

The patient undergoes endoscopic esophageal dilata-
tion, which markedly improves her oral intake. She
receives a therapeutic trial of prednisone at 20 mg/day.
After 3 months, no significant improvement is noted
and the drug is tapered off. The patient is referred for
physical and occupational therapy evaluations for
assessment of gait safety and the need for assistive
devices at her home. Three years later, she is still ambu-
latory but has had progressive difficulty with ambula-
tion.

SUMMARY POINTS

AMYOTROPHIC LATERAL SCLEROSIS

• ALS is clinically characterized by the presence of
  UMN and LMN signs and the absence of any other
  system involvement.
• Approximately 10% of ALS cases are familial, and
  approximately 20% of familial cases are associated
  with a mutation in the SOD1 gene.
• Nerve conduction studies and needle EMG should
  be performed in all patients with suspected ALS.
  Electrodiagnostic evaluation may reveal evidence of
  muscle denervation in clinically unaffected muscles
  and help rule out alternative diagnoses.
• MRI of the brain and spinal cord should be consid-
  ered in patients with suspected ALS to rule out focal
  lesions that may mimic ALS.
• Mild elevation of CK is not unusual in ALS. Muscle
  biopsy to rule out myopathy should be considered in
  some patients, especially when signs of UMN involve-
  ment are absent.
• A high index of suspicion is necessary to rule out
  IBM because it may mimic ALS in terms of both clin-
  ical and electrophysiologic features.
• There is no effective treatment for ALS. Manage-
  ment emphasizes diligent symptomatic and palliative
care to minimize secondary complications. Riluzole
  may prolong survival by 3 to 6 months.

INCLUSION BODY MYOSITIS

• IBM is the most common form of acquired myopa-
  thy in patients older than age 50 years.
• Growing evidence suggests that IBM is a myodegen-
  erative condition and inflammatory reaction may be
  an epiphenomenon of the degenerative process
  affecting the skeletal muscle.
• Distal and proximal lower extremity weakness is a
  common finding in IBM, and many patients develop
  characteristic weakness of the knee extensors and
  long finger flexors in the forearm.
• Characteristic light microscopic findings in IBM in-
  clude endomysial inflammatory infiltrates (often
  with evidence of invasion of non-necrotic muscle
  fibers), rimmed vacuoles, eosinophilic inclusions,
  and groups of atrophic fibers.
• Electron microscopy in IBM may reveal 15- to 20-nm
  filamentous inclusions. These inclusions may be
  located in the myonuclei or in the sarcoplasm.
• EMG in IBM may show a mixed myopathic and neu-
  rogenic pattern of motor unit potentials and may be
  misinterpreted as indicative of motor neuron dis-
  ease.
• There is no effective treatment for IBM. In contrast
to other inflammatory myopathies (eg, polymyositis,
dermatomyositis), IBM does not respond to immu-
notherapy.

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