TABLE 121-2 CLINICAL FEATURES OF THE NEUROMUSCULAR DISEASES

CLINICAL FEATURE	ANTERIOR HORN CELL	PERIPHERAL NERVE	NEUROMUSCULAR JUNCTION	MUSCLE
DISTRIBUTION OF WEAKNESS	Asymmetrical limb or bulbar	Symmetrical, usually distal	Extraocular, bulbar, proximal limb	Symmetrical, proximal limb
ATROPHY	Marked and early	Mild, distal	None (or very late)	Slight early; marked later
SENSORY INVOLVEMENT	None	Dysesthesias, loss of sensation	None	None
REFLEXES	Variable (depending on degree of upper motor neuron involvement)	Decreased out of proportion to weakness	Normal in myasthenia gravis, depressed in Lambert-Eaton syndrome	Decreased in proportion to weakness
CHARACTERISTIC FEATURES	Fasciculations, cramps	Combined sensory and motor abnormalities	Fatigability	Usually painless

DISEASES OF THE MOTOR NEURON (ANTERIOR HORN CELL)

Amyotrophic Lateral Sclerosis

Definition and Epidemiology

The most common *acquired* motor neuron disease, amyotrophic lateral sclerosis (ALS), is a progressive, typically fatal disorder. The incidence is approximately 2 per 100,000 population, and there is a slight male predominance. The peak age of onset is in the sixth decade, although the disease can occur at any time throughout adulthood. Epidemiologic studies have incriminated risk factors for ALS including exposure to insecticides, smoking, participation in varsity athletics, and military service in the Gulf War. The cause of ALS is largely unknown, with 95% of cases considered "sporadic," and 5% related to an autosomal dominant disease (familial ALS [FALS]). FALS is an adult-onset disease that is clinically and pathologically indistinguishable from sporadic ALS. FALS is caused by mutations in many genes, including the C9orf72, SOD1, TARDBP, FUS, ANG, ALS2, SETX, and VAPB genes. Mutations in C9orf72 can also cause sporadic ALS. (E-Table 121-1).

Pathology

ALS results from degeneration of the cortical motor neurons originating in layer five of the motor cortex and descending via the pyramidal tract (resulting in upper motor neuron signs and symptoms) and from degeneration of the anterior horn cells in the spinal cord and their brainstem homologues innervating bulbar muscles (resulting in lower motor neuron signs and symptoms) (Table 121-3).

Clinical Presentation

Clinical symptoms relating to the upper motor neuron degeneration include loss of dexterity, slowed movements, muscle weakness, stiffness, and emotional lability. Signs on neurologic examination that confirm an upper motor neuron lesion include pathologic hyperreflexia, spasticity, and extensor plantar responses (Babinski's sign). Lower motor neuron signs and symptoms caused by anterior horn cell degeneration include weakness, muscle atrophy, fasciculation, and cramps. Fasciculations in the absence of associated muscle atrophy or weakness are usually benign and may be aggravated by sleep deprivation, stress, and excessive caffeine ingestion. Muscle weakness in patients with ALS usually begins distally and asymmetrically and may manifest as a monoparesis, hemiparesis, paraparesis, or quadriparesis. It may also be limited initially to the bulbar region, resulting in difficulty with swallowing, speech, and movements of the face and tongue. For unclear reasons, ocular motility is spared until the very late stages of the illness. Bowel and bladder function and sensation remain spared throughout the course of the disease. Degeneration of the corticobulbar projections innervating the brainstem can lead to pseudobular affect causing difficulty controlling laughter and/or tearfulness. Up to 50% of patients with ALS may also have a component of frontotemporal dementia characterized by executive dysfunction, poor insight, personality changes (disinhibition, impulsivity, and apathy), abnormal eating habits, poor hygiene, and language dysfunction.

TABLE 121-3 SYMPTOMS AND SIGNS ASSOCIATED WITH AMYOTROPHIC LATERAL SCLEROSIS

SYMPTOMS	SIGNS
UPPER MOTOR NEURON DEGENERATION	
Loss of dexterity	Pathologic hyperreflexia
Slowed movements	Babinski's sign
Weakness	Hoffman's sign
Stiffness	Jaw jerk
Pseudobulbar affect	Spasticity
LOWER MOTOR NEURON DEGENERATION	
Weakness	Muscle atrophy
Fasciculations	Fibrillation potentials on electromyography
Cramps	Neurogenic atrophy on muscle biopsy

Diagnosis and Differential Diagnosis

The diagnosis of ALS remains one of "exclusion," in which other potential causes must be ruled out through a variety of neuroimaging, laboratory, and electrodiagnostic investigations (E-Table 121-2). For example, compression of the cervical spinal cord or cervicomedullary junction from tumors or cervical spondylosis can produce weakness, atrophy, and fasciculations in the upper extremities and spasticity in the lower extremities, closely resembling ALS.

Treatment

Specialized multidisciplinary clinic referral should be considered for patients with ALS to optimize health care delivery (Level B) and prolong survival (Level B). The only current U.S. Food and Drug Administration (FDA)–approved therapy for ALS is riluzole 50 mg twice per day, which in clinical trials prolonged