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Clinical Manifestation and Management of Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disease resulting in death in 2 to 4 years in most cases. There are several clinical subtypes of ALS depending on the degree of upper and lower motor neuron involvement, and recognition of these subtypes is important because certain subtypes have better prognosis. Without a reliable biomarker, ALS is a clinical diagnosis supported by laboratory investigations. The etiology of ALS remains unknown. However, mutations in certain genes cause ALS in about 5–8% of cases and understanding molecular pathogenetic pathways in these cases may pave a way for effective therapies. There is currently no cure or meaningfully effective therapy for ALS. Supportive and palliative measures in multidisciplinary ALS clinics are exceedingly important to maintain and improve the quality of life in patients with ALS. This chapter summarizes the clinical features and management of ALS.

Keywords: amyotrophic lateral sclerosis; motor neuron; muscular atrophy; primary lateral sclerosis; progressive bulbar palsy

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INTRODUCTION

Motor neuron diseases encompass a group of related degenerative disorders of motor neurons in the motor cortex, brainstem, and the spinal cord which manifest clinically by muscular weakness, atrophy, and corticospinal tract signs in varying combinations. Amyotrophic lateral sclerosis (ALS), a prototypic motor neuron disease (MND), is a progressive disease of middle life that leads to death in 2 to 4 years in most cases (1–3).

Jean Martin Charcot (1825–1893), a French neurologist, originally delineated the clinical and pathologic aspects of ALS and recommended the term amyotrophic lateral sclerosis (4). In a series of lectures given in the 1870s, he provided a lucid account of the clinical and pathologic findings of ALS. In the United States, Lou Gehrig, a baseball legend, suffered ALS at age 38 and died 3 years later, and ALS is also named Lou Gehrig disease. Although called Charcot disease in France, MND in the United Kingdom, and Lou Gehrig disease in the United States, ALS has been a preferred term all over the world.

The annual incidence rate of ALS is at 0.6 to 1.8, and prevalence at 4 to 8 per 100,000 population (5–8). The disease occurs in a random pattern throughout the world except for a clustering of patients among inhabitants of Guam, West New Guinea and Kii Peninsula where ALS is often combined with dementia and parkinsonism (9, 10). The ALS is about one-and-half times more common in men than woman (1). Most patients are older than 50 years, and the incidence increases further with later age (5). In 10–15% cases of ALS, an additional diagnosis of frontotemporal dementia (FTD) can be made (7, 11–13). FTD is characterized by the degeneration of frontal and anterior temporal lobes and presents clinically by behavioral changes, impaired executive function, and language dysfunction (12, 13). ALS and FTD are now considered two ends of a spectrum due to the overlap in genetic and molecular mechanisms underlying both these neurodegenerative disorders (12, 13). In 5–8% of cases the ALS is familial (fALS), being inherited in autosomal dominant trait with age-dependent penetrance. A hexanucleotide repeat sequence of C9orf72 gene mutation accounts for approximately 35% of fALS cases (7, 11, 12). Another 15–20% of fALS cases occur from SOD1 gene mutation (14). Over 20 additional genes are linked to fALS, chief among them being *TDP43, FUS, ANG, VCP,* and *OPTN* (7, 15–17). The familial cases as a group differ clinically from sporadic cases in their earlier age of onset, equally affected males and females, and slightly rapid disease progression.

CLINICAL FEATURES: ALS SUBTYPES BASED ON UPPER AND LOWER MOTOR NEURON INVOLVEMENT

ALS in its classic form with amyotrophy (denervation atrophy and weakness of muscles) and lateral sclerosis (corticospinal tract degeneration in the lateral columns of the spinal cord) occurs in approximately 85% of cases. Less frequent are cases in which weakness and atrophy occurs alone, without evidence of corticospinal tract dysfunction, and it is called progressive muscular atrophy (PMA).

When the predominant muscle weakness and atrophy occurs in bulbar territory muscles (muscles of the tongue, pharynx, larynx, jaw, and face), it is called progressive bulbar palsy or progressive bulbar atrophy (PBA). In minority of patients, the clinical state is dominated by pyramidal tract degeneration with spastic limbs and hyperreflexia, with lower motor neuron signs becoming apparent only at a later stage or not at all. This is called primary lateral sclerosis (PLS), an infrequent form of ALS in which the disease process involves only the corticospinal tract pathways, sparing the anterior horn cells in the spinal cord and brainstem. It is important to recognize these subtypes of ALS, because the prognosis in syndromes with the isolated upper or lower motor neuron degeneration is better than in classic ALS with mixed upper and lower motor neuron involvement (2, 3).

Classical amyotrophic lateral sclerosis

The ALS in classic form is insidious in onset and progressive in clinical course and consists of both upper and lower motor neuron involvement (1). Most typically, the disease onset is perceived by the patient as slight weakness in the distal part of one limb. It then progresses and spreads in the adjacent part of the affected limb. For example, it is noted first as an unexplained tripping from slight foot drop with atrophy and stiffness of leg muscles on one side. That is, features of lower motor neuron (weakness and atrophy) or upper motor neuron (stiffness) or both degenerations appear insidiously in one leg. A footdrop with weakness and wasting of the anterior tibial muscles may give an impression of peroneal nerve compression until painless weakness of the calf muscles and thigh muscles, along with normal sensory examination, declares more widespread involvement of lumbosacral neurons. As the disease progresses and spreads, the motor deficit is noted on the opposite side with the subsequent asymmetrical progression in both legs.

In hand-onset ALS, weakness is noted first by mild difficulty in tasks requiring fine finger movements (writing, buttoning, etc.), stiffness of fingers, and slight weakness or wasting of hand muscles on one side. Muscle contraction-induced cramps and fasciculation of the muscles of the shoulder girdle, upper arm, and the forearm may also arise. Thumb and finger abductors, adductors and extensors become weak while the long finger flexors are relatively spared with preserved hand grip. The weakness and atrophy of dorsal interossei and forearm extensor muscles resulting in hallowed intermetacarpal spaces and partial wrist drop may impart a cadaveric or skeletal hand (Figure 1). With further progression and over time, the constellation of atrophic hand and forearm muscles, fasciculations, along with slight spasticity of the arms and generalized hyperreflexia – without sensory or autonomic changes – leaves little doubt as to the ALS diagnosis. Later, the atrophic weakness spreads to the neck, tongue, pharyngeal, and laryngeal muscles and eventually those in the trunk and lower extremities, declaring the devastation of the disease. One of the hallmarks of the disease is despite the amyotrophy, the tendon reflexes are notably active. Babinski and Hoffman signs are variably present.

In about 25 percent of cases, the disease may first start in bulbar (lower brainstem) territory with the attendant difficulty in speaking, swallowing, and handling of saliva (1). Examination in such cases may show atrophic, shriveled and weak tongue (Figure 2) with fasciculation and saliva drooling from the angle of the mouth.

Figure 1. Hand-onset ALS showing asymmetric atrophy and weakness of hand and forearm muscles.

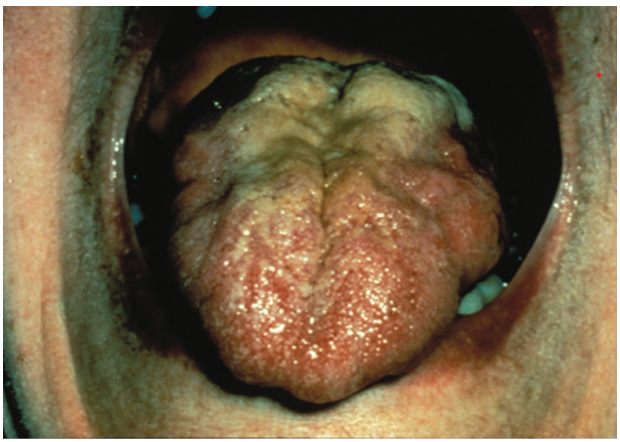

Figure 2. Bulbar onset ALS with tongue atrophy weakness.

Rarely, involvement of thoracic, abdominal, posterior neck muscles, or diaphragm muscle occurs in early course resulting in camptocormia (forward bending of the neck and trunk), head drop, or early respiratory failure in affected individuals (1).

The first and dominant manifestations of ALS may be a spastic weakness of the legs, in which case a diagnosis of PLS is tentatively made (1). Only after months or a year or so, do the hand and arm muscles weaken, waste, and fasciculate, making it obvious that both upper and lower motor neurons are diseased. On occasion, the disease may commence with spasticity of bulbar territory muscles with speech and swallowing difficulty, brisk jaw and facial reflexes, but without muscle atrophy, and it is called pseudobulbar palsy.

Coarse fasciculations are usually evident in the weakened muscles but may not be noticed by the patient until the physician calls attention to them (1–3). The weak and atrophied limb parts may feel cold and achy, but actual numbness or paresthesia, except from poor positioning of the weak limb and focal pressure or compression neuropathies, do not occur in ALS. Sphincter function is well maintained even after both legs have become weak and spastic.

The clinical course of ALS, regardless of its mode of onset and topography of spread and evolution, is progressive. Patient may sometimes observe short periods of stable weakness lasting for weeks or a few months; however, objective changes will be detected in almost all cases. Approximately 50% of patients succumb within 2 to 3 years and 90% within 5 years of disease onset, almost all from respiratory failure (1, 2, 3, 8, 18).

Progressive muscular atrophy

These purely lower motor neuron amyotrophies are more common in men than in women, they progress at a slower rate, and the majority of these patients survive more than 5 years (2, 18). In one large cohort of 155 patients with PMA (18), the authors reported a relatively more benign course in younger patients; 72% of patients with disease onset before age 50 survived over 5 years, compared to 40% of patients with onset after 50 years (18). In about half the patients, the PMA phenotype commences in distal arms with asymmetric weakness and atrophy of hand muscles and then it advances to forearm and arm muscles (Figure 1). Less frequently, the legs and thighs are the sites of the initial atrophic weakness, or the proximal parts of the arms are affected before the distal ones. Fascicular twitching and cramping are common. PMA typically differs from classical ALS in diminished or absent tendon reflexes and undetectable clinical signs of corticospinal tract involvement. However, at autopsy corticospinal tract changes are noted in these cases (19).

The PMA may clinically mimic immune-mediated motor neuropathy that occurs with or without multifocal motor conduction block of electrical conduction and less often inclusion body myositis (described below).

Progressive bulbar palsy

In progressive bulbar palsy, first and dominant symptoms relate to weakness and atrophy of muscles innervated by the motor nuclei of the lower brainstem.

This weakness gives rise to an early defect in articulation and swallowing. As the condition worsens, syllables lose their clarity and run together, until, finally, the patient's speech becomes unintelligible. Usually, the voice is altered by a combination of atrophic and spastic weakness. Defective speech modulation with variable degrees of rasping and nasality is another characteristic. Chewing of food and swallowing become impaired; the food bolus cannot be manipulated efficiently, and this can lead to lodging of food between the cheek and teeth and difficulty in propelling it properly into the esophagus. Liquids and small crumbs of food may find their way into the larynx and trachea with episodes of coughing and choking. Ineffective closure of nasopharynx can result in fluid regurgitation through the nose. Fasciculations and atrophy of the tongue muscle are usually early clinical signs in PBA (Figure 2). Eventually the tongue bulk is lost, and it lies useless on the floor of the mouth.

As the disease progresses in PBA, the pharyngeal reflex is lost, and the palate and vocal cords move imperfectly or not at all during attempted phonation. The jaw jerk may be present or exaggerated at a time when the muscles of mastication are markedly weak. Spastic weakness of the bulbar territory muscles may be the initial manifestation of bulbar palsy without regional muscle atrophy and in such cases the pseudobulbar signs (pathologic laughing and crying) may become a prominent and embarrassing clinical feature. As with other subtypes of ALS, the clinical course of bulbar palsy is relentlessly progressive. Eventually the weakness spreads to the respiratory muscles and deglutition fails entirely. In general, the earlier the onset of the bulbar weakness, the shorter the course of the disease (18).

Primary lateral sclerosis

PLS can be considered another subtype of ALS occurring in 2–4% of cases (1, 20). Most patients, in whom the early signs of corticospinal tract degeneration suggest the presence of ALS, will develop clinical or electromyographic evidence of lower motor neuron involvement within 6–12 months. Some cases, however, have a slowly progressive corticospinal tract disorder that begins with a pure spastic paraparesis; later, the arms and oropharyngeal muscles become involved, and the disease remains one solely of the upper neurons (20).

The typical case begins insidiously in the fifth or sixth decade with asymmetric stiffness in legs with slowing of gait; leg spasticity and imbalance predominates over weakness as the disease progresses. Walking is still possible with the help of a cane for many years after the onset, although falls become frequent. Eventually this phenotype acquires the characteristic features of a severe spastic paraparesis. Over the years, finger movements loose dexterity, the arms become spastic, and, if the illness persists for several years, spastic dysarthria and pseudobulbar palsy is added to clinical features. Infrequently, the PLS may begin with spasticity in one-sided limbs (Mill's hemiparetic pattern) or in bulbar territory muscles (pseudobulbar paresis).

Pathologic studies in a limited number of cases have disclosed a relatively stereotyped pattern of reduced numbers of Betz cells in the frontal and prefrontal motor cortex, degeneration of the corticospinal tracts, also evident on MRI (Figure 3), and preservation of motor neurons in the spinal cord and brainstem (20).

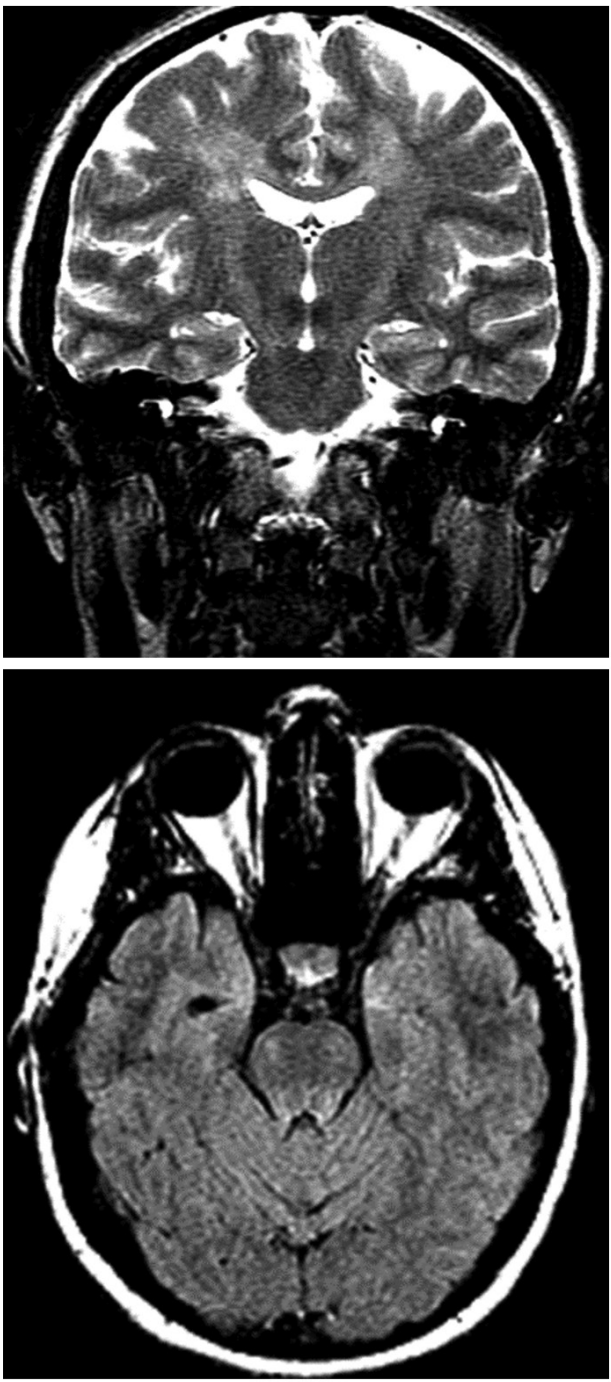

Figure 3. **T2-weighted coronal (3a, top) and FLAIR axial (3b, bottom) MRI showing signal changes that reflect Wallerian degeneration in the corticospinal tracts (Courtesy Dr. Rita G. Bhatia).**

PATHOLOGICAL FEATURES

The pathognomonic finding in ALS is loss of motor neurons in the anterior horns of the spinal cord, motor nuclei of the lower brainstem (lower motor neurons), and motor cortex of cerebrum (upper motor neurons). Large alpha motor neurons tend to be affected before small ones. In addition to neuronal loss, there is evidence of slight gliosis and proliferation of microglia cells. Many of the surviving nerve cells are small and shrunken. In the affected motor neurons, ubiquitin inclusions in threads or dense aggregates can be demonstrated by special stains (1, 3, 12). The anterior roots are thin corresponding to large axon loss, and there is a disproportionate loss of large myelinated fibers in motor nerves (21). The muscles show typical denervation atrophy of different ages.

The lower part of the spinal cord shows the corticospinal tract degeneration most prominently; however, the degeneration can be traced up through the brainstem to the posterior limb of the internal capsule and corona radiata by myelin stains. The loss of Betz cells in the motor cortex corresponds to corticospinal tract degeneration and this is manifested as a slight frontal lobe atrophy on the MRI, but it is not a prominent finding in most ALS cases. In FTD cases, in addition to the usual loss of cortical motor neurons, an extensive neuronal loss, gliosis, and vacuolation involving the frontal premotor area, particularly the superior frontal gyri and the inferolateral cortex of the temporal lobes, is evident (12).

Laboratory investigations and differential diagnosis

ALS is primarily a clinical diagnosis. The lack of a reliable biological marker, highly variable initial clinical presentation, and its clinical overlap with other late-age degenerative disorders make it difficult to diagnose ALS with certainty in early stages. There is an average delay of 6 to 15 months from the onset of symptoms to confirmation of diagnosis (2, 3, 18). The El Escorial criteria for diagnosing ALS was published in 1994 by the World Federation of Neurology (22). The hierarchical diagnostic categories were created chiefly for inclusion standards for patients entering research studies and clinical trials (22). The El Escorial ALS diagnostic criteria were revised to include laboratory features in Arlie House Criteria in 1998 (Table 1). The Awaji-Shima Criteria of 2000 consider electrophysiological features equivalent to clinical lower motor neuron involvement (23). A definitive diagnosis of ALS requires evidence of lower motor neuron and upper motor neuron involvement in at least three of four anatomic regions (cranial, cervical, thoracic, and lumbar regions). Clinically definite ALS shows progression and spread of degeneration or signs within or toward another anatomical regions. More importantly, the laboratory, electrophysiological, and neuroimaging results should not show evidence of other pathological processes that could explain the observed clinical presentation and thus exclude ALS.

Although, there is no definite marker to diagnose ALS, investigations provide useful confirmatory evidence even in the atypical clinical syndrome (1–3). The EMG, as expected, displays widespread fibrillations and positive sharp waves (evidence of active denervation) and fasciculations and enlarged motor units (denoting reinnervation). Motor conduction studies may show drop in combined muscle action potential (muscle atrophy) and only slight slowing, without focal motor

TABLE 1 **Revised El Escorial classification of ALS (22, 23). Four anatomical regions, bulbar, cervical, thoracic, and lumbar are included for disease stratification**

Diagnostic category	Inclusion criteria
Definite ALS	Presence of upper motor neuron and lower motor neuron signs in three anatomical regions
Probable ALS	Presence of upper motor neuron and lower motor neuron signs in at least two regions with upper motor neuron sign rostral to lower motor neuron signs
Probable ALS, laboratory results supported	Presence of upper motor neuron and lower motor neuron signs in one region with evidence by EMG of lower motor neuron involvement in another region
Possible ALS	Presence of upper motor neuron and lower motor neuron signs in one region or upper motor neuron signs in two or three regions, such as monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis

conduction block. If the atrophic paresis is restricted to an arm or hand, raising the question of cervical spondylosis, evidence of denervation in many widely separated somatic segments favors the diagnosis of ALS. Widespread denervation of the thoracic paraspinal muscles and the tongue muscle or facial muscles strongly suggest the disease, as these myotomal involvement is not a feature of cervical or lumbar spondylosis. Sensory nerve action potentials are typically normal in ALS. When in a typical case the amplitudes of sensory nerve action potentials are reduced, there is usually an underlying compression neuropathy or an unrelated neuropathy from diabetes or other cause. Serum creatinine kinase (CK) is moderately elevated in half of patients (1). The CSF protein is usually normal or marginally elevated. A muscle biopsy though helpful in corroborating neurogenic denervation is not needed in ALS.

In patients with prominent corticospinal signs, the MRI may show slight atrophy of the motor cortex and signal changes indicating Wallerian degeneration of the corticospinal tracts (Figure 3). These changes may be diagnostically useful when the presence of severe LMN deficit makes pyramidal tract signs unobvious. Corticospinal tract degeneration appears as an increased FLAIR and T2 signal intensity in the posterior limb of the internal capsule, descending motor tracts of the brainstem, and spinal cord (1–3). These MRI signs however are generally subtle and often missed.

The early clinical picture of ALS is closely simulated by cervical spondylosis or ruptured cervical disc with regional myeloradiculopathy, but with these conditions there is usually pain in the neck and shoulders, limitation of neck movements, sensory impairment, and the lower motor neuron changes are restricted to 1 or 2 spinal segments (1). The EMG showing multi-segmental ongoing active

denervation and reinnervation is particularly helpful in differentiating ALS from these disorders. An isolated and mild hemiparesis or monoparesis because of multiple sclerosis may be difficult to distinguish from early ALS and PLS. Leg-onset PMA may be differentiated from peroneal muscular atrophy (Charcot-Marie-Tooth disease) by asymmetrical clinical course, the complete lack of sensory change, lack of family history, and EMG pattern.

The differentiation of PMA from chronic motor neuropathies, particularly the form that displays multifocal conduction block, poses a major consideration (1–3). An extensive nerve conduction studies and EMG examinations are necessary to distinguish multifocal motor neuropathy from PMA. The presence of an IgM monoclonal paraproteinemia or of specific antibodies directed against the GM1 ganglioside are usually indicative of the immune motor neuropathy, but in half of the cases these laboratory tests are negative (1). A leg form of PMA may be confused with inflammatory myopathy, specifically inclusion body myositis. A rare form of subacute paraneoplastic poliomyelitis in patients with lymphoma or carcinoma that leads to an amyotrophy and progression to death over a period of several months has been reported (24). Another rare condition in young men with localized and asymmetrical amyotrophy of the forearm that became arrested and does not advance over a decade or more is called juvenile MND (25).

The main considerations in relation to progressive bulbar palsy are myasthenia gravis and especially the inherited type of bulbospinal atrophy, the Kennedy's disease (26). The spastic form of bulbar palsy may suggest the pseudobulbar palsy of lacunar disease and can be a prominent part of the progressive supranuclear palsy.

The differential diagnosis of the purely spastic state of primary lateral sclerosis is broad and includes compressive and noncompressive myelopathies, multiple sclerosis, adrenomyeloneuropathy, HTLV-1 associated myelopathy, vitamin B12 or copper deficiency states, familial spastic paraparesis, and lacunar states.

MANAGEMENT

The effect of available treatment for ALS is modest. Two drugs, Riluzole and Edaravone, are approved for ALS; they have modest effect in slowing the disease progression. The antiglutamate agent Riluzole, when given orally, was shown to slow the progression of ALS and improve survival in patients with disease of bulbar onset; it prolonged survival by about 3 months (27). The antioxidant Edaravone has been shown to slow the clinical progress of ALS in select patients in limited trials; but again, the benefit has been marginal (28).

In the absence of curative treatment, supportive and palliative measures are exceedingly important (29–33). Table 2 summarizes the range of symptomatic and palliative treatments in ALS. Regarding symptomatic treatment of spastic leg weakness, anti-spasticity medications, such as baclofen or tizanidine, or subarachnoid infusions of baclofen via an implanted lumbar pump can be helpful. Benzodiazepines may also be used to relieve limb and bulbar spasticity in some cases. These anti-spasticity approaches are most suitable for cases of PLS, which are expected to progress slowly over a long period.

TABLE 2 Symptomatic and palliative management of ALS

Symptoms	Management
Spasticity	• Baclofen • Tizanidine • Intrathecal baclofen pump • Physical therapy
Weakness and physical disability	• Orthotics (leg brace, neck brace) • Mobility aids (cane, walker, wheelchair) • Physical therapy
Dyspnea and poor cough	• Ventilatory support • Cough-assist device • Suction machine • Chest physical therapy • Morphine or benzodiazepine
Dysphagia	• Modified diet • Gastrostomy tube
Dysarthria	• Communication aids
Sialorrhea	• Tricyclic antidepressants • Glycopyrrolate bromide • Botulinum toxin injection • Salivary gland radiation • Suction machine
Emotional lability	• Tricyclic antidepressants • Dextromethorphan hydrochloride/Quinidine sulfate
Depression and anxiety	• Antidepressants • Benzodiazepines
End of life care	• Hospice services

The pseudobulbar syndrome can be ameliorated with dextromethorphan-quinidine compounds.

At all stages of ALS, physical therapy is useful in maintaining mobility. Physical therapy is invaluable, for example, for avoiding contractures of the fingers and shoulders. Occupational therapy is likewise helpful, particularly assessments of the patient's function in the home. A range of personalized orthotic devices, often guided by the physical and occupational therapists, may be of assistance to the patient as the disease progresses.

Important in the management of ALS is periodic monitoring of respiratory function and nutrition (33). Significant practical advances have been made in multidisciplinary ALS clinics with regard to respiratory and nutritional management in ALS. As the respiratory muscle weakness compromises breathing, the use of bilevel positive airway pressure (BiPAP) allows patients to sleep better and

reduce daytime somnolence. With effective noninvasive respiratory support, tracheostomy can be deferred for months or years in most cases. Ultimately, as the disease progresses further and diaphragm fails, BiPAP becomes necessary not only at night but also during the day. When BiPAP use approaches 20 to 24 h per day, patients and their families must address the difficult question of tracheostomy and mechanical ventilation or hospice care.

As oropharyngeal muscles become weak and dysphagia progresses, meals need to be modified to prevent choking, aspiration, and complications. In initial stages, fruits, vegetables and meat should be cut into small pieces and dry foods, such as toast should be avoided. Milk shakes and thicker consistency foods are ideal at this stage. Speech therapists at ALS clinics are helpful in teaching patients and their caregivers methods to adapt to declining bulbar function and minimizing aspiration. Eventually, most ALS patients will need a feeding tube to maintain normal hydration and caloric intake (33).

The American Academy of Neurology has published guidelines for management that have been of aid to patients and physicians; they emphasize the complex and multidisciplinary needs of ALS patients (34, 35)

CONCLUSION

ALS is a progressive neurodegenerative disease resulting eventually in respiratory failure and death in 2 to 4 years or longer in rare cases. Several clinical subtypes of ALS are recognized chiefly depending on the upper and lower motor neuron involvement, and some of these subtypes have better prognosis. The etiology of ALS is unknown, and there is currently no curative treatment of ALS. Supportive and palliative measures are exceedingly important to maintain and improve the quality of life in patients with ALS.

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