CHAPTER 32

Amyotrophic Lateral Sclerosis

Dale J. Lange

CLINICAL DEFINITIONS

Amyotrophic lateral sclerosis (ALS) was recognized as a distinct clinical and neuropathologic entity more than a century ago (1). The unique neuropathologic findings include anterior horn cell degeneration producing muscle atrophy or amyotrophy and degeneration and sclerosis of the corticospinal tracts. The clinical lower motor neuron (LMN) manifestations due to anterior horn cell loss include weakness, wasting, and fasciculation, with upper motor neuron (UMN) signs due to corticospinal tract degeneration recognized by hyperreflexia, spasticity, clonus, and Hoffmann and Babinski signs. The clinical spectrum of motor neuron disease (MND) is broad, with some patients manifesting LMN signs alone without signs of corticospinal tract dysfunction, so defining progressive spinal muscular atrophy (PSMA), and others demonstrating UMN without LMN signs in the syndrome of primary lateral sclerosis (PLS) (3). The signs of progressive bulbar palsy and bulbar-onset ALS reflect predominant motor neuron loss in the brainstem, supplying the lingual and pharyngeal muscles that leads to early or predominant dysarthria, dysphagia, and respiratory insufficiency (2). MND localized to a single limb is termed monomelic amyotrophy.

There is no marker that uniquely identifies the process of ALS during life; therefore, the diagnosis is absolutely confirmed at postmortem examination. However, in the presence of the classic clinical syndrome, confidence of the diagnosis probably approaches 98%. It is when portions of the clinical syndrome are missing that confidence decreases and the opportunity for other diseases masquerading as ALS becomes a significant issue. Brisk reflexes in limbs exhibiting weakness, wasting, and twitching are probable UMN signs (2). Patients with probable UMN signs and PSMA have the greatest likelihood of having an alternative diagnosis, for example, multifocal motor neuropathy, lymphoma, paraproteinemia, or endocrinopathy. Patients with UMN signs alone and pseudobulbar palsy probably have PLS (3).

The World Federation of Neurology El Escorial Diagnostic Criteria (Table 1) (4) provide a useful scheme for the clinical classification of ALS. For classification purposes, LMN signs consist of weakness, atrophy, and fasciculation. UMN findings consist of overactive tendon reflexes, spasticity, Hoffmann and Babinski signs, and pseudobulbar features. The regions of the body are classified into bulbar, cervical, thoracic, and lumbosacral. Patients with definite ALS have UMN and LMN signs in

| TABLE 1. El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis (ALS) |
|---------------------------------|-----------------------------------------------------------------------------------|
| The diagnosis of definite ALS requires |
| Signs of lower motor neuron degeneration by clinical, electrophysiologic, or neuropathologic examination |
| Signs of upper motor neuron degeneration by clinical examination |
| Progressive spread of signs within a region or to other regions |
| Bulbar and two body regions affected or three body regions affected |
| Probable ALS |
| At least two regions of the body affected by UMN and LMN signs |
| Possible ALS |
| UMN and LMN signs in one region |
| UMN signs alone are present in two or more regions |
| UMN signs are above UMN signs |
| Monomelic ALS, progressive bulbar palsy without spinal UM or LMN signs, and primary lateral sclerosis without signs of LMN signs may be classified as probable ALS |
| Suspected ALS |
| Manifested as LMN signs in two or more regions (UMN pathology may be demonstrated at autopsy but there are no clinical signs) |

UMN, LMN, upper and lower motor neuron.

three spinal regions or bulbar region and two spinal regions. Those with probable ALS have UMN and LMN signs in at least two regions. Possible ALS patients have UMN and LMN signs in one region and UMN signs alone in two or more regions. Suspected ALS has LMN signs in two or more regions. Prognosis is not clearly related to the particular clinical syndrome; however, long-term survival is best with PSMA followed by PLS, ALS, and bulbar palsy. The shortened survival of progressive bulbar palsy and bulbar-onset ALS is due to prominent involvement of swallowing and breathing.

In 5 to 10% of ALS patients, a genetic basis is demonstrable, so termed familial ALS (FALS). The mode of transmission is usually autosomal dominant. FALS-autosomal dominant behaves in a stereotypic manner in successive generations with similar age at onset and course. In 30 to 40% of patients so studied, there is a mutation in the copper/zinc superoxide dismutase (Cu/ZnSOD) gene located on chromosome 21 (5).

CLINICAL PRESENTATION

The annual incidence of ALS is approximately 1 to 2 per 100,000 in developed countries (range, 0.5 to 2.4 per 100,000) (6). The average age at onset is 56 and is more common in men than women (1.3:1). It is less common below the age of 40 and rare below 30. The youngest patient I encountered was 17 years old. The average duration of illness is 3 to 5 years with a large variation in the duration of disease course (7,8), with some patients expiring weeks to months after diagnosis and others surviving decades. Most patients complain of weakness or some functional impairment that results from weakness, such as difficulty writing, buttoning, or holding onto objects indicative of involvement of the arms and frequent stumbling, tripping, and occasionally falls reflecting involvement of the legs. ALS can be misdiagnosed as painless radiculopathy before electromyography (EMG) studies are performed, especially when the signs and symptoms are restricted to a single limb or adjacent root. Occasional patients have isolated weakness of neck extension muscles leading to forward drooping of the head or floppy head syndrome. Hoarseness, slurred speech, and drooling precedes frank respiratory and pharyngeal muscle involvement in patients with bulbar involvement and can lead to complaints of sleep disruption and easy fatigability. Asymmetry and relentless progression of symptoms is diagnostically important. Although fasciculation is common, seldom is it the presenting complaint; rather, it is usually pointed out by the physician to the astonishment of the patient. Muscle twitching without focal weakness or bulbar complaints at presentation is more likely due to a benign disorder rather than ALS. The neurologic examination provides the foundation for the diagnosis of ALS and should demonstrate the combination of LMN and UMN signs already described. EMG and nerve conditions should be performed in all patients with suspected ALS to confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TESTING

The recommended evaluation for suspected patients is summarized in Table 2. The singular role of testing in ALS is to confirm the diagnosis and confidently eliminate other disorders that may bear clinical resemblance to it and identify other potentially serious and treatable disorders toward which therapy might also be directed. Clinically apparent or occult Hodgkin and non-Hodgkin lymphoma or macroglobulinemia may be the cause of a motor neuron syndrome resembling PSMA or ALS. Motor neuropathy may be clinically indistinguishable from PSMA. Patients with multifocal motor neuropathy resembling ALS-probable UMN signs with or without GM1 antibodies may have overactive or retained tendon reflexes despite weakness, wasting, and twitching (9,10). The importance of making the diagnosis of multifocal motor neuropathy is that such patients respond dramatically to intravenous immunoglobulin (11). There is little rationale for the routine evaluation of antibodies to GM1 gangliosides and myelin-associated glycoprotein in otherwise typical cases of ALS, because they are rarely

<table>
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<th>TABLE 2. Diagnostic evaluation</th>
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<td>1. Blood: CBC, differential, ESR, chemistries (glucose, NA, K, Cl, CO2, BUN, creatinine, Ca, PO4, albumin, bilirubin, AST, ALT, LDH, alkaline phosphatase, CK), quantitative immunoglobulins, immunofixation electrophoresis, T-cell subsets, latex fixation, ANA, lyme, GM1, MAG antibodies.</td>
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<td>2. Muscle biopsy if an immunologically mediated disease or inflammatory myopathy is supported or to prove neurogenic abnormalities in an otherwise clinically unaffected limb.</td>
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<td>3. Lumbar puncture</td>
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<td>4. EMG and nerve conduction studies with proximal stimulation for multifocal conduction block and quantitative EMG if a myopathy (IBM) is suspected.</td>
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<td>5. MRI with MR spectroscopy if evidence of cortical cell death is required (especially for diagnosis of PLS or PSMA).</td>
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<td>6. Blood for genetic testing when appropriate</td>
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<td>7. Video swallowing tests to assess upper pharyngeal muscle strength and function</td>
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<td>8. Pulmonary function tests</td>
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CBC, complete blood count; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; AST, ALT; aspartate and alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; ANA, antinuclear antibodies; EMG, electromyography; IBM, inclusion body myositis; MRI, magnetic resonance imaging; PLS, primary lateral sclerosis; PSMA, progressive spinal muscular atrophy.
detected in significant titer to warrant serious consideration of treatment (12).

Disorders that may sometimes be confused with MND but are obvious after an appropriate history and evaluation include post-polio muscular atrophy, postirradiation atrophy or myelitis, myasthenia gravis, inclusion body myositis, and PLS. Patients with PLS complain of stiffness, diminution in fluidity of movement, and imbalance, without muscle twitching or atrophy. Reflexes are hyperactive with pathologic signs of corticospinal tract dysfunction, including Babinski and Hoffmann signs and abnormally active jaw jerk. Pseudobulbar palsy is typical with accompanying slurred speech, inappropriate affect, and hyperactive jaw jerk. EMG does not reveal denervation or fasciculation. The prognosis is one of continued progression of symptoms, but the rate is generally slow. PLS is a diagnosis of exclusion, but recent studies using magnetic resonance spectroscopy suggest that abnormalities in the NAA/creatine ratio in the frontal motor areas correlate with clinical signs of UMN degeneration and corticospinal tract signs. Nevertheless, until diagnostic specificity is proven, all patients should be screened for other causes, such as Chiari malformations, intrinsic lesions of the spinal cord, extrinsic tumors at the foramen magnum, syringomyelia, multiple sclerosis, and human T-cell lymphotropic virus type 1 infection. Therefore, magnetic resonance imaging of the brain and cervical cord, lumbar puncture, and EMG are necessary before the diagnosis is made. Sometimes separation from familial spastic paraparesis is difficult.

Genetic testing for FALS and Kennedy syndrome is indicated in selected situations. In sporadic ALS, it may be useful to screen for an SOD mutation when the family history is vague or incomplete. Kennedy syndrome should be clinically suspected in men with perioral fasciculation limb girdle and bulbar weakness, wasting, twitching, and gynecomastia. Genetic analysis shows more than 40 CAG repeats in the gene for the androgen receptor (13). Creatine kinase and serum gonadotropins may be elevated; however, serum testosterone levels are normal.

PROGNOSIS

The prognosis for an individual patient with ALS cannot be estimated from population studies. Rare patients have had reversible symptoms (14). Poor vital capacity, dysarthria, dysphagia, and four-limb fasciculation are considered poor prognostic findings. Studies regarding the prognosis of patients with progressive muscular atrophy vary. Some show prognosis to be similar to classic ALS, whereas others show a mean survival of 6.5 years. The variation is due to the fact that patients in this group include those with only anterior horn cell degeneration (spinal muscular atrophy), motor neuropathy, and ALS with pathologic involvement of the corticospinal tract without clinical expression. Patients with bulbar palsy also have a variable course with some dying shortly after onset and others having a very prolonged course.

SYMPTOMATIC TREATMENT

Fatigue and insomnia are disabling symptoms at any time in the course of the illness. One possible cause of fatigue is inefficient neuromuscular transmission in degenerating neurons, with symptoms reminiscent of myasthenia gravis. For this reason, some clinicians give pyridostigmine. Polysomnography occasionally shows disrupted sleep patterns due to airway obstruction and weak pharyngeal musculature; because of resultant hypoxemia, frequent awakenings and daytime fatigue results. Nocturnal noninvasive respiratory support is often therapeutic (15). As weakness worsens, physical activity decreases. The degree of exhaustion at the day's end may be less, and small naps during the day may detract from ease of entering sleep. Frequent nocturnal awakenings may cause insomnia. Therefore, proper diagnosis is essential. If falling asleep is deemed the problem, medications to facilitate sleep may be necessary, either trihexyphenidyl or triazolam (0.25 mg hs).

Patients with bulbar weakness have particular difficulty controlling secretions, and long-term control is often difficult to achieve. Amitriptyline is often used because of its anticholinergic properties. Atropine has recently returned to the pharmaceutical market and may also be helpful. As a last resort, some patients have opted for radiation of the parotid glands. However, because of totality of destruction of glandular tissue, excessive dryness is a common and troubling side effect because infection becomes a problem under such circumstances.

Cramps and fasciculation can be annoying symptoms but are never disabling. Nocturnal cramps are often the earliest symptom of ALS. Patients with cramps report immediate relief from drinking electrolyte-fortified drinks or use of quinine sulfate, and those with fasciculates generally find clonazepam to be helpful. Spasticity and muscle spasms are most often due to dysfunction of the corticospinal tracts. Therapy is usually through physical therapy and antispasticity agents. These include baclofen and tizanidine. Severely affected patients may require baclofen injected directly into the cerebrospinal fluid, administered through a computer-driven pumping system.

Although formal testing does not reveal excessively prevalent depression, it is a frequent enough complaint that antidepressant therapy is often warranted. It is clear that professional education and emotional support is essential for patients and families affected by ALS.

The natural end point of ALS is pulmonary failure. When breathing becomes sufficiently compromised, noninvasive ventilatory support is becoming increasingly
helpful. In severely affected patients, tracheostomy and mechanical ventilatory support is the only alternative. Many patients choose not to pursue this therapy because of its dramatic impact on quality of life.

SPECIFIC MEDICAL THERAPY

No known treatment stops or improves the symptoms of ALS or halts the progression of the classic disease. Recent studies have suggested that some agents may slow the progression of the illness, but this is based on statistical analyses of populations using an agent and comparing them with a placebo-treated population. Nevertheless, for the first time in our study of this illness, there are drugs that have a rational basis for use in this disease and have shown evidence that they do indeed affect the course of the illness. To understand the rationale of the use of these agents, we should review essential aspects of current theories of pathogenesis.

Excitotoxicity Theory and Glutamate Receptor Blockers

The excitotoxic theory has been reviewed extensively elsewhere (16). Glutamate is an excitotoxic amino acid that when present in the extracellular fluid is potentially toxic to nerve cells. It is increased in the cerebrospinal fluid of patients with ALS (17). Such patients may have a deficit in the ability to efficiently clear glutamate released into the extracellular space (18). The use of medications to block receptors for glutamate may interfere with its neurotoxicity. Rilutek (or riluzole) is the only approved medication for the treatment of patients with ALS. It blocks the toxic effect of glutamate in many animal models and has been shown to be effective in two clinical trials in ALS patients. One trial demonstrated an improved survival in patients with bulbar-onset disease but not limb-onset (19). A second trial showed significantly prolonged survival, but its effect was unexplained because there was no significant change in strength, respiratory function, or bulbar function in these patients compared with placebo. The most effective dose was 50 mg by mouth twice daily (20). Gabapentin (Neurontin) is also known to have antiglutamate effects. A recent double-blind placebo-controlled study showed that 2,400 mg of neurontin showed a trend but not statistically significant effect on the rate of deterioration. The drug is usually well tolerated, and a larger study is planned (21).

Neurotrophic Factor Deficiency

Another hypothesis is that patients with ALS have a deficiency of one or more nerve growth factors or neurotrophins critical for neuronal functioning. There are many different types of neurotrophins that support a wide array of function and cell types. These include motor neurons, muscle, sensory neurons, or sympathetic neurons. Adding nerve growth factor to nerve cultures dramatically promotes neuronal survival. In the chick embryo, NCF promotes survival of motor neurons and impedes normal programmed cell death during development by excessive amounts. When nerves are transected, adding nerve growth factors will enhance the rate of regrowth.

There have been several clinical trials of neurotrophic factors, and many are still ongoing. Ciliary neurotrophic factor was found to be ineffective in a large-scale trial (22). Higher doses proved to be too toxic to complete another study. Brain-derived nerve growth factor showed no clinical effect in a large multicenter, double-blind, placebo-controlled trial. Insulin-like growth factor type I (IGF-1) has shown conflicting results. One study showed a statistically significant change in the rate of progression in patients receiving high-dose IGF-1 (23), measured by the Appel ALS score (8), and a statistically significant slowing of progression of bulbar and limb weakness was also demonstrated. IGF-1 improved quality of life, but paradoxically, the improvement was not statistically significant in the motor portion of this analysis. A second trial in Europe using IGF-1 showed no effect (24). There was, however, a trend toward slowing in the treated group. An ipso facto survival analysis showed that IGF-1 promoted survival in patients taking this drug. Food and Drug Administration approval of this drug is pending at the time of this manuscript preparation.

Antioxidant Therapy

Because of recent evidence of impaired oxidative processes in FALS, attempts to treat patients with agents that interfere with oxidative processes have been of interest. Most investigators promote the use of high-dose vitamins known for their antioxidative properties, especially vitamin E (2,000 U/day), vitamin C (2,000 mg/day), and beta-carotene (25,000 U/day). Selegiline (Eldepryl) has been found to be ineffective as has N-acetyl cysteine (25–27).

Autoimmunity

There is circumstantial evidence to implicate a role for autoimmune processes in ALS. The apparently excessive prevalence of lymphoma and paraproteinemia in patients with ALS suggests an association. One group has reported lymphocytes and activated macrophages in ALS spinal cord and the presence of IgG within ALS motor neurons. IgG from patients with ALS interact with L-type calcium channels and promote entry of calcium into the cell (28). Increased intracellular calcium may overwhelm the intracellular control systems for oxidative processes and contribute to the process of cellular destruction. However, several therapeutic trials have used immuno-suppressant agents, including cyclophosphamide, intra-
venous immunoglobulin, prednisone, cyclosporin, and
total body irradiation. None have proven effective. Cal-
cium channel blockers have also proven to be ineffective
(29).

Future advances will continue to make symptomatic
care better in ALS and give hope that an understanding of
what causes this disease is near, clearing the way for an
effective therapy that does not slow progression but stops
or reverses the process (30).

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