# ALS, Motor Neuron Disease, and Related Disorders: A Personal Approach to Diagnosis and Management

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## ABSTRACT

Motor neuron disease, from diagnostic criteria, laboratory evaluation, communication with patients and their families, and the approach to long-term management represents a daunting challenge for many neurologists. Contained herein is a selective and biased discussion of several common dilemmas and questions that reflect recurring themes in the evaluation and management of patients with suspected motor neuron disease. The answers to these questions represent the author's opinions and are colored by personal experience, pearls graciously given to me by other experts in the field, and selected studies from the neuromuscular literature.

**KEYWORDS:** Management of motor neuron disease, ALS, multifocal motor neuropathy, Kennedy's disease

**Objectives:** Upon completion of this article the reader will be able to recognize the diagnostic features of the motor neuron diseases including ALS, PLS, Kennedy's disease, and multifocal motor neuropathy. A practical approach to the diagnostic workup and suggestions for symptomatic and primary management can be stated upon completion of this article.

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While amyotrophic lateral sclerosis (ALS) and related motor neuron disorders have been thoroughly reviewed in multiple superb publications (including a recent exhaustive compendium in *Seminars in Neurology*) the diagnosis, laboratory evaluation, approach to giving information to the patient, and management of the disease remains a daunting issue for many neurologists. Frequent questions posed to the ALS "expert" often lead one to site a recent study or paper, only to result in a follow-up question of "Yes, but what would you actually do with this patient? What do you do in your practice?" Contained herein is a selective and biased discussion of several common dilemmas and questions that reflect recurring themes in the evaluation and management of patients with suspected motor neuron disease.

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Common questions from referring physicians and neurologists follow.

## QUESTION 1: HOW DO YOU MAKE THE DIAGNOSIS OF ALS?

All good neurologists know when to suspect this diagnosis on clinical grounds. When the history is classic for gradual progressive painless loss of function due to weakness in multiple limbs and bulbar muscles without sensory, cognitive, and ocular involvement and when the associated exam shows widespread lower and upper motor neuron signs, there can be little doubt about the underlying diagnosis. Diagnostic problems center around patients with an atypical history (such as sudden onset or sudden awareness of symptoms), those with early or focal signs, or those in whom we struggle to find either the upper motor neuron or the lower motor neuron component. Also, with the trend toward performing a thorough if not massive laboratory evaluation, patients at times have the diagnosis become complicated due to a laboratory red herring.

Age of onset of ALS is highly variable. While in general it is a disease of older people (with more common age of onset in the 50s and 60s), all Neuromuscular Centers have experience with patients in their 20s and occasionally in their teens. Men outnumber women having ALS by nearly 2 to 1 for reasons that remain unclear. ALS affects about 1 in every 10,000 individuals (prevalence) and has an estimated annual incidence of onset of about 1 to 2/100,000/year.

Designed primarily for research purposes, the El Escorial Criteria for the diagnosis of ALS have allowed for some uniformity in classification and definition (Table 1).[1–3] I have often found these criteria a bit cumbersome and at times arguable, but overall, patients who meet the criteria for clinically definite and clinically probably ALS rarely are misdiagnosed. Table 1 summarizes my interpretation of the revised El Escorial Criteria for the diagnosis of ALS.

**Table 1 El Escorial Criteria for the Diagnosis of ALS**

| |
|---|
| The "regions" are defined as bulbar, cervical, thoracic and lumbosacral (there are four "regions"). |
| Clinically definite ALS: Both upper motor neuron and lower motor neuron signs in three separate regions. |
| Clinically definite familial-laboratory-supported ALS: Both upper motor neuron and lower motor neuron signs in at least one region along with abnormal DNA test for SOD mutation. |
| Clinically probable ALS: Both upper motor neuron and lower motor neuron signs in two different regions with some UMN signs rostral to some of the LMN signs. |
| Clinically probable laboratory-supported ALS: Upper motor neuron and lower motor neuron signs in one region with the addition of EMG in at least two limbs (with appropriate use of neuroimaging and other laboratory studies to exclude other causes). |
| Clinically possible ALS: Both upper motor neuron and lower motor neuron signs together in one region, or UMN signs alone in two or more regions, or LMN signs are found rostral to UMN signs. Other diagnoses must have been excluded to allow a diagnosis of "clinically possible ALS." |
| Clinically suspected ALS: Upper motor neuron signs only in one or more regions, or lower motor neuron signs only in one or more regions. |

## QUESTION 2: HOW MUCH LABORATORY WORKUP IS NECESSARY IN A PATIENT WITH SUSPECTED ALS?

Ideally, the amount of laboratory workup depends on how clear-cut the clinical signs and symptoms are in the context of the patient's history. I think that for a patient with the classical story of ALS: gradual progressive symptoms of upper and lower motor neuron dysfunction slowly spreading over time, whose examination shows widespread atrophy and fasciculations, including bulbar involvement, as well as the presence of hyperactive muscle stretch reflexes, including clonus at the jaw; without sensory, cognitive, or ocular abnormalities, the diagnosis is straightforward. The laboratory workup ends up being perfunctory.

It seems reasonable to define the appropriate workup based on whether or not the patient has fairly typical or classical ALS. Those with the typical or classical presentation should probably be evaluated with a number of studies (Table 2). Electromyogram (EMG) and nerve conduction studies are mandatory, being the only test that can provide laboratory evidence to support a diagnosis of ALS (there has been the occasional patient with familial ALS who has an identified SOD-1 mutation). Furthermore, the EMG and nerve conduction studies can be argued to be appropriate screening studies for other diseases of the motor unit that might mimic ALS to some degree. For example, multifocal motor neuropathy is best detected (from a laboratory standpoint) with nerve conduction studies showing multifocal major conduction block. In addition, the needle examination in the EMG study on a patient with sus-

**Table 2 The Routine Workup (Good History and Physical Exam and Re-Exam)**

| |
|---|
| EMG |
| MR of the appropriate region |
| Calcium, serum protein electrophoresis, thyroid function tests, complete blood count |

pected ALS may reveal the presence of widespread fibrillation but no clear-cut fasciculations; the voluntary motor units may appear more myopathic, indicating that the patient has inclusion body myositis or some other inflammatory myopathy (particularly for inclusion body myositis, given the gradual progressive course, the presence of atrophy can be—at times—a confounding diagnosis).[4] Furthermore, if there were a paucity of active denervation on the EMG studies, then it would seem sensible to be cautious about making a clinical diagnosis of ALS.

Magnetic resonance imaging (MRI) scan is performed on nearly all ALS patients looking for a focal structural lesion that might account for a significant portion of the patient's symptoms and signs. I think it is reasonable to determine the most likely location for a focal structural lesion; plan to scan that region with MRI just to make sure that there is not a foramen magnum lesion, Chiari malformation, cervical spondylosis with compressive myeloradiculopathy, coexisting cervical and lumbosacral spondylosis, syringomyelia, etc.[5] The other laboratory tests that seem reasonable to send, even though the yield is incredibly low in patients with a classical presentation, include: thyroid function tests (given the publication years ago that suggested that hyperthyroidism might mimic ALS); serum calcium level to screen for hyperparathyroidism (although the data available make it unclear to me that hyperparathyroidism really can produce a syndrome that is confused with ALS); and serum protein electrophoresis with immunofixation looking for a monoclonal gammopathy. I have personally never seen hyperthyroidism or hyperparathyroidism produce an ALS-like syndrome despite routinely screening patients for the past 17 years. Nor have I ever seen a patient with classical ALS having a monoclonal gammopathy improve following treatment of the gammopathy.

On the other hand, in patients who have an atypical presentation, an unusual examination, or some inconsistent clinical features, then a much more exhaustive diagnostic workup would seem appropriate (Table 3). For example, a patient with predominantly or exclusively upper motor neuron disease should be screened thoroughly with MRI scan looking for evidence of multiple sclerosis, multiple strokes, tumor, Chiari malformation, syringobulbia, etc. (Table 4). The patient should also be screened for vitamin $B_{12}$ deficiency, even in the absence of sensory disturbance. Hereditary spastic paraparesis should be considered, especially if there is a positive family history. Such patients typically have a very slow progressive course, often have some degree of sensory symptomatology or signs on examination, and tend not to have a significant degree of dysarthria. On the other hand, patients with primary lateral sclerosis do tend to have dysarthria. The general observation has been that most patients with primary lateral sclerosis do tend to eventually develop lower motor neuron signs if one waits long enough. My personal experience is consistent with that review. I am also in agreement with the notion that primary lateral sclerosis with or without the addition of some more mild lower motor neuron signs represents a slower form of motor neuron disease with a gentler slope of progressive disability.

Patients with predominantly or exclusively lower motor neuron disturbance should be screened for motor neuropathies including multifocal motor neuropathy, the motor neuronopathies associated with a monoclonal gammopathy, paraneoplastic motor neuronopathy, and a chronic inflammatory demyelinating polyradiculoneuropathy that might predominantly effect the motor over the sensory nerves. In addition, lead neuropathy tends to produce bilateral wrist drop as a subacute chronic course, is associated with reduced muscle stretch reflexes, and is also typically associated with significant anemia—probably sufficient to allow a complete blood count to be the screening test of choice for patients with suspected lead neuropathy (Table 5).

**Table 3 Tests to Be Checked Selectively**

| |
|---|
| Spinal fluid with viral studies (enterovirus) |
| HIV |
| SOD mutation (family history) |
| Kennedy's disease (pure lower motor neuron, bulbar involvement, gynecomastia, x-linked) |
| Anti-GM1 antibody (pure lower motor neuron, no bulbar) |
| Heavy metal screen |

**Table 4 Pure Upper Motor Neuron Syndrome (the Patient with Suspected PLS)**

| |
|---|
| B12 |
| MS |
| PLS |
| HSP |
| HTLV-I |
| Adrenomyeloneuropathy |
| Compressive cervical myelopathies (spondyslosis) |
| Lathyrism, Konzo |

**Table 5 Lead Poisoning**

| |
|---|
| Pure lower motor neuron |
| Classic lead neuronopathy, neuropathy, bilateral wrist drop |
| Blue lead line on gum |
| Best screening test CBC/anemia |
| Lead neuropathy exceedingly rare in adults |

**Table 6 Multifocal Motor Neuropathy**

| |
|---|
| Slow progressive weakness, atrophy, and fasciculations, arms more than legs |
| Pure motor neuron |
| No bulbar involvement |
| Look for selective patterns of atrophy |
| Large conduction block |
| Multiple nerve conduction studies may be necessary |
| GM-1 antibody in 50% |
| Treatment IVIg |

## QUESTION 3: WHICH PATIENTS SHOULD BE SCREENED FOR MULTIFOCAL MOTOR NEUROPATHY, AND HOW SHOULD THEY BE SCREENED?

According to the literature since the mid-1980s, along with the experience here at Indiana, patients with multifocal motor neuropathy (MMN) have a pure lower motor neuron type of syndrome (Table 6). They have no upper motor neuron signs (although they may well have preserved muscle stretch reflexes), and they have no bulbar involvement.[6,7] Therefore, in a patient with suspected ALS, if there are clear-cut upper motor neuron signs and certainly if there are significant bulbar signs, then the diagnosis of MMN would seem so unlikely as to make it unnecessary to perform methodical screening. The patients with MMN followed at our center tend to have predominance of involvement initially in the distal forearm and hand muscles, although we do have some with substantial lower extremity involvement. Muscle bulk may appear preserved relative to the severity of weakness on exam (due to the demyelinating nature of the neuropathy).

On the other hand, patients with pure lower motor neuron involvement restricted to the limbs should be considered for MMN. I think the patients can have obvious fasciculations; they certainly can have atrophy. It is said that the atrophy is more selective for distal or peripheral nerve involvement as opposed to a more proximal anterior horn cell lesion. In other words, there might be severe atrophy of the ulnar innervated C8- and TI-level muscles but not the median innervated C8 and TI muscles. On the other hand, in some patients it is just less clear. In my experience, the arms are typically more affected than the legs, and the findings are more distal than proximal. On occasion we have found people who have sensory symptoms and signs, although they are usually mild. The best screening test clearly is a thorough exploration of nerve conduction studies. Although it can be argued that physicians who perform electrodiagnosis sometimes go a bit overboard in their studies, it should not be argued that one can go overboard when looking for multifocal neuropathy. The hallmark is conduction block; the conduction block is not minor or subtle, it is what I would call massive conduction block. The problem is that one may have to go on a witch-hunt looking for dramatic conduction block. Checking two motor nerves may be insufficient, although one can target the electrodiagnostic study to focus on those nerves associated with muscles that are clinically weak or atrophic. I would emphasize that this is a case where the more motor nerve conduction studies done the better in trying to find absolutely clear-cut documentation of major conduction block. I believe over 90% of patients with multifocal motor neuropathy have obvious major conduction block if sufficient motor nerve conduction studies are performed.

The presence of elevated levels of anti-GM1 ganglioside antibodies is another useful diagnostic test. The problem centers on sensitivity, with only about half of all patients having markedly elevated levels of GM1 antibodies. Therefore, the more sensitive test is a motor nerve conduction study.

## QUESTION 4: WHAT ABOUT THE TREATMENT OF MULTIFOCAL MOTOR NEUROPATHY?

The treatment of choice is clearly high-dose intravenous gamma globulin. The exact schedule and regimen varies markedly from center to center and patient to patient; of course, there is not much science behind dosing and regimen. My own view is to start off with the usual 0.4 gm/kg/d for 5 consecutive days and then observe the patient's response. I will often decide to give an additional 0.4 gm/kg weekly for 2 weeks, then every other week for two cycles, and then once per month. That allows for 3 months of fairly aggressive therapy, at which point it should be fairly clear whether or not the patient is improved.

There are three responses that have different implications. Some patients have no improvement whatsoever. Some patients have objective improvement in strength and function, usually associated with improvement in the degree of conduction block as seen by the nerve conduction studies. Those patients obviously should continue on treatment as needed down the road. We have had some patients who have only required treatment on an as-needed basis every 6 to 12 months; other patients have required monthly maintenance doses. The third group is the toughest. These are patients who are not sure they are improving but think they may be a bit better or more "stable" yet there is no clear-cut objective improvement, either by the bedside examination or by repeat nerve conduction studies. Often these are patients who desire to continue therapy; given our emphasis on hope and the potential for them having some benefit, it is difficult in many cases to withhold contin-

ued therapy. I will make a judgment call in these situation and try to work with the patient's insurance in trying to continue therapy on an empirical basis for another 3 months, then reevaluate.

I am less enthusiastic about the use of other immunosuppressive regiments for treating multifocal motor neuropathy. I have treated occasional patients with long-term corticosteroids, methotrexate, and cyclophosphamide in the past but have never been impressed that any of those therapies were particularly helpful. It should be acknowledged that there are some experts who have reported very favorable results with cyclophosphaminde.[7] In my admittedly limited experience I have been uniformly impressed that the side effects were more problematic than any degree of potential benefit.

## QUESTION 5: WHEN SHOULD ONE SUSPECT KENNEDY'S DISEASE AND HOW SHOULD SUCH PATIENTS BE MANAGED?

In 1968 Kennedy et al[8] reported an x-linked recessive form of spinomuscular atrophy with bulbar involvement and gynecomastia (Kennedy's disease).[8] Occasional patients have sensory symptoms and endocrine abnormalities (such as diabetes mellitus).[9] Men can present in teenage years or in later life. The gynecomastia is typically noted in teenage years with symptoms from progressive limb weakness years to decades later. It affects only males, and neuromuscular symptoms generally begin in older age (after age 30 years). Fasciculations tend to be abundant in the tongue and facial muscles. In spite of prominence fasciculations and atrophy, the patients tend to have only mild dysarthria and dysphagia. Weakness is of a pure lower motor neuron type and tends to be symmetrical in the limbs. Respiratory muscle weakness is uncommon or mild. Mild distal sensory involvement should not dissuade one from the diagnosis. Although gynecomastia is present in 90% of patients, it can be mild and in many patients is missed on the initial neurological evaluations. The diagnosis has been missed or delayed in young men who have undergone bilateral mastectomy in teenage years. Other endocrine abnormalities include testicular atrophy, some degree of testicular feminization and infertility, and diabetes mellitus. Not all patients are sterile. In general, Kennedy's disease progresses much more slowly than ALS or progressive muscular atrophy (PMA) (Table 7).

**Table 7 Kennedy's Disease**

| |
|---|
| Slow progressive limb weakness and fasciculations |
| Almost always tongue atrophy and fasciculations |
| Not much dysarthria |
| Pure lower motor neuron |
| Gynecomastia in most |
| X-linked recessive |
| Presents in teens to 60s, slow course, decades |
| ? androgen therapy |

Kennedy's disease is due to an expanded CAG trinucleotide repeat expansion in the first exon of the androgen receptor gene, providing a sensitive and specific diagnostic test. A normal number of repeats is up to 27, and in Kennedy's disease patients the repeats tend to range from 40 to 65. The exact pathogenesis is unclear. Although the feminizing features are logical based on the abnormal androgen receptor abnormality, the motor neuron involvement may have a separate mechanism. The prevailing opinion is that the abnormal repeat expansion leads to a gain of function that is somehow toxic to lower motor nerves.

Androgen therapy (such as testosterone) has been suggested and used in some centers as a strategy to stabilize the disorder. To date, I am unaware of any convincing outcome data or prospective trial to support or refute the use of androgen therapy. I have tended to favor using androgen therapy in my patients but my neuromuscular colleagues at Indiana tend to hold off, reflecting the difference of opinion around the country in management of this disorder. Symptomatic treatment for limb weakness (physical therapy/occupational therapy) and medication for muscle cramps (quinine) are central to management of these patients, along with genetic counseling and awareness of the propensity for endocrine problems. Thus far I have been unable to determine if these men are at increased risk for developing breast cancer and whether or not they should be screened periodically.

## QUESTION 6: DO YOU BELIEVE IN THE DIAGNOSIS OF PRIMARY LATERAL SCLEROSIS?

Pure progressive upper motor neuron disease is rare, if it exists at all. My neuromuscular mentor had doubts about the existence of primary lateral sclerosis (PLS) even though we all learn about it. One needs to be aware of the high likelihood of another underlying identifiable diagnosis. Fortunately, the majority of "PLS" patients eventually develop some degree of lower motor neuron symptoms and signs, which makes me feel more comfortable about the original diagnosis. Some experts define PLS as "predominant upper motor neuron (UMN) disease" as opposed to exclusive UMN disease. Others refer to "PLS-Plus" to reconcile the existence of some lower motor neuron (LMN) signs. An important feature of PLS (regardless of how one defines it) is the tendency for a relatively slow course compared with patients having typical ALS. PLS patients tend to develop dysarthria and dysphagia in contrast to those with hereditary spastic paraparesis, who only rarely have bulbar involvement.

## QUESTION 7: WHAT ARE THE OTHER "ALS VARIANTS" THAT YOU SEE?

The most common form of focal motor neuron disease tends to affect a single limb, usually an arm, with several months to several years of progressive predominantly lower motor neuron disease. Men are more commonly affected than women, with onset in the second or third decade.

Bi-brachial amyotrophy or "flail-arm syndrome" represents another variant of motor neuron disease in which the abnormalities are predominantly in both arms and characterized by a relatively slow clinical course (compared with ALS).

Progressive bulbar palsy starts with slow progressive dysarthria and dysphagia but eventually the patient develops more widespread involvement (at which point we call it "bulbar onset ALS"). Some patients have what appears to be ALS except for the absence of clear-cut UMN signs. The literature refers to this as PMA and in general is felt to be one end of the clinical spectrum of ALS.

## QUESTION 8: WHERE DOES THE DIAGNOSIS OF SPINOMUSCULAR ATROPHY FIT IN?

Spinal muscular atrophy (SMA) is a genetically based progressive lower motor neuron disorder. It has a prevalence of 8/100,000. The primary gene responsible for SMA has been cloned [survival motor neuron (SMN) gene] and serves as the basis for a valuable diagnostic lab test. The SMN gene is deleted or mutated in over 98% of SMA patients. Most patients experience clinical onset in childhood and demonstrate autosomal recessive inheritance. Weakness is symmetric, hypotonic, and proximal more than distal. Legs are more involved than arms and the axial or trunk muscle are often affected.

### Childhood-Onset SMA

Childhood-onset SMA is classified as type I (onset 0 to 6 months, patient never sits, death by 2 years), type II (onset 7 to 18 months, never stands, death beyond 2 years), and type III (onset after 18 months, stands alone, death in adulthood). With later onset the disease is more benign. Bulbar and respiratory involvement is a prominent feature only in early-onset SMA.

### Adult-Onset Spinal Muscular Atrophies (SMA Type IV)

Adult-onset SMA is responsible for approximately 10% of all SMA cases. Although almost all childhood-onset SMA (types I, II, and III) cases are autosomal recessive in inheritance, only 70% of adult-onset SMA (type IV) patients inherit the disease by the autosomal recessive mode. The remaining 30% are autosomal dominant. Another important difference is that a minority of adult-onset SMA has an associated abnormality of the SMN gene. The age of clinical onset in SMA type IV ranges from the third to the sixth decade. The clinical course is variable but usually much slower than ALS. Typically, there is slowly progressive limb-girdle weakness beginning in the lower limbs. Difficulty in walking, climbing stairs, and rising from a chair are the main symptoms in the early stages, and bulbar weakness involvement is less commonly a problem.

## QUESTION 9: WHAT ARE THE MOST IMPORTANT ISSUES REGARDING FAMILIAL ALS AND WHICH PATIENTS SHOULD HAVE DNA TESTING?

Around 5 to 10% of all ALS cases are familial, most demonstrating an autosomal dominant pattern of inheritance. About 20% of patients with familial ALS have a mutation of the gene coding for superoxide dismutase 1 (SOD1) on chromosome 21.[10] Treatment of such patients with antioxidants including SOD is ineffective due to the presumption of a toxic gain of function from the defective gene (as opposed to the simple absence of normal SOD function). Patients with familial ALS tend to have a somewhat younger age of onset than those with sporadic ALS. The clinical course and manifestations are indistinguishable from sporadic ALS. A major spin-off from the discovery of human SOD1 mutation is the subsequent development of the SOD mouse model of ALS. Although it may not be a perfect animal model for the sporadic form of the disease, it does offer a major advance for study of pathogenesis, and at this juncture is an important tool for the rapid screening of potential new therapies.

Neurologists should be aware that of all the SOD1 mutations associated with ALS, the A4V subtype is notorious for resulting in a very rapidly progressive form of the disease, typically with survival of less than a year from the onset of symptoms.[11] In addition, the A4V patients tend to have predominantly if not exclusively lower motor neuron involvement (at times causing confusion about the diagnosis). From a pragmatic standpoint, if we know a patient has early symptoms consistent with motor neuron disease and a positive family history, and we confirm the presence of the A4V mutation in the patient, it behooves the clinician to discuss the unusually rapidly progressive prognosis with the patient (instead of the usual 2 to 5 years or longer). Patients deserve to know realistically how much quality physical time they have left to plan their upcoming months appropriately.

Those patients with a first-degree relative affected with ALS are appropriate candidates for genetic testing. Patients with a negative family history are gen-

erally not tested. As with genetic testing in other progressive degenerative conditions, considerable time should be spent with the patient discussing the implications of the test results.

## QUESTION 10: WHAT IS THE STATUS OF RECENT OBSERVATIONS SUGGESTING A "VIRAL" CAUSE FOR ALS?

### ALS and the Viral Hypothesis

For 50 years investigators have searched for a viral cause of ALS, a logical assumption given the specificity of polio and other enteroviruses to motor neurons. In 2000 Berger et al[12] reported the association between enterovirus and ALS by finding a sequence of echovirus using reverse transcriptase polymerase chain reaction (PCR) testing of spinal cord samples from 13 of 17 patients who had died with ALS compared with only 1 of 29 patients who had died of other neurological disorders.[12] Such findings have yet to be confirmed. Subsequently, Walker et al[13] reported no echoviral sequences in 20 spinal cord and 10 motor cortex samples from autopsy-confirmed cases of ALS, nor did they find echoviral sequences in testing of 13 spinal cord and 5 motor cortex samples from patients without motor neuron disease.[13]

The likelihood of a cause and effect relationship between enteroviruses (such as echovirus) and ALS is of even greater clinical significance with the advent of antiviral drugs such as pleconaril, which would be expected to be successful in treating such a viral infection.[14]

### HIV and Antiviral Therapy in ALS

In a recent widely publicized report, Moulignier et al[15] from Paris reviewed all patients with HIV infection who had neurologic symptoms seen over a 13-year span. Out of 1700 patients with HIV infection and neurologic symptoms, all having been referred to the lead author, there were six patients who developed a distal motor weakness mimicking a monomelic amyotrophy that subacutely progressed regionally or assumed a symmetric distribution on more than one region. The EMG was indicative of motor neuron disease and no multifocal conduction block was seen. Other causes of motor neuropathy were ruled out. There was observation of "positive response to antiretroviral therapy," suggesting that this ALS syndrome in HIV infection might be etiologically related. MacGowan et al[16] reported benefit from antiretroviral therapy in a patient with HIV and a paralytic illness resembling ALS. The role of viruses, be they enteroviruses or HIV, as well as the role of antiviral therapy remains unclear.

## QUESTION 11: WHY IS A CYCLOOXENGENASE-2 INHIBITOR BEING TESTED FOR THE TREATMENT OF ALS?

Almer et al[17] reported on "Increased Expression of the Pro-Inflammatory Enzyme Cyclooxengenase-2 in Amyotrophic Lateral Sclerosis," noting that in transgenic mice with superoxide dismutase and mutations during the course of their illness, the expression of the cyclooxengenase-2 (Cox-2, a key enzyme in the synthesis of prostanoids, which are potent mediators of inflammation) is dramatically increased. In both early and end-stage transgenic SOD mice, the neurons and to some degree the glial cells in the anterior horn area of the cord show increased Cox-2 immunoreactivity. Cox-2 messenger RNA and protein levels and catalytic activities are also increased. The time course of spinal cord Cox-2 up-regulation parallels that of motor neuron loss in these transgenic mice. In addition, the same authors showed an increased Cox-2 activity in postmortem spinal cord samples from patients who had sporadic ALS.

In a separate study by Yasojima et al[18] the spinal cord from 11 ALS patients and 27 controls were studied for Cox-2 messenger RNA levels with findings that Cox-2 mRNA was up-regulated seven-fold in the ALS spinal cords. Western blots of the protein products showed up-regulation of Cox-2 protein levels in the ALS patients.

Furthermore, a Cox-2 inhibitor has been reported to be neuroprotective in organotypic spinal cord cultures exposed to the toxic astroglial glutamate transport inhibitor threo-hydroxy-aspartate.[19]

The observation of a beneficial effect in the ALS mouse model completes the data in support of a clinical trial in ALS.

## QUESTION 12: HOW OFTEN DO ALS PATIENTS HAVE AN ASSOCIATED DEMENTIA?

About 1 to 3% of ALS patient have an associated frontal lobe dementia. Most such patients have prominent bulbar involvement. The onset of dementia usually parallels the development of neuromuscular symptoms. Occasional patients with Creutzfeldt-Jacob disease (CJD) have anterior horn cell involvement. Such patients typically have a rapidly progressive clinical course and the other classical features of CJD (such as stimulus responsive myoclonus).

Also, patients with respiratory insufficiency may manifest cognitive problems as a result of hypercarbia or hypoxia.

## QUESTION 13: WHEN THE DIAGNOSIS OF ALS IS MADE, WHAT IS THE APPROPRIATE TREATMENT?

There are two different strategies for the management of ALS.

## Strategy One: The Attempt to Protect, Save, and Salvage as Many Motor Neurons as Possible

### RILUZOLE

Riluzole blocks the presynaptic release of glutamate. Evidence-based reviews indicate that use of riluzole prolongs survival by about 2 to 3 months in the average patient.[20–22] Further analysis would suggest that the chance of surviving 1 year is better on riluzole than not (57% in the placebo and 66% in the riluzole group). To date there is no convincing data to show a benefit in quality of life or in function. Side effects are usually mild. About 10% of patients experience fatigue and 5 to 10% experience loss of appetite or other gastrointestinal symptoms. Patients with mild side effects may do better by taking the dose after a meal instead of prior, and after a month or two switching to a prior to meal dosing schedule. In addition, we have treated some patients with a single dose of 50 mg daily instead of the recommended 100 mg due to intolerance of the larger dose and absence of side effects with the lower dose. The company recommends checking liver function tests monthly for the first 3 months and every 3 months thereafter. As about a third of ALS patients have chronic elevation of skeletal muscle enzymes, the presence of an elevated transaminase sometimes erroneously leads to discontinuation of riluzole even though the elevation may be from muscle as opposed to liver. Therefore I would suggest in such patients to monitor gamma as opposed to SGOT, SGPT, or LDH (as the latter can all be elevated from skeletal muscle). There is no convincing study to date to indicate an impact on quality of life, and the cost remains an issue for many patients (about $850/month). The pros and cons of riluzole should be discussed with patient and family, and riluzole should be offered, particularly if the cost is not a hardship. Around 10 to 15% of patients will discontinue treatment because of side effects (nonspecific fatigue, anorexia, gastrointestinal problems), and a few will have to stop because of liver enzyme elevation, which requires monitoring. If patients choose to take the drug, then I support their decision and even point out that they might have a better response than the average patient. I try to maximize the benefits from any therapy including the nonspecific therapeutic effect and psychological effects. On the other hand, if the patient chooses not to take the drug, especially when the patient is paying out of pocket, I completely support that decision as well and try to make certain they are comfortable with their decision one way or the other. Patients must be told up front of the realistic expectations of treatment in order to make an informed decision.

Although I can cite no data, I believe in the logic that patients with a larger number of intact and viable motor neurons (those early in the course of the disease) are better candidates for riluzole than those with severe or end-stage disease.

More on the survival issue: My own view is that discussion of prolonged enhanced survival as a reason to take a drug should be followed by some additional comments. It is helpful to point out to the patient that if prolonged survival is their major priority (to survive for a number of additional months or indefinitely) then the option of tracheostomy with mechanical ventilation is appropriate. I would argue that the additional survival time might logically be associated with a better overall functional level and quality of life in the setting of mechanical ventilation than whatever degree of prolonged survival can be expected from a medication alone.

### CREATINE

Creatine is commonly used by ALS patients for a variety of reasons. Patients with a variety of neuromuscular diseases (other than ALS) have been reported to display improved muscle bulk and in some cases strength in the setting of creatine use.[23] Athletes across the country commonly use this supplement for the same reason. Creatine prolongs survival of SOD1 mice about twice as long as does riluzole.[24] The most common empirical dose is 5 g/d. Side effects are usually minimal. Prospective double-blind trials with creatine in ALS are approaching completion such that actual data should be available by the end of 2002 to answer the questions (1) Does creatine really help ALS patients?; (2) If so, to what degree?; (3) Is there an optimal dosage or regimen?; (4) Are there particular patients in whom it is particularly helpful?; and (5) Are we sure it is as safe as we assume?

Antioxidant vitamins (vitamin E, vitamin C, beta carotene, etc.) are used by many patients even though there are no data to confirm clinical benefit in patients with ALS.

## Strategy Two: Attack the Symptoms That the Disease Creates

The wide variety of treatable symptoms of ALS is best addressed with the establishment of a multidisciplinary management clinic.[25] Tables 8 through 17 summarize many of the management issues that are central to the day-to-day management of our ALS patients. With sufficient expertise from physical, occupational, speech, and respiratory therapy, along with input from neurology, physical medicine, social service, and a link to support groups and research centers, the patient can receive the appropriate interventions at the optimal time to enhance and enrich their quality of life.

### MANAGEMENT OF LIMB WEAKNESS

A physical medicine and rehabilitation physician is an integral part of our multidisciplinary clinic in the management of ALS patients. A skilled physical therapist can be most helpful in assessing gait and judging when to use canes, walkers, and manual and motorized wheel-

**Table 8 Checklist of Treatable Associated ALS Symptoms and Suggestions for Management**

| | |
|---|---|
| Depression | SSRI, if trouble with sleep then TCA |
| Pseudobulbar affect, treat when severe | SSRI or TCA |
| Anxiety | Benzodiazepine (I liberally use alprazolam, diazepam, and lorazepam; the drug can also help with nighttime sleep problem and also with spasticity) |
| Constipation (aggravated by immobility, decreased oral intake/dehydration, and also by the anticholinergic effects of other meds) | Colace<br>Sorbital 70% 15 cc (1 tablespoon), one or two daily<br>1–2/d and increase as needed |
| Thick mucous secretions | Guaifenesin<br>Nebulizer inhalation treatment (can be given with Atrovent or bronchosol), home suction machine<br>N-acetylcysteine |

chairs to keep the patient as functional as possible while minimizing the chances of injury from falling. Similarly, a skilled occupational therapist can not only teach patients how to accomplish activities of daily living with reduced muscle power but also assist with selection and instruction of a large variety of tools (for opening jars, buttoning clothes, eating utensils, etc.). The home typically will need adaptive devices to enhance function including lift chairs, Hoyer lift, hospital bed, bars for stability, elevated commode seats, and so on. Heavy weight training or graded physical therapy, as is common in stroke patients, is typically unhelpful. Although light exercise is fine, patients should be advised not to exercise to extremes of physical exhaustion. Simple measures such as splint for wrist drop and/or flexion contractures of the hands and ankle-foot-orthosis for foot-drop can make a major functional difference for the patient and are often overlooked.

#### DYSPHAGIA AND PEG

For mild dysphagia in ALS, simple chin-tuck maneuver can be taught by specialized speech therapists or physiotherapists and can reduce the risk of aspiration (Table 18).

The two most obvious indications for percutaneous enterogastrostomy (PEG) are the presence of frequent choking with eating and the presence of unacceptable weight loss. There have traditionally been two schools of thought with regard to timing of PEG. One view is that being an invasive procedure, and given the occasion regrettable complications (such as aspiration from the procedure, respiratory arrest, gastrointestinal infection, peritonitis, etc.), it should not be performed until it is clearly needed. Why take the chance of giving the patient more problems than he or she needs? The other extreme seems to be to place the PEG as early as possible, as the procedure typically has fewer complications when performed on a healthier patient. Most neuromuscular specialists can identify the occasion patient with poor pulmonary function who decompensated for one reason or another during or shortly after PEG placement. Most patients are reluctant to jump right in and have the procedure in the absence of significant dysphagia. It seems logical to me to recognize that if the patient is struggling with frequent choking, or if their weight is declining to a degree consistent with malnutrition, that PEG should be strongly encouraged. For patients who are uncertain, arrange for them to meet with a surgeon, gastroenterologist, or interventional radiologist to discuss the procedure in more detail. Consider, for more advanced patients, having pulmonary consultation before and during the procedure. We have instituted BiPAP in the hospital in some patients, followed the next day by PEG (and continued BiPAP post-procedure). I would also emphasize to the patient that PEG is not necessarily performed as a measure to ensure or prolong survival—just as often it is chosen as a method of improving patient comfort (choking and malnutrition are logically unpleasant for the patient).

**Table 9 Pain Management**

| | |
|---|---|
| Muscle cramps | See Table 10 |
| Spasms/spasticity | See Table 11 |
| Musculoskeletal pain | Nonsteroidal anti-inflammatory medication for musculoskeletal pain (note recent interest in COX-2 inhibitors) |
| Muscle relaxers (such as Flexeril) | |
| Narcotics (start with low dose and escalate as needed) | Propoxyphene<br>Codeine with acetaminophen<br>Stronger narcotics if needed, especially for qhs dose |

**Table 10 Medication for Muscle Cramps (Pascuzzi's Preferences)**

| | |
|---|---|
| Quinine sulphate | 260–520 mg daily |
| Carbamazepine (or oxcarbazepine) | 200 mg bid (150 mg bid for oxcarbazepine) |
| Vitamin E | 400–800 IU bid |
| Gabapentin | 300 mg bid or qid |
| Diphenhydramine | 25–50 mg qhs |

## QUESTION 14: WHAT IS YOUR APPROACH TO THE USE OF TRACHEOSTOMY AND MECHANICAL VENTILATION IN PATIENTS WITH ALS?

It is said, and probably correctly, that this topic should be discussed and addressed early after the diagnosis is made so that the patient has a chance to think through it in a methodical fashion and his or her wishes can be made quite clear to the family and physicians. In some patients, however, one should temper these discussions, particularly with someone who has just recently been diagnosed and someone who is not having significant respiratory involvement. The patient may have so much information to work through and so many decisions to consider that to bring up a lengthy discussion of mechanical ventilation at the first visit, or even the second, may in some cases be counterproductive. The patient may become so anxious, frustrated, or depressed that his or her overall management is hindered. I try to measure each patient in this regard and get a feel for what he or she wants to know. In general I ask the patient what we can do for him or her and what he or she would like from us. Otherwise, I'll try to emphasize the importance of long-term monitoring of respiratory function. I certainly mention the routine use of BiPAP or CPAP when the patient's pulmonary function drops off significantly, but I hold off on an in-depth discussion of tracheostomy and mechanical ventilation until I have a reasonably good rapport with the patient and have come to know him or her well. The discussions, like many in medicine, can take different shapes and forms. I'm convinced that the vast majority of ALS patients can either be talked into tracheostomy with mechanical ventilation or talked out of it simply by the way in which it is presented by the physician. Informed consent in this area is complicated; how much information can the average neurologist impart to the patient about what it would be like to have a tracheostomy with mechanical ventilation? The patient can hear from the neurologist, can be sent to a pulmonologist who is experienced with home ventilators, can speak with other patients and "caregivers" who have made such a decision, but in the end the patient still is guessing what it would be like to have a trach and ventilator. Ideally, unless a patient has been on a mechanical ventilator in the past, the only truly informed decision the patient can make for long-term management is giving it a try to really experience it firsthand.

I use the following principles in approaching this dilemma.

1. Mechanical ventilation tracheostomy is a reasonable option for patients who have ALS.
2. Although it is the case that the vast majority of ALS patients prefer not to pursue a tracheostomy with mechanical ventilation, some of them do and there is no "correct decision" in this matter other than what the patient chooses.
3. I generally tell patients that while the majority are not interested in this form of treatment because of the concern that they will simply be prolonging survival with a poor quality of life, some patients do prefer this form of management and that quality of life is all relative and some patients are quite pleased with their decision in this regard.
4. There is no fundamental difference in deciding to withhold the treatment and deciding to withdraw the treatment and this should apply to mechanical ventilation just as much as it should apply to any

**Table 11 Spasticity Management (Medications)**

| | |
|---|---|
| Baclofen | 10–80 mg daily in divided doses |
| Tizanidine | 4–24 mg daily (in divided doses with an evening load) |
| Diazepam | 5 mg qhs with gradual increase with gradual increase as needed |

**Table 12 Management of Sialorrhea (Excessive Saliva/Drooling)**

| | |
|---|---|
| Glycopyrrolate (Robinul) | 1–2 mg po q 6–12 hours |
| Amitriptyline/nortriptyline | 10–75 mg qhs |
| Transdermal hyoscine patches | 1–2 patches |
| Atropine (Saltropine) | 0.5 mg po q 4–12 hours |
| Parotid gland botulinum toxin injections | Contact you local Botox authority for help |
| Home suction machine | |
| Avoid sweets and sour foods in the evening | |

**Table 13 Chronic Respiratory Failure Symptoms**

| |
|---|
| Morning headache |
| Daytime fatigue and sleepiness, concentration problems |
| Difficulty falling asleep, disturbed sleep, nightmares |
| Nervousness, tremor, increased sweating, tachycardia |
| Depression, anxiety |
| Dyspnea and tachypnea |

**Table 14 Respiratory Insufficiency: Management Options**

| |
|---|
| BiPAP, CPAP |
| Elevate head of bed (hospital bed) |
| Home supplemental low flow oxygen (2 liters NC) |
| If symptoms of infection, bronchitis, pneumonia, exam, and chest X-ray indicated; low threshold for empirical course of oral broad-spectrum antibiotics |

**Table 16 Sleep Quality and Comfort (Should Be Used with Caution)**

| Drug | Dosage (at Night) |
|---|---|
| Zolpidem tartrate | 5–10 mg qhs |
| Zaleplon | 5–10 mg qhs |
| Restoril | 15–30 mg qhs |
| Chloral hydrate | 500–1000 mg qhs |
| Diphenhydramine | 25–100 mg qhs |
| Nighttime pain pill (propoxyphene or acetaminophen with codeine) qhs, stronger narcotic qhs if needed | |
| Hospital bed | |

other form of treatment of ALS. In other words, if a patient chooses to take riluzole, then he or she should take it. If he or she should choose not to use the drug, then that should be the case. Should he or she starts the drug and does not like it due to side effects, expense, or any other decision, then the drug should be stopped with the full support of the physician. Riluzole has proven to prolong survival. There is never a quandary over a decision to stop riluzole. The same should apply for mechanical ventilation. If the patient chooses to take the treatment, it should be attempted. If he or she chooses not to pursue it, it should be avoided if possible, and should he or she start on mechanical ventilation and decide to discontinue it, it should be discontinued. It is simply a treatment in a condition in which the patient's cognitive function is not impaired. The patient is in the best position to decide if the treatment is in their best interest or not. A patient should know up front that in agreeing to have tracheostomy with mechanical ventilation that should at some point down the road he or she wishes to stop the treatment, it will be done. Protocols with hospice programs, palliative therapy groups, and a large number of neurologists and pulmonologists who deal with ALS patients recognize the importance of patient autonomy, ensuring that patients do not suffer when and if mechanical ventilation is withdrawn. One of the major reasons why so many ALS patients are fearful of having tracheostomy with mechanical ventilation is the notion that should they go on a ventilator, they can never come off, and that they might therefore be looking at many years of long-term indefinite suffering and poor quality of life against their will. In my view, while this is a very commonly held belief, even among many physicians, it is a very poor way to make such a major decision. Therefore, I would propose the following.

5. After discussion with the neurologist, if the patient is interested in hearing more about long-term mechanical ventilation, he or she should be referred to a pulmonologist who has expertise and experience in this area, especially with home ventilators.
6. Should the patient decide he or she does not want to pursue mechanical ventilation, then that should be clearly documented and noted by the family and physicians and the patient's wish should be followed. Should the patient clearly wish to have mechanical ventilation, then that should be planned and performed prior to the patient developing acute pulmonary decompensation if possible. The earlier it is done, the better the patient will probably sleep at night with ventilatory support. Many such patients ventilate at night or while resting during the day and come off the ventilator during their waking hours.

**Table 15 Respiratory Failure: Medicare Guidelines for Reimbursement for CPAP/BiPAP in ALS Patients**

All of the following conditions must be met:

1. There is documentation in the patient's medical record of a progressive neuromuscular disease or severe thoracic cage abnormality, and
2. One of the following conditions are met:
   A. An arterial blood gas $PaCO_2$ done while awake and breathing the patient's usual $FIO_2$, is ≥45 mm Hg, or
   B. Sleep oximetry demonstrates oxygen saturation ≤88% for at least 5 continuous minutes, done while breathing the patient's usual $FIO_2$, or
   C. For progressive neuromuscular patient only, maximal inspiratory pressure is <60 cm $H_2O$ or forced vital capacity is <50% predicted, and
3. Chronic obstructive pulmonary disease does not contribute significantly to the patients pulmonary limitation

These guidelines are for Bi PAP S or BiPAP ST machines! There are other guidelines that are to be used in other situations but this is the one we usually use for our patients.

**Table 17 Other Therapeutic Options in the Home**

| |
|---|
| Hospice services |
| Computer/internet |
| Massage therapy |

7. If the patient is uncertain about how to proceed, then he or she should be offered the option of a therapeutic trial of mechanical ventilation with the thought that it is a difficult decision and the patient can give it a try. A trial from several weeks to several months would put a patient in a far better position to decide if it is a good form of treatment or one that he or she would prefer to avoid on a long-term basis. Many patients going this route will be pleased with the overall results and stay on the mechanical ventilator indefinitely. Just as many will be pleased for some period of time with the use of the mechanical ventilator but will reach a point where they feel they have had enough and would like to have the ventilator withdrawn. We have some patients who desire to have their survival extended with mechanical ventilation in order to experience a personal milestone or event such as a child's wedding or graduation, birth of a grandchild, etc. Other patients reach a point where they feel that length of survival is no longer a priority, but rather quality of life on earth. Another group of patients give mechanical ventilation a try but feel that it is a poor option for them and within a few weeks to a few months choose to withdraw the treatment.
8. Decision making and management of patients should be oriented around one of two principles (and many times both). Survival as the primary driving factor is a factor in most of the decision making we make on a daily basis with the management of patients in general. However, in many patients who have chronic or progressive disabling or uncomfortable conditions, the emphasis of management shifts. Survival is no longer the issue but rather comfort as the primary goal becomes the focus. With many ALS patients there comes a point in time where survival is no longer the emphasis of their management but rather it shifts over to comfort and any decision that is made should pass the test of whether or not it is expected to enhance the patient's comfort level. There are occasional patients in whom a tracheostomy and mechanical ventilation may be pursued for comfort measures more so than for prolongation of survival.

**Table 18 Dysphagia Management**

| |
|---|
| Work with a speech therapist with experience in motor neuron disease |
| Work with a dietician |
| Chin tuck maneuver for swallowing (I tell the patient about it, the speech therapist shows them how to do it, reduced risk of aspiration) |
| Modify diet (mechanical soft, pureed) |
| Thicken up liquids |
| Suction machine |
| PEG tube |

The vast majority of patients with ALS die peacefully (usually in their sleep) and do not strangle or choke. In patients with end-stage ALS, unless they choose mechanical ventilation, the development of hypercarbia leads to sedation. It is appropriate to focus on comfort measures, as opposed to survival measures, and liberal use of benzodiazepines for anxiety or restlessness, as well as use of analgesics including morphine for musculoskeletal pain or dyspnea. Hospice and palliative care services allow for the majority of patients to be managed at home for their end of life care. Administration of oxygen may be helpful. Patients with chronic hypoventilation who use hypoxic drive for breathing may decompensate if given high-concentration supplemental oxygen.

Pitfall scenario: An ALS patient has chronic dyspnea due to diaphragm weakness. In an effort to provide maximum comfort he or she is given supplemental oxygen. Over the next hour the patient appears much more comfortable and less short of breath. Two hours later he or she appears more peaceful and is finally able to go to sleep. Several hours later he or she has a respiratory arrest and dies. Comment: The problem here is that the patient with chronic hypoventilation may have a chronic elevation of $pCO_2$, leading to "hypoxic drive" of respiration. The supplemental oxygen raises the $pO_2$ and the patient loses their "hypoxic drive." Therefore the patient further hypoventilates, leading to increasing levels of $CO_2$. The patient appears more comfortable, in part because of the sedating effects of hypercapnia. Such sedation becomes increasingly profound, and over the next few hours the patient follows a vicious cycle of increased sedation leading to reduced ventilation, which in turn raises the $pCO_2$ even further, producing increasing sedation and ultimately a respiratory arrest. The solution is to utilize noninvasive ventilation (such as BiPAP) prior to adding the supplemental oxygen. Also, starting with lower concentrations of supplemental oxygen may be prudent.

## CONCLUSION: THE BIG PICTURE

ALS is a very serious diagnosis and the reality is that the patient, family, and health care team should anticipate the progressive nature of the patient's weakness. Although one can focus on the fact that the diagnosis is progressive and can lead to death, I think it is better to use one's energies to focus on being alive and quality of life. I have heard

some refer to the treatments for ALS as being nothing more than Band-Aids, not a cure. I would counter that point by suggesting that a lifetime of health care is nothing more than a series of Band-Aids. Band-Aids can be great. Furthermore, if a patient has 20, 10, 5, 2, or 1 year of life, it is best to focus on ways to enhance or enrich the patient's level of function and quality of experience. In our view, there are two primary goals that serve as the basis for decision making. One involves survival. Many of the treatments that we offer patients are based on trying to extend or prolong someone's survival. Another goal is that of comfort; there are circumstances in which survival at all cost is not the main goal but the emphasis shifts to comfort as the deciding factor in their management. Therefore, if a patient is diagnosed with ALS, it is important to respect the fact that the clinical course can be unfortunately rapid but also recognize that 10% of patients have a course that runs longer than 10 years and elderly patients may outlive the condition. In my view, the emphasis should be placed on trying to enhance and enrich the patient's level of function and overall comfort.

Each patient should be viewed separately with an eye toward determining how the disease is affecting the individual and then come up with a plan for treating the various symptoms that are significant for that particular patient.

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