

MANAGEMENT STRATEGIES IN AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is an irreversible degenerative disorder characterized by loss of upper and lower motor neurons, finally culminating in respiratory insufficiency and death. In different series, median time from onset of symptoms until death varies from 23 to 48 months, 5-year survival rates range from 9% to 40%, and 10-year survival rates between 8% and 16% (1, 3). There are currently no medications to firmly stop or reserve the progressive course of the disease. However, there are a number of management strategies optimizing the quality of life (1). This obliges the physician to play a role which requires broad thinking about pharmacologic and non-pharmacologic measures and collaboration with other physician and non-physician healthcare providers. The purpose of this review is to provide current data for the development of optimal management strategies.

Key words: Amyotrophic lateral sclerosis, management, treatment, quality of life

QUALITY OF LIFE OF THE PATIENT WITH ALS

Because ALS cannot be cured or its progression definitely stopped, the primary goal in caring for patients with this disease is the optimization of quality of life (QOL).

QOL for all individuals reflects more than simply the person's health status and depends on non-medical factors, including psychological state, level of independence, social relationships, personal beliefs and their relationships to environment. Thus, overall QOL consists of health-related factors (physical, functional, emotional, and mental well-being) and non health-related factors (jobs, family, friends, and other life circumstances). This implies individual variability, and two individuals with similar physical limitations may have very different QOLs. In this respect, a number of studies have demonstrated that QOL in patients with ALS does not correlate with measures of physical strength and function, and does not necessarily decline over time despite progressive weakening (1). Psychological, religious/spiritual factors, and support systems appear to play major roles in the potential for individuals with ALS, including those with tracheostomy/mechanical ventilation (TMV), to have a high QOL. It

has to be emphasized the fact that people in good health surrounding patients with ALS frequently underestimate the QOL of individuals with chronic disease (2).

To measure QOL in patients with ALS, several types of scales are used, trying to circumscribe all the aspects influencing QOL: general QOL instruments such as the McGill Quality of Life Questionnaire (MQQOL), which incorporate domains outside of physical strength and function; general QOL instruments such as the Schedule for the Evaluation of Individual Quality of Life (SEIQOL), which permit individuals to identify and score those domains that are of most importance to them; ALS-specific QOL instruments such as the ALSAQ-40, with use domains that are believed to be most important to the majority of patients with ALS (3).

The ALSQ – Specific Quality of Life Questionnaire (ALSSQOL) is a toll that may be of value in research as well as in clinical practice. It reflects patients' own assessments of their QOL based on the MQOL, measures of religiosity and spirituality, and items that patients with ALS identified as being of importance to them in semi-structured interviews. This scale has been validated in ALS patients (4).

It has to be emphasized once more that QOL in ALS patients does not correlate with measure of physical strength and function, and does not necessarily decline over time despite the progression of motor weakness (3).

ANNOUNCING THE DIAGNOSIS

An important moment is the announcement of diagnosis, since this will determine the patient's initial reaction to the diagnosis of ALS and the ability to work collaboratively with his or her physician during the evolution of the disease. The difficulties the physician is facing are fear of getting blamed for the diagnosis, the perceived lack of time, lack of training, fear of causing distress, and concerns about being asked difficult questions and not having the answers (3). However, most patients want to know their diagnosis and want information on their condition, even when the news is bad. Guidelines have been proposed for breaking the news to a patient with ALS, with goal to convey accurate information while providing hope (3).

The physician should avoid phrases such as "there is nothing more we can do" and reassure the patient of his availability to continue caring for them or desire to refer them to a specialized center that can provide such care, even this last is difficult in Romania. Ideally, the neurologist should make patients aware that there is medication that may prolong life, and care is available to control symptoms and optimize QOL, discussing clinical treatment trials and offer to refer patients for enrolment. A recent study in USA showed that 44% of ALS patients thought that physician did a good job of breaking the news, whereas 31% rated their physician's approach as average and 25% gave a poor rating (5).

MEDICATIONS

Riluzole, a glutamate antagonist, is currently the only drug available in USA approved for the treatment of ALS. A double-blind, placebo-controlled trial demonstrated that it slowed the decline in muscle strength, improved the survival rate at 1 year, and lengthened median survival by 83 days (3). A larger follow-up study demonstrated an improved survival rate at 12 and 18 months when given a daily doses of 50,100, and 200 mg, with the best benefit-to-risk ratio seen in the group taking 100 mg daily. Consistent with these findings, a population-based outcome study in Ireland concluded that riluzole reduced the mortality rate by

23% and 15% at 6 and 12 months, respectively, and prolonged median survival by 4.2 months (6). Riluzole may be most useful in those with early and less severe disease; a vital capacity survey demonstrated no effect on survival or rate of deterioration muscle strength (6). Riluzole was generally well tolerated, abnormalities in liver tests that led to discontinuation (ALAT greater than 5 times the upper limit of normal) occurred in less than 4% of patients. Recently, case reports of neutropenia and possible hypersensitivity pneumonitis have been published (7,8). Riluzole is not available in Romania.

Minocycline has been shown to delay disease onset and prolong survival in the SOD1 transgenic mouse model of ALS (16,17,18). A recent phase I and II study has established the safety and dose range in the treatment of ALS, and a phase III trial is ongoing (19).

Antioxidant compounds are often recommended by physicians treating ALS based on the possible pathogenetic role of oxidative stress in ALS and in other neurodegenerative disorders. In Parkinson disease, coenzyme Q10 was found to be safe and well-tolerated at doses as high as 1200 mg daily (20). Combination therapy looks promising because multiple pathways may be involved in ALS pathogenesis. A "3-drug cocktail" of minocycline, riluzole, and nimodipine showed efficacy in transgenic SOD1 mouse model of ALS in disease onset slowing decline in muscle strength and increasing lifespan, but has not yet undergone trials in human with ALS (21). It has to be emphasized that it does not exist at the moment a medication that can halt or reverse the course of the disease, and that the survival prolongation obtained with riluzole does not mean an improvement in QOL for the period of this survival.

MANAGEMENT OF THE RESPIRATORY PROBLEMS

Most patients with ALS die of progressive respiratory failure. In this spirit, assessment and management of respiratory function are important. Forced vital capacity (FVC) is most commonly used to assess respiratory function in the patients with ALS, and shorter survival is associated with lower FVC. Although it is unclear whether non-invasive positive pressure ventilation (NIPPV) actually slows the rate of decline of FVC over time, it has been shown to have many benefits in patients with ALS when used for at least 4 consecutive hours in each 24-hour period. NIPPV have to be instituted when a decline in FVC of patients with ALS to 50% of predicted value occurs, because these values are

associated with respiratory symptoms and with a poor prognosis (9).

It has to be noted that there is no consensus on using FVC as unique measure of respiratory distress, because FVC correlates poorly with other measures of respiratory function and with symptoms of early respiratory insufficiency. A number of other measures have been proposed as better indicators of respiratory function. One simple variant is FVC while supine, which is lower than erect FVC in patients with ALS with dyspnea, orthopnea, and daytime fatigue. Nocturnal oximetry, maximal inspiratory pressure (MIP), and maximal sniff nasal inspiratory force (SNIF) appear to be more sensitive indicators of early respiratory insufficiency than FVC and have been recommended for deciding when to initiate NIPPV (10,11). SNIF has good prognostic value, can be obtained more readily than FVC in patients with advanced disease, and is more sensitive to changes in respiratory muscle strength than FVC (10).

Because NIPPV in ALS patients will not sustain life indefinitely, they will require tracheostomy/long-term mechanical ventilation (TMV) to survive. Use of TMV in ALS is rare in USA (3). In one study, 8,6% of patients with ALS in a large geographic region chose TMV (3). The ALS CARE database indicates that 3.2% of ALS patients with FVC of less than 40% of predicted was being treated with TMV. TMV represents an entirely different, and much more complex, level of support than NIPPV, and may substantially prolong life. In one Japanese study of 70 patients placed on TMV, 33 (47%) survived more than 5 years, but many of these patients effectively lost their ability to communicate (12). Also, TMV is very expensive and difficult to be used in Romania (the costs in USA published reports vary between \$155,000-\$180,000), and insurance often does not cover these costs (3). On the other hand, TMV has unique implications with respect to issues of quality of life for both the patient and the caregiver.

NUTRITION

Approximately 20% to 30% of patients with ALS present with bulbar dysfunction and affects during the course of the disease nearly all patients, placing them at risk for malnutrition (3). Many series demonstrate a poorer prognosis for patients with bulbar-onset disease. Dysphagia in ALS usually begins with liquids and then progresses to solid aliments. Tongue weakness may limit the patient's ability to move food around in the mouth, coughing

and choking may become frequent with a progressively increasing risk of aspiration. Malnutrition, dehydration, and weight loss often are consecutive to dysphagia: in one series, 16.4% of patients with ALS were found to be malnourished (3). Malnutrition was an independent prognostic factor for survival, with a 7.7-fold increased risk of death in patients with ALS who were malnourished. Thus, management of dysphagia has important prognostic implications. It initially consists of recommendations for changes in food consistency. Patients are encouraged to take smaller, more frequent meals, thicken their liquids, and make sure solid foods are moist and soft. Liquids are taken through a straw using a chin-tuck maneuver. When these methods fail, a feeding gastrostomy tube can be introduced, inserted surgically, endoscopically or radiologically. The surgical approach requires general anesthesia and has been replaced with the endoscopic method, known as percutaneous endoscopic gastrostomy (PEG). PEG has been shown to improve survival in some series of patients with ALS, but not if inserted late in the disease (13). PEG improves nutritional status enhance QOL.

It is not entirely clear the timing and indication of PEG placement. This is clear when attempts at swallowing result in choking and gagging or when patients are no longer able to swallow at all, but weight loss, respiratory function, and meal times should be considered. It was reported that the risk of death in patients with ALS increases when body mass index (BMI) is less than 18 to 18.5 kg/m² and recommended PEG placement before that point (3), but other reports suggest PEG placement before body weight loss reaches 10%. The importance of considering respiratory function when making a PEG recommendation has been emphasized as a means of minimizing the risk of PEG placement, and because of a positive correlation between survival and the FVC at the time of PEG insertion (14). PEG is indicated in patients who have lost more than 10% of their body weight, have average meal times of more than 30 minutes, or have episodes of choking when trying to take food and fluids by mouth (3).

Many patients experience a decline in their FVC to fewer than 50% of the predicted value before agreeing to PEG. An alternative for such patients is percutaneous radiologic gastrostomy (PRG), with reduced or no sedation needed, so with a low risk of aspiration (14,15). PRG can be also a useful alternative when PEG placement is unsuccessful because of anatomy (14).

MANAGEMENT OF SECRETIONS

Sialorrhea with associated drooling is not the result of saliva overproduction, but related to an inability to adequately handle and swallow saliva. More, saliva production is lower than normal in patients with ALS (3). The traditional pharmacologic treatment of sialorrhea involves the use of anticholinergic agents, including amitriptyline, atropine, trihexyphenidyl, hyoscyamine, and transdermal scopolamine (where available). Common side effects include excessive drying of nasopharynx, constipation, urinary retention, confusion, and sedation, particularly in the elderly. Unfortunately, these agents may further thicken the mucous that accumulates deep in the throat.

When oral medications fail to control sialorrhea, botulinum toxin is an alternative treatment. A number of uncontrolled observational studies have found that botulinum toxin type A is safe and is beneficial at reducing refractory sialorrhea in some patients with ALS at doses ranging from 7.5 units to 20 units into each parotid gland (22). Submandibular gland injection should be considered if injection into the parotid glands alone is not beneficial. Radiation therapy is another option for treating sialorrhea. It has been shown to be effective and safe in patients with a variety of neurological diseases, including ALS, when directed at the parotid glands. Side effects are transient and include pain in the parotid area, dryness of the mouth, burning of the skin, sore throat, and nausea (3).

Thick mucous which the patient is unable to cough up or clear, is particularly bothersome and poses a risk of aspirations. It is the result of secretion of the glands with beta adrenergic receptors, and using of a beta blocker (propranolol, metoprolol) may be helpful. A mechanical cough-assist device (insufflation-exsufflation device) may provide symptomatic relief by increasing peak cough expiratory flow (3).

COMMUNICATION

Bulbar involvement in ALS is most commonly a combination of upper and lower motor neuron dysfunction, resulting in a mixed dysarthria with both spastic and flaccid components affecting muscles of the face, tongue, and throat. A hoarse quality to the voice, often combined with a decrease in speech volume, is common, and may be followed as disease progresses by complete loss of speech. Loss of the ability to communicate effectively can have devastating psychological and social consequences.

Other forms of communication may be substituted for speech. The speech language pathologist have to be involved, and strategies to maximize speech intelligibility are the first techniques used, followed by augmentative and alternative communication (AAC) (3). This implies writing, hand signals, head nodding, but electronic AAC devices are suitable for some individuals and must be adapted taking into account physical function, level of education, and comfort with technology (3).

PSEUDOBULBAR EMOTIONAL INSTABILITY (AFFECT)

Most treatment reports for this kind of emotional instability are small, non-controlled studies in patients with stroke, dementia, and multiple sclerosis, although there are some double-blind studies and some non-controlled studies involving patients with ALS (3). SSRI are used as initial treatment of pseudobulbar affect, although tricyclic antidepressants may be particularly useful when sialorrhea is bothersome or there are sleep disorders (3). The response of pseudobulbar affect to antidepressants is more rapid than that seen in depression, usually occurring in less than a week within 48-72 hours. Medications other than antidepressants have occasionally been reported to be effective, including levodopa and lithium (3).

PHYSICAL THERAPY AND EXERCISE

The overall goals of physical and occupational therapy should be maximized comfort and independence. An evaluation by a physical therapist early in the course of the disease is necessary. Initially, a straight cane or quad cane may be helpful, and ankle foot orthoses are used. However, a walker, manual wheelchair, or power chair may be most appropriate during the evolution. The progressive nature of ALS must be kept in mind to avoid large expenditures on equipment that will soon be rendered unusable by additional loss of function (3).

Exercise in ALS has not been widely studied, but studies in other slowly progressive neuromuscular disorders generally showed that moderate resistance exercise can be beneficial (23). In contrast, high-resistance exercise programs do not clearly offer advantages over moderate resistance training and may have some negative effects (23). Regular moderate-resistance exercise results in improvements in static force in some muscle groups and slows the deterioration in the ALS Functional Rating Scale and the Ashworth Spasticity Scale (23). Even

patients with respiratory insufficiency can benefit from modest exercise while wearing NIPPV devices (23). Animal models of ALS have not revealed harm in exercise (23).

SPASTICITY, CRAMPS, AND OTHER SOURCES OF PAIN

Pain is common in ALS, ranging from 23.9% to as high as 73% of patients. Pain may result from spasticity and cramping even in the early stages of ALS. There are few articles in the literature on treating spasticity in patients with ALS. A recent review identified only one technically acceptable randomized, controlled trial who found that individualized moderate-intensity endurance-type exercise for the trunk and limbs may help to reduce spasticity in motor neuron disease (3). For the treatment of nocturnal muscle cramps, stretching and massage may be helpful, and some reports showed that quinine sulphate may provide relief. Most commonly, stretching is used in combination with muscle relaxants: baclofen, tizanidine, dantrolene sodium, and diazepam may provide relief. Combinations may be beneficial because of different mechanisms of action and different side effect profiles. Intrathecal baclofen is a treatment option for intractable spasticity in some patients. Botulinum toxin injection can be directed toward specific muscle groups in an attempt to reduce pain or improve function (3). As mobility decreases, pain becomes more common, and relief may be provided by properly fitted cushions on chairs and bed, or the medication use: non-narcotic analgesics and antispasticity agents produce relief of pain in approximately 55% of patients. Narcotic analgesics are the next line of treatment and are very effective (good relief achieved in 74%), although they depress respiration, decrease airway protection, and suppress coughing (3).

DEPRESSION

Very interesting, the prevalence of depression in ALS patients largely varies, from 2% to 75%, but always associated with a poor QOL (24). An approach to treatment should include not only antidepressant medication, but also professional counseling and identification and management of correctable factors such as community supports (24).

It is very important to differentiate hopelessness from depression, in the spirit of some countries regulations who permit euthanasia. Hopelessness implies negative expectations about the future, and

predicts suicidal intents and suicide better than depression. Euthanasia is not permitted in Romania, but physicians treating individuals with ALS should be aware of the literature involving euthanasia and physician-assisted suicide. In a survey in Netherland, 20% of patients with ALS died as a result of euthanasia or physician-assisted suicide (3, 24). In a study of 100 patients with ALS in USA, 56% said they would consider assisted suicide. Very important, only 11% of the patients in this series were depressed. In this spirit, it is important to assess for hopelessness, which usually requires a non-pharmacologic approach.

SPIRITUAL AND RELIGIOUS FACTORS

Spiritual and religious factors have to be taken into account, since relationships have been identified between religiousness or spirituality and the attitude of patients with ALS toward the use of PEG and NIPPV. Although QOL may not be correlated with religiousness early in the course of ALS, a significant relationship develops over time (25, 26).

COGNITIVE CHANGES

Cognitive changes most commonly take the form of frontotemporal lobar degeneration (FTLD), particularly frontotemporal dementia (FTD). FTD is characterized by changes in personality and social conduct, particularly social disinhibition, distractibility, and loss of insight with relatively well-preserved memory. There is loss of executive functioning with deficits in attention, abstraction, planning, and problem solving and patients with ALS may demonstrate deficiencies in social judgment (27, 28).

The overlap between FTD and ALS is substantial. 14% of patients with FTD met criteria for definite ALS, and conversely, 52% of patients with ALS met criteria for probable or possible FTLD (29). Patients with bulbar ALS are overrepresented in the FTLD group (30). Probably in the future, brain metabolites studies will offer the possibility to detect changes earlier in the course of the disease, but this is not actual in clinical setting (37).

This has significant implications for management, because individuals with ALS and FTD will need simpler tools for communicating when speech is lost and have to be observed more closely to watch for impulsive behavior. FTD also has implications for end-of-life decisions regarding PEG, TMV, etc. (30)

OTHERS

In USA, *advance directives* are documents whose purpose is to assure that the provision or withdrawal of medical care is performed with a person's wishes in the event that person is unable to communicate those wishes. Advance directives can be general or disease-specific and include living will, durable powers of attorney for health care, and advance medical care directives (32). In Romania, family members are usually those who fulfill advance directives, but it has to be emphasized that, in the settings of an often lack of legislative rules or the lack of knowledge of the patient of this rules, sometimes family directives will prevail. Among patients with ALS on TMV who survive for more than 5 years, the chance of developing severe difficulty communicating or of completely losing the ability to communicate is high: 18.2% develop a totally locked-in state, whereas 33.1% develop a minimal communication state (32). As TMV will become in the future available in Romania, the need to specify wishes for discontinuation of TMV will be another problem to be faced by the physician.

In the future, the need for *specialized centers* for ALS management will probably generate such units. This implies a multidisciplinary team composed by neurologist, nurse, physical therapist, speech pathologist, nutritionist, social worker, pneumologist, gastroenterologist, and psychologist. The goals of such clinics are to provide optimal care and to serve as the nidus for clinical and basic ALS research. Comparing patients with ALS receiving care at a multidisciplinary clinic with those followed in a general neurology clinic, studies found median survival to be 7.5 months longer, or being 9.6 months for patients with bulbar ALS (32).

However, very recent data show that management of ALS by MDC does not always improve survival (35). Thus, in a setting characterized by low frequency of riluzole prescription and low frequency and late implementation of PEG and NIV (and Romania is the case), there is no additional benefit for patients attending MDC compared with general neurologist. On the other hand, it has to be emphasized that these results have no implication on a possible role of MDC on the quality of life of ALS patients (36). The conclusion that emerges is

that only using maximum of all the possibilities and items (medications, interventional, psychological) in management of ALS, we can obtain some result, and that the issues revised by used are not replaceable and alternative.

QOL of the caregiver is an important issue. QOL of caregivers is below that of the general population, even lower than for patients with ALS, and declined over time. QOL of the caregiver is important not only for that individual, but for the patient with ALS as well; there is high concordance between patient and caregiver distress (33).

The terminal phase of ALS is another problem to be faced, with difficult issues in a sometimes cynical society. Defining a "good death", an author emphasized: "dying persons should be aware of and at peace with their impending deaths; the dying should be surrounded by loved ones; death should occur at the end of a long and full life; the dying process should not be burdensome to others; death should be relatively pain- and distress-free" (34). Symptom management will also play a role in enhancing the quality of death. Pain and suffering at the end of life can be reduced by the use of narcotic analgesics, usually morphine for pain and dyspnea and benzodiazepines for restlessness and anxiety. A referral to hospice can optimize symptom control and increase the likelihood of a peaceful death. Of those patients dying at home in the United States and Canada, only approximately half to two thirds receive hospice services (3, 33). The earlier and more aggressive use of palliative treatments, in conjunction with earlier referral to hospice, would help to achieve a more peaceful terminal phase in the patient with ALS.

To conclude, a well-coordinating, multidisciplinary approach to care will provide ALS patients with the best possible QOL, while maintaining their dignity and making the burden on caregivers more manageable. It is emphasized the necessity to use all known levers of ALS therapy and management at their maximum possibilities, because they are not equivalent, but complementary. Even this apparently implies less "scientific" tasks to be considered by the neurologist and a stricter follow-up, the issues are important in management of ALS, until new medical therapies will influence more radically the course of the disease.

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