Doi: 10.11606/issn.2317-0190.v15i3a102947

REVIEW ARTICLE

Rehabilitation in Amyotrophic Lateral Sclerosis: literature review

Reabilitação na Esclerose Lateral Amiotrofica: revisão da literatura

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ABSTRACT

Amyotrophic Lateral Sclerosis is a motor neuron pathology that results in a high degree of impairment. There is a worldwide tendency to create standardization manuals regarding the approach of this population, mainly on the subject of rehabilitation and quality of life. We conducted a review of the published guidelines related to this issue in a strict, non-systematic way and based on this published material, created a proposal for an up-to-date, comprehensive and simple manual adapted to the Brazilian reality.

KEYWORDS

Amyotrophic Lateral Sclerosis, rehabilitation, review literature as topic

RESUMO

A Esclerose Lateral Amiotrófica é uma patologia do Neurônio Motor que traz um grande grau de incapacidade. Em todo o mundo existe uma tendência a elaborar manuais de uniformização na abordagem desta população, principalmente no que se refere à reabilitação e qualidade de vida. Levantamos os guidelines publicados para este fim, de maneira não sistemática estrita, e elaboramos a partir destes, uma proposta de manual adaptado a realidade brasileira, atualizado, abrangente e simples.

PALAVRAS-CHAVE

Esclerose Amiotrófica Lateral, reabilitação, literatura de revisão como assunto

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Manuscript received on May 26, 2008; accepted on July 18, 2008.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease is considered the disease with the most devastating characteristics. Its diagnosis is considered a fatal one and its research has been the object of study of countless researchers worldwide. In order to systematize the attention to this group of patients, several guidelines have been published in many countries, including in the rehabilitation area. Our objective is to conduct a non-systematized review of the literature dedicated to rehabilitation in ALS published in the last decade, as there is only one study in our country that describes a sample of patients from South America.[1]

The focus of these tools is to improve the quality of life and reduce the degree of dependence and disability of patients with ALS and, therefore, most of them were carried out in the rehabilitation area. Although the mean survival is 2 to 5 years, there are groups of patients that survive for more than a decade and thus, a long and careful assistance is predicted.

ALS is a motor neuron disease, which, due to its range, allows the study of all the other diseases in this group. The most prevalent form is known as the classic form and is characterized by presenting signs related to the lesion in the lower motor neuron (amyotrophy), upper motor neuron (spasticity) and bulb (dysarthria/dysphagia).

The incidence is quite variable per studied geographic region, with an apparently higher incidence in Caucasian individuals from America and Europe. International studies describe an incidence of 1 to 2 cases per 100,000 inhabitants. In Brazil, the incidence is of 1.5 cases per 100,000 inhabitants, with most of the cases being in the 8th decade of life.[2] Worldwide, the calculated prevalence is of 4 to 6 cases per 100,000 inhabitants. In Brazil, the incidence is of 1.5 cases per 100,000 inhabitants, totaling 2,500 new cases a year. The mean age at diagnosis is 62 years and the mean survival is 2 to 5 years, with differences observed in different age ranges. The correlation between the incidence and gender varies from 1.2 to 1.6, and it is always higher in the male sex and Caucasian individuals.[2]

To date, no pathogenic mechanism has been described for ALS. There is a degeneration of the motor neurons of the mesencephalus and medulla, with atrophy of the great pyramidal pathways in the primary motor cortex and pyramidal tract. There is an accumulation of glutamate in the neuron body that leads to its degeneration. A genetic mutation responsible for this degeneration has been described in the familial forms.[3]

Clinical Picture

The main initial complaint is muscular weakness, which, at the physical examination, shows to be amyotrophy, muscular strength decrease and myofasciculation. The muscular tonus can be high or reduced in the areas of intense amyotrophy according to the evolution of the disease, followed by the exacerbation or slowing down of deep reflexes. The bulb involvement is normally manifested as dysarthria (spastic) or dysphagia for liquids, presenting at the physical examination initially as fasciculation and tongue atrophy. Frequently, the onset of the muscular weakness is focal and tends to spread out symmetrically, but the sensibility and the sphincter functions are preserved.

Traditionally, the reviewed El Escorial diagnostic criteria are accepted, which are shown below: [4]

Chart 1
Diagnostic Criteria

Classic ALS Signs of de UMN and LMN in more than 3 regions
Clinically defined and laboratory-supported ALS Signs of UMN and/or LMN in one region and the patient carries a genetic mutation
Clinically probable ALS Signs of UMN and LMN in two regions with some sign of UMN rostral to the LMN
Clinically probable - laboratory-supported ALS Signs of UMN in one or more regions and LMN sigs defined by ENMG
Clinically possible ALS Signs of UMN and LMN in one region and signs of UMN in at least two regions or signs of UMN and LMN in two regions with the UMN rostral to the LMN

UMN - Upper motor neuron; LMN - lower motor neuron; ENMG - electroneuromyography

In the rehabilitation area, tools are used for the functional assessment that allow the classification and follow-up of functional losses[5,6] in the several involved areas. The ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Scale - revised), is one of the most often mentioned tools, due to its being simple to apply and interpret and it is being validated for our language, showing a high correlation with the traditionally used functional assessment tools7. Due to the prognosis associated to this disease, it is not usual to present to the patient the diagnosis that is yet to be defined. The diagnostic delay and the large number of mistakes have been the theme of several studies. The concern with the theme is so disseminated that an algorithm has been created (Figure 1) to allow other professionals, rather than neurologists, to suspect ALS.

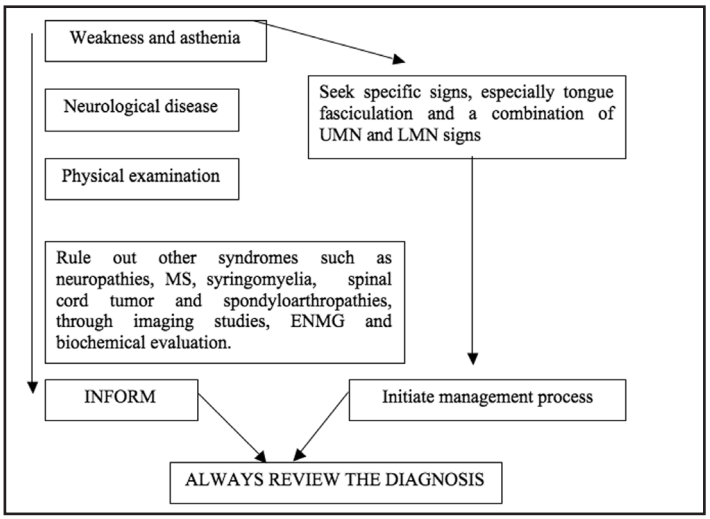

Figure 1
Diagnostic Algorithm.[8]

Since 1999, several guidelines have been published in the USA, Europe and Asia, where groups of researchers have established a consensus of what would be a "good practice" regarding the management of a patient with ALS, as in most cases there is no type I and type II evidence (double-blind randomized studies). These guidelines deal with essential points of the patients' follow-up and describe, whenever possible, the level of evidence of the procedure. We will discuss the items highlighted in the international tools, mentioning, whenever possible, the existing level of evidence. In most, the recommendations are based only on the consensus of "good practice".

Diagnosis

Although the diagnosis of a generalized picture is considered easy, one can observe a delay of 13 to 18 months between symptom onset and diagnosis confirmation. This can be attributed to the fact that the patient presents the symptoms gradually, but, additionally, one can observe a large number of ALS patients that are initially treated based on a wrong diagnosis, notably spondyloarthropathies. Although there is no etiologic treatment, the neuroprotective therapy must be started as soon as possible, allowing the deceleration of the neuronal loss rate.

Recommendations regarding the diagnosis:

1. It must be carried out as soon as possible; the suspected cases must be promptly referred to an experienced neurologist.
2. All clinical and complementary tests must be performed (Chart 2).
3. Some cases require specific tests.
4. The tests must be repeated if the diagnosis is not confirmed after the first series of tests.
5. It is advisable to review the diagnosis if the picture does not progress or the patient presents atypical forms of the disease.

Informing the patient

The neurologist is expected to give the diagnosis to the patient, but it is not rare that the latter will arrive at the rehabilitation center totally unaware of his/her physical condition. The following were considered good clinical practice items, although cultural adaptations are necessary:

1. The news must be given by a doctor that has had a longer contact with the patient.
2. The doctor must initiate the visit by asking what the patient really knows about it.
3. Respecting his or her social-cultural background, the patient must choose between receiving the diagnosis him or herself or through a family member.
4. The doctor must give the diagnosis and gradually explain its implications, always asking if the patient has understood what has been said.
5. The diagnosis must be given personally, never by phone or e-mail. Set aside 45 to 60 minutes to do it.
6. Supply instructional material, web addresses and association phone numbers, everything that is available in the region.
7. Promise your patient that he/she and his/her family will be

Chart 2
Complementary Tests.

ASSESSMENT	TEST	EVIDENCE	RECOMMENDED	ADDITIONAL
SANGUE	VHS	IV	X	
	PCR	IV	X	
	WHOLE BLOOD COUNT	IV	X	
	TGO, TGP, LDH	IV	X	
	TSH, T3, T4	IV	X	
	VIT. B12, FOLATE	IV	X	
	PROTEIN ELECTROPHORESIS	IV	X	
	IMMUNOGLOBIN ELECTROPHORESIS	IV	X	
	CPK	IV	X	
	CREATININE	IV	X	
	ELECTROLYTES	IV	X	
	GLUCOSE	IV	X	
	ANGIOTENSIN-CONVERTING ENZYME	IV	X	
	LACTATE	IV	X	
	HEXOXYDASE A AND B	IV	X	
	ANTI-GANGLISIDE GM-1	IV	X	
	ANTI-DNA	IV	X	
	ANTI-ACHR, ANTI-MUSK	IV	X	
	SEROLOGY (BORRELIA, VIRUS)	IV	X	
CSF	CELLULARITY	IV		X
	CYTOPATHOLOGY	IV		X
	TOTAL PROTEIN CONCENTRATION	IV		X
	GLUCOSE, LACTATE	IV		X
	PROTEIN ELECTROPHORESIS	IV		X
	SEROLOGY (BORRELIA, VIRUS)	IV		X
	ANTI-GANGLIOSIDE	IV		X
URINE	CADMIUM	IV		X
	LEAD (24 HRS)	IV		X
	MERCURY	IV		X
	MANGANESE	IV		X
	IMMUNOELECTROPHORESIS	IV		X
NEUROPHYSIOLOGY	ENMG	IV	X	
	NERVOUS CONDUCTION VELOCITY	III	X	
	EVOKED MOTOR POTENTIAL	IV		X
RADIOLOGY	MAGNETIC RESONANCE IMAGING	IV	X	
	CHEST X-RAY	IV	X	
	MAMMOGRAPHY	IV		X
BIOPSY	MUSCLE	III		X
	NERVE	IV		X
	BONE MARROW	IV		X
	LYMPH NODE	IV		X

followed throughout all the phases of the disease. Set up a new visit between 2 and 4 weeks later.
8. Avoid: a) minimizing the severity of the diagnosis by omitting data; b) not supplying enough material; c) taking away hope and help. Do not forget to turn off mobile phones and pagers and put up a "Do not disturb" sign.

Multidisciplinary care

1. It must be available for all patients with ALS, as the care provided neuromuscular disease clinics improve survival.[9]
2. The following specialist must be promptly available for the neuromuscular disease team: neurologist, pneumologist, gastroenterologist, rehabilitation doctor, social worker, occupational therapist, speech therapist, physical therapist, nutritionist, specialized nurse and dentist.
3. Clinical consultation must be scheduled every 2-3 months or more frequently, if necessary. This time span must be shorter in the first semester after the diagnosis and at the late stages of the disease. Patients with the slow progression form can be seen twice a year.
4. It is important for the support team to keep in touch with the patient and family members between visits (telephone, letter, e-mail).
5. Ideally, externally, the patient can be followed by a single neurologist in contact with the general practitioner.
6. The channels of communication and coordination must be effective between the hospital that shelters the neuromotor disease clinic, the primary care teams, the palliative care team and the community services.

Treatment with neuroprotectors

To date, only riluzole has presented evidence of changing ALS evolution.10 The drug is a glutamate release antagonist and, when used at a dose f 100 mg/day at the initial phase of the disease, it increases survival between 6 and 20 months. The adverse effects are widely known (gastrointestinal effects, anorexia, asthenia, paresthesia, dizziness, increase in liver enzymes),11 and to date, there is no consensus regarding the optimum time to withdraw the therapy, as it has shown to be useless at the later stages.

1. All patients must receive 50 mg of riluzole twice a day (class 1 A evidence)
2. The patients undergoing treatment must be regularly monitored regarding the safety (class 1 A evidence)
3. The treatment must be initiated as early as possible, taking into account the risks and expectations (Class 1 A). These potential risks and benefits must be discussed with the patients and their families.
4. The therapy with riluzole must be considered in patients with primary lateral sclerosis or progressive spinal atrophy, with first-degree relatives with ALS.
5. Patients with sporadic primary lateral sclerosis (PLS) or progressive spinal amyotrophy (PSA) must not undergo treatment with riluzole.
6. Regardless of the family history, all patients with a neuron motor disease with a genetic mutation in the Superoxide Dismutase 1 (SOD1) gene must initiate treatment with riluzole.
7. To date there is no favorable evidence for the treatment with vitamins, testosterone, anti-oxidants such as the Q-10 co-enzyme, Ginkgo biloba, intravenous therapy with immunoglobulins, interferon, cyclosporine, copaxone, ceftriaxone, minocycline, vascular endothelial growth factor (VEGF), or stem cells

Symptomatic treatment

Sialorrhea

The increase in the production of or difficulty to eliminate saliva brings great social limitations to the patient and must be treated whenever there is a complaint.

1. Treat the Sialorrhea with oral or transdermal hyoscine or atropine drops, Glycopyrrolate or amitriptilin.[12]
2. Supply home aspirator.
3. Botulinum toxin injections in the parotid glands can be used,13 but to date, there not enough evidence on the safety and long-term effects of its use, and thus, it remains classified as experimental.
4. The irradiation of the salivary glands can be considered, when the clinical treatment fails.
5. The surgical intervention is not recommended.

Bronchial secretions

The constant flow of secretion, in addition to the increase in its consistency due to its drying up, makes this a crucial point in quality of life.[14]

1. Teach the patient and caregivers the assisted respiratory movement techniques, using the manually assisted coughing (MAC); this can also be done by the physical therapist.
2. Supply a home aspirator and humidifier.
3. Consider the use of 200-400 mg of N-acetylcysteine, 3 times a day. If these doses are insufficient, try a saline solution nebulizer with a beta-receptor antagonist and/or cholinergic and/or mucolytic bronchodilator and/or combined furosemide.
4. The use of a mechanical insufflator/exsufflator (AMBU) can be useful, mainly during respiratory infections.
5. The cricopharyngeus muscle myotomy can be indicated in rare cases of cricopharyngeus spasm and continuous secretion retention.

Pseudobulbar lability

Pseudobulbar symptoms such as pathological screaming, crying and cackling can occur in 50% of patients with ALS, even without

bulbar motor signs.[15]

1. Inform the patient that this picture is caused by a brain lesion, and not by mood alterations.
2. Only emotional symptoms that bring problems must be treated when necessary; the use of anti-depressive medication such as amitriptyline, fluvoxamine or citalopram, is sufficient.
3. A combination of quinidine and dextromethorphan showed to be effective in a Class IV study.[16] Data on tolerability and long-term effects are still lacking.

Muscular Cramps

Sometimes the muscular cramp complaint precedes the others and it is more important at night. A Class I study on muscular cramps in non-ALS patients receiving quinine and vitamin E showed that the first can be effective in symptom reduction.[17]

1. Treat muscular cramps in ALS with physical therapy and/or physical exercises and/or hydrotherapy.
2. If necessary, use quinine.
3. Magnesium, carbamazepine, phenytoin, verapamil and gabapentin are the alternatives.

Spasticity

pasticity is very disabling in ALS and, although there are no controlled studies with an ALS population, the results obtained regarding spasticity in other clinical conditions such as spinal cord injury and cerebral palsy can be extrapolated to ALS. Physical therapy and oral baclofen have been used in consensus, but there are also studies with gabapentin, tizanidine, diazepam, dantrolene, memantine and botulinic toxin.

1. When the spasticity is intense, the physical therapy must be carried out regularly.
2. Hydrotherapy in a warm pool at 32-34o or cryotherapy can be used.
3. Anti-spastic drugs such as baclofen and tizanidine must be tried.

Depression, anxiety and insomnia

They can occur at any time of the pathology evolution, but they get worse at the respiratory failure onset.

1. Treat depression in ALS with amitriptyline or selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertralin)
2. Treat insomnia with amitriptyline or adequate hypnotic drugs such as zolpidem.
3. Treat anxiety with bupropione or benzodiazepine 2 to 3 times a day.

Pain

Neuropathic pain can occur in ALS, mainly in some familial forms of the disease. The use of opioids has been approved for this class of patients and the treatment follows the specific protocol. Initiate treatment with acetaminophen; add mild opioids such as tramadol and, if necessary, add more potent opioids such as morphine.[18] Constipation can be a limiting factor.

Deep Venous Thrombosis (DVT)

The lack of movement in the lower limbs increases the risk of DVT. General measures, such as upper limb elevation, physical therapy and the use of support hose are recommended. The prophylactic use of anticoagulants is not recommended.

Genetic analysis and counseling

The number of familial ALS cases in the different populations reaches 10% of the total number of cases. To date, four groups of genes have been identified as the cause of ALS: Superoxide Dismutase 1 (SOD1) gene; VAPB (vesicle traffickling protein B), SETX (senotoxin gene) and ALSIN (gene related to the recessive forms of ALS), but only the first one is routinely screened and 116 mutations have been described for it, with at least 4 different types of inheritance. In ALS familial cases, up to 23% of the cases present SOD1 mutations, whereas in the sporadic forms, they are present in only 2-7% of the cases.

1. The clinical analysis of SOD1 must be carried out only in cases with a family history or those in whom the sporadic form presents a phenotype that is typical of D90A mutation.
2. This analysis must not be carried out in sporadic cases with the typical ALS phenotype.
3. Before the blood is collected for analysis, the patient must receive counseling, with time given for conclusion. The analysis cannot be carried out without consent.
4. The pre-symptomatic genetic analysis can only be carried out in adults, first-degree relatives of the patients with a known mutation of SOD1. This analysis is voluntary.
5. The results of the DNA analysis in patients and relatives carried out as research must not be disclosed to the non-affected relative and must not be part of the medical file.

Non-invasive Ventilation (NIV)

Respiratory failure in ALS is mainly due to the loss of strength in the respiratory muscles, but it becomes worse due to the accumulation of secretions and by bronchoaspiration. Normally, the non-invasive ventilation is preferable and it is initiated before a picture of respiratory failure is established, but sometimes it is not possible in patients with significant atrophy of the facial musculature. The signs of hypoventilation must be part of the routine assessment of the patient.

1. Signs and symptoms of respiratory failure (including nocturnal hypoventilation) must be verified at each visit.
2. The vital capacity (VC) is the most practical available parameter to follow and whenever possible, it must be checked in the standing, sitting and lying positions.
3. The sniff nasal pressure (SNP) can be used, mainly in those individuals with bulbar innervations that is so impaired that it does not allow VC measurement.
4. The nocturnal oxymetry (measured at home) can be used to monitor the symptoms of nocturnal hypoventilation.
5. The signs and symptoms of respiratory failure must allow a discussion with the patients and caregivers on the available therapeutic options and their consequences. The early discussion allows a pondered decision to be made. The patient must be informed about the temporary characteristic of the non-invasive ventilation (which aims at improving quality of life and not prolonging it, as the invasive ventilation does). This therapy must be adapted to the changes in the clinical picture and that is accomplished throughout life.
6. The NIV must be considered before the IV, in the presence of respiratory failure symptoms.
7. The tracheotomy can increase survival by many months and also the quality of life. The procedure has a big impact on the level of care given to the patient and must be considered only after a methodical discussion with the persons involved in it.
8. The emergency tracheotomy must be avoided at all costs through discussions about the terminal phase of the disease, palliative care and anticipative measures.
9. Isolated oxygen therapy must be avoided as it increases the retention of CO2 and dry-mouth condition.
10. Clinical treatment of the dyspnea crises:
a. Short crises: relive anxiety and administer lorazepam (0.25-0.5 mg sublingual).
b. Longer crises (>30 minutes) - use morphine
11. Clinical treatment for chronic dyspnea: start with oral morphine, 0.25 mg every 4 - 6 hours. If the clinical picture worsens, start subcutaneous or intravenous administration (0.5 mg/hour) and titer

Chart 3
Non-invasive ventilation.

1- Symptoms related respiratory muscle weakness (at least one)
dyspnea
orthopnea
sleep loss without pain
morning headache
loss of concentration
loss of appetite
excessive daytime sleepiness
2- Signs of respiratory muscle weakness
FVC<80 or SNP<40 cm of H2O
3- evidence of both
Significant nocturnal desaturation by oximetry or morning pCO2 >6.5 Kpa

Enteral Nutrition

1. Bulbar dysfunction and nutritional profile, at least weight, must be reviewed at each visit.
2. The patient and spouse must be referred to a nutritionist as soon as the dysphagia appears. The speech therapist can also help with deglutition techniques.
3. The moment for the gastrostomy is based on individuals factors that take into account the bulbar symptoms, nutritional status (weight loss > 10%), respiratory symptoms and the patient's general status. However, the early procedure is the most recommended.
4. When the endoscopic gastrostomy (PEG) is indicated, the patient and caregivers must be formally informed of the risks and benefits of the procedure, that the patient will be capable of receiving food orally as long as possible and that delaying the procedure to a later phase can bring additional risks.
5. The radiological gastrostomy (PRG) is an alternative to the PEG when the risk is too high.
6. Relatively large-diameter tubes must be used (18-22) to prevent obstruction.
7. The antibiotic therapy carried out together with procedure reduces the risk of infection.
8. The use of NG tube for feeding must be restricted to a short-term period or when the indicated procedures (PEG/PRG) are not possible.

Communication

1. A routine assessment (every 3-6 months) by an experienced speech therapist is recommended.
2. Alternative means of communication must be adapted, whenever necessary (from the communication table to computerized vocalizers).

Palliative and terminal care

1. Whenever possible, information must be provided with a palliative care team at the early stages of the disease.
2. Initiate discussions about the end of life as soon as the patient manifests interest on it.
3. Discuss the options of respiratory support if the patient presents dyspnea, other signs of hypoventilation or VC<50%.
4. Inform the patients on the legislation about anticipation measures and tutoring assignment.
5. Re-discuss the patient's preferences about life support measures every 6 months.
6. Initiate early referral to the hospital admission unit along with the guidance for the terminal phase.
7. Attention to the spiritual support of the family and advice to the members of spiritual communities to give support to the families.
8. For the treatment of dyspnea and pain, use opioids alone or with benzodiazepines if the anxiety is severe.

9. For the confusion and insomnia resulting from hypercapnia, use mild neuroleptics (chlorpromazine 12.5 mg every 4-12 hrs by oral or parenteral administration)
10. Oxygen therapy is restricted to proven cases of hypoxia.

CONCLUSION

These directives must guide the establishment of Brazilian directives of care to the population with ALS. However, the need for clinical research in the area is observed worldwide and the standardization of the data regarding this population would allow the identification of these requirements. Therefore, it would be extremely appropriate to establish groups that could construct the standardized tools, allowing the exchange of information between the national and international research groups.

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