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AMYOTROPHIC LATERAL SCLEROSIS: AN UPDATE ON CLINIC AND REHABILITATION

Marco Orsini*[1], Mauricio Sant'Anna Junior[2], Acary Bulle de Oliveira[3], Adriana Leico Oda[3], Cristina Salvioni[3], Jacqueline Fernandes do Nascimento[4], Antônio Marcos da Silva Catharino[4], Nicolle dos Santos Moraes Nunes[4], Valéria Camargo Silveira[4], Carlos Eduardo Cardoso[5], Marcos RG de Freitas[1] and [6]Carlos Henrique Melo Reis

[1]PhD Federal University of Rio de Janeiro; [2]Federal Institute of Rio de Janeiro – IFRJ –Physiotherapy School; [3]Federal University of São Paulo – Medical School; [4]Iguaçu University – Medical School; [5]Vassouras University –Rio de Janeiro – Brazil, [6]Professor - Unig University, Brazil

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Corresponding author:** ***Marco Orsini

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a inexorable and degenerative disease that affects the neurons of the anterior horn of the spinal cord, brainstem and motor cortex. The main initial complaint is muscle weakness, with amyotrophy, reduced muscle strength, and myofasciculations revealed by physical exam. It is worth mentioning that when the early signs of paresis are noticed, commonly as loss of dexterity in the hands or unexplained tripping, the patients have already lost about 80% of the motor neurons in this region. This principle is valid for the muscles of the upper and lower limbs, for breathing and swallowing. The possibility of inducing an injury by "overtraining", that may cause intense metabolic demand on already ailing motor units is the primary concern of the professionals that deal with motor rehabilitation. The exercises (type, frequency and intensity) must respect the peculiarities of patients, by performing frequent revaluations.

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INTRODUCTION

Since the initial description of Amyotrophic Lateral Sclerosis by Jean Martin Charcot, theories and shortcuts in the pathophysiological framework have signaled us to a mechanism of neuronal apoptosis that permeates the depletion of upper and lower motor neurons[1]. Previously considered a progressive, degenerative and inexorable disease of the neurons of the anterior tip and of the pyramidal bundle in varying degrees, a "superficiality" in this title is already notorious[1]. The technological advances, researchers' relentless search for biomarkers, stem cell therapy and possible disease-modifying drugs, makes a light emerge at the end of the tunnel; the one that was once blackened and clouded by hopelessness. The (ALS) that we leafed through in the oldest books, no less important, was a death sentence. Obviously, it is a cruel, inexorable disease, but it does not present itself equally among all affected patients; so there is a paradigm shift.

The ALS can already be considered a multisystem disease; not only because of the new discoveries that circumvent motor manifestations, such as, for example, the conditions associated with dementia, neuropathies and disorders of the autonomic nervous system[2,3]. Let us not forget the genetic codes that signal a new form of evolution of hereditary cases; a "gift" of molecular biology[4]. There is sadness and nostalgia when the diagnosis certain, however an overwhelming science and readiness to unravel complex systems. We are still tiny doctors for this complex that culminates in the death of neurons; however we are brave; we hold our patients tooth and nail – with scientific content, nobility in treating, cordiality and love. We are already able to understand the small steps of this "chess game" as we seek to extend longevity, improve the quality of life of patients, conduct clinical studies and compile population records[5]. We will certainly look in detail for triggers for this rapid disorder that involves calcium influx, mitochondrial damage, glutamate excitotoxicity – in

addition to epigenetic triggers and innate DNA errors[6,7,8]. In cases of hereditary ALS, advances in molecular biology have been rampant. Expanded genetic panels opened up a multifaceted view of variants and markers. In patients with ALS/FTD (Frontotemporal Dementia), for example, the neuroinflammation mechanism characterized by innate immune responses of glial cells that "dwell" in the tissue is uniformly present in advanced-stage disease[9,10]. Neuroinflammation, initially observed in animal models, begins in the early stages of disease pathogenesis[11]. Added to these findings are changes in populations of circulating immune cells and cytokines found in patients with ALS/FTD. Increased levels of pro-inflammatory IL-6, IL-8 and nitrite and significantly reduced levels of endogenous GSH antioxidant can identify these humoral constituents as systemic biomarkers in ALS[11,12]. However, systemic alterations in the levels of IL-2, IL-5 and IL-6 may indicate adaptive immune system-dependent responses at specific stages of the disease. In summary, ALS has broad hypothetical genetic and environmental causes as well as phenotypic variability[9-12]. Damage to the endoplasmic reticulum (ER) in sporadic forms of ALS has been documented based on experimental models[13]. The spinal cord of these patients shows signs of stress in the cell communication system, from the cytoplasm to the karyothek[11]. Among the potential causes of proteasomal involvement (ER), some factors are relevant: increased immunoreactivity to ubiquitin and lipo-oxidative or glyco-oxidative proteins, when compared to control groups, as evidenced by mass spectroscopy and immunological methods[13,14]. We took the opportunity to praise, already in the introduction, the support offered by all professionals of the interdisciplinary team regarding daily care, palliative care and, above all, the extension of the functionality of these patients. Without them, we would be, like doctors, infinitely smaller in everything. In all aspects; in all spheres. We recognize that ALS does not only affect the individual with the disease. It has a profound impact on the family and especially on those closest to the patient who often become "hidden" caregivers and patients[15]. We have learned that those who develop ALS should not walk alone. In fact none of us should walk or fly in solitude.

Pathophysiology

Before we dissect what exists in the pathophysiological framework in Amyotrophic Lateral Sclerosis, a pause must be provided for a possible villain. Oxidative stress is considered a metabolic disorder in which unstable molecules, too (reactive species), promote cell damage due to oxidation-reduction reactions with organic molecules such as phospholipids, proteins and DNA[16]. The outcome is the loss of cellular function and dysfunctions in organ systems. Due to the potential toxicity of these molecules, endogenous and exogenous protection mechanisms, represented by antioxidant agents, are recruited to neutralize these compounds and slow down cellular injury. When the production of these species exceeds the body's antioxidant capacity, cell metabolism goes into oxidative stress and collapse[16,17]. Much is lost in this process, especially the synchrony in the functioning of upper and lower motor neurons – they go into apoptosis. Theories that can cause ALS are: genetics, glutamate excitotoxicity, trophic factors, cell biology, mitochondrial damage, epigenetic factors, neuroinflammation, autoimmunity, retrograde axoplasmic flow damage, among others[16-18]. Epidemiological studies suggest that patients with sporadic ALS may have been exposed to environmental toxins[19]. Exposure to tobacco, intense physical activity, work with heavy metals, agricultural chemicals, radiation/electromagnetic fields, and certain types of diet (high levels of glutamate) have been speculated to be associated with the risk of developing ALS[19]. The CNS and the peripheral nervous system (PNS) are made up, in addition to nerve cells (neurons), by supporting cells, such as astrocytes and microglia, among others[17]. These have the function of providing physical, trophic and immune support to the surrounding nerve cells[17]. An imbalance in their functions can leave neurons vulnerable and cause neuronal damage[17]. Immunological dysfunctions together with neurovascular alterations are other probable mechanisms of neuronal damage that can increase the progression and incidence of the disease[17-19]. It was also found that viral infections also influence the degeneration of motor neurons[19].

Epidemiology: The incidence is around 1-2 cases per 100,000 inhabitants and the prevalence is 3-8 cases per 100,000 inhabitants[20]. ALS usually affects people between 40 and 60 years of age, but it can also develop in younger or older people[7,8]. In 90% of ALS cases, the disease happens sporadically, and about 10% of ALS cases are familial[10]. In some countries and regions these values fluctuate, for example, in the Islands of Guam; subject that will not be explored in this chapter. More generally, the ALS study shows that males are more compromised than females in a 2:1 ratio and whites are more affected than blacks, with an average age of onset at 57 years old. , a little earlier in men[20]. About 6% of affected cases are people under 40 years of age[20]. The sporadic form is the most common form of this disease, accounting for about 90% of total cases worldwide[10,12].

Genetic Forms of als: Despite the marked heterogeneity of familial ALS, it can be said that most cases are related to genes encoding proteins C9orf72, SOD1, fused in sarcoma (FUS), TARDBP and UBQLN2[4]. It is known that up to 32% of familial cases and up to 11% of sporadic cases still do not have a definitive genetic diagnosis of ALS[9]. Most mutations are transmitted by autosomal dominant inheritance[9]. Currently, a large number of mutations are involved in neuronal death mechanisms[9]. In addition to the mutation that interferes with the function of the SOD1 protein, others have been found that interfere with the coding and formation of other protein[4,5s]. Mutations in the genes encoding TARDBP-43, FUS/TLS, optineurin (OPTN), valosin-containing protein (VCP) and UBQLN2, for example, lead to specific alterations[7]. The presence of protein aggregates at sites of neuronal destruction can be considered a possible mechanism involved in neuronal death[7,9].

Clinical Condition: The clinical picture of patients with Amyotrophic Lateral Sclerosis is directly related to the depletion of upper|lower motor neurons in spinal cord, oblong, and pyramidal bundle segments[2,3]. Signs of lower motor neuron injuries are: disuse atrophy, areflexia, fasciculations and paresis; on the other hand, the involvement of upper motor neurons is marked by: spasticity, hyperreflexia, clonus and cutaneous-plantar extension (Babinski's sign)[2]. Commonly, patients start the disease with impairment of muscle strength in the flexor muscles of the fingers (difficulty in grasping objects), with foot slipping (unexplained tripping) or with changes in swallowing (dysphagia) or breathing (dyspnea)[2]. The initial symptoms are asymmetric and develop progressively and generally, with disuse as the main marker of the disease[3]. In summary: the signs and symptoms of the upper motor neuron (UMN) occur due to injuries to the corticospinal and corticobulbar tracts, on the other hand, those of the lower motor neuron (LMN) occur due to injury to the anterior tip of the spinal cord or cranial nuclei (brainstem)[2,3]. In classic ALS, there is rarely peripheral nerve damage; although cases have already been described[2]. The same occurs with cognitive function, as it is known that about 10% of cases have some degree of dementia syndrome and/or behavioral changes[2]. We emphasize that in pseudobulbar palsy there is emotional lability, hyperreactivity of the masseterine reflex, dysphagia (difficulties in swallowing, more for liquids) and dysarthria (difficulties in articulating words – nasal voice)[3]. Bulbar palsy is associated with paralysis of the palate, oropharynx, in addition to tongue fasciculations[2]. Sialorrhea is also frequent in these cases; specific interventions are common due to the risk of bronchoaspiration[9]. Fasciculations are usually visible in more than one muscle group and sometimes in the muscles of the tongue[2,3]. We must distinguish the typical fasciculations of ALS with the cramp-fasciculation syndrome and Benign Fasciculations[15]. The tendon reflexes can be increased or decreased, depending on the preferential involvement of the anterior tip of the spinal cord or the pyramidal pathway. Weakness of the cervical and thoracic segments of the paraspinal muscles (muscles that start and end in the spine) leads to "Drop Head Syndrome" – many patients need to wear a cervical collar. Pulmonary complications often end the lives of these patients[20,21]. We will not talk about survival in ALS, mainly due to the broad spectrum of the disease associated with the individuality of patients[2]. We keep in mind that it is a neurological disease, progressive and inexorable.

Cramps are associated with muscle denervation and pain from contractures and/or myo-articular problems resulting from confinement to a wheelchair or bed[9]. The decision to perform tracheostomy and/or gastrostomy is a delicate matter to be addressed, as patients are fully aware of participating directly in this process.

ALS clinical and laboratory diagnosis: The diagnosis of ALS is based on the patient's clinical history, electrophysiological studies, neuroimaging studies, genetic studies and appropriate laboratory studies[2]. It is noteworthy that an unarmed neurological examination is capable of providing the diagnosis in 80% of cases. In these patients, an association between damage to the anterior tip of the spinal cord (atrophy, areflexia, fasciculations, paresis) and to the pyramidal bundle (hyperreflexia, spasticity, clonus and extended plantar cutaneous) is enough[22]. We cannot forget MRI exams of the cervical spine and skull, electroneuromyography, hemogram and, in a few cases, cerebrospinal fluid[23]. As the purpose of the chapter is to provide a general notion, I will not expose differential diagnoses, even if they are scarce.The Awaji or EL Escorial Revised criteria. Experts have demonstrated how the interpretation of the clinically probable laboratory supported (PRLS) category in the updated Awaji criteria can affect the diagnosis rates of amyotrophic lateral sclerosis (ALS)[24]. However, several studies have reported that the Awaji criteria are less sensitive than the R-EEC criteria due to exclusion from the clinically probable-laboratory supported (PRLS) category, which requires upper motor neuron (UMN) signals in a region[6]. We consider the choice of criteria to be a decision of the neurologist. To date, there is no test that is a definitive marker of ALS. Several tests were presented with a good potential diagnostic or follow-up marker of the disease, also allowing to distinguish predominant involvement of UMN or LMN: • Magnetic Resonance with MTC / SET1 technique: it is useful to demonstrate involvement of the cortical tract spinal cord when patients have UMN involvement[2,3,6].Magnetic Resonance Imaging with MTC / SET1 technique: is useful for demonstrating spinal cortical tract involvement when patients have UMN involvement[2]. • Magnetic Resonance with spectroscopy: a decrease in the NAA / Cr ratio is indicative of UMN impairment; • Diffusion tensorimaging (DTI): which analyzes the presence of diffusion anisotropy, resulting from the preference of water molecules to diffuse along axons instead of crossing them, allows early diagnosis of impairment of the axon in the CNS[2]. This technique also allows for the study of the entire cortical-spinal tract, associating volumetric analysis of this tract, allowing not only topographic diagnosis, but also longitudinal study in clinical trials[3-6].

DISEASE MODIFYING DRUGS, VALIDATED IN CLINICAL AND SYMPTOMATIC STUDIES

Disease Modifiers

Riluzol: Although we have not been successful in using this medication, it is part of the group of drugs that cause a certain "inhibition" of excitotoxicity by glutamate[25]. As a beneficial effect, they have a slight slowdown in the evolution of the disease (a few months)[25,26]. Prolonging survival is a generic term and not necessarily linked to a better quality of life[27]. To date, this drug remains the only registered drug that has been proven to be effective in the treatment of ALS[25-27]. In this context, a drug synthesized by the SANOFI Laboratory (RILOZOLE) was produced, approved by the FDA on December 12nd, 1995 and in Europe in 1997, as ALS therapy. It is used in a dosage of 50 mg for 12-12 hours[25-27].

Edaravone: Considered a potent inhibitor of free radicals, it had been registered in Japan and the USA as a drug for the treatment of ALS[26]. Used, in the form of infusion (intravenous), 14 days a month, with a break of another 14 days, for 24 consecutive weeks, a "possible stabilization" of motor and ventilation in the functional scales in treated patients was verified in a double-blind randomized study had early stage disease (Milan stage 1/Japanese scale) and preserved initial ventilatory capacity (CVF or VEF1 >80%) and no bulbar involvement[26,27].

Non-Modifiers

Methylcobalamin: We commonly use it intra-muscularly (gluteal region), twice a week with a dosage of 50mg per application. Currently, oral vitamin B12 replacement has also been considered. It acts to inhibit neuronal degeneration by reducing homocysteine levels, whose accumulation has already been correlated with neuronal apoptosis in Amyotrophic Lateral Sclerosis. Preclinical studies revealed that the use of methylcobalamin protects the neurotoxicity of glutamate, in addition to promoting nerve regeneration[28].

Tudca: The justification for such use, usually 250mg or 500mg twice a day, stems from the demonstration of antioxidants, anti-apoptotic and neuroprotective properties of TUDCA in the central nervous system (CNS), in vitro and in vivo models[28,29]. TUDCA inhibits mitochondrial-associated apoptosis through many pathways: 1) it inhibits Mitochondrial Permeability Transfer (MPT) and cytochrome C release, 2) it inhibits mitochondrial membrane depolarization, and 3) it antagonizes Bax translocation of activation of mitochondria and caspases in hepatocytes and the central nervous system[28-31].

Tudca + Sodium Phenylbutyrate: A clinical trial, seeking to associate the use of such compounds for patients with ALS, was formulated and named AMX0035. These are oral medications composed of (sodium phenylbutyrate and taurursodiol), with different cellular targets than the previous ones, but which also reduce the death of motor neurons[29,30].

Naltrexone: Naltrexone is classified as a long-acting, competing antagonist of opioid receptors (Mu, delta and Kappa)[28,29]. It had been approved by the FDA for the treatment of alcohol and opioid addicts[28,29]. Some neurologists use doses of 4.5mg in a single dose or even every 12 hours. Others with larger doses. Both approaches without results based on science and method. In vitro studies have already revealed that opioid drugs were capable, for example, of inhibiting the activity of non-activated macrophages and inhibiting the chemotaxis of neutrophils and monocytes to complement-derived factors[29]. There is a consensus that ALS is a multifactorial degenerative disorder, with autoimmune components under investigation[29].

L-Serine: The amino acid called L-serine has emerged as a possible adjuvant in the treatment of ALS[28,29]. The first study, a phase 1 clinical trial, was conducted to assess the safety of 0.5mg, 2.5mg, 7.5mg and 15g twice-daily doses[29]. Patients who received L-serine (experimental group) were compared to patients who received a placebo in 5 other ALS clinical trials[28]. Preliminary results showed that L-serine was safe at all doses, although some patients mainly reported abdominal pain and discomfort[29].

Neurotrophic Factors: The use of neurotrophic factors, especially the ciliaryneurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF1) and glial cell line-derived neurotrophic factor (GDNF) bring up the word hope[32]. These have allowed, especially in clinical trials (animal models), a neurotrophic and neuroprotective activity, minimizing the degree of amyotrophy and paresis[29,32]. These results justify the most recent therapeutic trials with neurotrophins in ALS. We can mention: CNTF (ciliaryneurotrophicfactor); BDNF (brain-derived neurotrophicfactor); IGF-1(insulin-like growth factor-1); GDNF (glial derived neurotrophicfactor); GM604[32].

Symptomatic Treatment: In the absence of curative treatment or new disease-modifying drugs, symptomatic therapy and supportive care are of fundamental importance in the management of signs|symptoms and prevention of related episodes, for example, with bronchoaspiration, pain of various causes and sialorrhea, anxiety, depression. Anxiety: Buspirone (5 to 20 mg/day); Alprazolan (0.25 to 2.0 mg/day); Clonazepam (0.25 to 2.0 mg/day). The prescribing physician must individually assess the need and risks of medications[29].

Cramps: Baclofen (10 to 30 mg 3x daily); Diazepam (2 to 5 mg 3x daily); Phenytoin (100 mg 3x daily); Quinidine (300 mg at night)[29,32]. The prescribing physician must individually assess the need and risks of the medications. Depression: Citalopram (20 to 60 mg/day); Fluoxetine (20 to 60 mg/day); Sertraline (50 to 100 mg/day); Venlafaxine (75 to 225 mg/day)[29]. The prescribing physician must individually assess the need and risks of medications. There are other antidepressants that can also be used. Spasticity: Spasticity can be relieved with daily use of Baclofen (2 to 4 tablets a day); Diazepam (10 to 30 mg/day); Dantrolene sodium (25 to 400 mg); Tizanidine (2mg to 10mg/day)[32]. The prescribing physician must individually assess the need and risks of the medications. We cannot fail to mention the applications of botulinum toxin in specific muscle groups – the objectives are several, such as self-care, walking, changes in decubitus and transfers, sialorrhea, among others[28,29]. Fasciculations: Carbamazepine (200 to 800 mg/day); Gabapentin (300 to 1200 mg/day)[33,34]. The prescribing physician must individually assess the need and risks of medications. Insomnia: Amitriptyline (12.5 to 50 mg/day); Nortriptyline (12.5 to 50 mg/day); Zolpiden (5 to 10 mg/day); Trazodone (50 to 100 mg/day)[28,29]. The prescribing physician should individually assess the need for and risks of the medications.Emotional Lability: Amitriptyline (12.5 to 50 mg/day); Dextromethorphan (20mg); Quinidine sulfate (10mg)[28,29]. The prescribing physician must individually assess the need and risks of medications. Sialorrhea: Amitriptyline (12.5 to 50 mg/day); Atropine (0.3 to 0.6 mg twice daily); Hyoscine (0.3 mg 3 times a day); Adhesive scopolamine (once/week). 1% atropine eye drops and botulinum toxin application in the parotid glands should also be considered[32]. The prescribing physician must individually assess the need and risks of the medications. Other medications should also be taken in the presence of infectious and inflammatory processes, among others. Many patients use fluid thickeners, vitamin complexes, specific amino acids and food supplements.

Motor Rehabilitation: Physiotherapy is an area of health sciences that becomes of fundamental importance for the patient with ALS and should be started at the time of diagnosis so that its contribution can be more effective both in matters related to the musculoskeletal and respiratory systems. It will be up to the physiotherapist to make an assessment capable of covering the entire spectrum that encompasses ALS, as well as predicting future limitations. For such questions to be possible, the ideal way to conduct the assessment is through the use of the International Classification of Functioning, Disability and Health (ICF) described by the World Health Organization (WHO)[34], in 2001, thus being able to explore aspects related to the domains "activity" and "participation", so fundamental to the physiotherapist. An adequate physical-functional evaluation allows the professional to more solidly outline the treatment program, as well as the establishment of goals and prognosis. For this to occur, the physiotherapist must use the appropriate tools for assessment, such as instruments, scales, and technologies necessary for an individualized prescription. ALS can compromise upper motor neurons of the spinal cord, brainstem, and motor cortex, in addition to the fact that patients can evolve with a series of motor symptoms[35,36] of the lesion, such as: signs of upper motor neuron (spasticity and hyperreflexia), lower motor neuron (muscle atrophy, myofasciculations, cramps, among others), bulbar changes (dysarthria, dysphagia, sialorrhea), respiratory changes (dyspnea and use of accessory muscles) in addition to fatigue, weight loss, and muscle contractures.

The determination of how the assessment will be conducted by the physiotherapist must take into account the evolution of the disease, which considers the loss of progressive function in the trunk, upper and lower limbs. This evolutionary process was elegantly described by Sinaki and Mulder[37]. The authors describe 6 stages of ALS as described below. Therapeutic goals can be proposed according to each stage. Among the instruments that can be used to assess patients with ALS, the following stand out: Falls Efficacy Scale — International (FES-I), developed by Tinetti Richman and Powel 37 and later modified by a group of European researchers and which presents the possibility of evaluating activities and social participation[39].

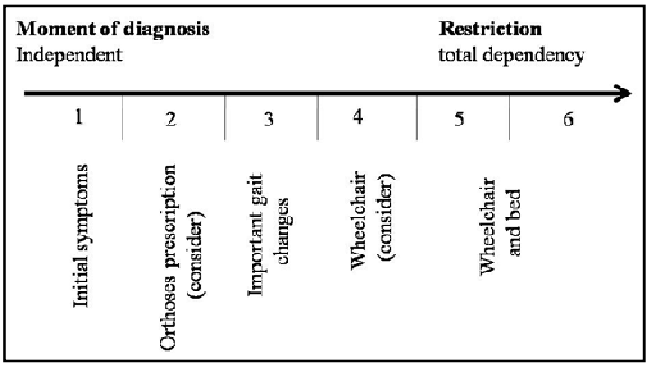

Figure 1. Adaptations of ALS stages

The ALS Severity Scale was created by Hillel et al and can also be used, and was developed to evaluate the clinical and functional evolution of ALS with a focus on the lower extremity; upper end; speech, and swallowing.[40,41] The Short Form-36 (SF-36) is a quality of life questionnaire that was designed to measure functional capacity, physical, emotional, pain, and mental health, and aimed to be a generic health-related assessment tool, easy to administer and understand, in addition to high reproducibility.[42] The 6-minute walk test (6MWT), which was first proposed by Balke in 1963[43], has since been used in various clinical conditions, and in 2002, the American Thoracic Society (ATS)[44] created a guideline for its performance. of the TC6M. According to the ATS guidelines, the 6MWT is a simple, practical, and low-cost test that aims to assess functional capacity at submaximal intensity through the distance an individual can travel, in addition to evaluating the overall condition and the integration between the responses. pulmonary, cardiovascular, and neuromuscular systems, in addition to being directly correlated with oxygen consumption (VO_2). In addition to the Mini-balance Evaluation Systems Test (Mini-BESTest), it was developed from The balance evaluation systems test (BESTest) to evaluate balance.[45]

The prescription of muscle strengthening and physical reconditioning over the years has become part of the goals of physical therapy. Behaviors aimed at strengthening were considered inappropriate for a while for patients with ALS; however, this perception has recently changed with the emergence of new studies with a consistent level of evidence. The first prospective, randomized study that considered the effects of muscle strengthening on ALS was published in 2001.[46]Droy et al. randomized 25 patients into two groups, one participating in the intervention with strengthening exercise and the other not exercising. A moderate-intensity program was developed individually and practiced by patients at home for 15 minutes twice a day. After three months, it was possible to verify a functional difference between the group that performed the exercises and the control group using the ALS functional rating scale (ALSFRS) and the Ashworth spasticity scale. In the study, it was not possible to observe differences in muscle strength scales or reports of fatigue and improvement in quality of life. After six months, it was no longer possible to see any difference between the groups. Unfortunately, in this study, the authors did not define well the exercise protocol used (load, number of sets, interval between sets and number of repetitions, and other variables for the prescription of strength training), nor, clearly, the training time. duration of the protocol. Thus, the reproduction of the study and even more careful and constructive criticism were not possible. The multicenter, randomized study conducted by Hass[47] on therapeutic interventions in patients with ALS was the first to use a training protocol described by the American College of Sports Medicine. Twenty-seven ALS patients were randomly allocated into two groups: a treatment group with an individualized resistance exercise program performed at home 3 times a week, associated with a daily stretching program; a control group, which performed only the daily stretching program. Treatment time was six months. The group submitted to the strengthening exercise protocol had significant improvement in both the ALSFR and the quality of life assessed by the SF-36 after six months.

Respiratory Rehabilitation: At any of the stages of ALS, patients can experience respiratory problems, so there should be specific assessments and goal setting and appropriate physical therapy interventions to minimize these problems. The impairment of the respiratory system is the most common cause of death in patients with ALS, therapeutic strategies are aimed at improving the quality of life of patients.[48,49] ALS does not directly affect the lungs or airways, the dysfunction occurs in the muscular sphere, more specifically in the ventilatory pump, thus compromising its function. It is known that there are disorders of cough and inspiratory functions. Such mechanisms will be briefly described below.[50] Due to bulbar involvement, laryngeal and pharyngeal muscles, glottic control, and saliva production are impaired. As a result, sialorrhea occurs, an impairment of the cough mechanism (compressive phase). With the involvement of the trunk muscles, especially the abdominal muscles, coughing is compromised, this time due to the inefficiency of the exhalation phase. It is essential that peak expiratory flow (PEF) can be monitored. When the patient reaches a degree of impairment, the risk of pneumonia increases considerably.[51,52] The cough mechanism is also influenced by inspiratory muscle weakness. The affection of the external intercostal muscles, such as the diaphragm, leads to impairment of the inspiratory phase of the cough. The restrictive disorder observed in inspiratory impairment also causes carbon dioxide (CO_2) retention and type II insufficiency (IRpAII), as well as the occurrence of atelectasis. The main symptom is dyspnea.[50,52] Disorders associated with sleep can also be found, which, in many cases, are revealed early in ALS patients. Examples of sleep disturbances include hypopneas, alveolar hypoventilation, triggering increased CO_2 levels, and atelectasis.

Daytime symptoms should also be taken into accounts, such as nocturnal restlessness or insomnia, nocturnal dyspnea or orthopnea (dyspnea occurring in the low position), and headache.[49,50] To assess the effectiveness of cough, it is recommended to use the PEF as a cutoff point for therapeutic interventions when it is less than 270L/min.[50,51] Regarding the assessment of the inspiratory function, FVC is a functional marker that helps to guide support strategies, especially regarding the use of non-invasive positive pressure ventilatory support. The American Society of Neurology indicates that values lower than 50% of the predicted FVC would already be a parameter for indicating ventilatory support. In addition to FVC, other functional variables may be reduced, such as: total lung capacity (TLC); forced expired volume in one second (FEV_1); maximum voluntary ventilation (MVV), which indicates the endurance behavior of the respiratory muscles. The measurement of respiratory muscle strength is also carried out by measuring the maximum inspiratory pressures (MIP) and maximum expiratory pressures (MEP), taking into account respective losses of 34 and 47% of the predicted values - used as a point of cutoff for decision making regarding the evolution of respiratory muscle function.[49,52]

The Approach in Cases of Cough: About cough optimization strategies, it is recommended, as described, that interventions start when the patient reaches PEF lower than 270L/min. In these situations, guidance and instructions to caregivers about maneuvers such as Heimlich's can be of great value. Manual hyperinflation, performed with a resuscitation bag adapted to mouthpieces, optimizes the maximum lung volume, aiding the insufflation phase of the cough. However, if added to the expiratory flow acceleration maneuver, through thoracic maneuvers, the effectiveness of coughing will be greater. Mechanical resources such as Cough Assistance have shown greater efficiency when compared to manual maneuvers.[54] In addition to these benefits in the exhalation phase of cough, such equipment with an inspiratory pressurization system is capable of reversing atelectasis resulting from respiratory failure.[55–58] When inspiratory impairment sets in, in addition to atelectasis and hypoventilation, an increase in CO_2 rates and dyspnea are also evident, which must be monitored because they can trigger hypercapnic respiratory failure. As previously reported, when FVC is below 50% of predicted, noninvasive positive pressure ventilation (NIPPV) is the therapy of choice.[54] The effect of NIPPV on the survival of patients with ALS is well established in the literature, as well as its results in the quality of life of these people. The NIPPV is indicated for patients with or without bulbar involvement, as long as they are mild, and the most suitable equipment is portable ventilators, generally, pressure ventilators, which have mouthpieces or masks (nasal or facial) as an interface. Therapy is usually started with nighttime support, which can be extended to the daytime.[58,60] As the disease progresses, bulbar involvement becomes largely responsible for the ventilatory failure, and the patient, even with PNIPP throughout the day, evolves with the need to use an artificial airway with a tracheostomy tube. The literature describes that, even in continuous non-invasive support, SpO_2 declines over time, and bronchoaspiration inevitably occurs, putting the patient's life at risk.[58] With the use of tracheostomy, a considerable increase in the survival of patients with ALS has been demonstrated. Life expectancy is even increased by 20 years.

However, due to the progression of the disease, many patients present incarceration syndrome and a significant decline in quality of life. This leads experts and authorities around the world to consider with the family the benefits of prolonging life with TQT for such a long time. For these patients, volume-cycled household respirators are used.[60] Other strategies aimed at optimizing respiratory functionality are being proposed. One of them is the use of a diaphragmatic pacemaker. The current hypothesis would be the possibility of maintaining the inspiratory muscle function as it occurs in patients with high spinal cord injury. However, so far, there has been no improvement in survival or ventilatory independence; on the contrary, it was shown that mortality was significantly higher in the group of patients who used the device.6[1] Another proposal to optimize respiratory functionality would be to establish an inspiratory training protocol for patients with ALS. The hypothesis would be in promoting a delay in the loss of inspiratory muscle function. It was investigated whether a protocol that used a device capable of generating a linear pressure load adjusted to approximately 30% of MIP would be able to cause such a result. Although effective, especially when evaluating MLV, MIP, and FEV_1, the results were not sustained, showing that the evolution would happen anyway. A criticism made to the use of resistive loads for patients with ALS is the possibility of overtraining, which could bring negative results.[63]

Nutrition: Changes in nutritional status and poor food intake are related to ALS / NMD progression, resulting in weight loss and changes in body composition. In addition to the loss in function of motor neurons that affect food and water intake, through changes in swallowing that are harmful to skeletal muscle mass due to muscle atrophy and eating error, these patients also present in a hypermetabolic state[64-66]. Reasons for changing the nutritional status of these patients go far beyond the increase in the basal metabolic rate. Upper limb weakness with reduced dexterity compromises automatic feeding ability. Furthermore, malnutrition is further aggravated by the loss of appetite, which represents a multifactorial component of the secondary disease, the increasing difficulties brought about by dysphagia, depressive symptoms and also by impairment of the hypothalamus[67-69]. Nutritional disorders have a direct impact on the duration of the disease, since nutritional status is an independent prognostic factor for survival in patients with ALS[70-74]. A 5% reduction in the usual weight at the time of diagnosis increased the risk of death in this population by 30%, and a decrease of one kg/m2 in the body mass index would be associated with 20% of the risk of death71. In addition, changes in body compartments, regardless of weight loss, are also points that deserve attention because they are associated with disease progression[75-77.] Thus, systematic nutritional assessment added to nutritional intervention are essential components for the treatment of patients with ALS/DNM. The periodicity and regularity of follow-up are part of this treatment and should not occur in a period longer than three months78. The general characteristics of the oriented diet should include: greater fractionation, avoiding prolonged periods of fasting, high-calorie, high-protein, normal to high-fat diet, rich in fiber, with adequate water supply and ideal consistency against the dysphagia presented.[79] With the progression of the disease, oral food intake becomes inefficient to meet nutritional needs, there are clinical signs

of aspiration and the need to modify the consistency of food, at this time, the indication of an alternative feeding route is considered. In ALS/DNM, the indication for percutaneous endoscopic gastrostomy (PPE) is sovereign over other forms of access to the digestive tract for nutrition purposes 80-83. Commonly, ALS patients tend to undergo gastrostomy relatively late, that is, after the disease has run its course by approximately 80% (Figure 2)[84]. Able to stabilize the weight and BMI in the evaluated sample, bringing benefits and giving more quality to the patient's life.

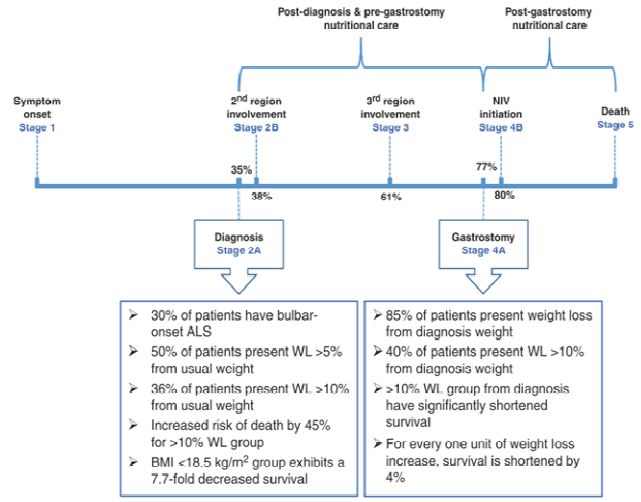

Figure 2. Diagram describing the main stages of ELA/DNM[84]

The GEP indication criteria consider a 10% reduction in body weight in the last three months, the presence of moderate dysphagia and assessment of respiratory function, with emphasis on the forced vital capacity measure with values close to 50% of the predicted value.78 A more prospective study recent, suggests that the indication of the enteral route should be considered with a basal body weight loss of only 5%[85.] Enteral nutritional therapy is directed maintaining the same characteristics of dietary guidelines given orally, considering a polymeric, hypercaloric, hyperprotein diet ranging from normo to hyperlipidae with fiber. There are studies showing that high-fat diets could benefit the treatment of these patients[86-87]. Finally, the importance of nutritional intervention performed from diagnosis onwards is highlighted, considering that the early identification of nutritional disorders creates the possibility of adequate intervention, in order to aid in the recovery and/or maintenance of the nutritional status in ALS/DNM, bringing impact on the survival of these patients.

Speech Therapy: Speech therapy can contribute to the treatment of patients with ALS in two major dimensions of care: Food and Communication. This implies a motor approach, focused on dysphonia, dysarthria and dysphagia. At the same time, a non-motor approach, focused on communication. In addition, there is the work of language and cognition, especially in patients who have some cognitive deficit associated with motor impairment. Dysphonia can manifest itself by alteration in vocal quality (source) and also by alteration in resonance (filter) and the clinical characteristic will depend on whether there is a predominance of alteration in the upper motor neuron (spastic pattern, which gives the voice a more vocal quality tense, acute and hypernasal resonance or, in other cases, laryngopharyngeal) or lower motor neuron (flabby pattern, which gives the voice a breathy, asthenic and hypernasal resonance). In both cases, there is a reduction in vocal intensity, which is due to the ventilatory alteration, with a reduction in the inspiratory volume and also pneumophonoarticulatory incoordination, due to the imbalance between the myoelastic and aerodynamic forces of the vocal tract[88]. The initial picture of dysarthria is characterized by phoneme distortion and alteration in articulatory precision. Over time, there is a reduction in intelligibility and understandability components, limiting the patient's participation in social, work or even family contexts. Despite the evolution of dysarthria towards the absence of speech for neuromotor reasons (anarthria), it is It is important that the speech therapist is aware of the best time to prescribe and develop, together with the patient, an alternative communication system (ACS)[89]. Such resource should be developed in a joint action between Speech Therapy and Occupational Therapy. However, it is of fundamental importance to assess whether the changes related to communication are related only to dysarthria, or whether there is a parallel change in language and/or cognition. It is known that around 35% of ALS patients develop cognitive alterations and 15% reach the diagnosis of Frontotemporal Dementia[90]. Often, this condition starts with subtle changes in language (such as anomie episodes) and cognition (such as memory, praxis, temporal or spatial orientation, among other cognitive dysfunctions) and executive functions, which must be identified early, so that the conducts outlined by the team can be readjusted. There is a tendency for patients with executive dysfunction not to follow the clinical guidelines given by the professionals, which has an impact even on their survival[91]. It is up to the speech therapist to identify and treat, during the therapeutic process, issues related to language and also to cognition. Language alterations must be carefully mapped and the professional must make the differential diagnosis between speech and language alterations[92]. For example: syntactic reduction can be a strategy to limit the complexity of the sentence, due to a language alteration, but it can also be due to a speech alteration, as a resource that the patient uses to help the interlocutor to better understand the message . In turn, cognitive alterations restrict the possibility of using alternative communication. Such cognitive changes can also impact the recognition of difficulties related to dysphagia and this is another factor that points to the need for a detailed assessment of clinical signs, which may be present in chewing and swallowing functions.

Dysphagia is one of the factors that most impact the patient's survival and quality of life, due to its implications both in the nutritional and respiratory aspects. The patient may present alterations both in the oral and pharyngeal phases of swallowing, with episodes of difficulty in prehension of the food, anterior escape, difficulty in handling the bolus inside the cavity, reduction in masticatory force, difficulty in preparing, accommodating and ejecting the bolus towards the pharyngeal cavity, nasal reflux, reduction in pharyngeal elevation and stabilization, difficulty in opening the pharyngoesophageal transition, occurrence of food stasis in the laryngopharyngeal region, incoordination of breathing-swallowing, laryngeal penetration or bronchoaspiration. It is up to the speech therapist to assess which clinical events occur, according to different food volumes and consistencies, in order to establish a more assertive conduct in each case[93]. Some strategies that can be used in speech therapy include: indication of myofunctional exercises, swallowing maneuvers, hygiene maneuvers, adequacy of food volume and consistency, fatigue management and environmental management, such as limiting distracting elements during meals, among others. It is noteworthy that exercises that use counter-resistance or increased overload or even the use of peripheral electrical stimulation are contraindicated, given the occurrence of fatigue and the deleterious impact it can cause on the body of the patient with ALS[94]. Moderate dysphagia is already considered a clinical criterion for indication of gastrostomy. Other criteria should also be considered in this indication, such as nutritional status and the occurrence of severe weight loss in the last three months; in addition to the respiratory condition, such as reduced forced vital capacity[77]. Dysphagia is one of the factors that most impact the patient's survival and quality of life, due to its implications both in the nutritional and respiratory aspects. The patient may present alterations both in the oral and pharyngeal phases of swallowing, with episodes of difficulty in prehension of the food, anterior escape, difficulty in handling the bolus inside the cavity, reduction in masticatory force, difficulty in preparing, accommodating and ejecting the bolus towards the pharyngeal cavity, nasal reflux, reduction in pharyngeal elevation and stabilization, difficulty in opening the pharyngoesophageal transition, occurrence of food stasis in the laryngopharyngeal region, incoordination of breathing-swallowing, laryngeal penetration or bronchoaspiration. It is up to the speech therapist to assess which clinical events occur, according to different food volumes and consistencies, in order to establish a more assertive conduct in each case[93]. Some strategies that

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