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Review Article

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Move Toward to Non Invasive Mechanical Ventilation in Amyotrophic Lateral Sclerosis: A Clinical Review

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Abstract

Subjects with amyotrophic lateral sclerosis (ALS) can have fast or slow evolution. Precocious diagnosis significantly impacts on natural history, even though the prognosis remains severe, indeed the mortality rate at 5 years is higher than 80%. Progressive weakness of bulbar, limb, and respiratory muscles is characteristic. Death generally occurs from 2 to 4 years following symptom onset, primarily owing to respiratory failure. Treatments for respiratory aspects of ALS are evolving. This manuscript that recapitulates the current indications is aimed to define a rational basis for a patient-oriented approach to treatment of ALS, mainly focused on non-invasive mechanical ventilation (NIV).

Keywords

Amyotrophic Lateral Sclerosis; Mechanical ventilation; Hypercapnia

Introduction

The correct diagnosis and clinical management of patients suffering from Amyotrophic lateral sclerosis (ALS) remains an important challenge in this field. The ALS onset occurs usually in middle aged patients and the disease leads to death after 3-5 years. In most epidemiologic reports there is an incidence of 1-3 cases/ 100000 / year and a prevalence of 3-5 / 100,000. The clinical scenario of presentation is unpredictable, depending on the predominant initial involvement of the upper or lower motor neurons [1,2].

Common starting symptoms include hyposthenia, hypotrophy, stiffness, cramping and collision of the muscles of the hands and arms (often seen at the level of the intrinsic muscles of the hand). Lower limbs (stiffness, cramps, and hyposthenia) are less severe than the ones in upper limbs. Symptoms of cerebral trunk include dysphagia, which can lead to aspiration pneumonia and impairment of energy supply; the tongue can undergo a pronounced atrophy, which causes difficulty in the word articulation (dysarthria), phonation and swallowing [1,3].

Hypersensitivity to respiratory muscles leads to respiratory failure. Other characteristic features of ALS are the absence of sensitive abnormalities, pseudobulbar paralysis (with lax and involuntary tears) and the absence of intestinal or bladder dysfunction. Dementia is not a component of sporadic ALS. In some families ALS is inherited along with a frontotemporal dementia, characterized by secondary behavioural alterations to frontal lobe dysfunctions [1]. Precocious diagnosis has a significant impact on natural history, even if the prognosis remains severe, in fact the mortality rate at 5 years is higher than 80% [3].

Progressive weakness of bulbar, limb, and respiratory muscles is characteristic. Death generally occurs from 2 to 4 years following symptom onset, primarily owing to respiratory failure. Only 20% of patients live more than 5 years. The disease mostly appears at 43-52 years of age if it is familiar, otherwise at 58-63 years for the sporadic cases [4]. Regrettably, if the skeletal muscles are implicated, the respiratory apparatus could determine a rapid respiratory degeneration. This may because a decrease in general condition and a higher risk of aspiration pneumonia due to dysphagia, an exaggerated modification in the response to muscle relaxants, and, among other adverse side effects, a delayed recovery of spontaneous breathing after general anesthesia [5]. Consequently, anesthetic approach in ALS should include cautious monitoring and proper drug choice, in order to avoid severe complications [5]. This review is aimed to update on the new therapeutic landscape for pulmonary aspects of ALS which is still an unachieved medical goal.

Pathophysiology of ALS

If on one side ALS lacks predictable biomarkers, on the other side one common guideline to a correct diagnosis of the disease is missing. We are still far away from the identification of a single gene responsible for disease progression, even though the latest findings revealed a pattern of genes involved in the same manner [5]. The identified pattern of genes seems to share some cellular functions such as RNA metabolism, protein degradation, ER-Golgi pathway, trafficking and endosomal sorting complexes required for transport. Guerriero R. et al. have drawn up a complete table with all the genes involved in ALS and Frontotemporal dementia and the possible pathways connected. Regarding ALS the most reliable genes are TAR DNA Binging protein (TARBDP) and FUS RNas Binding protein; they both confirm the involvement of DNA/RNA metabolism [6]. Unfortunately, their specific role and how their dysfunction regulates ALS development are still unknown. Also protein accumulation seems to affect the disease progression. It has been shown that the accumulation of filaments of ubiquitinated material on motor neurons is associated with ALS [7]. The evidences that characterize the mechanism behind these accumulations is still scanty. Nevertheless, the disease progression with the increasing instability of the genome, seem to be responsible for the production of material aggregates destined for degradation [8,9]. In this scenario, it is worth highlighting even the possible involvement of autophagy deregulation as a cause of the disease [10,11]. Research in this field is growing very fast due to the role of autophagy in the elimination of cellular damaged components and the evidence that neurodegenerative diseases are connected with accumulation of material that has not been wasted. In ALS it seems that autophagy is enhanced by an accumulation of LC3-II protein in mouse models for the disease [12,13]. Notwithstanding the promising

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hypothesis and the early evidence in animal models, still there are no therapeutic results regarding autophagy-modulation drugs [2] (Figure 1).

Clinical remarks

Subjects with ALS can have rapid or slow evolution. Symptoms could be muscular weakness, loss of coordination, spasticity, atrophy, fasciculation and hyperreflexia that lead to a progressive degeneration of motor neurons. In this scenario the patient could develop a progressive asymmetric limb weakness and bulbar manifestations such as difficulty in speaking (dysarthria), problems in swallowing (dysphagia) and in some cases problems related to respiratory muscle with consequent difficulty in breathing [14,15]. The distinctive anatomy-pathological characteristic of the ALS is the death of both lower motor neurons (spinal cord horn cortex cells and their counterparts in the cerebral trunk that innervate the bulbar muscle), as well as upper or corticospinal motoneurons (which originate in the fifth layer of the cortex motor and descend through the pyramidal beam to contract synapse with the lower motoneurons). Although initiating ALS may cause a selective loss of only lower motor carcasses or only upper motor neurons, it ultimately results in a progressive loss of both types [1]. The absence of a clear involvement of both motor neurotic populations must lead to questioning the possible diagnosis of ALSs. Liquor is usually normal. Muscle enzymes (e.g. CK) can be elevated. Many types of secondary motor neurone disorders, similar to ALS, are curable [2,3].

MRN or myelo-CT is often necessary to exclude compression lesions of the forearm magna or cervical column. When only inferior motoneurons are affected, another important clinical issue to consider is motor multifocal neuropathy with conduction block. ALS-like lower axonal motor neuropathy sometimes can be associated with hematopoietic disorders such as lymphomas or multiple myeloma; the presence of a serum monoclonal component should bring to a rapid execution of a bone marrow biopsy. Lyme disease can also cause axonal lower motor neuropathy, typically with intense proximal limbs in the limbs and pleural effusion. Other benign conditions that rarely imitate ALS are chronic lead poisoning and thyrotoxicosis [3].

Pulmonary evaluation in ALS

Premature decline of the respiratory components (muscles and neuromuscular degeneration) may determine death before the disease involves additional sites [16]. A mask based evaluation can be used to obtain measures (as indicated in bulbar ALS) that are fundamental to motivate non invasive mechanical ventilation (NIV) [17]. Nonetheless, frequent intensive monitoring and following up adjustments when necessary, are a valuable choice in a multidisciplinary clinic field [18]. Certainly providing extensive and detailed education, selecting the interface carefully, and controlling sialorrhea, are fundamental topics [19]. However, the role of early NIV is debated [3,20,21]. It is worthwhile to plan the ventilation program in a patient oriented manner. Therefore the appropriate strategy to initiate ventilation has to be discussed well in advance. Ventilation capacity (FVC), mean inspiratory pressure (MIP), and expiratory CO2 level (ETCO2) are fundamental parameters to take into account in order to better plan the neurologic approach.

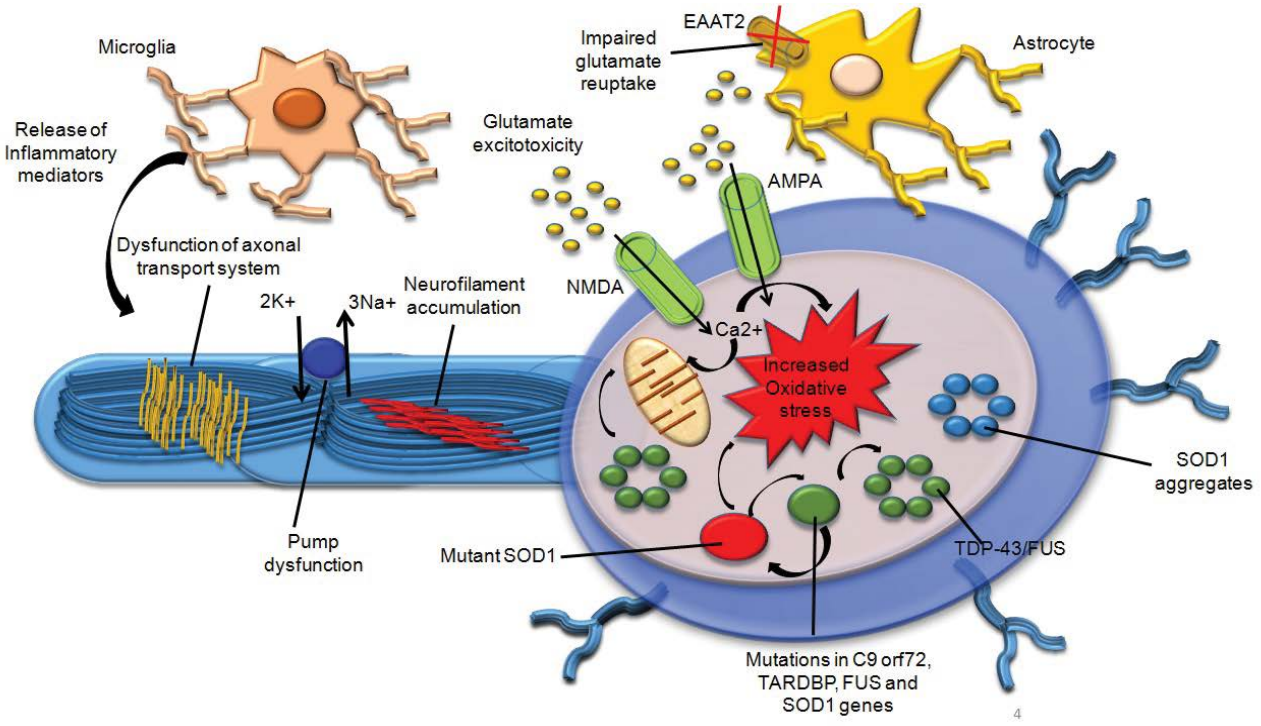

Figure 1: The ALS disease biology. A multifaceted interaction between genetic factors and molecular pathways has a pivotal role. Mutations in DNA/RNA-regulating genes including the recently reported c9orf72 (chromosome 9 open reading frame 72) gene, suggesting an important role for dysfunction of RNA metabolism in ALS pathogenesis. Further, dysfunction of molecular pathways, including glutamate-mediated excitotoxicity, has been identified in sporadic and familial ALS, indicating the existence of a common pathogenic pathway.

Clinical studies evidences

Long-term mechanical ventilation is exceptionally used [22]. Nevertheless this approach can considerably boost life expectancy. Remarkably, most patients cannot be weaned from ventilator support [23]. Early decision making should include thorough documentation of discussions [24]. Studies demonstrate patients' preference for physician to initiate the discussion [22-25]. Diaphragm pacing option demonstrated conflicting results [26]. Three studies were halted for increased mortality in treatment arm [26-28]. A meta-analysis from all studies examine reasons for disparities and attempt to identify subgroups of patients who may benefit [29]. Death in ALS is in most of the cases linked to the respiratory function: people die because of respiratory failure. An intervention that could impact respiratory function would be incredibly important in ALS, which raises the stakes in terms of effectively measuring respiratory capacity [30]. The most commonly used measure in clinical trials is the vital capacity VC, however there is a difference between the experimental and clinical way used to measure VC [31].

Respiratory function tests can be useful for ventilation management. The swallowing assessment allows the identification of patients at risk of aspiration. A genetic test is available for the mutations of superoxide dismutase 1 (SOD1) responsible for 20% of the family forms of ALS, as well as for rare mutations of other genes [32].

There is no treatment that blocks the basic pathological process of ALS. Riluzole produces a modest elongation of survival; in a study, 18-month survival in riluzole (100 mg / day) subjects was similar to the one in15-month-placebo-treated patient. Its mechanism of action very likely decreases the release of glutamate thus reducing the excitotoxic death of neuronal cells. Riluzole toxicity profile can comprise weight loss, dizziness, nausea, and liver toxicity [33].

Currently, several therapeutic agents for ALS are being studied in clinical trials, including ceftriaxone, pramipexole and tamoxifen. Interventions such as the use of antisense oligonucleotides, which are able to reduce the expression of the mutant SOD 1 protein, are currently undergoing clinical trials on ALS cases associated with mutated forms of SOD1 [32,34]. Several rehabilitative aids can substantially help ALS sufferers. Showers to prevent foot falls make walking easier, while the ones suitable for the extension of patients' fingers strengthen their grip.

In the cases with bulbar involvement, normal chewing and swallowing can be affected and gastrostomy may be useful in restoring normal nutrition and hydration. Voice synthesizers increase the chances of speaking in the advanced stages of bulbar paralysis. Respiratory care can ensure survival. For patients who choose to avoid long-term ventilation through tracheostomy, positive pressure ventilation through the nose or mouth provides transient relief (a few weeks) from hypercapnia and hypoxia. Respiratory devices that cause artificial cough are also useful: they help release the respiratory tract and prevent pneumonia from aspiration [35,36]. The variability in the clinical approach to the patient with ALS highlights the lack of guidelines in the long-term integrated approach [37]. The available data suggest that the early use of non –invasive ventilation (NIV) can change clinical outcome and improve quality of life [38].

Discussion and Outlook

In ALS respiratory failure is the most important co-morbidity affliction in patient survival. A useful tool in this setting is ventilation. It could be managed both in invasive (using tracheostomy ventilation - TV) and in NIV manner. In ALS patient management more intensive treatments, such as a feeding gastrostomy or TV, are associated with numerous side effects both in early and late stage of the disease. Also NIV entails many problems and does not ensure a later use of TV; therefore physicians should ask themselves if the decision to treat is reasonable and when to perform the treatment [37]. Respiratory failure is often related to hospitalizations, with more frequent bulbar onset [39]. Actually in those who were hospitalized the use of TV larger than in NIV, mainly in the cases with spinal onset. Respiratory failure and pneumonia (both infective and aspiration) are the most common cause of emergency and death [39]. It takes time to discuss the different therapeutic approaches with the patient but if respiratory failure occurs and hypercapnia confusion arises, patients could not be able to provide adequate informed consent for treatment [37].

The sooner a closely monitored disease progression and respiratory function are set the better in order to provide an adequate follow-up and to estimate the risk of decompensating. A FVC less than 50% and/or symptoms of hypoventilation are signals suggesting a respiratory failure: physicians have to prompt a discussion on therapeutic options allowing patients, their families and care-givers to have enough time for a constructive discussion avoiding hasty decisions in a life-threatening emergency setting [3].

TV is the most effective choice for life-long survival but it also results in an intensive resource utilization, an increase in ventilator entrapment risk and finally in an emotionally difficult acceptance, in fact; despite a very high increase in life survival [40,41]. TV enhances disability and dependency, consequently decreasing the quality of life. On the contrary NIV does not affect significantly the use of facial, nasal or mouthpiece tools which are therefore more useful and manageable. Via these different types of masks NIV system provides a ventilator-assisted support using a volume cycled or a bi-level pressure volume ensuring an intermittent positive pressure to support patient ventilation.

A few trials have tried to understand which is the best ventilation to be used in ALS patients. One of them showed an increase in median survival associated to a better quality of life [42,43]. The above result was mostly due to a benefit in a patient with mild-to-moderate bulbar impairment but, notably, in the standard treatment group, 67% of patients died within two weeks after randomization which prompted an accurate appraisal of the presumably overrated positive effect of NIV. Moreover authors had found an improvement in sleep-related symptoms but not in life survival in patients with severe respiratory dysfunction. In another double-blind single-center trail, patients were randomized to NIV use or placebo [44]. The majority of patients in both groups reported no and only mild problems with NIV treatment. The most common complaints were about dry eyes, nose, or mouth and facial discomfort. Authors described that an increase in FVC% after one month of NIV treatment was found compared to placebo but this result did not involve a difference in survival between the two groups. This could be due to the mild ALS dysfunction (evaluated by the specific score) of the patients and because the study was not based on clinical outcomes.

Some authors have also suggested the possibility of using NIV to prevent respiratory failure. In fact, according to Bourke results, a non-randomized study described a decrease in FVC decline and an increase in survival in ALS patients if NIV was used at an earlier stage in disease progression [45]. Some RCT are ongoing to explore the impact of early NIV use in mild respiratory failure ALS patients

but exhaustive results are not available yet. Some retrospective series have explored the outcome of ALS patients receiving NIV, finding that most of those who experience this type of ventilator support need a TV after one month of NIV [46,47].

In a French retrospective cohort study researchers found that NIV was mostly used in late stages of disease when severe respiratory symptoms (orthopnea, respiratory-related nocturnal symptoms and hypercapnia) are present [48]. This management is mostly due to the adherence of the prescribers to the French guidelines and to a not strictly surveillance of respiratory function. However in this study authors had also found that in the 90% of patients NIV was not performed in case of acute respiratory distress. In particular they had found that NIV was initiated when a decreased FVC or other parameters such as the presence of daytime or nocturnal symptoms, daytime hypercapnia, decreased maximal inspiratory pressures (Pimax and SNIP), isolated nocturnal desaturations, and polysomnography results occurred. Even the definition of volume needed to perform adequate ventilation is still on debate. In fact many authors suggest low tidal volume ventilation in this particular setting. A more accurate evaluation needs to be performed on both inspired and E-spired volume to avoid a lung dysfunction in particular in patients with a sufficient muscular strength. Maintaining an optimal tidal volume has to be the aim of the use of ventilation. In this prospective it has to be used NIV with a volume-assured pressure support via a pressure-cycled mode (VAPS). In fact, another retrospective single-center cross-sectional cohort study making a comparison between VAPS and a pressure support (PS) had shown that an higher tidal volume was achieved with VAPS [49]. Additionally it has to be stressed that the same authors have described a decreased spontaneous breath cycling not related to the type of ventilation, even if the triggering is less severely impaired in the main percentage of patients under scrutiny [49].

In a retrospective study on ALS patients receiving either NIV or TV authors try to identify the best volume to use [50]. They found that only in the patients who performed TV and not in those with NIV there was a significant positive correlation between body weight (both actual and predicted) and volume both in tidal and minute volume inspired. On the contrary no difference was found in Positive Inspired Pressure (PIP) used for both the groups. It could be noted that PIP appears to be a relatively constant and important parameter when compared to tidal volume and it is not related to severity of bulbar dysfunction in initial NIV treatment or shifting to TV. Moreover in order to ensure an adequate ventilation volume it is essential to take into account the body weight. Body weight is also a clue to acceptance of ventilation particularly in outpatients. It has been highlighted that low body weight and female sex as well as spinal onset imply a lower tolerance to NIV use [51].

Clinical judgment directed approach

One of the most important debates is centered on the best timing for NIV initiation. Many evidences suggest that an earlier initiation of NIV ensures a change in the course of the disease based on a favorable effect on the rate of lung function decline. On the contrary the present guidelines allow physicians to start NIV in only 21% of patients with ALS and only if they qualify for it [52]. Many efforts have been made to access to the best way to drive respiratory management in ALS. A Revised Amyotrophic Lateral Sclerosis Functional Rating Scale score, (ALSFRS-R) has also been proposed to be used in order to identify the possible risk population. This score is not only referred to respiratory functional description but it also explores twelve working items [53]. However even if it may be useful in patient stratification it varies from time to time also with the same patient [54].

Before starting NIV it is necessary an accurate evaluation of pulmonary function. A lung capacity prediction in ALS and functional vital capacity (FVC) measured in an erect posture are the most frequently used procedures. In fact baseline FVC has been found as a predictor of survival in several studies on ALS and it was confirmed in a 20-year cohort study: FVC reduction impacts as a negative prognostic indicator. On the other hand, supine measurement of FVC could be an important marker because the imitation of the sleeping position provides information about diaphragm functionality. Starting NIV in patients performing a FVC shows that about 65% obtains a one-year survival increase compared to those who start NIV later. After NIV treatment was settled, the rate of FVC reduction was statistically significantly lower than in patients without NIV [52].

Several symptoms described in ALS patients (i.e. excessive daytime sleepiness, morning headache and orthopnea) are a consequence of sleep disturbances associated to nocturnal desaturation. Nocturnal respiratory functions in ALS are more sensitive measurements of FVC. In particular maximal inspiratory pressure (MIP) is a more sensitive indicator of respiratory decline compared to FVC, while Sniff nasal inspiratory pressure (SNIP) measurement has been shown to be more sensitive than MIP and FVC in predicting hypercapnia in ALS patients also when there is no significant bulbar involvement. SNIP should be considered as a marker of diaphragm muscular fatigue, in particular when there has been found a measurement of 40 cmH_2O which is related to nocturnal hypoxemia [55].

An RCT meant to study evaluate if polysomnography could be useful to guide the NIV treatment is still ongoing [51].

Performing a full polysomnography (PSG) is much more effective than measuring sleep quality subjectively, Nocturnal desaturation and apnea/hypopnea index are useful parameters to decide when to start NIV [52].

However in clinical practice most of the neurologists base their decision on nocturnal hypoxemia but only 39% perform also a FVC and just 13% use SNIP [56]. Abnormalities in respiratory functional tests (such as a supine drop in FVC, a reduced SNIP, or prolonged nocturnal desaturation) are considered a red mark for initiation of NIV in less than 10% of cases [48]. SNIP is a good tool to quantify the decline in respiratory function. In a retrospective study it has been found that SNIF declined to the utmost in the three months before NIV treatment compared to FVC or inspiratory/expiratory pressure [57].

Another parameter which appears to be effective in decision making is Peak cough flow (PCF) which estimates the efficacy in cough and airway clearance. PCF is measured by performing a maximal inspiration, followed by a cough as forcefully as possible, while the lips are sealed tightly around the tube. It results lower in those who start a NIV treatment compared to those who have not yet had indication to NIV [57]. In other retrospective studies the evaluation described was done on arterial blood gas (ABG) analysis to drive the NIV: even though no significant differences have been found in arterial gas mean values, bicarbonate >30 mg/dL, PCO2 >50 mmHg and pH <7.30 were associated with an increased death risk [46,47]. In ALS patients a delay in initiation of NIV treatment mostly results negative because a poor surveillance of pulmonary function has been performed. The main difficulties are related to patient's mobilization as well as technical difficulties to perform respiratory

tests. A standardized method to study, follow and screen ALS respiratory function is needed to avoid the difficulty to decide when to start NIV. In the retrospective study on the French registry authors had analyzed the importance of guideline use for NIV treatment in ALS patients [48]. After the guideline acceptance they described a less frequent indication to NIV for daytime hypercapnia while a larger number of patients had a poor quality sleep related symptoms associated to a decreased ALSFRS-R score, suggesting a trend to an earlier initiation of ventilation.

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