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Assessment and Management of Respiratory Dysfunction in Patients with Amyotrophic Lateral Sclerosis

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a relatively rare neurodegenerative disorder that causes progressive dysfunction of voluntary muscle groups secondary to motor neurons death. The relentless involvement of all skeletal muscles of the body, characterized by weakness and atrophy to complete paralysis, invariably involves respiratory muscles (particularly the diaphragm) resulting in a failure to deliver adequate amounts of oxygen to, and remove carbon dioxide from blood. As a result, respiratory failure, frequently complicated by pneumonia related to respiratory muscle weakness and ineffective cough, is the most frequent cause of death in these patients (Lo Coco et al., 2008).

Considering the natural history of ALS, only a few number of patients shows respiratory muscle dysfunction at the onset of the disease (Marti-Fabregas et al., 1995; De Carvalho et al., 1996), and the majority of patients maintains an almost normal pulmonary function for months or years. Patients thus need to be regularly and progressively evaluated to identify early signs of respiratory muscle weakness so that adequate treatment can be implemented. Indeed, in the last few years it has been repeatedly shown that non-invasive positive-pressure ventilation (NIPPV), the treatment of choice for chronic hypoventilation and respiratory failure in ALS, allows a significant improvement in survival and quality of life (Heiman-Patterson & Miller, 2006). Many tests are available to objectively assess the performances of the respiratory system, and there is increasing interest toward those able to sensitively detect mild impairment. Moreover, great attention has to be put on monitoring of cough effectiveness, management of respiratory secretions and prevention of respiratory infections. For all these reasons the management of respiratory dysfunction has become a

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major issue in the multidisciplinary assessment of patients with ALS, and the pulmonologist has gained an increasing role in this process. However, there is still little consensus on pulmonary care worldwide, and clinical practice varies widely from country to country, especially when NIPPV becomes inadequate to support respiratory muscle failure. It is, then, good practice to discuss respiratory issues in advance with the patients and their carers in order to avoid emergency interventions or unwanted treatments, and frequently review these decisions during the course of the disease.

This chapter focuses on the recent advances that have emerged in the management of pulmonary dysfunction in patients with ALS with emphasis on respiratory evaluation and mechanical ventilation.

2. Evaluation of pulmonary function

As already mentioned, when patients with ALS seek medical attention, they do not usually display signs of pulmonary involvement, and do not refer respiratory complaints. However, during the progression of the disease all patients eventually complain of dyspnea with exertion, orthopnea, and poor sleep quality with frequent awakenings, nightmares, early morning headaches or excessive daytime sleepiness (Heffernan et al., 2006; Beneditt & Boitano, 2008). A clinical examination at this point might show respiratory paradox, rapid shallow breathing or accessory muscle contraction. Nevertheless, the observation that many patients may remain asymptomatic even when there is a marked reduction of vital capacity limits the reliability of these signs and symptoms. There are, however, several dyspnea rating scales, such as the Borg dyspnoea score, the baseline dyspnea index and the transition dyspnea index, that have been recently reconsidered and their implementation has been encouraged (Lechtzin et al., 2007a; Just et al., 2010).

In addition to respiratory symptoms and signs, many exams are used in the evaluation of pulmonary function in patients with ALS (Heffernan et al., 2006; Beneditt & Boitano, 2008; Lo Coco et al., 2008; Miller et al., 2009a).

The most widely available measure for detecting respiratory decline is forced vital capacity (FVC) sitting and/or supine. FVC is correlated with survival, and usually presents an almost linear decrease during the course of the disease, but with a marked variability from patient to patient (within 2% to 4% of predicted value per month) (Fallat et al., 1979; Munsat et al., 1988; Schiffman & Belsh, 1993; Stembler et al., 1998; Czaplinski et al., 2006; Lo Coco et al., 2006a).

FVC, however, has some well known limitations, such as low sensitiveness in patients with bulbar involvement, because of reduced buccal strength, or cognitive involvement, and a relative insensitiveness to detect mild or moderate diaphragmatic dysfunction. According to many specialists, supine FVC, although more difficult to perform, has superior sensitivity over seated FVC in predicting survival, is closely correlated with transdiaphragmatic pressure, and then should be always executed in the evaluation of patients with ALS (Varrato et al., 2001; Schmidt et al., 2006; Baumann et al., 2010).

Maximal inspiratory and expiratory pressure (MIP and MEP) are other sensitive measurements, and it has been shown that many patients with an FVC > 70% had abnormal MIP (< -60 cm) (Jackson et al., 2001). However, since many patients are unable to perform the test with the progression of disease, in many centres these two tests are not routinely executed.

Arterial blood gas analysis may also be of help in the evaluation of patients with ALS, especially in those with severe bulbar involvement, since it could reveal resting hypercapnia ($PaCO_2$ > 6.5 kPa) and/or hypoxemia (PaO_2 < 80 mmHg). However, these are usually very late signs of respiratory failure in ALS.

Sniff nasal inspiratory pressure (SNIP) is regarded as a good measure of diaphragmatic strength, and is probably more accurate than FVC, especially at later stages, although even SNIP may underestimate respiratory function in patients with bulbar involvement, because of upper airway collapse. However, a sniff nasal pressure test < 40% of predicted value (or < 60 cmH_2O) is a significant predictor of sleep disordered breathing, nocturnal hypoxemia, hypercapnia and mortality (Fitting et al., 1999; Lyall et al., 2001b; Carrat et al., 2011).

Finally, nocturnal hypoventilation and sleep-disordered breathing are common problems in ALS with the progression of the disease, and can occur even when respiratory muscle function is only mildly affected and in the presence of normal daytime gas exchange (Gay et al., 1991; Ferguson et al., 1996; Arnulf et al., 2000). Nocturnal hypoventilation is particularly severe during rapid eye movements (REM) sleep, when all postural and accessory muscles are physiologically atonic, and only the diaphragm, which may itself be impaired, is left to sustain ventilation and overcome any upper airway resistance (Ferguson et al., 1996). Then, since nocturnal oximetry is easily performed and can be executed domiciliary, it has become frequently used in clinical practice for the evaluation of respiratory involvement in patients with ALS and as a guide to initiate mechanical ventilation. Nocturnal oximetry correlated with survival (mean SaO_2 < 93 mmHg was associated with mean survival of 7 months vs 18 months when mean SaO_2 > 93 mmHg) (Velasco et al., 2002), and nocturnal desaturations < 90% for 1 cumulative minute was a more sensitive indicator of nocturnal hypoventilation than either FVC or MIP (Jackson et al., 2001). Polysomnography is not routinely performed, because is costly and demanding, although it can reveal causes of poor sleep quality different from disordered breathing, such as motor activity during sleep (Lo Coco et al., 2011).

3. Non-invasive mechanical ventilation

Long-term mechanical ventilation in patients with neuromuscular problems was first introduced between 1950 and 1960 in France and Sweden as a consequence of the poliomyelitis epidemics. During the following decades, the concept of home mechanical ventilation expanded rapidly, and long-term non-invasive positive-pressure ventilation (NIPPV) was implemented in many other countries and for many other conditions, including ALS, to treat chronic alveolar hypoventilation.

Chronic alveolar hypoventilation is a state characterized by reduced arterial oxygen tension and increased carbon dioxide tension, which the patient may correct at least partially by voluntary hyperventilation. The underlying mechanisms are not yet fully understood and may involve impairment of lung mechanics or airway function and cough, ventilation-perfusion mismatch, blunted central ventilatory drive, or respiratory muscle fatigue. Abnormalities may occur while awake or during sleep. In most cases, chronic alveolar hypoventilation leads to daytime fatigue, hypersomnia, and changes in psychological function.

The application of ventilatory assistance in ALS, most frequently non-invasively, has led in the last fifteen years to a revolution in respiratory assistance and ventilatory support in these patients, with a significant impact on the natural history of the disorder. Indeed, NIPPV has been shown to alleviate respiratory symptoms, to extend survival considerably,

and to improve quality of life and cognitive functions in most patients (Miller et al., 2009a). At present time, NIV, usually via nasal mask with Bi-level Positive Airway Pressure (BiPAP) machines, is the most effective treatment available for ALS patients (Heiman-Patterson & Miller, 2006).

The first study that investigated the effects of NIPPV in patients with ALS dates back to 1995. In a non-randomized trial of NIPPV, Pinto and colleagues showed that survival was significantly longer in the nine patients that received NIPPV compared to the nine patients that received standard care (Pinto et al., 1995). In the following years, many cohort and retrospective studies, and a single randomized trial confirmed these results in those patients that used the ventilatory device for more than 4 hours/night (defined as tolerant patients) (Aboussouan et al., 1997, 2001; Kleopa et al., 1999; Bourke et al., 2003, 2006; Farrero et al., 2005; Gruis et al., 2005; Lo Coco et al., 2006b). In general, these studies demonstrated a median survival of 10 to 15 months in those who were able to tolerate NIPPV. It was also pointed out that NIPPV treatment could slow the rate of respiratory impairment, while severe bulbar impairment could affect NIPPV tolerance (Pinto et al., 1995; Aboussouan et al., 1997, 2001; Kleopa et al., 1999; Bourke et al., 2003, 2006; Farrero et al., 2005; Gruis et al., 2005; Lo Coco et al., 2006b). Furthermore, many recent studies showed that NIPPV therapy could improve quality of life of patients with ALS (Gelinas et al., 1998; Lyall et al., 2001a; Kaub-Wittemer et al., 2003; Bourke et al., 2003, 2006; Mustfa et al., 2006), although some suggested that the caregivers' burden could become heavier (Gelinas et al., 1998; Kaub-Wittemer et al., 2003). Finally, it has been reported that mechanical ventilation could improve cognitive function after some months of treatment (Newson-Davis et al., 2001).

Notwithstanding the aforementioned effects on respiratory symptoms, quality of life, and survival many studies suggest that the employment of NIPPV in ALS is poor worldwide (Bourke et al., 2002; Lechtzin et al., 2004), with a need for more education of clinicians and patients regarding the benefits of mechanical ventilation earlier in the course of the disease (Bradley et al., 2001). The reasons for such low uptake of NIPPV treatment are multifactorial but are influenced by differences in the experience of physicians, its availability and cost, uncertainty of the benefits and timing for starting ventilation, and concerns that ventilatory support might prolong suffering, render home care less feasible, and lead to dependency or ventilator entrapment (Radunović et al., 2007).

Moreover, there is still debate about the optimal timing to introduce ventilation in these patients and whether early NIPPV initiation could actually lead to increased survival rates. With regard to the first aspect, as previously discussed, there are at present many different guidelines that suggest numerous exams to be performed, including upright and supine spirometry, nocturnal oximetry, blood gas analysis and MIP (Andersen et al., 2005, 2007; Miller et al., 2009a).

Concerning to the effects of early NIPPV introduction in patients with ALS, there are some studies that reported increased compliance, quality of life and survival in those patients that received earlier treatment (mainly defined by the evidence of significant desaturations at nocturnal oximetry) (Velasco et al., 2002; Jackson et al., 2001; Pinto et al., 2003; Lechtzin et al., 2007b; Carratù et al., 2009), encouraging earlier use of NIPPV or the use of more sensitive tests to detect chronic alveolar hypoventilation.

According to recently published guidelines, all patients with ALS could benefit from NIPPV therapy, and a trial with this appliance should never be discouraged, although marked bulbar involvement could be associated with reduced tolerance and maybe survival (Miller

et al., 2009a). Indeed, the increased risk of aspiration in patients with bulbar onset and problems because of difficulties in clearing secretions or obstructions, such as those related to abnormal function of the vocal cords, should be considered.

In our experience NIPPV can be well tolerated by both patients and caregivers, even in patients with bulbar involvement, especially if an intensive educational training and adaptation on NIPPV can be performed (Volanti et al., 2011). Special importance, then, should be deserved to adaptation and compliance during the first few weeks of NIPPV use, since this could be a crucial step in determining the efficacy of the treatment.

Factors predicting survival following NIPPV include advanced age, airway mucus accumulation and lower body mass index (Peysson et al., 2008; Lo Coco et al., 2006). Noncompliance with NIPPV has been related to frontotemporal dysfunction and severe bulbar involvement, whereas compliance with the treatment was associated with young age, preserved upper limb function, symptoms of orthopnea and dyspnea, use of percutaneous endoscopic gastrostomy (PEG), speech devices, and riluzole (Bourke et al., 2003, 2006; Gruis et al., 2005; Olney et al., 2005; Jackson et al., 2006). Nocturnal hypercapnea has also been recently indicated as a predictor of good compliance with subsequent NIPPV treatment (Kim et al., 2011). Oxygen supplementation should be avoided unless provided with mechanical ventilation or to treat dyspnea as a palliative, periodically monitoring CO_2 levels. In fact oxygen therapy may reduce respiratory drive particularly during sleep and has been associated with CO_2 retention and a less favourable outcome than ventilation (Bach et al., 1998; Gay & Edmonds, 1995).

At present, worldwide accepted guidelines propose NIPPV initiation in the presence of respiratory symptoms, and/or evidence of respiratory muscles weakness (FVC ≤ 80% of predicted or SNIP ≤ 40 cmH_2O), evidence of significant nocturnal desaturation on overnight oximetry (< 90% for > 5% of the time asleep) or a morning arterial $PaCO_2$ > 6.5 kPa (Radunović et al., 2007; Miller et al., 2009a).

4. Physiotherapy and management of airway secretions

Physiotherapy is a useful palliative adjunction in the treatment on ALS, in particular in the management of respiratory secretions (Lo Coco et al., 2008). Indeed, during the course of the disease progressive inspiratory and expiratory muscle weakness and bulbar innervated muscle dysfunction result in ineffective cough reflex. Coughing, an important part of the airway defence aiding in the removal of secretions, consists of three components: an inspiratory phase, a compressive phase with glottic closure, and an expulsive phase resulting from sudden glottic opening. Patients with ALS may develop impairment of any of these three phases, and as a result, clearance of respiratory secretions may become problematic, leading to further pulmonary complications.

The effectiveness of mucus clearance is largely dependent on the magnitude of peak cough flows (PCFs) (King et al., 1985), which can be measured using a standard peak flow meter adapted to an anesthesia face mask. A PCF of < 2.7 L/s has been suggested to indicate an ineffective cough (Bach & Saporito, 1996; Tzeng & Bach, 2000). However, since PCF decreases during respiratory tract infections, when the pressure generated by expiratory muscles is reduced (Poponick et al., 1997), it has been suggested that once a patient's PCF is < 4.5 L/s, particularly in the presence of bulbar dysfunction, there is a risk for pulmonary complications (Bach et al., 1997; Sancho et al., 2007). That threshold could be an appropriate time to implement assisted cough techniques. Moreover, patients with a mean PCF above

337 L/min had a significantly greater chance of being alive at 18 months (Chaudri et al., 2002).

Methods of treatment include breathing exercises, postural drainage, exercise regimens and the use of assisted cough techniques (Lo Coco et al., 2008).

Medications with mucolytics like guaifenesin or N-acetylcysteine, a β-receptor antagonist (such as metoprolol and propanolol), nebulized saline, or an anticholinergic bronchodilator such as ipratropium are widely used, although no controlled studies exist in ALS (Miller et al., 2009a).

The benefit of breathing exercises is difficult to evaluate but their main aims can be summarized as: to promote a normal breathing pattern; to teach controlled breathing for use during attacks of dyspnoea; in conjunction with forced expiration technique and postural drainage to assist the removal of secretions; and to maintain the mobility of the chest wall. Patients must be carefully instructed by a physiotherapist and should practise these exercises regularly.

Patients who have excess secretions in the bronchial tree or difficulties in secretions removal may benefit from postural drainage. Postural drainage can be defined as the placement of a patient in various positions so that, with the aid of gravity, secretions may drain from the peripheral to the more central areas of the lung and thus become more easily expectorated. The positions to be used and also the length of time spent in each position must be determined for each patient by a skilled physiotherapist. Clearance of bronchial secretions by postural drainage may be further assisted by the use of deep breathing, percussion and chest vibration, which may be combined with compression of the chest wall and also with the use of the forced expiration technique. However, patients with limited mobility and muscle weakness have difficulty with postural drainage and generally do not benefit from chest physical therapy (Kirilloff et al., 1985). Moreover, intensive cycles of physiotherapy may be exhausting for many patients, particularly those with advanced disease, and may cause arterial desaturation.

Interestingly, a recent double-blind, randomized-controlled trial showed that inspiratory muscle training may potentially strengthen the inspiratory muscles and slow the decline in respiratory function in patients with ALS (Cheah et al., 2009).

Among non-invasive expiratory aids, manually assisted coughing techniques, such as anterior chest compression and abdominal trust, have been shown to be effective in facilitating the elimination of airway secretions in patients with neuromuscular diseases (Massery & Frownfelter, 1990; Bach, 1993a). Nevertheless, manually assisted coughing is labour intensive and often difficult for non-professional caregivers, both during outpatient and in-hospital management, and it depends on precise care provider-patient coordination (Vianello et al., 2005).

The mechanical in-exsufflator (MI-E) is a device that assists patients in clearing bronchial secretions. It consists of a two-stage axial compressor that provides positive pressure (that causes a deep insufflation), thereby generating a forced expiration in which high expiratory flow rates and a high expiratory pressure gradient are generated between the mouth and the alveoli. It is usually applied via a facemask. The use of MI-E has been described to be simple and safe enough for application by non-professional caregivers (Bach, 1993a, 1994), and has been proposed as a complement to manually assisted coughing in the prevention of pulmonary morbidity in neuromuscular patients (Tzeng & Bach, 2000; Bach et al., 1993b). MI-E has also been shown to be helpful in the

management of patients with ALS (Sancho et al., 2004) and to be effective in prolonging non-invasive respiratory aids delaying the need for tracheostomy (Bach, 2002). However, this device seems to be ineffective in patients with severe bulbar dysfunction (Bach, 2002; Sancho et al., 2004), perhaps because the application of the exsufflation cycle of MI-E for those patients with weakness of the genioglossus activity due to bulbar dysfunction might produce a dynamic, total, or partial collapse of the upper airway (Sancho et al., 2004).

It is useful to remember that for patients whose vital capacities are less than normal, manually assisted coughing is not optimally effective unless preceded by a maximal lung insufflation, and MI-E is not optimal unless an abdominal trust is applied during the exsufflation (Goncalves & Bach, 2005). Then abdominal trusts and MI-E should be combined together for effective prevention of lower respiratory tract infection and respiratory insufficiency. Failure to correctly administer physical medicine aids continues to make respiratory failure inevitable for the great majority of people with neuromuscular diseases (Goncalves & Bach, 2005).

Finally, high-frequency chest-wall oscillation (HFCWO), another airway-clearance technique, has been recently evaluated in a 12-week randomized, controlled trial on 46 patients with ALS (Lange et al., 2006). HFCWO is a technique that, through generation of high flow in the small airways, is thought to mobilize secretions from the distal airways to the larger airways, from where they can be more easily removed. It has been reported that HFCWO is well tolerated, considered to be helpful by a majority of patients, and decreases symptoms of breathlessness, suggesting that the intervention was useful in the clearance of airway secretions in patients with ALS (Lange et al., 2006). Another study, however, failed to show any benefit in loss of lung function or mortality in 9 patients with ALS (Chaisson et al., 2006).

A part from sustaining respiration with mechanical devices, special consideration should be given to prevention of aspiration and development of pneumonia (Radunović et al., 2007; Miller et al, 2009 a,b). In this regard, it is of fundamental importance the reduction of the amount of salivary secretions through the use of several medications (such as amitriptyline and botulinum toxin injections), devoting adequate amount of time in teaching proper swallowing technique, and maintaining hydration. It is also useful to provide a portable mechanical home suction device. In addition, when dysphagia worsens, placement of a PEG tube should be the preferred option, especially when the respiratory function is not too much compromised. Smoking cessation advice should be offered to all patients who are current smokers. Influenza and pneumococcal immunization should be encouraged during the progression of the disease, although ALS has not been included in specific risk-group recommendations available so far. In case of acute pneumonia, adequacy and length of treatment, proper dosages and intervals of administration, and reduction of delay of initial antibiotic treatment are all important issues (American Thoracic Society, 2005; Lim et al., 2009).

Antibiotic prophylaxis strategies are especially useful to prevent ventilator-associated pneumonia, whereas passive humidifiers or heat–moisture exchangers decrease ventilator circuit colonization, but have not consistently reduced the incidence of ventilator-associated pneumonia, and thus they cannot be regarded as a pneumonia prevention tool (American Thoracic Society, 2005).

5. Invasive mechanical ventilation

ALS is a relentless pathology that causes progressive muscle dysfunction. Therefore respiratory capacity eventually fails, despite NIPPV treatment. Indeed, at first, NIPPV is generally used for intermittent nocturnal support to alleviate symptoms of nocturnal hypoventilation, although as respiratory function worsens, patients tend to require increasing daytime support and eventually continuous support. When all the respiratory aids fail to maintain adequate blood oxygen saturation, the only intervention that allows survival of these patients is invasive mechanical ventilation through a tracheostomy tube. Treatment failure seems not to be dependent on lung or respiratory muscle function but on bulbar dysfunction (Bach et al., 2004).

When placed on invasive ventilation patients are supported from a respiratory point of view; however, the loss of motor neurons goes on progressively, leading to complete paralysis and muscular atrophy. Some patients may eventually reach a "locked in" state in which they cannot communicate at all, because there is also total paralysis of the extraocular muscles. When connected to tracheostomy tubes patients may survive for many years, with respiratory tract infections the most frequent cause of death (Bradley et al., 2002; Hayashi & Oppenheimer, 2003; Lo Coco et al., 2007; Marchese et al., 2008; Vianello et al., 2011). Median survival time usually ranges from 2 to 4 years. Interestingly, the amyotrophic lateral sclerosis functional rating scale (ALSFRS), a disease-specific rating scale that assesses functional impairment, has been shown to predict both length of hospital stay as a result of acute respiratory failure and survival after initiation of invasive ventilation in these patients (Lo Coco et al., 2007).

Notwithstanding its effect on survival, only a minority of patients with ALS receive invasive mechanical ventilation, at least in the western Countries (Moss et al., 1993; Miller et al., 2000; Neudert et al., 2001). On the contrary, in Japan the frequency of invasive ventilation is considerably higher. Many patients are treated in emergency without advance planning, because of a respiratory crisis, whereas the number of patients that electively choose this treatment is low (Moss et al., 1993, 1996; Cazzoli & Oppenheimer, 1996; Lo Coco et al., 2007). Socio-economic reasons may be one of the possible explanations for the low prevalence of invasive ventilation in ALS, given the relatively high costs of this treatment. Moreover there is a need for 24-hour-caregiving, which could be perceived by caregivers and relatives as extremely burdensome. A recent study suggested that the choice of invasive ventilation was consistent with a sustained sense that life was worth living in any way possible, at least for some time and within certain boundaries, although it may involve unrealistic expectations of cure by some (Rabkin et al., 2006). Moreover, the attitudes of the treating physician have also a great influence (Moss et al., 1993), and there is concern that tracheostomy will prolong life beyond the point that the patient can communicate or interact with others.

Despite these many doubts and concerns, the majority of patients that underwent invasive ventilation were positive about their choice (Moss et al., 1993), reporting a satisfying quality of life (Cazzoli & Oppenheimer, 1996; Kaub-Wittemer et al., 2003), and indicating that they would repeat the choice again in the same situation. Caregivers were more frequently burdened and distressed by this intervention and they frequently witnessed a marked reduction of social life activities (Cazzoli & Oppenheimer, 1996; Gelinas et al., 1998; Kaub-Wittemer et al., 2003; Rabkin et al., 2006).

It is good practice that patients together with their families discuss end-of-life issues and preferences with the physician, so that advance directives and patient's wishes are well

known in advance of a respiratory crisis (Silverstein et al., 1991; Andersen et al., 2005, 2007). Indeed, once intubated, patients can rarely get free from the ventilator. These preferences should also be reviewed periodically during the course of the disease, since patients' desires concerning life-sustaining interventions might change with disease progression. Ideally, emergency intubation and tracheostomy should be avoided (Andersen et al., 2005, 2007), but this is a much debated question, since there is not universal consent from public authorities. As a result, the percentage of patients that had been tracheotomized without informed consent is very high across studies (Moss et al., 1993, 1996; Cazzoli & Oppenheimer, 1996; Lo Coco et al., 2007).

Symptomatic treatment of severe dyspnea includes use of opioids (morphine) alone or in combination with benzodiazepines (such as lorazepam, diazepam or midazolam), if significant anxiety is present (Voltz & Borasio, 1997; Miller et al., 1999; Andersen et al., 2007; Clemens et al., 2008). Relief of dyspnea using opioids was rated as good by 81% of hospice patients with ALS. (O'Brien et al., 1992). Dose titration against clinical symptoms is recommended and rarely results in life-threatening respiratory depression. Anxiety of choking correlated highly significantly with the intensity of dyspnea (Clemens et al., 2008).

Terminal relentlessness and confusion secondary to hypecapnia could be relieved by administration of neuroleptic drugs (Voltz & Borasio, 1997; Miller et al., 1999; Andersen et al., 2007).

There are some case series offering practical advice for withdrawing both invasive and non-invasive ventilation, including frequent and repeated discussions and counseling with the patient and his family, assessment for discomfort, such as dyspnea, agitation, or anxiety, and symptom management during the withdrawal process with morphine and benzodiazepines (such as diazepam) (Borasio &, Voltz, 1998; Ankrom et al., 2001; O'Mahony et al., 2003). However, there are no controlled studies specifically examining withdrawal of ventilation in ALS (Miller et al., 2009b).

6. Conclusion

Recent publications provided important contributions to many aspects of respiratory care for patients with ALS, such as non-invasive ventilation and assisted cough. There is a need for regular assessment and follow up of respiratory function, and investigations should include daytime assessment of respiratory function (including FVC and SNIP) as well as sleep studies in order to ensure early recognition of patients with respiratory muscle impairment (Lo Coco et al., 2008).

At present time the only approved pharmacological treatment for ALS is riluzole, which extends survival by about 2 months (Miller et al., 2007). On the other hand, NIPPV treatment allows survival for longer periods of time, improves quality of life, and may probably alter the disease course. As a consequence, NIPPV should be considered a major treatment option in patients with chronic hypoventilation or in whom respiratory impairment has become evident during sleep despite normal diurnal respiratory function. Every effort, then, should be made to improve NIPPV implementation in the management of patients with ALS worldwide, since it is still underutilized. The degree of hypoventilation that should prompt introduction of NIPPV must be defined further, even if there is a general tendency toward earlier intervention. Nocturnal hypoventilation could be particularly useful for this purpose.

Prevention of aspiration and pneumonia, and adequate management of bronchial secretions are two other important issues. Adequate treatment of sialorrhea and dysphagia are important in the reduction of pneumonia risk. Insufficient cough is a condition that can be diagnosed by measuring peak cough flow and should, whenever present, be treated in patients with ALS. There is some evidence that the MI-E device could be of help in cough assistance, except for patients with severe bulbar dysfunction, but further research is needed, as well as randomized trials that compare the MI-E with other techniques of assisted coughing.

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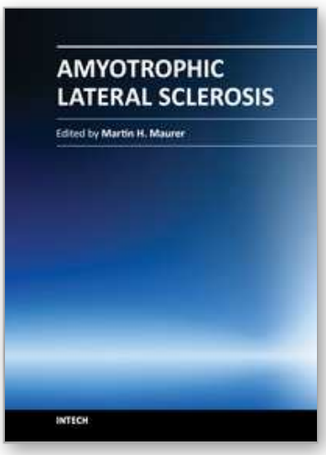

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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