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Multidisciplinary Rehabilitation in Amyotrophic Lateral Sclerosis

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is the most common chronic neurodegenerative disorder of the motor system in adults. It is a relatively rare disease with a reported population incidence of between 1.5 and 2.5 per 100,000 per year worldwide and a gender ratio of 3:2 men: women. Amyotrophic Lateral Sclerosis is characterized by the loss of motor neurons in the cortex, brain stem, and spinal cord, manifested by upper and lower motor neuron signs and symptoms affecting bulbar, limb, and respiratory muscles. Death usually results from respiratory failure and follows on average two to four years after onset, but some may survive for a decade or more.

Amyotrophic Lateral Sclerosis is a devastating condition with unknown aetiology and no current cure. The symptoms in ALS are diverse and challenging and include weakness, spasticity, limitations in mobility and activities of daily living, communication deficits and dysphagia, and in those with bulbar involvement, respiratory compromise, fatigue and sleep disorders, pain and psychosocial distress. The International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001), defines a common language for describing the impact of disease at different levels: impairment (body structure and function), limitation in activity and participation (see Figure 1). Within this framework ALS related impairments (weakness, spasticity), can limit "activity" or function (decreased mobility, self-care, pain) and "participation" (driving, employment, family, social reintegration). "Contextual factors", such as environmental (extrinsic) and personal factors (intrinsic) interact with all the other constructs to shape the impact of ALS on patients and their families. The impact of ALS upon patients, their caregivers (often family members) and on society is substantial, often beginning long before the actual diagnosis is made, and increasing with increasing disability and the need for medical equipment and assisted care (Klein and Forsheew, 1996).

Given the broad spectrum of needs, current management spans from diagnosis (acute neurological needs) through to symptomatic and supportive rehabilitation and palliative care. The interface between neurology, rehabilitation and palliative care is of utmost importance to ensure co-ordinated care for persons with ALS rather than duplicating services (Royal College of Physicians National Council for Palliative Care and British Society of Rehabilitation Medicine, 2008). It should be noted however that the focus of this chapter is on the rehabilitation phases, hence discussion of acute neurological and palliative care aspects are limited.

Rehabilitation is defined as “a problem solving educational process aimed at reducing disability and increasing participation experienced by someone as a result of disease or injury” (Wade, 1992). Although it is sometimes effective in reducing impairment, its principal focus is to reduce symptoms and limitations at the level of activity and participation, through holistic interventions, which incorporate personal and environmental factors. The multidisciplinary rehabilitation team (see Figure 2) comprises of a group of clinical professionals with expertise in ALS, directed by a physician, who work as an integrated unit to provide seamless care which is patient-centred, flexible and responsive to the evolving nature of the condition (Hardiman, 2007). The role of multidisciplinary rehabilitation in ALS is supported by a recent Cochrane review (Ng et al., 2009) which suggested some advantage for quality of life without increasing healthcare costs, reduced hospitalisation and improved disability with conflicting evidence for survival.

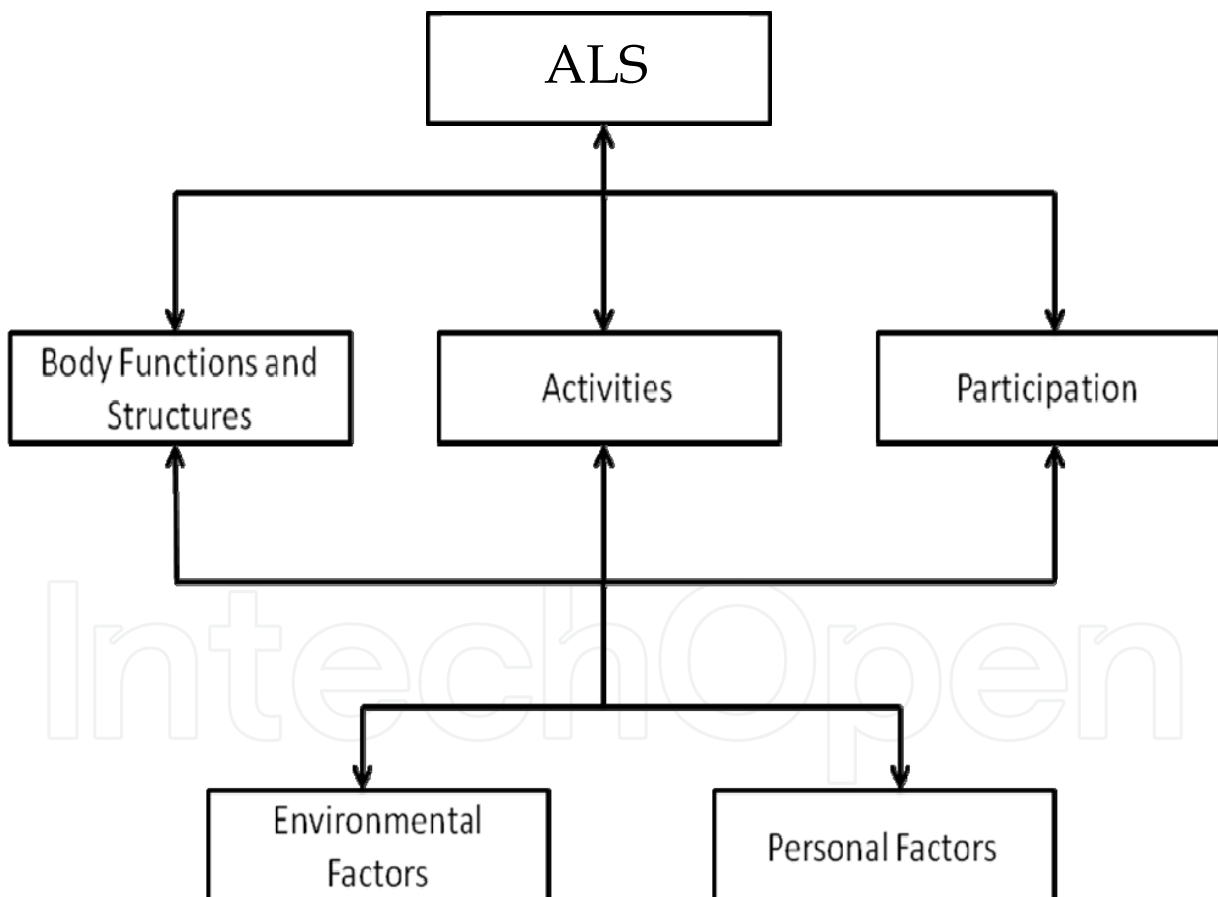


Fig. 1. The interaction between the various domains of the International Classification of Functioning, Disability and Health (adapted from (World Health Organization, 2001))

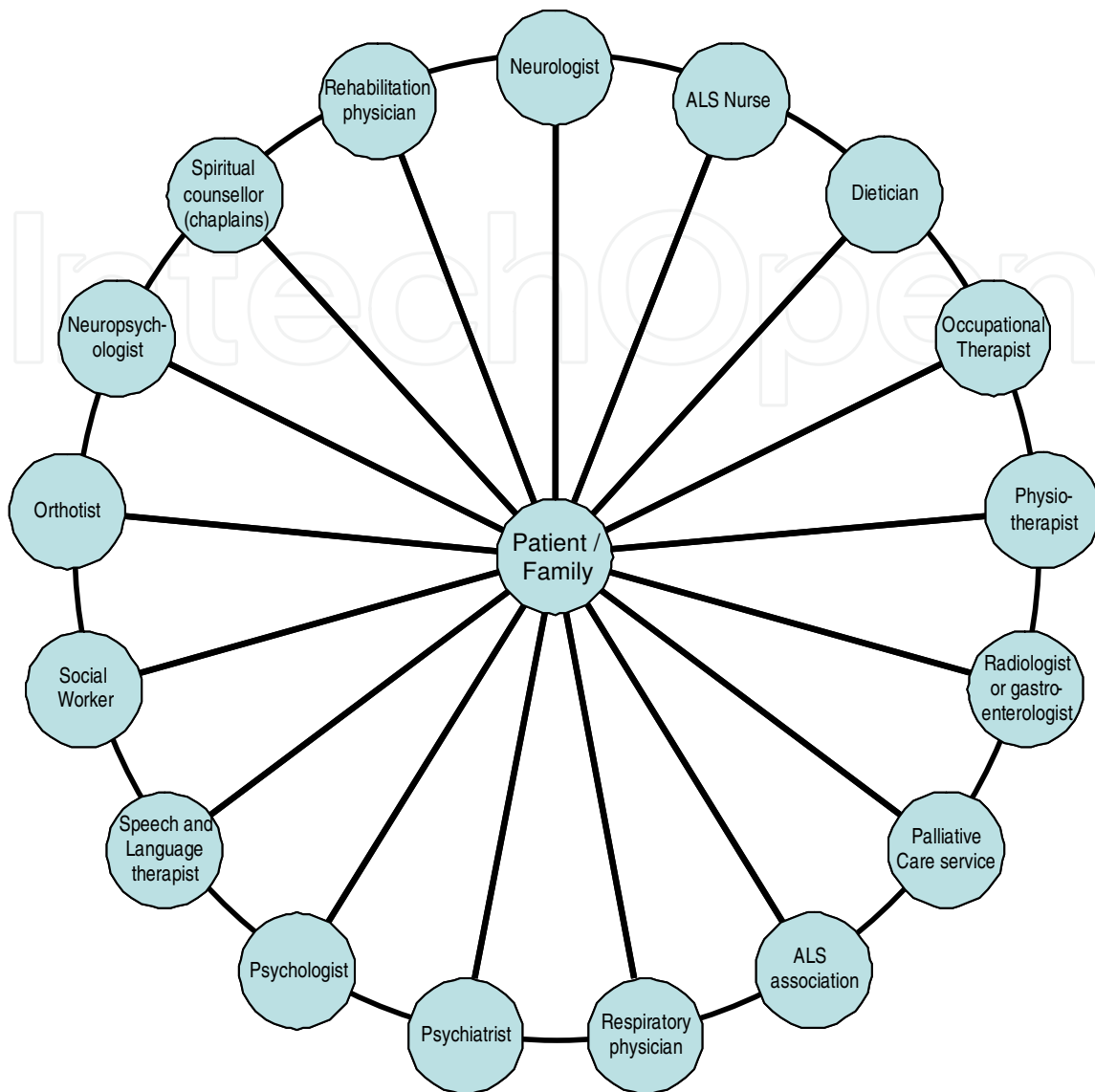


Fig. 2. The multidisciplinary rehabilitation team in ALS (adapted from (Hardiman, 2007))

A proposed model for service interaction in caring for persons with ALS shows involvement of neurologists and palliative care teams in the acute and terminal phases of care, with a relatively smaller role for rehabilitation physicians. However rehabilitation plays a major role in long-term care and support (over years) in the more slowly progressive phase (Royal College of Physicians National Council for Palliative Care and British Society of Rehabilitation Medicine, 2008). Early rehabilitation intervention and treatment has much to contribute to improve health and quality of life prior to accumulation of disability through symptomatic and supportive therapies to enhance functional independence and community integration and reduce barriers (such as lack of knowledge about treatment, economic constraints) (Kemp, 2005). Disability management in ALS should also be planned, with deficits should be anticipated (over time) to avoid “crisis management”. As patients deteriorate the rehabilitation and palliative care approaches can overlap, i.e. “neuropalliative rehabilitation”. Key skills in neuropalliative rehabilitation include: understanding disease progression, symptom control,

managing expectations, issues relating to communication, addressing end of life issues, legal issues (mental capacity, wills), specialist interventions (ventilation), equipment needs, counselling and support, and welfare advice (Royal College of Physicians National Council for Palliative Care and British Society of Rehabilitation Medicine, 2008).

The literature presented in this review includes all levels of evidence for multidisciplinary rehabilitation of ALS (including randomised and clinical controlled trials, case studies and expert opinion).

2. Rehabilitation issues in ALS

Amyotrophic Lateral Sclerosis is a fatal disease with a challenging progressive course that results in a broad and ever-changing spectrum of care needs. Symptoms are varied (see Table 1) and need to be carefully assessed and managed. The timing of provision of appropriate care is important as whilst information needs to be provided when patients are psychologically in the right frame of mind, the options of certain interventions may be time-limited as the disease continues to progress.

Weakness	94%
Dysphagia	90%
Dyspnoea	85%
Pain	73%
Weight loss	71%
Speech issues	71%
Constipation	54%
Cough	48%
Sleep issues	29%
Emotional lability	27%
Drooling	25%

Table 1. Symptoms experienced by ALS patients (adapted from (Oliver, 1996))

2.1 Respiratory dysfunction

Most deaths in ALS are due to respiratory failure from respiratory muscle weakness, hence the diagnosis and management of respiratory symptoms is important (Figure 3) (Miller et al., 2009a). Counselling may be initiated at the time of diagnosis especially if respiratory symptoms are present and/or forced vital capacity (FVC) is <60% of predicted. Early symptoms may be suggestive of nocturnal hypoventilation (eg. frequent arousals, morning headaches, excessive daytime sleepiness, vivid dreams) rather than overt dyspnoea (Miller et al., 2009a). It is important to discuss the options of respiratory choices, including tracheostomy and ventilatory support well before these are clinically indicated to enable advance planning or directives. It is also important to offer patients information about the terminal stages of ALS and reassure regarding terminal hypercapnoeic coma and resulting peaceful death, as many may fear "choking to death" (Borasio et al., 2001b).

Respiratory function should be evaluated every three months from the time of diagnosis. Whilst FVC is the most commonly used (Melo et al., 1999) and significantly predicts survival (Czaplinski et al., 2006), it can be insensitive to slight changes in muscle strength (Fitting et al., 1999). The maximal sniff nasal inspiratory force (sniff nasal pressure) may be more

appropriate especially in those with bulbar weakness (no mouthpiece) and may be more sensitive to changes in diaphragmatic and respiratory muscle strength (Stefanutti et al., 2000; Lyall et al., 2001). It is also more reliably recorded in the later stages of ALS (Morgan et al., 2005).

Initial management can include chest physiotherapy and postural drainage, especially if the patient has difficulty clearing secretions from the chest (Shaw, 2003). A suction machine may also be helpful. Preventing respiratory infections is a primary goal and pneumococcal and influenza vaccines should be administered. Respiratory muscle exercise can be instituted and may delay the onset of ventilatory failure (Schiffman, 1996).

Non-invasive ventilation (NIV) should be considered in respiratory dysfunction (see Figure 3) especially for nocturnal symptomatic respiratory compromise. A recent Cochrane review concluded that NIV significantly improves quality of life when tolerated and may prolong survival in those with normal to moderately impaired bulbar function especially if used for ≥ 4 hours/day (Radunovic et al., 2009). Successful use of NIV is dependent on respiratory therapists and patients working closely and patiently through the adjustment phase of NIV, especially with selection and tolerance of face masks. A small dose of anxiolytic may assist with the process in select patients. Bulbar involvement and executive dysfunction may also reduce compliance (Miller et al., 2009a).

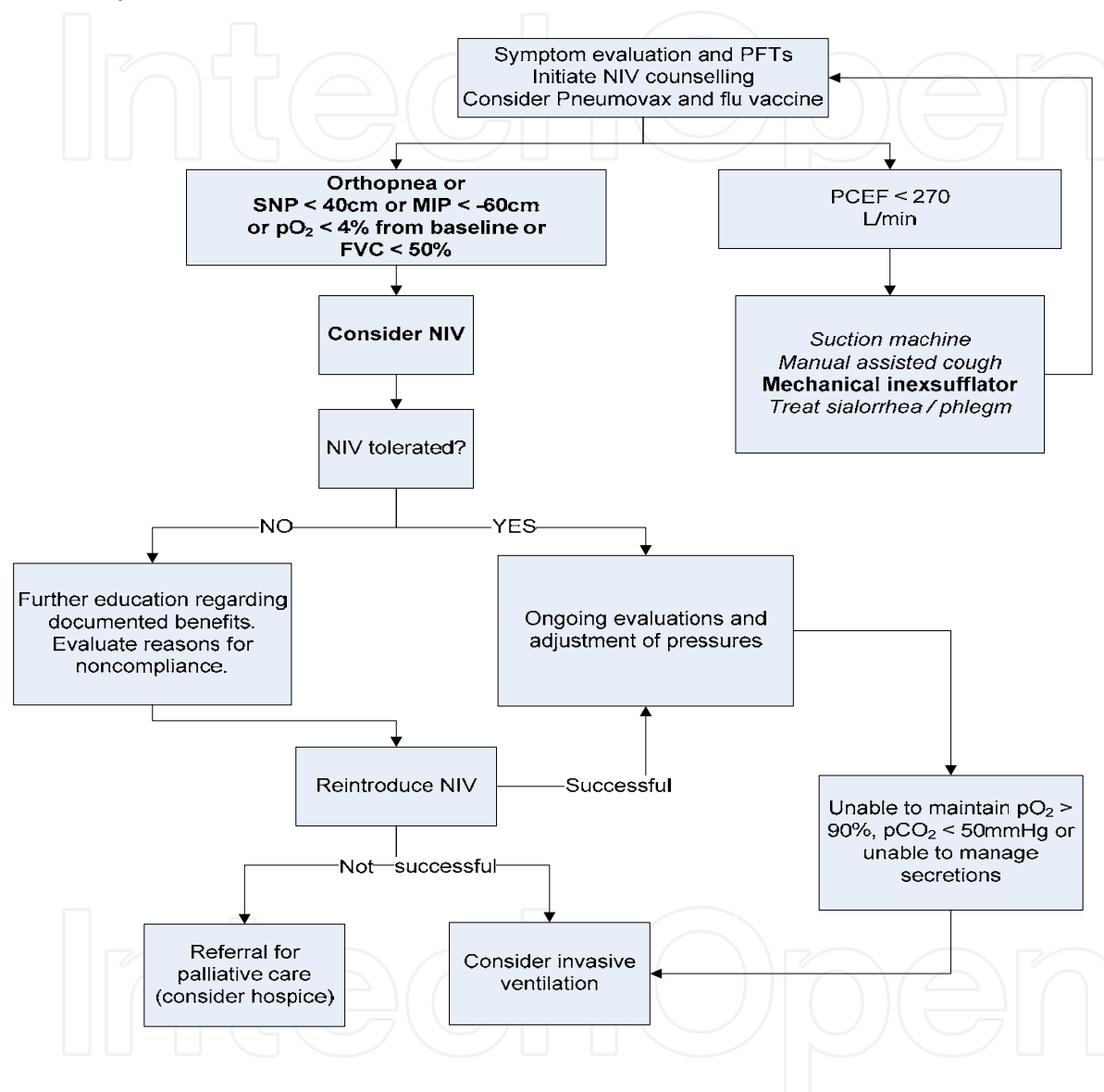
Invasive ventilation should be offered when longer-term survival is the goal. Counselling is necessary with regards to benefits and burden (expense, intensive physical support with suctioning and nursing care, high caregiver burden) as many may not be able to manage invasive ventilation at home, thus requiring nursing home placement (Kaub-Wittemer et al., 2003; Miller et al., 2009a). There is evidence however that the 10-20% of persons with ALS who undergo invasive ventilation (including those administered at the time of acute respiratory failure without advance discussion) appear to have good acceptance and satisfactory quality of life (Vianello et al., 2010).

2.2 Communication

Dysarthria is common as a result of bulbar involvement and is often a source of significant frustration to the persons with ALS and their families. Early changes include nasality or reduced vocal volume and changes in oral movement rates and speech rates (Yorkston et al., 1993). As weakness and spasticity of the oral and laryngeal muscles increase, imprecise consonant production, hypernasality, harsh vocal quality, slowed rate of speech and breath volumes affect intelligibility (Hillel and Miller, 1989). Speech pathologists can teach the patient to slow speech rate, exaggerate articulation and improve respiratory efficiency through phrasing (Francis et al., 1999). Palatal lift and palatal augmentation prostheses may also be of some use to reduce the hypernasal aspect of dysarthria (Esposito et al., 2000).

As intelligibility in ALS worsens, Augmentative and Alternative Communication (AAC) is required. AACs can improve quality of life by optimising function and assisting with decision making (Brownlee and Palovcak, 2007). AACs range from no or low technology (gestures, communication boards with letters) to high-tech electronic communication devices that allow the user to have voice output (Brownlee and Palovcak, 2007). For example, speech-generating devices such as LightWRITERS are commonly used. These devices can be used as long as there is voluntary motor movement (including eye gaze). The specific access method depends on the abilities of the patient – for example, pointing with a body part or pointer, adapted mice or joysticks or switches and scanning technology can be used. For those who have no voluntary

motor control for communication, a recent case study using a brain-computer interface system has been reported and appears promising (Sellers et al., 2010). The emotional aspect of using an alternative form of communication however can result in significant patient resistance and acceptance as the ability to speak and use language is what distinguishes us from all other species (Pinker and Jackendoff, 2005; Brownlee and Palovcak, 2007). Hence, acceptance of an AAC may take weeks to months.



Text in bold = evidence-based
Text in italics = consensus-based

PFT = pulmonary function tests; PCEF = peak cough expiratory flow; NIV = noninvasive ventilation; SNP = sniff nasal pressure; MIP = maximal inspiratory pressure; FVC = forced vital capacity (supine or erect)

Fig. 3. Respiratory management algorithm in ALS (adapted from (Miller et al., 2009a))

A source of significant frustration for those with speech difficulties is use of the telephone. Technology is available and varies from country to country. In the United States, "Speech to Speech" technology can be used, where trained communication assistants are used by the patient to complete phone calls. They are trained to use superior equipment to hear the caller and place the call, then repeat verbatim what the caller says so the call is completed successfully.

2.3 Swallowing and nutrition

Dysphagia affects a third of persons with ALS at onset and the majority by late disease (Higo et al., 2004). It increases the risk of suboptimal caloric and fluid intake and can worsen weakness and fatigue (Borasio, 2001). Aspiration pneumonia (13%) is a contributor to respiratory complications and is associated with increased mortality with mean survival time post-infection of 2 months (Sorenson et al., 2007).

Difficulties in the oral preparatory stage of swallowing (preparation of food for propulsion to the pharynx) is common (Mayberry and Atkinson, 1986). Symptoms include jaw weakness, fatigue, drooling, choking on food and slow eating. In addition, loss of upper limb function and fear of choking or depression can further impact on self-feeding abilities and oral intake (Slowie et al., 1983). A speech pathologist can evaluate the degree of dysphagia through bed-side assessments and/or further imaging (eg videofluoroscopy). Mild dysphagia can be managed with specific interventions such as alteration of food consistency, upright positioning, small bolus size, soft collar for neck extensor weakness and the chin-tuck technique, in which the person flexes their neck to the anterior chest wall as they swallow, narrowing the inlet to the larynx and reducing the chance of food aspiration. Dieticians monitor nutritional status through body weight, percentage weight loss and body mass index. Common advice includes high calorie diets, texture modification and prescription of nutritional supplements (Rio and Cawadiaz, 2007). Patients may show nutritional compromise even before bulbar symptoms become significant (Slowie et al., 1983) as in addition to muscle wasting, persons with ALS at all stages of disease often do not meet their energy requirements (Kasarskis and Neville, 1996). Dehydration is also a common and important problem contributing to fatigue and thickened secretions (Francis et al., 1999).

As dysphagia progresses, evidence (Level B) suggests a percutaneous endoscopic gastrostomy (PEG) or equivalent (eg. radiologically inserted gastrostomy) is indicated to supplement oral intake (as long as this remains safe) for weight maintenance (Loser et al., 2005). PEGs prolong survival but there is currently little evidence regarding the impact of PEG on quality of life (Langmore et al., 2006). Timing of a PEG can be challenging. Indicators may include weight loss (5-10% of body weight loss implies nutritional risk (Francis et al., 1999)) and reduced FVC. If FVC falls below 50% of predicted (Kasarskis et al., 1999), risks of laryngeal spasm, localised infection, gastric haemorrhage, technical difficulties of PEG placement and respiratory arrest increase (Mazzini et al., 1995; Mathus-Vliegen et al., 1994)).

Sialorrhoea can be a significant issue in ALS and is generally not related to increased saliva production but rather to impaired ability to swallow saliva, combined with facial weakness causing labial incompetence and neck weakness causing the head to tip forward (Francis et al., 1999). Improved positioning, use of a cervical collar and orolingual exercises may be helpful. Medications such as anticholinergics and tricyclics can also be trialled (Schiffman

and Belsh, 1996), as can suction machines. In the US, most commonly used medications are amitriptyline, glycopyrrolate, atropine and propantheline (Forsheiw and Bromberg, 2003). However, medications may further thicken secretions, hence should be used with caution in those with respiratory insufficiency or poor cough. More recently, botulinum toxin injected into the salivary glands (parotid, submandibular) appears to be safe and has been used to treat sialorrhea with beneficial effects lasting approximately 3 months (Verma and Steele, 2006; Contarino et al., 2007). Thick oropharyngeal secretions may be treated with increased fluid intake, humidification of air, cough augmentation, suction machines and guaifenesin (Forsheiw and Bromberg, 2003).

2.4 Exercise

The effects of exercise and safe therapeutic range in ALS are poorly understood. It is generally thought that weakness and muscle fibre degeneration may be accelerated by overwork or heavy exercise as it is already functioning close to its maximal limits (Johnson and Braddom, 1971). However, inactivity leads to deconditioning and disuse weakness. In addition, muscle and joint spasticity can cause pain, contractures and further loss of function. A recent Cochrane review (Dalbello-Haas et al., 2008) identified two trials (n = 52), which addressed therapeutic exercise in ALS. The trials examined the effects of moderate intensity, endurance type exercise on spasticity, and effects of moderate intensity resistance type exercises in ALS. Although one of the trials reported improvement in function and quality of life, both trials were too small to determine to what extent strengthening exercises were beneficial or harmful in this population (Dalbello-Haas et al., 2008). A more recent pilot study demonstrated that repetitive rhythmic exercise - supported treadmill ambulation training was feasible, tolerated and safe for patients with ALS and appeared to improve work capacity and gait functioning in patients with ALS who were dependent on assistive devices for ambulation (Sanjak et al., 2010). In view of the paucity of evidence to guide exercise prescription, the current recommendations are (Chen et al., 2008):

- Stretching exercise to improve flexibility to maintain muscle length and joint mobility and prevent contractures.
- Strengthening exercise of sub-maximal (low, non-fatiguing) intensity, with degree of resistance tailored to muscle strength.
- Aerobic/endurance exercise may improve cardio-respiratory fitness and is probably safe but adequate oxygenation, aeration and carbohydrate load is important to reduce oxidative stress load. Supported treadmill ambulation training can be considered if available.

2.5 Mobility and activities of daily living

In early stages of disease, rehabilitation aims to prolong independence in mobility and activities of daily living, prevent complications such as falls, contractures, and musculoskeletal pain, maintain strength, range of movement and conditioning through an appropriate exercise program, educate the patient and family about the disease, provide psychological support, evaluate the home for safety and teach energy conservation techniques (Khanna et al., 2007).

As weakness worsens, the physiotherapist can instruct the patient and family in safe transfer techniques (eg. between bed and chair, in and out of cars), optimise gait pattern and provide gait re-training with appropriate gait aids (eg. walking frame, sticks) and orthoses (ankle-foot

orthosis to facilitate foot clearance during gait and stabilise knee to prevent falls). Occupational therapists can fabricate with upper limb orthoses to assist with fine motor function. For example, patients with distal weakness can improve hand function with wrists braced in 30° extension which improves efficiency of grip and addition of a universal cuff can assist those with weak grasp in feeding and typing (Francis et al., 1999). Other adaptive equipment is also provided, such as built-up cutlery for eating, Velcro fasteners for dressing, long-handled aids, and bathroom equipment (rails, over-the-toilet frames, bath boards, shower chairs, commodes). Wheelchairs are generally eventually required although introduction of a wheelchair whilst a patient is still ambulant, for intermittent community use, is important to enhance energy conservation. Future needs should be anticipated and considered when prescribing a powered wheelchair (eg. reclining, tilt-in-space, custom seating, and modifiable control system) to optimise independence and social interaction whilst preventing contractures, compression nerve palsies, skin breakdown and aspiration. A motorised scooter may be more appropriate for some patients (Francis et al., 1999). Other equipment such as hospital beds with pressure-relieving mattress and hoists for lifting might also be required. Caregiver training in the use of hoists is important to prevent injury.

A recent study (n=44) (Ng et al., 2011) showed that a small but significant gap exists from the perspective of persons with ALS with regards to advice and assistance relating to continued employment and driving. Healthcare providers may underestimate the importance of maintaining employment as a priority in a fatal condition such as ALS and hence under treat this issue. For these persons, the use of assistive technology may be particularly useful, especially in employment where computer use is crucial. Computer technology is fast advancing and options include different types of keyboards, mouse alternatives, switches, interfaces, mounting systems, integrated communication/computer access packages, software and systems. For those who have some proximal arm control, track balls, type writing sticks and forearm supports may be useful. In persons with ALS who have more severe upper limb weakness, head tracking systems, on-screen keyboards and voice recognition software may be required. Text-entry software such as Dasher (which is free) can be used whenever a full-size keyboard cannot be used such as on a palmtop computer or with a joystick, touchscreen, trackball, headpointer, or eyetracker. There are also many mouse alternatives available -- eyegaze system, foot control mouse, head tracking mouse, joysticks and switch-adapted mouse.

Assistive technology can have a dramatic effect on restoring and maintaining independence, a sense of control and quality of life. Apart from technologies that assist with mobility and communication which have already been discussed, other forms of assistive technology such as environmental control units (ECU) should be considered. Environmental control systems offer sophisticated electronics to enable people with a range of impairments and severe disability to use a wide variety of electrical devices. Aids may include unobtrusive control units (eg. remote control for TV), home security (door intercoms, door release and alarms), adapted telephones (such as hands-free control) and lighting and heating/cooling systems (Wellings and Unsworth, 1997). These environmental control units may be used to facilitate function and decrease reliance on carers, improve family dynamics and improve patients' self-esteem (Wellings and Unsworth, 1997). It is important for patients, families and therapists to work closely together when prescribing and using assistive technology to ensure the correct, safe and optimal use of such aids and equipment; and to anticipate future needs especially with the expense of such technology. Close collaboration with specialised providers of assistive technology that can provide back-up technical support is also crucial.

2.6 Bladder, bowel and sexuality

Although bowel and bladder sphincters are generally spared, bowel, bladder and sexual dysfunction may be much more common (30%) than reported to health professionals by persons with ALS (Ng et al., 2011). These areas are in general poorly studied in ALS. Constipation is common with inactivity and poor nutritional intake, and can be treated with a regular bowel program with intake of fibre/bulking agents and adequate fluids. Suppositories, stool softeners and enemas should be considered. In one of the few studies addressing bladder function in ALS (n=38), 47% had micturition symptoms and urodynamics studies found a range of UMN abnormalities (Hattori et al., 1983). Where urinary urgency is an issue, oxybutinin may be helpful. Contributory factors to incontinence, such as urinary tract infections, drinking large amount of fluids late in the day and dependent oedema causing nocturia when the legs are elevated overnight should be considered and treated. Wasner et al (Wasner et al., 2004) suggested a prevalence of 62% (n=62) in sexual dysfunction with issues including decreased libido and passivity of the patient and partner due to physical weakness and the body image changes. The wide variation in reported prevalence in bowel, bladder and sexual dysfunction suggests that patients may not volunteer this information; hence its inclusion in routine enquiries might help to encourage reporting and thus the facilitation of appropriate treatment, such as sexual counselling and suggestion of specific techniques.

2.7 Pain

Pain is common in ALS (50% in a recent study (Ng et al., 2011)), especially in the later stages. Fatigue and depressive symptoms may also worsen a patient's experience of pain.

Spasticity and muscle spasms are not an uncommon source of pain and with the current paucity of supporting evidence, this is often treated with stretching exercises in combination with a muscle relaxant (baclofen is the drug of choice) (Ashworth et al., 2006). Baclofen should be started at low doses (5mg twice to three times daily) and slowly increased (up to 100mg a day in divided doses). Baclofen however can be associated with muscle weakness. Tizanidine (2mg twice daily up to 24 mg a day) is likely as efficacious but it is associated with dry mouth. Other options include clonidine (25 µg twice a day) which can cause hypotension, drowsiness and bradycardia and benzodiazepines which can cause sedation and habituation and respiratory depression. Dantrolene is not recommended as it can cause excessive muscle weakness in ALS (Krivickas and Carter, 2005). Intrathecal baclofen is rarely required but may be indicated in those with intractable spasticity, needing more than the maximum oral dose (Marquardt and Seifert, 2002). There are few reports of use of botulinum toxin for spasticity in ALS in literature. Caution is advised as persons with ALS may be more prone to developing generalised weakness after being injected with botulinum toxin A to treat spasticity (Mezaki et al., 1996).

Muscle cramps can cause severe pain and discomfort and are a result of spontaneous activity of motor units induced by contraction of shortened muscles (Norris et al., 1957). The list of potentially useful drugs for cramps is extensive, implying efficacy of individual agents is low and variable and the evidence base weak. In the US, quinine (35%), baclofen (19%), phenytoin (10%), and gabapentin (7%) were the preferred agents (Forshever and Bromberg, 2003); in Europe, choices were quinine (58%), benzodiazepines (40%), magnesium (25%) and carbamazepine (23%) (Borasio et al., 2001a). In 2006 however, the US Food and Drug administration restricted the use of quinine sulfate in the US to treatment of

malaria falciparum because of concerns regarding severe adverse events, including cardioarhythmias, thrombocytopaenia, severe hypersensitivity reactions and serious drug interaction (U.S. Food and Drug Administration, 2006).

In advanced disease, pain often results due to immobility. Musculoskeletal pain from weakness and resulting postural changes can be ameliorated with range of motion exercises, adequate support in sitting and supine positions and proper lifting and transfer techniques to prevent undue traction on weakened joints. Equipment such as motorised beds that slowly rotate from the side to side can be useful for reducing caregiver burden (Francis et al., 1999). Analgesia such as nonsteroidal anti-inflammatory drugs or narcotics (oral or sublingual) may also be required (with careful respiratory status monitoring in the latter). Intramuscular delivery of medications should be avoided due to muscle wasting (Mayadev et al., 2008).

2.8 Fatigue and sleep disorders

Fatigue is a common disability in ALS – 77-83% in recent studies (Ng et al., 2011; Ramirez et al., 2008) but understudied and often overlooked by clinicians (Lou, 2008). It is unrelated to clinical strength as a large component of fatigue in ALS has a central origin (Kent-Braun and Miller, 2000). Fatigue in ALS does not correlate directly with gender, educational level, disease duration, physical function, quality of life, dyspnoea, depression or sleepiness (Ramirez et al., 2008). However, contributory factors may include sepsis (including aspiration), depression and/or anxiety, pain, hypoventilation, positioning, sleep disruption and effortful activity and these should be treated where possible. It may manifest as reduced energy, difficulty in maintaining sustained attention and increased motor weakness, incoordination and gait difficulties. No double-blind, placebo-controlled trials have been performed for treatment of fatigue. Physostigmine is sometimes prescribed but not necessarily effective (Norris et al., 1993). Modafinil appears to be well-tolerated in a recent small open-label study (n=15) and may reduce symptoms of fatigue (Carter et al., 2005). Rehabilitation strategies involve pacing activities (regular rest breaks), energy conservation and fatigue management strategies, addressing sleep disorders, consideration of exercise to improve fitness if appropriate and treating other exacerbating factors.

High incidence of sleep disturbance in ALS has been reported with pain, micturition, and choking listed by patients as the most common causes for awakening (Kinnear et al., 1997 Nov 3-5). Other contributors to poor sleep include abnormal nocturnal movements such as periodic leg movements or fragmentary myoclonus, which was demonstrated on polysomnography in almost all patients with fatigue (Kinnear et al., 1997 Nov 3-5). Such movements may be treated with controlled release carbidopa-levodopa (Sinemet CR) (Sufit, 1997). Antihistamines (eg. diphenhydramine) and other sedatives (eg. Chloral hydrate 250-500mg, benzodiazepines) can also be considered once respiratory causes for sleep disturbance have been ruled out.

2.9 Cognition and behavioural impairment

Cognitive impairment is increasingly recognised in ALS – 50% are thought to have frontal executive deficits (see Table 2) (Lomen-Hoerth et al., 2003). Visuospatial function, praxis and memory storage are usually spared (Massman et al., 1996; Abrahams et al., 2005; Ringholz et al., 2005). Use of memory aids such as diaries, planners and structured daily routine is encouraged. Other conditions (depression, anxiety, fatigue) and medications

(anticholinergics, benzodiazepines) should be monitored as they can worsen cognitive function.

Behavioural changes unrelated to mood or cognition has also been noted although estimates of prevalence vary widely (Woolley and Jonathan, 2008). Marked apathy occurs in an estimated 55% of persons with ALS (Grossman et al., 2007). This correlates with deficits in verbal fluency but not depression, disease duration, FVC or ALSFRS scores and may be related to fatigue, respiratory weakness, impaired sleep, anxiety or medication (Woolley and Jonathan, 2008). It may also be a psychological coping mechanism (Woolley and Jonathan, 2008).

In a subset of persons with ALS (approximately 5%), clear fronto-temporal dementia (also known as fronto-temporal lobar degeneration) is the presenting picture with severe behavioural dysfunction (insidious onset with gradual progression, altered social conduct, impaired regulation of personal conduct, emotional blunting, loss of insight) that begins before motor weakness becomes obvious (Woolley and Jonathan, 2008). In addition, those with fronto-temporal dementia may exhibit disinhibition, restlessness, reduced empathy, lack of foresight, impulsiveness, social withdrawal, verbal stereotypes, verbal or motor perseveration and/or sexual hyperactivity (Neary et al., 1998).

Management of behavioural and cognitive deficits can be challenging and begins with the identification of these issues. An assessment by a neuropsychologist is often helpful in terms of defining the deficits and provision of cognitive and behavioural remediation strategies. Education and counselling of the patient and family is important. No trials have been conducted in efficacy of pharmacological interventions in this area; however the use of antidepressants and antipsychotics may be considered.

Attention and concentration Working memory Cognitive flexibility (rigidity) Response inhibition "Executive function" - Planning/problem/solving/abstract reasoning Visual-perceptual skills Memory Word generation (fluency)

Table 2 Cognitive deficits in ALS (adapted from (Woolley and Jonathan, 2008))

2.10 Pseudobulbar affect

Pseudobulbar affect describes sudden uncontrollable outbursts of laughter or tearfulness and is a result of bilateral corticobulbar tract degeneration (Rosen and Cummings, 2007). It is common, affecting between 50-70% of persons with ALS (Palmieri et al., 2009) especially those with the bulbar form of ALS. Pseudobulbar affect can have a significant impact on anxiety and emotional frailty (Palmieri et al., 2009), social functioning and relationships in persons with ALS as these sudden, frequent, extreme, uncontrollable emotional outbursts may lead to severe embarrassment and social withdrawal (Moore et al., 1997).

Despite the prevalence of this issue, less than 15% ask for treatment (Meininger, 2005). Education of the persons with ALS and their family and friends assists with understanding and acceptance of these pathological and involuntary outbursts and is an important component of the appropriate treatment of pseudobulbar affect. Crying associated with

pseudobulbar affect is easily incorrectly interpreted as depression; laughter may be embarrassing. Pharmacological treatment can include amitriptyline (10-150mg nocte, starting with 10mg and slowly increasing the dose) which also has the positive benefit on weight loss and loss of appetite (Meininger, 2005) or fluvoxamine (100-200mg daily). A more recent study (n=140) showed that dextromethorphan and quinidine in combination appears to be more effective in reducing the frequency and severity of pseudobulbar affect and to improve quality of life (Brooks et al., 2004). However, side effects are also more common (nausea, dizziness, gastrointestinal complaints) (Brooks et al., 2004).

2.11 Psychosocial issues

ALS is a devastating condition, which takes its toll on the patient and family especially as the disease progresses, and loss of independence occurs. Rates of depression and anxiety are reported to be 0-44% and 0-30% respectively in persons with ALS (Kurt et al., 2007) and depression does not appear to increase in more advanced disease (Rabkin et al., 2005). Quality of life also appears to be more dependent on psychological and existential factors than physical factors (Goldstein et al., 2006b; Simmons et al., 2000). Amongst caregivers, 23% are depressed (Rabkin et al., 2009) and caregiver strain is often significant as a result of increased caregiving time, cognitive impairments in persons with ALS, emotional labour and socio-economic considerations (Chio et al., 2006; Goldstein et al., 2006a; Ray and Street, 2006). Hence, referrals to support groups and counselling and education of patients and their families (often their caregivers) are essential. Frank discussions facilitate understanding of the disease and improve coping skills. Carer support (both physical and emotional) and respite care should be discussed. Referrals to the local ALS associations are also recommended as these provide patients and families with ongoing support, resources and equipment needs. Psychotherapy should also be considered to assist with coping strategies (Matuz et al., 2010). Antidepressants such as amitriptyline and selective serotonin reuptake inhibitors may be used, the former being also useful for other symptoms such as drooling, pseudobulbar affect and insomnia. Anxiety is difficult to measure due to physical confounding symptoms such as shortness of breath, muscle cramps and restlessness. Anxiety can be treated with psychotherapy and training in relaxation and breathing techniques, as well as participation in support groups. It is generally thought that the rates of anxiety increase in the pre-terminal stage (Kurt et al., 2007), hence anxiolytics at this time such as benzodiazepines should be offered. With good support, mental health and quality of life can remain stable despite deteriorating physical health (De Groot et al., 2007).

2.12 End of life issues

It is important to establish an open environment of communication with persons with ALS and their families from the time of diagnosis. Specialist palliative care providers should be involved as early as possible. Discussions should take place early, well before specific decisions need to be made. The actual timing of when to introduce these discussions however can be challenging and will depend on a number of factors including coping skills, depression and anxiety, cultural issues and functional status (Mitsumoto et al., 2005). Some triggers may include the patient or family initiation of discussion, severe psychosocial distress, pain requiring high dosages of analgesia, dysphagia, dyspnoea and functional loss in two body regions (Mitsumoto et al., 2005). Given the progressive nature of the disease, the patient eventually has to choose between life-sustaining therapies (respiratory

assistance, feeding tubes) and terminal palliative care whilst considering issues relating to quality of life, burden of therapies, their own wishes and those of their family. It is important that clinicians caring for ALS patients and their families appreciate and communicate the significance of life-threatening symptoms, monitor decision-making capacity, ensure that multiple possible end of life scenarios are anticipated and managed with all options provided (including hospice care), review advance care directives and comprehensively consider and aggressively manage symptoms (McCluskey, 2007).

Medications should be available for all patients who are deteriorating and may be approaching the terminal phase, although the terminal phase may be difficult to recognise as there is usually slow deterioration until a quicker change leads to death within a few days or less (Oliver, 2007). Medications should include morphine to relieve dyspnoea and pain, midazolam to relieve distress and agitation and glycopyrronium bromide or hyoscine hydrobromide to reduce chest secretions, delivered parenterally (Oliver, 2007). Cultural and spiritual issues should also be addressed (Mitsumoto et al., 2005; Albert et al., 2007). Although many persons with ALS fear the terminal stages of ALS, with good palliative care, the later stages can be a time of fulfilment and peace for both persons with ALS and their families (Oliver, 2007).

Bereavement in ALS occurs in both the patient and their family and continues, in families, after the death of the patient. Some families feel relieved of their caregiver burden and the burden of losses for the patient but also have feelings of guilt that they feel these emotions; hence support is vital in this area (Skyles, 2006).

3. Conclusion

ALS is a complex and challenging condition with no cure. Current “gold-standard” management is “multidisciplinary care” which includes neurological, rehabilitative and palliative care. As consistent with the guidelines from the American Academy of Neurology (Miller et al., 2009b) and the World Federation of Neurology (Andersen et al., 2007), multidisciplinary care should be available to all persons with ALS. Where multidisciplinary care is currently available, it should be delivered with a high level of coordination and integration, with evidence-based intervention to ensure holistic and seamless care for persons with ALS and their caregivers. Many areas in ALS are poorly understood, with research often further hindered by the logistical and ethical difficulties. Much more work is needed in the area of evidence-based interventions. At present, much of the evidence has been concentrated in areas such as respiratory and nutritional management. There is paucity of information on effective rehabilitation interventions and very little is understood with regards to the “black box of rehabilitation”. For example, evidence to guide exercise prescription (such as strengthening, stretching, aerobic/endurance exercises) is much needed. The use and development of assistive technology is another area that warrants much more attention, as is a better understanding of bowel, bladder and sexuality issues. Further research is also needed into appropriate study designs; outcome measurement; the evaluation of optimal settings, type, intensity or frequency and cost-effectiveness of multidisciplinary care; and the different phases of ALS, covering the spectrum of care required for this patient population. The interface between neurological, rehabilitative and palliative components of care, and caregiver needs should be explored and developed to provide long-term support for this population. Last but not least, national and international guidelines incorporating evidence-based practice in rehabilitation should be further developed to enable optimisation of clinical care and practice.

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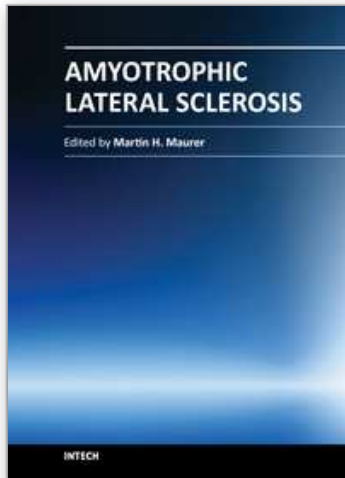
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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop 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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