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Management of Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons, in both the spinal cord and medulla (lower motor neurons) and cerebral cortex (upper motor neurons). Even though ALS remains fatal, several advances have been made during the last decade in improving the consequences of motor dysfunction, quality of life and survival time of patients. Treatment of ALS cannot be restricted to riluzole, the only molecule that has been proved to modify the evolution of the disease. Symptomatic treatments have an important role in controlling the major consequences of the disease, such as pain, sleep disorders, spasticity, hypersialhorroea, emotional lability, depression and digestive disorders (constipation and reflux). All these symptoms need to be recognized and their

possible causes identified in order to provide the most appropriate management of patients with ALS.

However, an advance in the daily care of patients is the identification of two important phenomena that occur during the evolution of the disease: swallowing difficulties and the occurrence of diaphragmatic dysfunction. For both, specific medical interventions have been developed to allow correction of the consequences (i.e. weight loss and respiratory insufficiency). Although no controlled trials have been performed, observational studies suggest that gastrostomy and non-invasive ventilation may improve at least quality of life and survival.

All of these various approaches, pharmaceutical and non-pharmaceutical therapies, are prescribed according to individual symptoms and require the involvement of a large range of health professionals. This multidisciplinary approach in ALS clinics is considered to be one of the more important factors impacting on survival rate and appears to be the gold standard of medical care of ALS patients.

Important findings have been made in understanding the nature of the degenerative process that affects the motor neurons. All these data have allowed new therapeutic molecules to be tested alone or in combination with riluzole. Despite the negative results obtained until now, we hope to demonstrate very soon a greater improvement in therapy.

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease or motor neuron disease, is the most frequent motor neuron disorder in adults. The cardinal pathological features of ALS are loss of anterior horn cell and motor cells in the lower cranial motor nuclei, and degeneration of the corticospinal tracts, which is associated with ubiquinated inclusions in motor neurons. Its main clinical features are a combination of upper and lower motor neuron degeneration in bulbar and spinal territories, and a constant evolution. Death related to respiratory insufficiency is almost inevitable after a median survival time of 36 months.[1] However, 5–10% of patients may survive for more than 10 years.[2]

Currently, the pathophysiology of ALS remains unknown, although there is growing evidence of it being a polyfactorial and probably multigenic disease. Although around 90% of cases are sporadic,[3] there is familial inheritance of the pathological trait, mainly through a dominant autosomal pattern.[4]

ALS predominates in males, with a 1.6 : 1 sex ratio (males to females).[5] The incidence of ALS is more or less uniform worldwide, around 1.1 in 100 000, varying from 0.2 in 100 000 to 2.4 in 100 000 in industrialized countries, with prevalence rates of around 6 in 100 000 worldwide.[5]

1. Diagnosis of Amyotrophic Lateral Sclerosis (ALS)

Diagnosis of ALS is mainly based on clinical criteria. These criteria were defined in 1994 and revised in 1998 during two workshops held in El Escorial in Spain and in Airlie House in the US. These workshops led to the establishment of the El Escorial criteria and the El Escorial revisited criteria, respectively (table I). Four stages are defined from definite to probable, probable with laboratory support, and possible based on the presence of upper and lower motor neuron signs in three to one of the anatomic regions bulbar, cervical, thoracic, lumbosacral, respectively.[6] Even though the key feature of the disease is a pure motor syndrome, it remains possible to observe extra motor involvement such as sphincter abnormalities or dysautonomia.[7]

Cognitive impairment and dementia appear in ALS patients. A range of cognitive and behavioural changes are related to frontal lobe dysfunction and occur in up to 30% of individuals with ALS not meeting criteria for dementia. The most frequent association is with frontotemporal lobar dementia (FTLD), as demonstrated by clinical, genetic and neuropathological investigations.[8] Frontotemporal cognitive impairment produces changes in behaviour, personality, planning, organization and lan-

guage, with relatively intact memory. Cross-sectional studies estimate that FTLD might occur in as many as 25–33% of ALS patients. Experience shows that this association is more frequent in females with a speech disorder as an initial symptom of the disease. The ubiquitinated inclusions of both ALS and FTLD contain the same protein, TDP-43.[9]

At the earlier stages of the disease, diagnosis is not very easy, and around 10% of patients for whom ALS is the first diagnosis later develop another disease.[10] One of the main reasons to explain this misdiagnosis is the absence of a biological marker. Laboratory assessments may be necessary to rule out alternative diagnoses. Electrophysiological investigations are particularly useful because they confirm the existence of pure motor neurogenic changes even at the early stages of the disease. They exclude conduction blocks suggestive in this context of multifocal motor neuropathy with conduction blocks.[11]

The absence of sensory involvement is currently an definitive characteristic of the diagnosis of ALS according to the El Escorial criteria. However, a recent report demonstrated sensory axonal loss without the features of an alternative aetiology, supporting the hypothesis that ALS is a multisystem neurodegenerative disorder that may occasionally include sensory neuropathy among its non-motor features.[12] Neuroimaging is performed to exclude cerebral disorders such as stroke, multiple sclerosis, tumours and skull base lesions, or spinal cord diseases such as cervical myelopathy or tumours. Biological screening is carried out to exclude other motor neuron disorders related to plasma cell dyscrasia, infectious disorders (human T-lymphotrophic virus type 1 and HIV), autoimmune diseases (Sjögren's disease), endocrinopathies such as hyperparathyroidism, heavy metal intoxications (lead and mercury) and paraneoplastic syndromes respective to past medical history or occupational activities.[10,13] Muscular disorders such as myasthenia gravis, hyperthyroid myopathy or inclusion myositis may also be investigated based on clinical presentation.[13]

Molecular biology can be helpful in various situations. A multisystem disorder with anterior horn cell involvement can suggest a spinocerebellar ataxia. A pure lower motor neuron involvement without any immunological markers can suggest an adult form of spinal muscular atrophy related to an SMN 2 deletion. The existence in humans of gynaecomastia and/or testicular atrophy suggests a Kennedy's syndrome, which requires looking for the identification of an abnormal CAG triplet expansion on exon 1 of the androgen receptor gene.[14]

2. Management of ALS Patients

2.1 Presenting the Diagnosis

Once the final diagnosis has been firmly established, it is the responsibility of the neurologist to inform the patient and immediately start treatment, mainly based on a multidisciplinary approach to care. Caregivers have to keep in mind that this disease is specific regarding its constant and frequently high rate of evolution.

Informing the patient is the first step of ALS management and the diagnosis of ALS needs to be established indisputably. This step needs time, and the diagnosis must be given only during a consultation and never by telephone. Empathy is essential and the neurologist needs to avoid doing too much or too little. Too much is tracing a future without

Table I. El Escorial revisited criteria for amyotrophic lateral sclerosis (ALS)[6]

Type of ALS	Criteria
Definite ALS	Upper motor neuron and lower motor neuron signs in three spinal regions or two spinal regions and the bulbar area
Probable ALS	Upper motor neuron and lower motor neuron signs in two regions with at least some upper motor neuron signs rostral to lower motor neuron signs
Probable ALS (laboratory supported)	Upper motor neuron signs in one or more regions and lower motor neuron signs defined by electromyogram in at least two regions
Possible ALS	Upper motor neuron and lower motor neuron signs in the same region or Upper motor neuron signs in at least two regions or Lower motor neuron signs rostal to upper motor neuron signs

any hope; too little is hiding the absence of recovery and the risk of worsening symptoms. It is mandatory to inform patients clearly and honestly about ALS, its possible evolution and therapeutic possibilities. However, patients must be aware that the absence of improvement does not mean that there is nothing that can be done. It should be clarified that a multidisciplinary approach provides a longer duration and a better quality of life (QOL).[10,15] Neurologists must ensure that all the information that the patient and relatives need is provided in a comprehensive manner. Initial recommendations may be made, such as avoiding all sustained exertion. Psychological support may be proposed to the patient and relatives.

During the whole course of evolution, each step of the disease should be discussed honestly, leaving open the future and offering reasonable hope.

2.2 Aetiologically Based Medical Therapies

Numerous compounds have been evaluated in ALS, but riluzole remains the only one that is licensed since it was proven to modify the rate of evolution. Riluzole is known as a glutamate-modulating drug but it probably acts through other mechanisms such as the stimulation of production of neurotrophic factors[16] and cell signalling by acting on a large variety of ion channels.[17] In two clinical trials, riluzole was shown to increase mean survival time compared with placebo at a daily dose of 100 mg.[18,19] Adverse effects such as asthenia, nausea and increased hepatic enzymes remain rare. They occur mainly during the first 3 months of treatment and reverse when drug treatment is stopped. However, monitoring of blood count and liver function is recommended at the beginning of the treatment. The effect on survival is a 7% difference between placebo and treated groups after 18 months of treatment, without adjustment. After adjustment, the difference reached 35% with riluzole 100 mg/day.[19] These results mean that 12 treated patients are needed to avoid one death after 12 months of follow-up.[20] The efficacy of treatment with riluzole is independent of site of onset and there is no improvement in functional status.

2.3 Symptomatic Treatments

In ALS, symptoms are not disease specific but they need to be managed. The treatments proposed here are not based on controlled trials specific for ALS but on their largely accepted efficacy for a given symptom.

2.3.1 Asthenia and Fatigue

These symptoms are frequent and related to multiple causes. Many drugs have been tried with limited success. Even if acetylcholinesterase inhibitors such as pyridostigmine at a dosage >80 mg/day have been proposed at initial stages of the disease,[21,22] it is our clinical impression that these treatments are able to worsen symptoms if used for more than a few days. Modafinil (200 or 400 mg/day) might be an alternative, given the results of an open trial performed for a short period of 2 weeks showing a dose-dependent decrease of asthenia.[23]

2.3.2 Depression and Anxiety

The frequency of depression may reach 30% in ALS,[24] without correlation with the severity of the disease. Despite the absence of clinical trials, preferential use of drugs with anticholinergic activity and selective serotonim reuptake inhibitors (SSRIs) has been suggested.[25] Our preference is to use drugs with anticholinergic activity in patients losing weight, given the metabolic adverse effects of SSRI that promote weight loss.[26] For anxiety, benzodiazepines can be used on an as-needed basis.

2.3.3 Drooling

Sialorrhoea is the most frustrating and socially embarrassing complication of ALS. It results both from facial muscle weakness and the impairment of spontaneous swallowing of saliva. Amitriptyline is commonly used at a dosage of 25–50 mg three times daily based on its anticholinergic side effect.[26] Atropine (drops or subcutaneously administered) or scopolamine (subcutaneous or transdermal) can be used in patients in whom amitriptyline is inadequate or not tolerated.[27] When a drug treatment approach is insufficiently effective, botulinum toxin[28] or, as a last resort, subsalivary gland irradiation may improve symptomatology.[29] Several open trials reported efficacy of irradiation in ALS.[25,29-31] Doses range from 7 to 14 Gy (table II). Transitory burning

Table II. Treatment of sialorrhoea

Drug	Dosage	Reference
Amitriptyline	25–50 mg tid	27
Atropine	Atropine eye drops sublingual: 0.25–0.75 mg tid Scopalamine transdermal patch: 1 patch for 3 days	26
Botulinum toxin A	6–20 mU in each parotid 5 mU in each submaxillary gland	28
Radiotherapy[a]	7–14 Gy	25,29,30

a Recommended only as a last resort.

tid = three times daily.

and xerostomia have been reported as adverse effects.[31]

2.3.4 Bronchial Secretions

There are two distinct types of secretions in patients with ALS: (i) thick secretions; or (ii) thin, serous secretions. The former results from β-adrenergic stimulation, whereas the latter results from cholinergic stimulation.[3]

For thick secretions, β-blockers (e.g. metoprolol, propanolol) should be given.[32] If they are contraindicated, a humidifier prescription can be useful.

Expectorations of serous secretions are more difficult to manage. They may be decreased by an anticholinergic bronchodilatator, amytriptyline, theophylline or even furosemide.[13] Small periods of nebulized breathing treatments with small amounts of corticosteroids can help.

For both secretions, coughing assistance techniques and mechanical respiratory assistance provide beneficial help.[33]

2.3.5 Pain

Pain occurs in 43–73% of ALS patients, more frequently at advanced stages of the disease.[34,35] The main cause is the inflammatory processes resulting from the lack of mobility of the joints (mainly the shoulders). The lack of ability to spontaneously change the position of the limbs leads to pain at points of pressure. Physiotherapy and passive stretching are essential to prevent and treat the joint retractions.

Whatever the cause of pain, NSAIDs should be initiated first. Other agents can be used, such as antiepileptic drugs or tricyclic antidepressants; opioids are used in patients in whom these agents are insufficient.[29] Electric transcutaneous neurostimulation may be useful in treating musculoskeletal pain through the stimulation of endogenous opioids.[36]

2.3.6 Pathological Laughing

Pathological laughing or crying occurs in up to 50% of patients with ALS.[4] This symptom is often misinterpreted by relatives, and neurologists must explain that it does not mean a mood disorder or a cognitive impairment, but an abnormal display of emotions. Amitriptyline 50–150 mg/day, SSRIs (e.g. fluvoxamine [100–200 mg/day]), lithium (400–800 mg/day) and levodopa (500–600 mg/day) may control this emotional lability.[37] Recently, a randomized trial showed that a combination of dextromethorphan and quinidine was useful for this symptom.[38]

2.3.7 Constipation

Constipation is nearly constant in ALS and its causes are multiple (i.e. immobility, difficulties with water intake, iatrogenic and diet modifications). However, its impact is high on both QOL and respiratory function.

Prevention is essential, even at initial stages of the disease. Recommendations have to be made on liquid intake, abdominal massage and diet (increasing fibre). Osmotic laxatives, even when administered long term, are very useful.[39]

2.3.8 Gastro-Oesophageal Reflux

Gastro-oesophageal reflux is nearly constant in ALS patients. Signs and symptoms are sometimes troubling, such as nausea, insomnia and lingual mycosis. Anti-acid agents are reasonably effective.

Laryngospasm may affect around 20% of ALS patients and its symptoms are frequently misdiagnosed.[40] When related to acid gastric reflux, it is spontaneously alleviated with treatment of that symptom. Spicy foods, strong smells and alcohol should be avoided and the use of anti-acids help to reduce its consequences.[41]

2.3.9 Sleep Disturbances

Many factors lead to sleep disturbances: depression, restless legs syndrome, pain, mobility restriction, drooling, respiratory insufficiency and nocturnal decreased oxygen saturation. All of these possible causes need to be recognized and specifically treated. Nocturnal oxymetry is essential before any

hypnotic administration, because these drugs are contraindicated in patients with hypopneas.

Depression and anxiety respond well to tricyclic or SSRI antidepressants. Restless legs syndrome will be improved with dopaminergic agonists (ropinirole 0.25–4 mg/day and pramipexole 0.125–0.75 mg/day).[42,43] Nocturnal hypopneas are an indication for non-invasive ventilation (NIV) such as non-invasive positive pressure ventilation. When all these causes have been discounted, short-acting sedatives are preferred to other drugs.

2.3.10 Bedsore Prevention

Bedsores are rare in ALS, even in bedridden patients.[44] This is explained by the increase in dermal collagen and of an apomorphous substance that protects skin against sustained pressure and prevents the occlusion of skin blood vessels.[45]

Nevertheless, bedsores may occur in patients who are bedridden for a long time.[46] The best way to prevent such complications is to promote passive physiotherapy and prevention of complications of decubitus.

2.3.11 Venous Thrombosis and Pulmonary Embolism

The frequency of venous thrombosis is estimated to be 2.7% in ALS, which is higher than in the general population.[47] Moreover, pulmonary embolism is certainly underestimated and masked by respiratory disturbances as a result of ALS.

Although there is no recommendation for the prescription of anticoagulants in ALS, we suggest initiating low-molecular-weight heparin treatment when in any doubt of venous thrombosis or embolism.[48]

2.3.12 Spasticity

Spasticity corresponds to an increase in velocity-dependent muscle tone related to a pyramidal syndrome. It is frequently experienced by patients as stiffness or tightness, and increases functional disability and promotes joint retractions with a major negative impact on QOL.

Table III. Treatment of spasticity

Drug	Dosage	Reference
Baclofen	10–80 mg/d orally	48,50
	Intrathecally: 160–540 μg/d	51
Dantrolene	100–400 mg/d	29
Diazepam	5–20 mg/d	29
Memantine	10–60 mg/d	13
Tizanidine	6–24 mg/d	29

Management of spasticity combines drugs and physiotherapy. Myorelaxants, such as baclofen, dantrolene, benzodiazepines, memantine or tizanidine, may help, but physicians must keep in mind that myorelaxants in excess increase weakness (table III).[13,29] Baclofen, a GABA agonist, is the only agent to have been evaluated in a randomized study in ALS.[49] However, because of bias, this study does not allow any recommendation in ALS.[50] Because high dosages are required, it has been proposed to use baclofen intrathecally in order to circumvent major adverse effects such as sleepiness and an increase of weakness. In spastic tetraplegic patients, it demonstrated a positive effect on symptoms.[51,52] However, our opinion is that this therapy is very invasive and requires a very sensitive benefit-to-risk approach.

Physiotherapy is essential to reduce or prevent stiffness and contractures by promoting passive stretching.[50] Prevention and management of retractions require daily or twice-daily sessions of physiotherapy, performing essentially passive joint mobilization. Other physiotherapy techniques, such as botulinum toxin, need to be evaluated.

2.3.13 Cramps

Cramps are frequent at the initial stages of the disease and are sometimes extremely painful. They can be managed through correct hydration and manual stretching. No treatment has been evaluated in a trial in ALS. The most frequently used drug is quinine sulfate (200 mg twice daily) promoted by clinical practices in ALS management.[40] Other drugs can help, such as baclofen, dantrolene and benzodiazepines, and other agents such as carbamazepine, tocopherol (vitamin E; 400 UI twice daily), magnesium (5 mmol three times daily) or verapamil (120 mg/day) [table IV].[29]

2.4 Multidisciplinary Approach

During the last few years, several publications have demonstrated the importance of a multidisciplinary approach in the management of ALS.[53] Comparing the survival curves of ALS patients in

Table IV. Treatment of cramps

Drug	Dosage	Reference
Quinine sulfate	200 mg bid	40
Carbamazepine	600 mg/d	29
Phenytoin	300 mg/d	29
Tocopherol (Vitamin E)	400 UI bid	29
Magnesium	5 mmol tid	29
Verapamil	120 mg/d	29

bid = twice daily; **tid** = three times daily.

multidisciplinary clinics and general neurology clinics showed that the multidisciplinary approach offered a 29.7% decreased rate of death with a 7.5-month higher median survival.

The basis of this care approach is that ALS patients must be followed-up closely during the whole course of their disease in order to detect impeding problems in motor function, nutrition or respiration. The multidisciplinary team in the ALS clinic has to provide the most efficient answer to the alteration of each of these functions.

2.4.1 Physical Therapy Management

Physical therapy aims to avoid joint contractures and stiffness that increase the disability of the patient. Physical therapy is based mainly on passive mobility and avoids exertion against resistance, which increases the denervation process.[50]

In patients with spasticity, massage must include the antagonist muscular area in order to promote muscular relaxation. Physical exertion is an important part of physiotherapy but needs to be correlated to the patient and re-evaluated during the whole course of ALS. Joint mobilization is essential to circumventing joint contractures and secondary pain.

Electric stimulation remains debated and avoided because of the risk of worsening the denervation process in ALS.[54] Balneotherapy may be proposed in spastic patients.[55]

Occupational therapy may complete physical therapy. Its aim is to help the patient to improve performing skilled tasks, and to provide adaptive equipment and recommendations that help patients in daily activities.

2.4.2 Speech Therapy

Approximately 80% of ALS patients will experience speech disturbances during the evolution of ALS.[21] Speech therapy is necessary to maintain and facilitate communication.

Both speech therapists and physiotherapists need to coordinate their efforts to encourage the activity of diaphragmatic and intercostal muscles during breathing and speech. In the advanced stage of the disease, communication aids can be suggested and discussed with patients.

2.4.3 Respiratory Management

Management of respiratory function is one of the key points of the management of ALS because of the constant respiratory involvement as the disease progresses and its consequences on survival. Respiratory impairment is related to respiratory muscle weakness leading to difficulties with coughing, bronchial super- or secondary infection and hypoxic/hypercapnoeic death.

Evaluation of pulmonary function is mandatory every 3 months. Clinical evaluation should assess the existence of signs of diaphragm dysfunction and hypoventilation. Diaphragm muscle weakness leads to dyspnoea and orthopnoea, and finally to paradoxical breathing (as shown with an abnormal sniff nasal inspiratory pressure [SNIP] test).[56] Hypoventilation is suspected in the presence of morning headaches, daytime somnolence and poor concentration related to hypercapnoea.[57]

Laboratory assessments are required for measuring respiratory function (by spirometry, blood gas analysis and blood bicarbonate level), inspiratory muscle strength (by maximal inspiratory pressure [MIP], transdiaphragmatic pressure and SNIP test), expiratory muscle strength (by maximum expiratory pressure [MEP]) and sleep quality (by nocturnal oximetry and polysomnography).

Blood gas analysis checks for the presence of hypoxia and hypercapnoea. A partial pressure of arterial CO_2 ($PaCO_2$) >45 mmHg is one of the major parameters used when deciding whether to initiate NIV.[56] However, the sensitivity of this test is rather weak because of the late onset of hypercapnoea in ALS. In the absence of hypercapnoea, measurement of HCO_3 may be very useful and a value >30 mmol/L is a criterion of hypoventilation.[58] Spirometry is an important laboratory assessment. The threshold under which NIV may be proposed remains confused. Although some authors recommend a forced

vital capacity (FVC) value <75% or even 80% as a threshold,[13,59] this appears to be too stringent in clinical practice. We recommend considering FVC <50% as a good criterion for NIV.[60]

MIP and MEP values <80 and 100 cm H_2O, respectively, confirm respiratory muscle dysfunction.[60,61] Because MIP is effort dependent, it must be restricted to patients who are able to sustain effort.[62] The SNIP test emerges as the more sensible test in ALS. It is strongly correlated with diaphragm muscle strength and a value <65 cm H_2O is an indication of diaphragmatic dysfunction.[58] This test is the most sensitive to predict respiratory insufficiency: 66% of ALS patients with a SNIP test <40 cm H_2O had FVC >50%.[63] This test affords prognostic information: if the SNIP is <40 cm H_2O, the hazard ratio for death is 9.1 and the median survival time is 6 months.[63] Nocturnal oximetry detects nocturnal hypoventilation and can be performed at home. Pathological values for oxygen saturation (SaO_2) are <90% for more than 5% of recording time spent or SaO_2 <88% for more than 5 consecutives minutes.[64]

Proposed criteria in favour of NIV include blood bicarbonates >30 mmol/L if $PaCO_2$ is ≤45 mmHg, morning blood $PaCO_2$ >45 mmHg, FVC <50%, SNIP test <60 cm H_2O and SaO_2 <90% for more than 5 minutes of recording time spent.

Tracheotomy remains rare in most countries (between 0% and 2% in Europe). Prognosis remains poor with invasive ventilation.[65] Fifty percent of patients died after 1 month of invasive ventilation and 20% of patients have survival exceeding 2 years.[66] This procedure needs to be discussed in advance and patients need to be aware that they will lose the ability to communicate and will have to undergo a gastrostomy.

2.4.4 Nutritional Management

Denutrition is a major issue in the management of ALS, and weight loss a key prognostic indicator with the risk of death increased 7-fold when body mass index is <18.5 kg/m^2.[67] Denutrition is related to multiple factors such as bulbar involvement, upper limb disability, depression and/or hypermetabolism.[68] Although respiratory insufficiency represents the major cause of death, aspiration pneumonia, denutrition and dehydration can contribute.

It is mandatory to check nutritional status at regular intervals, focusing on weight loss, choking and duration of meals as well as diet assessment checks for caloric intake. In the first stages of the disease, modification of the texture and consistency of food may be sufficient to control weight loss. As dysphagia progresses, dietetic complements need to be proposed to compensate for caloric intake. We recently showed that hyperlipaemia significantly prolongs survival in ALS, suggesting the value of increasing lipid intake or promoting lipid rich nutriments.[69]

Gastrostomy should be proposed and discussed with patients sooner rather than later. Criteria for gastrostomy are loss of >10% of bodyweight since the onset of the disease, frequent choking or aspiration pneumonia, or the inability of the patient to feed themselves. Percutaneous radiological gastrostomy (PRG) may be preferred if the FVC is <50%. There are different types of gastrostomy: percutaneous endoscopic gastrostomy (PEG), classic surgical gastrotomy or PRG.

Gastrostomy should be performed before the FVC falls below 50% of the predicted value. When the FVC is <50%, PEG placement must be performed through NIV support.[70,71] To date, there is no evidence of an increase in survival through PEG, but several studies lead us to consider that PEG improves QOL.[72] PRG represents a reliable alternative when PEG is technically risky or impossible.[73,74] When gastrostomy is formally contraindicated, nasogastric tube feeding represents a reliable alternative, as does intravenous catheter nutrition.[75]

2.5 Management of Terminal Stage ALS

Advance directives should be promoted in order to respect the wishes of the patient and family concerning end-life management. These directives need to be reassessed at regular intervals.

Most ALS patients die peacefully.[76] In the absence of NIV, death occurs during sleep, probably as a result of hypoxia/hypercapnoea. However, for approximately 40% of ALS patients, respiratory insufficiency leads to bronchial superinfection associated with dyspnoea and anxiety. For these patients, the main objective is to provide comfort and control of symptoms. In the absence of ventilatory support,

appropriate anxiolytics and morphine should be given at increasing doses (starting with 0.5 mg/hour for morphine).[60] For terminal discomfort, chlorpromazine should be prescribed at the dosage of 12.5 mg intravenously every 4 or 12 hours.[60]

Palliative care provides symptomatic treatment and psychological and spiritual support to the patients and relatives in order to decrease the emotional burden.

3. Genetic Counselling and *SOD1* Mutation Research

Approximately 10% of ALS patients have a familial history of ALS.[77] Inheritance is mainly autosomal dominant.[78]

Even if the phenotype of the disease is similar in both sporadic and familial ALS (FALS), some characteristics are more frequent in familial forms: an earlier age of onset (46 years vs 56 years), a more frequent lower limb onset and two peaks of evolution (<2 years and >5 years).[77]

There is no reliable test that allows us to clearly detect relatives of ALS patients who will be at risk of developing ALS. In FALS pedigrees, *SOD1* mutation is detected in about 15–20%.[79] Although more than 120 *SOD1* mutations are currently described, causative effect of mutations is not systematic.[80] Although it is possible to perform *SOD1* genetic studies, we must keep in mind that we have to be cautious before drawing any conclusion concerning the risk of ALS. The weak and variable penetrance of *SOD1* mutations makes genetic counselling difficult.[80,81] For most patients, genetic counselling will be different from most other monogenic disease counselling (as in Huntington's disease).[82-84] Genetic counselling must take into account the type of *SOD1* mutation and be addressed exclusively to first-degree blood adult relatives of patients with a clear pathogenic *SOD1* mutation.

In conclusion, it seems unreasonable to perform a systematic test for *SOD1* mutation in asymptomatic patients belonging to a FALS pedigree. Because of the absence of recognized treatment and the unpredictable delay of the preclinical stage of ALS, such analysis seems unjustified.[85] Because of the exceptional occurrence of the *SOD1* mutation in patients with sporadic ALS, it is accepted that no systematic screening of the *SOD1* mutation be performed in these patients.[26]

4. Conclusion

Management of ALS has improved considerably during the last 10 years. Currently, expert opinions promote a multidisciplinary approach to the management of ALS patients, which improves QOL and, to a lesser extent, survival.[53,86] Because aetiologically based treatment of ALS for the moment remains limited to riluzole, there is an urgent need for more effective agents that can affect both survival and functional status.

In the future, a promising area of research for ALS therapy may be neuroprotective agents. There was growing evidence of inflammatory processes and microglia activation in ALS.[87] This led to the development of therapeutic trials based on anti-cyclo-oxygenase 2 molecules[88] and minocycline, although their effect appeared to be unsatisfactory.[89] Recently, a placebo-controlled, double-blind, multicentre study established the harmfulness of minocycline in ALS, with a more severe decline of the ALS functional rating scale (ALS-FRS) score in the minocycline group than in placebo group.[90] There is no clear explanation for this negative effect. In their conclusion, the authors stressed that this study underlined that animal models might not be considered a reliable model of sporadic ALS in humans.

Nevertheless, research efforts need to be continued in this manner. Other approaches are possible, thereby increasing the number of potential therapeutic trials. However, the recent results obtained in combining drugs with riluzole raise important methodological questions. To date, no agents appear to be effective on both survival and function.[91] Some molecules tested with riluzole worsened the function and/or survival.[91]

Stem cell implantation represents another potential and promising method of treatment in ALS. Stem cells correspond to self-renewing progenitor cells that can generate specialized cell types. The role of stem cells in ALS might be the release of neurotrophic factors or the replacement of lost motor neurons.[4] There are two main stem cell types (embryonic and multipotent cells), and two different

types of implantation of stem cells (intrathecally or intraparenchymally) could be used in ALS. Rare studies have been conducted in human ALS to assess the efficacy of stem cells. Implantation of mesenchymal stem cells into the spinal cord in seven patients was safe. Although four of seven patients showed a slowing of the decline of both FCV and ALS-FRS score, efficacy remains to be demonstrated.[92]

To date, stem cell therapy appears premature in ALS. Many points need to be highlighted before assessing efficacy in human ALS (e.g. type of stem cell and site of implantation).[93] Finally, ethical problems need to be resolved before any clinical trials are carried out. These questions and the pressing demand of patients necessitate an academic study in a large sample in order to avoid unrealistic hope by patients and their families.

Considering the multidisciplinary approach, several aspects could and should be improved. Well defined procedures need to be drawn up concerning the tube feeding procedure and the initiation of NIV. The psychological approach to ALS management should be developed further. Finally, ethical concerns about the end of life being ventilatory withdrawal or tracheostomy should be debated in order to propose a standardized procedure. Besides somatic management, which remains important, we have to improve the QOL of the patients but also of the caregivers, whose involvement is significant.

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References

1. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. N Engl J Med 2001; 344: 1688-700
2. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population: validation of a scoring system and a model for survival prediction. Brain 1995; 118: 707-19
3. Andersen PM, Borasio GD, Dengler R, et al., on behalf of the EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis. Guidelines for diagnosing and clinical care of patients and relatives. Eur J Neurol 2005 Dec; 12 (12): 921-38
4. Kurland LT, Mulder DW. Epidemiologic investigations of amyotrophic lateral sclerosis: 2. Familial aggregations indicative of dominant inheritance part II. Neurology 1955; 5: 249-68
5. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. Lancet 2007; 369: 2031-41
6. Brooks BR, Miller RG, Swash M, et al. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic Lateral Scler 2000; 1: 293-9
7. Pradat PF, Bruneteau G. Clinical characteristics of ALS subsets. Rev Neurol 2006; 162: 4S29-33
8. Ringholz GM, Greene SR. The relationship between amyotrophic lateral sclerosis and frontotemporal dementia. Curr Neurol Neurosci Rep 2006; 5: 387-92
9. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006; 314: 130-3
10. Traynor BJ, Codd MB, Corr B, et al. Amyotrophic lateral sclerosis mimic syndromes: a population based study. Arch Neurol 2000; 57: 109-13
11. Lewis RA, Sumner AJ, Brown MJ, et al. Multifocal demyelinating neuropathy with persistent conduction block. Neurology 1982; 32: 958-64
12. Isaacs JD, Dean AF, Shaw CE, et al. Amyotrophic lateral sclerosis with sensory neuropathy: part of a multisystem disorder? J Neurol Neurosurg Psychiatry 2007; 78: 750-3
13. Leigh PN, Abrahams S, Al-Chalabi A, et al. The management of motor neurone disease. J Neurol Neurosurg Psychiatry 2003 Dec; 74 Suppl. 4: iv32-47
14. La Spada A, Wilson EM, Lubahn DB, et al. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 1991; 352: 77-9
15. Chio A, Bottacchi E, Buffa C, et al. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. J Neurol Neurosurg Psychiatry 2006; 77: 948-50
16. Mizuta I, Ohta M, Ohta K, et al. Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. Neurosci Lett 2001; 310: 117-20
17. Beltran-Parrazal L, Charles A. Riluzole inhibits spontaneous Ca2+ signaling in neuroendocrine cells by activation of K+ channels and inhibition of Na+ channels. Br J Pharmacol 2003; 140: 881-8
18. Bensimon G, Lacomblez L, Meininger V, et al. A controlled trial of riluzole in amyotrophic lateral sclerosis ALS/riluzole Study Group. N Eng J Med 1994; 330: 585-91
19. Lacomblez L, Bensimon G, Leigh PN, et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Lancet 1996; 348: 336-7
20. Miller RG, Mitchell JD, Lyon M, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev 2007; (1): CD001447
21. Francis K, Bach JR, DeLisa JA. Evaluation and rehabilitation of patients with adult motor neuron disease. Arch Phys Med Rehabil 1999; 80: 951-63
22. Voltz R, Borasio GD. Palliative therapy in the terminal stage of neurological disease. J Neurol 1997; 244 Suppl. 4: S2-10
23. Carter GT, Weiss MD, Lou JS, et al. Modafinil to treat fatigue in amyotrophic lateral sclerosis: an open label pilot study. Am J Hosp Palliat Care 2005; 22: 55-9
24. Miller RG, Anderson Jr FA, Bradley WG, et al. The ALS patient care database: goals, design and early results. ALS C.AR.E. Study Group. Neurology 2000; 54: 53-7
25. Kurt A, Nijboer F, Matuz T, et al. Depression and anxiety in individuals with amyotrophic lateral sclerosis: epidemiology and management. CNS Drugs 2007; 21: 279-91
26. Vojtech H, Kabrnova K, Aldhoon B, et al. Serotonin and norepinephrine reuptake inhibition and eating behavior. Ann NY Acad Sci 2006; 1083: 252-69

27. Talmi YP, Finkelstein Y, Zohar Y. Reduction on salivary flow in amyotrophic lateral sclerosis with Scopoderm TTS [letter]. Head Neck 1989; 11: 565
28. Verma A, Steele J. Botulinum toxin improves sialorrhea and quality of living in bulbar amyotrophic lateral sclerosis. Muscle Nerve 2006; 34: 235-7
29. Borasio G, Voltz R. Palliative care in amyotrophic lateral sclerosis. J Neurol 1997; 244: S11-7
30. Stalpers LJ, Moser EC. Results of radiotherapy for drooling in amyotrophic lateral sclerosis [letter]. Neurology 2002; 58: 1308
31. Cintas P. Drug therapy for symptomatic relief in ALS. Rev Neurol 2006; 162: 4S235-43
32. Newall AR, Orser R, Hunt M. The control of oral secretions in bulbar ALS/MND. J Neurol Sci 1996; 139 Suppl.: 43-4
33. Sancho J, Servera E, Diaz J, et al. Efficacy of mechanical insufflation-exsufflation in medically stable patients with amyotrophic lateral sclerosis. Chest 2004; 125: 1400-5
34. Newrick PG, Langton-Hewer R. Pain in motor neuron disease. J Neurol Neurosurg Psychiatry 1995; 48: 838-40
35. Ganzini L, Johnston WS, Hoffman WF. Correlates of suffering in amyotrophic lateral sclerosis. Neurology 1999; 52: 1434-40
36. Stefanovska A, Rebersek S, Bajd T. Effect of electrical stimulation on spasticity. Crit Rev Phys Rehabil Med 1991; 3: 59-99
37. Ukada F, Yamao S, Nagata H, et al. Pathologic laughing and crying treated with levodopa. Arch Neurol 1984; 41: 1095-6
38. Brooks BR, Thisted RA, Appel SH, et al. Treatment of pseudobulbar affect in ALS with dextrometorphan/quinidine: a randomized trial. Neurology 2004; 63: 1364-70
39. Tariq SH. Constipation in long-term care. J Am Med Dir Assoc 2007; 8: 209-18
40. Forshew DA, Bromberg MB. A survey of clinician's practice in the symptomatic treatment of ALS. Amyotroph Lateral Scler 2003; 4: 258-63
41. Bortolotti M. Laryngospasm and reflex central apnea caused by aspiration of refluxed gastric content in adults. Gut 1989; 30: 233-8
42. Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord 2007; 22: 213-9
43. Walters AS, Ondo WG, Dreykluft T, et al. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord 2004; 19: 1414-23
44. Ono S. The skin in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2000; 1: 191-9
45. Watanabe S, Yamada K, Ono S, et al. Skin changes in patients with amyotrophic lateral sclerosis: light and electro microscopic observations. J Am Acad Dermatol 1987; 17: 1006-12
46. Sasaki S, Tsutsumi Y, Tamane K, et al. Sporadic amyotrophic lateral sclerosis with extensive neurological involvement. Acta Neuropathol 1992; 84: 211-5
47. Qureshi M, Cudkowicz ME, Zhang H, et al. Increased incidence of deep venous thrombosis in ALS. Neurology 2007; 68: 76-7
48. Kimura F, Ishida S, Furutama D, et al. Wheelchair economy class syndrome in amyotrophic lateral sclerosis [letter]. Neuromuscul Disord 2006; 16: 207
49. Norris Jr FH, U KS, Sachais B, et al. Trial of baclofen in amyotrophic lateral sclerosis. Arch Neurol 1979; 36: 715-6
50. Ashworth NI, Satkunam LE, Deforge D. Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease (Review). Cochrane Database Syst Rev 2006; (1): CD004156
51. Marquandt G, Lorenz R. Intrathecal baclofen for intractable spasticity in ALS. J Neurol 1999; 256: 619-20
52. Marquandt G, Seifert V. Use of intrathecal baclofen for treatment of spasticity in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2002; 72: 275-6
53. Traynor BJ, Alexander M, Corr B, et al. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. J Neurol Neurosurg Psychiatry 2003; 74: 1258-61
54. Desnuelle C, Bruno M, Soriani MH, et al. What physical therapy techniques can be used to improve airway freedom. Rev Neurol 2006; 162: 4S244-52
55. Johnson CR. Aquatic therapy for an ALS patient. Am J Occup Ther 1988; 42: 115-20
56. Howard RS, Orrell RW. Management of motor neuron disease. Postgrad Med 2002; 78: 736-41
57. Bourke SC, Gibson GJ. Non-invasive ventilation in ALS: current practice and future role. Amyotroph Lateral Scler 2004; 5: 67-71
58. Lyall RA, Donaldson N, Polkey MI, et al. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain 2001; 124: 2000-13
59. Radunovic A, Mitsumoto H, Leigh PN. Clinical care of patients with amyotrophic lateral sclerosis. Lancet Neurol 2007; 6: 913-25
60. Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidenced-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology 1999; 52: 1311-23
61. Polkey MI, Lyall RA, Green M, et al. Expiratory muscle function in amyotrophic lateral sclerosis. Am J Crit Care Med 1998; 158: 734-41
62. Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. Thorax 1995; 50: 1131-5
63. Morgan RK, McNally S, Alexander M, et al. Use of SNIP nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. Am J Resp Crit Care Med 2005; 171: 269-74
64. Perez T. Amyotrophic lateral sclerosis (ALS): evaluation of respiratory function. Rev Neurol 2006; 162: 4S188-94
65. Pinet C. What is the role of life support systems? Rev Neurol 2006; 162: 4S266-68
66. Lechtzin N, Weiner CM, Clawson L, et al. Hospitalization in amyotrophic lateral sclerosis: causes, costs and outcomes. Neurology 2001; 56: 753-7
67. Desport JC, Preux PM, Truong TC, et al. Nutritional status is a prognostic factor for survival in ALS patients. Neurology 1999; 53: 1059-63
68. Desport JC, Torny F, Lacoste M, et al. Hypermetabolism in ALS: correlations with clinical and paraclinical parameters. Neurodegener Dis 2005; 2: 202-7
69. Dupuis L, Corcia P, Fergani A, et al. Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. Neurology 2008; 70: 1004-9
70. Boitano LJ, Jordan T, Benditt JO. Non invasive ventilation allows gastrostomie tube placement in patients with advanced ALS. Neurology 2001; 56: 413-4
71. Gregory S, Siderowf A, Golaszewski AL, et al. Gastrostomy insertion in ALS patients with low capacity: respiratory support and survival. Neurology 2002; 58: 485-7
72. Bouteloup C. What are the means of alimentary function supply and their indications? Rev Neurol 2006; 162: 4S309-19
73. Desport JC, Mabrouk T, Bouillet P, et al. Complications and survival following radiologically and endoscopically-guided gastrostomy in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2005; 6: 88-93
74. Thornton FJ, Fotheringham T, Alexander M, et al. Amyotrophic lateral sclerosis: enteral nutrition provision-endoscopic or radiologic gastrostomy? Radiology 2002; 224: 713-7
75. Couratier P, Desport JC, Antonini MT, et al. Review of nutritional and respiratory support in ALS. Rev Neurol 2004; 160: 243-50

76. Neudert C, Olivier D, Wasner M, et al. The course of the terminal phase in patients with amyotrophic lateral sclerosis. J Neurol 2001; 248: 612-6

77. Camu W, Khoris J, Moulard B, et al. Genetics of familial ALS and consequences for diagnosis. J Neurol Sci 1999; 165: S21-6

78. Hand C, Rouleau GA. Familial amyotrophic lateral sclerosis. Muscle Nerve 2002; 25: 135-59

79. Orrell RW, Figliewicz DA. Clinical implications of the genetics of ALS and other motor neuron diseases. Neurology 2001; 57: 9-17

80. Mayeux V, Corcia P, Besson G, et al. N19S, a new superoxide dismutase gene mutation in sporadic amyotrophic lateral sclerosis: no evidence for disease causation. Ann Neurol 2003; 53: 815-8

81. Rezania K, Yan J, Dellafave L, et al. A rare Cu/Zn superoxide dismutase mutation causing familial amyotrophic lateral sclerosis with variable age of onset, incomplete penetrance and a sensory neuropathy. Amyotroph Lateral Scler 2003; 4: 162-6

82. Andersen PM, Forsgren L, Binzer M, et al. Autosomal recessive adult-onset amyotrophic lateral sclerosis associated with homozygosity for Asp90Ala Cu,Zn superoxide dismutase mutation: a clinical and genealogical study of 36 patients. Brain 1996; 119: 1153-72

83. Cudkowicz ME, McKenna-Yasek D, Sapp PE, et al. Epidemiology of mutations in SOD in ALS. Ann Neurol 1997; 41: 210-21

84. Regal L, Vanopdenbosch L, Tilkin P, et al. The G93C mutation in superoxide dismutase 1: clinicopathologic phenotype and prognosis. Arch Neurol 2006; 63: 262-7

85. Corcia P. Methods of the announcement of ALS diagnosis in familial forms. Rev Neurol 2006; 162: 4S122-6

86. Van den Berg JP, Kalmijn S, Linderman E, et al. Multidisciplinary ALS care improves quality of life in patients with ALS. Neurology 2005; 65: 1264-7

87. Nirmalananthana N, Greensmitha L. Amyotrophic lateral sclerosis: recent advances and future therapies. Curr Opin Neurol 2005; 18: 712-9

88. Cudkowicz ME, Shefner JM, Schoenfeld DA, et al. Trial of celecoxib in amyotrophic lateral sclerosis. Ann Neurol 2006; 60: 22-31

89. Gordon PH, Moore DH, Florence JM, et al. Results of the phase III randomized controlled trial of minocycline in ALS [abstract]. Neurology 2007; 68 Suppl. 1: 90

90. Gordon PH, Moore DH, Miller RG, et al. Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial. Lancet Neurol 2007; 6: 1045-53

91. Meininger V, Bensimon G, Bradley WR, et al. Efficacy and safety of xaliproden in amyotrophic lateral sclerosis: results of two phase III trials. Amyotroph Lateral Scler 2004; 5: 107-17

92. Mazzini L, Mareschi K, Ferrero I, et al. Autologous mesenchymal stem cells: clinical applications in amyotrophic lateral sclerosis. Neurol Res 2006; 28: 523-6

93. Lepore AC, Maragakis NJ. Targeted stem cell transplantation strategies in ALS. Neurochem Int 2007; 50: 966-75

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