Amyotrophic lateral sclerosis: new perpectives and update

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Abstract

Amyotrophic lateral sclerosis (ALS), Charcot's disease or Lou Gehrig's disease, is a term used to cover the spetrum of syndromes caracterized by progressive degeneration of motor neurons, a paralytic disorder caused by motor neuron degeneration. Currently, there are approximately 25,000 patients with ALS in the USA, with an average age of onset of 55 years. The incidence and prevalence of ALS are 1-2 and 4-6 per 100,000 each year, respectively, with a lifetime ALS risk of 1/600 to 1/1000. It causes progressive and cumulative physical disabilities, and leads to eventual death due to respiratory muscle failure. ALS is diverse in its presentation, course, and progression. We do not yet fully understand the causes of the disease, nor the mechanisms for its progression; thus, we lack effective means for treating this disease. In this chapter, we will discuss the diagnosis, treatment, and how to cope with impaired function and end of life based on of our experience, guidelines, and clinical trials. Nowadays ALS seems to be a more complex disease than it did two decades – or even one decade – ago, but new insights have been plentiful. Clinical trials should be seen more as experiments on pathogenic mechanisms. A medication or combination of medications that targets more than one pathogenic pathway may slow disease progression in an additive or synergistic fashion.

Introduction

The technological breakthrough in the field of neurolog /neuroscience, with modern imaging and genetic studies, may, sometimes, make the neurologist stay away from indispensable propaedeutic techniques for the correct diagnosis of amyotrophic lateral sclerosis (ALS). ALS is without doubt a disease of the central nervous system (CNS), which its natural history is one of the darkest in neurology. A progressive, devastating and inexorable disease, commonly leads to death by respiratory failure a few years after onset of first symptoms. Rowland,[1] centuries ago, defines its natural history well by stating that any notification of improvement in patients with this disease deserves careful review, because probably it is not a case of ALS. Prompt diagnosis, sensitive communication of the diagnosis, the involvement of the patient and their family, and a positive care plan are pre requisites for good clinical management. While ALS is an incurable disease, many symptoms are amenable to supportive and adjunctive therapies, some of which may even improve the disease course.[2] Nowadays, ALS is considered a multisystemic disease with broad pathophysiological framework and numerous theories that surround it, hampering a unique therapeutic target.[3] These pathophysiological mechanisms include oxidative stress, mitochondrial impairment, protein aggregation, cytoskeletal disruption, glutamate and neuronal cytotoxicity, altered regulation of gene expression, inflammation, and apoptotic cell death. An understanding of how these potential therapeutic targets interrelate will provide direction both in the development of a pharmacotherapy and in the design of clinical trials.[4] Countless experts in the field, for example, the group conducted by Oliveira and Pereira,[5] consider that a combination of drugs focused on more than one pathogenic pathway may slow disease progression in an additive or synergistic fashion. It is noteworthy that such combination therapy has been successful in oncology, though multiple drug interactions and increased incidence of drug side effects should be considered. The risk for benefit ratio should also be considered.

Histopathological findings reveal an impairment of the motor neurons of the pyramidal beam, the brainstem and spinal cord in varying degrees. Although ALS are readily recognized by neurologists, about 10% of patients are misdiagnosed, and delays in diagnosis are common.[5]

The disease has several features in the different presentation forms, course and progression. The incidence is approximately two cases per 100,000 inhabitants, which represents approximately 5000 patients per year in the U.S. alone.[6] A high prevalence of ALS cases is reported in certain geographical areas, for example the Pacific island of Guam (50 times that of ALS in western countries), leading to speculation about environmental and genetic factors as potential triggers for ALS. People over fifty are the most affected. Men are affected nearly twice as often as women, with no racial differences.

A study by Orsini *et al*.,[7] that aimed to delineate the clinical and functional profile of patients with ALS in Brazil and compare with other regions of the world, identified a rapid depletion of functional capacity, muscle strength, swallowing and breathing pattern. In that study, the onset of ALS is often insidious and can manifest by unexplained trip or motor disabilities, usually in the distal arm. Some patients with bulbar onset have difficulty in swallowing and changes in voice tonality. The time between the onset of first symptoms and seeking care services was 11.6±12.4 months. The time between the first symptoms and the diagnosis was 20.5±8.4 months. The author demonstrates that the findings related to ALS presentation in the subgroup of European countries (Italy, Germany, Spain) have some similarity with the characteristics of other industrialized countries as, for example, in Brazil. To sum up, ALS is part of the so-called motor neuron disease (MND) disease, along with progressive spinal amyotrophy (PSA) and primary lateral sclerosis. The progressive bulbar palsy (PBP), does not fail to take part in the spectrum of presentation of classical ALS, so, it should be studied together.[8]

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Key words: Amyotrophic lateral sclerosis; neurodegenerative diseases; diagnosis; treatment; rehabilitation.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 25 February 2015.
Accepted for publication: 15 June 2015.

Licensee PAGEPress, Italy
Neurology International 2015; 7:5885
doi:10.4081/ni.2015.5885

Classification and physiopathogenesis

The ALS cases can be classified into sporadic, familial, and from the western Pacific (ALS and Parkinsonism-Dementia Complex), the latter very common in Chamorro people of Guam and Marianas island, the Kii peninsula of Honshu Island, and the Auyu and Jakai people of south west New Guinea. In around 5-10% there is evidence of family history (familial ALS), and, approximately 20% of these variants are linked to the gene encoding the enzyme copper-zinc superoxide dismutase (*Cu-Zn SOD1*), and 2-5% have mutations of *TARDBP* (*TDP-43*) gene.

Commonly these cases show Mendelian autosomal dominant inheritance. However, autosomal recessive patterns have also been identified.[8] Investigations of mutant *SOD1* have illuminated crucial components of the death process including: a propensity for mutant *SOD1* to be unstable; a multiplicity of mitochondrial defects that predict cellular energy failure, enhanced glutamate sensitivity and activation of the machinery of programmed cell death; and a role for non-neuronal cells as modulators of neuron death.[9] Recently a mutation in the gene coding for the protein VAPB (vesicle-associated membrane protein-associated protein B), mapped at 20q13.3, was reported in a large white Brazilian family with ALS cases and traced to a common ancestor from the time of contact with Portugal.[5] Recently mutations in the gene *FUS* with involvement of TDP-43 and FUS proteins have been described. These cases are usually associated with frontotemporal atrophy. Sporadic ALS differs from familial ALS in some aspects. In sporadic ALS symptoms onset usually occur around the age of 55-65 years, with a mean of 64 years old; it is more prevalent in men than in women (1.5:1), probably due to a hormonal protection in women and a greater exposure among men to supposed risk factors; it also presents a mortality of 1.84 per 100,000 inhabitants. Differently, in familial ALS the age of onset of symptoms varies between 45-55 years, and the prevalence is similar between men and women, with a lower life expectancy. Both forms of the disease are similar in clinical and pathological presentation.[10] As stated previously, endogenous and environmental factors appear to be interrelate and contribute to the development and evolution of the disease neurotoxicity that ultimately culminates with the depletion of motor neurons.[11] Amongst others these include: oxidative stress, excitotoxicity mediated by glutamate, toxic effects caused by the mutation of super oxide dismutase (*SOD1*), inclusion of the abnormal protein aggregation, intermediaries filaments disorganization, changing the anterograde and retrograde axonal transport, microglial activation, inflammation, and growth factor deficiency.

Several factors are proposed to instigate these phenomena, including latent infections by viral and non-viral agents, toxins (for example, insecticides and pesticides) and autoimmune reactions.[9] Genetic factors, changes in intracellular calcium levels in motor neurons, and programmed cell death (apoptosis) have also been linked to the development of ALS.[12,13]

Clinical profile

The clinical presentations of patients do not follow a pattern, although some initial manifestations are present in most cases. Unexplained tripping (slight foot drop) with or without episodes of falls in addition to impairment of dexterity in distal crural are usually recounted by patients. This situation translates into an involvement of the motor cells of the anterior horn in L4 and C8-T1 segments respectively. Unfortunately, when muscle weakness becomes noticeable, patients have lost about 80% of the motor neurons in the corresponding myotomes.

The degree of involvement of the pyramidal beam and the ventral horn is variable and non-standardized. However, the fact of muscles that control eye movements and the urinary sphincters are spared. Cramps and fasciculations are frequent. Before long, the triad of *cadaveric* hands (atrophic weakness), hyperreflexia and spasticity – usually in absence of sensory changes – leaves little doubt as to diagnosis. It Is worth mentioning that although dominated by motor dysfunction, there is increasing evidence that ALS is a multisystem disorder in which the autonomic system, spinocerebellar tracts, dorsal columns, basal ganglia and extra motor cortex may also be affected.[14-17]

The occurrence of cognitive decline in ALS, especially in the form of frontotemporal dementia (FTD), notably with the behavioural variant FTD, has been described previously. Recent molecular biology and histopathology data suggest that both ALS and FTD may share common pathological pathways and may present two phenotypes of the same proteinopathy. Cognitive decline in ALS is characterised by personality change, irritability, obsessions, poor insight, and pervasive deficits in frontal executive tests.[18,19]

The association between neuropathy and ALS has been reported rarely and the line distinguishing from motor neuropathies is sometimes blurred. Among MND (Motor Neuron Diseases), the Patrikio's pseudopolyneuritic form of ALS strictly mimics a kind of neuropathy.[17,20] Neuromuscular diseases, as seem in ALS, lead to alveolar hypoventilation. When the onset is slow and progressive, alveolar hypoventilation typically goes undiagnosed and untreated until an episode of acute respiratory failure occurs. This episode of decompensation is frequently seen during common upper airway infections, and it results from patient incapacity to eliminate secretions. At the moment that the ventilatory muscles are compromised, individuals present pulmonary restrictions, characterized by reduced vital capacity (VC) and tidal volume (TV) with consequently chronic respiratory failure. Atelectasis, pneumonia and respiratory failure, initially during sleep and later on even during wakefulness, are the complications expected in this situation.[21]

ALS can produce sleep alterations, since alveolar hypoventilation is more intense during sleep. The worsening of alveolar air exchange presents subtle symptoms that can pass unnoticed if not directly analyzed. Hypoventilation during sleep can initially manifest as a progressively increasing number of nighttime awakenings, fatigue, daytime sleepiness and morning headaches.[22] In ALS, 30% of patients begin with bulbar symptoms including dysphagia, dysarthria, dyspnea and changes in phonation. It is unclear whether the bulbar involvement implies the simultaneous deterioration of the four functions or if they may have an independent evolution. Among these, dysphagia is one of the most important problems faced in ALS, not uncommon as the initial symptom. The presence of dysphagia and the aspiration pneumonia report are usually the biggest damages to the quality of patients' life, in addition to the risk of malnutrition and dehydration, occurring particularly in elderly.[23] To sum up, the majority (65%) of patients present limb symptoms, while 30% present symptoms of bulbar dysfunction in the form of dysarthria or dysphagia. 5% of patients have respiratory-onset disease. Initial symptoms of weight loss and isolated emotional lability have also been reported.[24] In some cases of ALS, the characteristic combination of upper motor neuron and lower motor neuron abnormalities may be absent, leading to diagnostic uncertainty for months or years.[25] It was not found in the literature a work that addressed all major emergency care in ALS for professionals in the health field. The Canadian Society has created a guideline for ALS patients living with ALS, which contains explanations of the disease, where to find help, signs and symptoms, mobility and independence, among other items geared to the patient and caregivers not portraying therefore, conducts to be taken by professionals in the health field in cases of emergency.[26,27]

Progressive muscular amyotrophy

Progressive muscular amyotrophy (PMA) is a heterogeneous syndrome that overlaps with

ALS. Although it is considered to carry a better prognosis than typical ALS, approximately 30% of patients with PMA develop upper motor neuron signs within 18 months, and progress to a diagnosis of ALS. Corticospinal tract involvement is demonstrated on autopsy in up to 50% of patients with an initial diagnosis of PMA.[28] Clinical manifestation is characterized by the involvement of lower motor neurons. It is genetically determined, with the absence or mutation of the survival motor neuron 1 (*SMN1*) as a hallmark. A similar copy of the *SMN1*, named *SMN2*, modulates the severity of the disease. Several types of the disease have been described along with several classification systems based either on the age at onset of symptoms or on the maximum function achieved. PMS presents itself in a wide clinical spectrum ranging from death in infancy (PMA type I) to a natural history characterized by only slight muscle weakness, with survival to adulthood (PMA adult onset). Currently, facing a phenotype suggestive, genetic study is performed to detect homozygous deletion of exons 7 and 8 of *SMN1* gene, with a sensitivity of about 95% and 100% specificity in the diagnosis of PMA.[29,30] Araújo described the clinical findings of patients with spinal muscular atrophy (SMA) with survival motor neuron (SMN) gene deletion.[31] All of the 22 included patients had symmetrical muscle weakness, which was diffuse in those with onset of symptoms up to 6 months of age (75%), and either proximal or predominant in lower limbs in the remaining group (67%). Fasciculations and atrophy were both frequent findings (82%). Laboratory tests findings were variable, with positivity of 57% for electrophysiology and of 58% for muscle biopsy.

Primary lateral sclerosis

Upper motor neuron involvement predominates clinically in patients with PLS, although, in some cases, slight lower motor neuron symptoms may be present. Clinical features include severe spasticity with slight weakness in the lower limbs and eventually pseudobulbar symptoms (dysarthria and compulsive laughing or crying). The course of the disease is slowly progressive. Pathologically, a selective involvement of the motor cortex is seen with degeneration of the Betz cells and demyelination of the descending motor tracts. Primary lateral sclerosis can be distinguished from ALS by the long duration of the disease, the extensive cortical atrophy and the considerable prolonging of the motor evoked potential (MEP). Motor nerve conduction velocity in PLS is normal or prolonged.[32]

Progressive bulbar palsy

We consider ASL and progressive bulbar palsy the same pathological entity. PBP predominates in females being characterized by emotional lability and early evolution of the respiratory muscles progressing to death around 6 months to 3 years of age.[8,33,34]

Diagnostic criteria

There is no definitive diagnostic test for ALS. The combination of suggestive clinical signs with negative laboratory tests and imaging studies for other pathologies supports the diagnosis, although disease progression is a pre requisite. The two conditions most commonly mistaken for ALS are multifocal motor neuropathy with conduction block, and cervical spondylotic myelopathy. Differentiating multifocal motor neuropathy from ALS is especially important, as patients with this neuropathy may benefit from intravenous immunoglobulin treatment. Generally, patients with common mimic syndromes do not progress as rapidly as those with ALS, and tend to survive for longer periods. Spinobulbar muscular atrophy (Kennedy disease) is also often misdiagnosed as ALS. Kennedy disease is an X-linked disorder associated with an expansion of trinucleotide repeats in the androgen receptor gene. The clinical features of this condition include slowly progressive lower motor neuron signs in the bulbar region and proximal limbs, and 50% of affected patients have gynecomastia. A pure lower motor neuron syndrome with a family history demonstrating no male-to-male inheritance should, therefore, alert the physician to this possible diagnosis.[35-37]

Several diagnostic criteria for ALS exist, namely, El Escorial criteria revised and Lambert criteria, however, these criteria may not be useful in early diagnosis. In December 2006, researchers around the globe met in Awaji Island, Japan to discuss about proposing a recent rationalisation of the El Escorial criteria (the Awaji consensus) to facilitate detection of ALS in an early stage.[36] The Awaji-Shima criteria was introduced in 2008, use of which improved diagnostic sensitivity without increasing false-positive rates (Table 1).[38]

Carvalho have tested the sensitivity of a recently published approach to combining clinical and EMG data in the *research diagnosis* of ALS, in 55 consecutive patients clinically diagnosed with ALS.[39] The application of this *Awaji algorithm* to the revised El Escorial diagnostic criteria for diagnosis of ALS, achieved a diagnostic sensitivity of 95% for definite ALS compared with 18% using the clinical El Escorial criteria and 53% when the EMG criteria as defined in the El Escorial criteria. This increased sensitivity was particularly relevant for bulbar onset patients (sensitivity improved from 38% to 87%) and for patients with El Escorial clinically possible ALS (from 50% to 86%).

Routine investigation

Routine investigation of a patient with apparently typical ALS should include measurement of erythrocyte sedimentation rate, serum and urine protein electrophoresis, thyroid function tests, serum calcium and phosphate measurements, and cerebrospinal fluid analysis. Infection-related tests: syphilis; Lyme; HIV; HTLV-1 and 2; hepatitis B and C are necessary; muscle enzymes: CK; ALT; AST; LDH.[5] Image evaluation is composed by: magnetic resonance investigation (brain and spine); DNA evaluation (SOD1, VAPB, Kennedy's disease – expansion of trinucleotídeo GCC on chromosome X). A heavy metal screen should be performed in individuals with a potential history of exposure. -hexosaminidase deficiency (Tay-Sachs disease) is common in some ethnic groups, and can mimic ALS. -hexosaminidase subunits and activity should be tested in patients of Ashkenazi Jewish extraction.[5]

Electrodiagnostic studies are the most critical ancillary tool in the investigation of ALS. Electromyography can identify loss of lower motor neurons, the hallmark of ALS, and it is particularly useful in clinically unaffected regions. The most frequently recognized abnormalities observed on electromyography are fasciculation, spontaneous denervation discharges (fibrillation potentials and positive sharp waves) indicative of ongoing motor neuron loss, and polyphasic units indicative of reinnervation.The measurement of central motor conduction has been refined and may, today, through transcranial electrical stimulation of the motor area, verify the slow transition through the I motor neuron. This exam can be useful in cases that the suffering from pyramidal tract is not clinically evident.[40]

Differential diagnosis

In patients diagnosed with ALS, theabsence of disease progression, the presence of an atypical history, or the presence of unusual symptoms should trigger a search for mimic syndromes. Generally, patients with common mimic syndromes do not progress as rapidly as those with ALS, and tend to survive for longer periods.[41]

Considering the clinical and laboratory findings, the motor neuron diseases have been classified as ALS/DNM (sporadic cases, family or genetically determined), ALS-plus syndromes (multisystem neurodegenerative disease affecting motor neurons), the ALS-related syndromes (represent symptomatic or secondary forms of motor neuron disease, with a known associated condition that may be caus-

ing the disease) and the ALS variants (are uncommon unless the patient lives in particular geographic locations) (Table 2).[41-44] Some clinical features are inconsistent with the diagnosis of ALS, although still possible, they are: anterior visual pathway abnormalities, autonomic nervous system dysfunction; cognitive abnormalities associated with Alzheimer's disease; movement abnormalities associated with Parkinson's disease; sensory disturbance; sphincter abnormalities. As mentioned previously, recent studies suggest that the pathogenic processes of ALS LS are more extensive, involving dysfunction of cortical grey and white matter with clinical correlates of impairment in cognition and language. In reality, at least a subgroup of ALS LS patients experience personality changes and cognitive problems consistent with fronto-temporal dementia (ALS LS-FTD).[5] Reports suggest that in some specific settings (especially in monomelic forms, ALS syndrome and some neuropathies), a search for HIV infection is warranted, especially in young individuals.[44]

Clinical treatment: therapeutic targets and control-submitted symptomatology

We reinforce that although ALS has no cure. Symptom control and anticipation of clinical problems are extremely important for this clientele. Many doctors believe that even today the provision of an early diagnosis does not change the patient's history as far as the disease goes. Fortunately, this fact is not true, since there is strong evidence that early detection prolongs survival of patients.[45] Other professionals still wonder if such survival is with good quality of life. Unfortunately our role is to provide the best in the treatment and contribute to mitigating their pain. Considering the quality of life, it is variable and changeable between ALS patients during the natural history of the disease.

A good doctor monitors the patient towards their difficulties. Unfortunately, riluzole remains the only evidence-based disease-modifying drug for ALS.[46]

Management of respiratory problems

The indication of NIV (non-invasive ventilation) in ALS patients has been recommended when there is a reduction of 50% of the predicted value for forced vital capacity (FVC), and/or a decrease of SpO_2 below 88% for more than five consecutive minutes during the night and/or increased partial pressure of oxygen in arterial blood (PaCO2) greater than 45 mmHg and/or increase in maximal inspiratory pressure of inspiratory muscles (MIPIM) above −60 cm H_2O. Besides these, there are indications related to possible signs and symptoms such as: dyspnea, fatigue, morning headache, aggravated sleepiness among others. Respiratory failure and pulmonary complications of bulbar paralysis (*i.e.* aspiration pneumonia) are the most common causes of death in ALS.[47,48]

Despite being a palliative care, the application of NIV in ALS patients can improve quality

Table 1. El Escorial and Awaji-Shima criteria.

Criteria	Definite ALS	Probable ALS	Possible ALS	Suspected ALS
El Escorial	Upper and lower motor neuron signs in 3 regions	Upper and lower motor neuron signs in at least 2 regions, with upper motor neuron signs rostral to lower motor neuron signs	Upper and lower motor neuron signs in 1 region, upper motor neuron signs alone in 2 or more regions, or lower motor neuron rostral to upper neuron signs	Lower motor neuron signs only, in 2 or more regions
Awaji-Shima	Clinical or electrophysiological evidence, demonstrated by the presence of upper and lower motor neuron signs in the bulbar region and at least 2 spinal regions, or the presence of upper and lower motor neuron signs in 3 spinal regions	Clinical or electrophysiological evidence, emonstrated by upper and lower dmotor neuron signs in at least 2 spinal regions, with some upper motor neuron signs necessarily rostral to the lower motor neuron signs	Clinical or electrophysiological signs of upper and lower motor neuron dysfunction in only 1 region, or upper motor neuron signs alone in 2 or more regions, or lower motor neuron signs rostral to upper motor neuron signs	NA

ALS, amyotrophic lateral sclerosis; NA, not available.

Table 2. Differential diagnoses of amyotrophic lateral sclerosis.

Hereditary conditions	Spinobular muscular atrophy (Kennedy disease); hereditary spastic paraparesis; acid maltase deficiency; facioscapulohumeral muscular dystrophy; adrenomyeloneuropathy; Huntington disease; hexosaminidase deficiency
Metabolic conditions and toxic effects	Hyperthyroidism; hyperparathyroidism; heavy metal intoxication; lathyrism; organophosphate toxic effects
Immune and/or inflammatory conditions	Multifocal motor neuropathy with conduction block; chronic inflammatory demyelinating polyneuropathy; myasthenia gravis; inclusion body myositis; polymyositis; multiple sclerosis; paraneoplastic disorders
Structural disorders	Cervical spondylotic myelopathy; syringomyelia or syringobulbia; postirradiation myelopathy and/or plexopathy; tumor
Cerebrovascular disease	-
Other neurodegenerative diseases	Corticobasal degeneration; multiple system atrophy; progressive supranuclear palsy; Parkinson disease; Huntington disease
Other motor neuron diseases	Primary lateral sclerosis; progressive muscular atrophy; spinal muscular atrophy; post-polio spinal muscle atrophy; benign fasciculation syndrome; Hirayama disease
Infections diseases	HIV; HTLV; Lyme disease; Syphilis

of life and prolong survival in some cases, in more than 12 months in patients with impairment of respiratory function. Eventually, when the need for HMV exceeds 16-20/24 hours, some centers would consider a change to invasive ventilation. Tracheostomies hinder the normal defense mechanisms of the trachea, increase secretion, rapidly colonize with difficult to control germs, impede swallowing and impair speech.[22] A more proactive attitude to treat respiratory infections, avoiding bronchopneumonia and/or pneumonia conditions, could have a significant impact on survival. Patients should also participate in the annual vaccination campaign against influenza and other infectious agents (Table 3).

Dysphagia management and support in amyotrophic lateral sclerosis nutrition

Drooling, dehydration, malnutrition with weight loss and aspiration are all associated with dysphagia.[5] ALS patients, especially with bulbar involvement, demonstrate more severe problems swallowing (such as aspiration). Early leak is more common with thin liquids and a major cause of tracheal aspiration, even at early stages of the disease and mild abnormalities of the oral musculature. Swallowing alterations occur due to the inefficiency of oral transit, the reduction of the movement of the tongue base, laryngeal elevation and anteriorization reduction and pharyngeal contraction.[49] The loss of body weight associated with bulbar disorders (dysphagia and breathing), demonstrates the need for early and specific nutritional care at every stage of the disease. It is possible to do body energy reserve in patients with ALS by minimizing significant loss of lean body mass and total body fat.[49]

Nutritional support comprises the early detection of the decrease in food intake, particularly in kilocalories, the change in the consistency of the diet and the early indication of alternative feeding ways. The alternative feeding ways of patients with ALS include gastrostomy or jejunostomy. The advantages of gastrostomy include improved nutrition, although evidence to support a substantial effect on survival remains to be firmly established.[50]

The guidelines for nutrition as well as the directives for implementation of enteral nutrition/parenteral follow in Table 4.[51,52]

Speech management

When speech can no longer be understood, adaptive strategies such as sign language, mime, posture and alternative communication by computer systems, may be used by patients with ALS. Most devices now offer a range of access methods, starting with keyboards, touch screens, a head mouse, and Morse code.[53,54]

Therapeutic trials in amyotrophic lateral sclerosis

Riluzole

Riluzole is a benzothiazole derivative that modulates glutamatergic activity, thereby suppressing excitotoxicity. This drug modifies the course of ALS, but this treatment achieves only a modest improvement in survival (3-6 months). The recommended dosage of the drug is 100 mg/day, split into two dosages of 12 hrs/day. This drug seems to be well tolerated, although it has some side effects such as: asthenia, nausea, vomiting, dizziness, drowsiness and perioral paresthesia. Cases of pneumonitis have been reported following the use of the drug. Patients may show an increase of hepatic markers, therefore, a control of liver function in an average period of three months is necessary. In case of significant increase, the drug should be discontinued. After demonstrating of decline in mortality, Riluzole, most likely related to its anti-excitotoxic properties, was approved by the United States food and Drug Administration in December, 1997. Later meta-analysis indicates that the effect was real, and that there may have been a small effect on function (Table 5).[55,56]

Drugs used for control of symptoms

We alert that the therapeutic options for the management of clinical problems presented by patients with ALS is wide, therefore, we mention just a couple of drugs that can attenuate them (Table 6).[57]

Emergency situations in amyotrophic lateral sclerosis

In cases of respiratory failure, it is common in ALS patients to arrive at emergency departments where healthcare professionals ignoring the concept of ventilation failure, treat the symptoms with the administration of oxygen. This leads to an exacerbation of hypoventila-

Table 3. Respiratory guidelines.

Respiratory function	Indications for non-invasive ventilation and tracheostomy
Non-invasive ventilation	Reduction of 50% of the predicted value for forced vital capacity; decrease of SpO2 below 88% for more than five consecutive minutes during night; increased partial pressure of oxygen in arterial blood greater than 45 mmHg; increase in maximal inspiratory pressure of inspiratory muscles above –60 cm H2O. Dyspnea, fatigue, morning headache, aggravated sleepiness among others.
Tracheostomy	When the need for home mechanical ventilation exceeds 16-20/24 hours
Respiratory therapy	The selection of physical therapy techniques , the work at submaximal limits, the variation in time of application, in addition to particular features of the patients are essential
Vaccination schedule	Influenza and Pneumococcal must be performed (unless there are specific contraindications).

Table 4. Guidelines for nutrition and directives for implementation of enteral nutrition/parentera.

General guidelines	Patients that feed or are fed quickly, are more susceptible to episodes of bronchial aspiration. Food should be well cut. Nutritional supplementation is necessary. ALS patients may have increased nutritional requirements, since they have loss of total body mass, even in the presence of adequate protein-calorie intake. To offer powder supplementing diluted in whole milk, or adding fruit in its preparation seem to be good strategies. For patients with frequent gagging, thickeners should be introduced in liquids. Soft food is easier to swallow and should be encouraged. Offer food in small amounts at regular intervals.
Percutaneous endoscopic gastrostomy	Such procedure should be considered when weight loss of over 10%; severe dysphagia; inadequate energy intake; functional vital capacity of less than 50% of predicted; history of aspiration and a body mass index of less than 20
Speech therapy	Early detection of these disorders allows speech therapists to objectively evaluate functional impairment and set realistic goals of rehabilitation

tion and sudden failure with subsequent need for intubation (rarely necessary for these patients) or even death. In these cases one should remember that the important thing is to ventilate and not oxygenate the patient. Also it is emphasized the importance of manual and mechanical aid to the cough through the air-stacking, abdominal press or cough assist (auxiliary cough) made by health professionals when patient does not reach the minimum flow of cough: 160l/min or 2.7 l/sec.[26]

Study medications for patients with amyotrophic lateral sclerosis: tamoxifen

Tamoxifen is an important drug in the treatment and prevention of breast carcinoma dependent of hormonal regulation, because it is a selective estrogen-receptor modulator (SERM). Despite its effectiveness depend on the metabolic activation of this prodrug, predominantly via cytochrome P450 2D6, the active metabolite endoxifen and 4-hydroxytamoxifen. Tamoxifen has an anti-estrogen action by binding to the first receptor of estrogen than estrogen, the level of the tumor cell itself. If we are considering an estrogen-dependent tumor, tamoxifen will prevent the binding of estrogen and, consequently, the tumor is decreasing. It is also believed that tamoxifen affects the most important factor in the regulation of angiogenesis is vascular endothelial growth factor (VEGF). Therefore, it is considered that the drug prevents tumor-induced angiogenesis.[58] On the other hand, propably has neuroprotective action because of its ability to inhibit protein kinase C, which mediates inflammation in spinal cords of patients with ALS.[59] The serendipitly way, in a patient with breast cancer and ALS who was treated with tamoxifen experienced marked slowing in progression of the ALS. The drug was well tolerated in both sexes and data from an extended follow-up period, suggested that patients receiving 20 to 40 mg per day may have longer survival compared to patients receiving only 10 mg per day (Dr. Ben Brooks, reported at the 15th International ALS/MND Symposium, Philadelphia, 2004).[56]

Stem cells in patients with amyotrophic lateral sclerosis

The relentless pursuit of treatment for this

Table 5. Medications and therapeutic targets.

Medicamento	Mechanism of action	Posology	Side effects	Target
Riluzole*	Modulates glutamatergic activity suppressing excitotoxicity	100 mg/day in 2 dosages of 50 mg	Conditions of elevated liver enzymes, and pneumonitis are the most serious side effects	Alleviate neuronal death
Lithium**	Activation of autophagy and na increase in the number of the mitochondria in motor neurons and suppressed reactive astrogliosis	Daily doses, leading to plasma levels ranging from 0.4 to 0.8 mEq/liter, delay disease progression in human patients affected by ALS	Acne, itching, confusion, dry mouth, memory problem, loss of apetite, Delirium, siarrhoea	Increased autophagy of abnormal cellular components and potentiation of mitochondrial activity

*The only drug that modifies the course of ALS, increasing survival in a short period of time. **Despite its use in animal models have been successful, the risk-benefit ratio in humans is still not satisfying.

Table 6. Therapeutic options for the management of clinical problems presented by patients with amyotrophic lateral sclerosis.

Clinical problems	Drug and/or guidelines
Sialorrhea Pain (commonly triggered by contractures, immobility or associated with spasticity)	Botulinum toxin type B; Tricyclic antidepressants (Amitriptyline) Non-narcotic analgesics, and antispasticity agents (baclofen) for initial treatment. Administer opioids liberally, following the WHO HO guidelines, when non-narcotic analgesics fail. Physiotherapy is also necessary for management of conditions (stretching, passive mobilisations and Transcutaneous Electrical Neurostimulation) in some cases
Bowel function (commonly is not affected in ALS, however paresis of the abdominal muscles, on the part of patients)	Increased Hydro Intake, Increased Intake of Dietary Fiber or even use of compost (sachet) Fibers.
Fasciculations (do not harm patients functionally, however they are subject of seizures and irritability on the part of patients)	Gabapentin; other drugs used are also phenytoin and pregabalin. There comes a moment that fasciculations cease in patients with ALS, because they are due the frustrated attempt of reinnervation. When the muscles become totally denervated, such mechanism does not happen. Excessive and strenuous physical activities in patients with ALS may potentiate deflagrate fasciculations
Fatigue (several mechanisms are associated with fatigue in patients with motor neurone disease, which can be of central or peripheral origin)	Amantadine is an example of medicine for this purpose. Antidepressants such as venlafaxine are also used. Other strategies for easing of fatigue are quality and duration of sleep. Also, to avoid exhaustive and strenuous physical activities during rehabilitation and rest periods during the day are needed, saving energy for priority activities
Depression (by the tragic outcome of ALS, it is common for many patients to have episodes of depression)	Despite existing several medications for this purpose, we chose to mention the SSRI e Tricyclic antidepressants. Patients may also experience emotional lability, most often controled with the use of SSRIs. We emphasize that psychotherapy is also extremely important for this clientele. Families and caregivers should, if possible, actively participate in this process.
Cramps (patients with ALS may present episodes of cramps or rest or when performing functional activities)	Vitamin E and diazepam are widely used drugs for this purpose. Other medications may also be used, for example clonazepam. Stretching and massage therapy can also be performed by the physiotherapist
Spasticity (patients with spastic muscle groups can experience pain and myo-joint contracturesin addition to loss in performing basic and instrumental activities of daily living)	The use of Baclofen has been proved to be effective in the management of spasticity in some cases. When patients have severe contractures and severe spasticity uncontrolled by the use of oral medications, botulinum toxin type A may be an alternative treatment. The physiotherapist plays an important role in the management of spasticity through stretching, weight transfer and other manual. 10-60 mg TID

inexorable condition has been based on solid principles related to probable multiple and certainly not mutually exclusive physiopathologic mechanisms, the complex interaction of genetic, epigenetic, metabolic and pathophysiological factors that can initiate or propagate the process in ALS has allowed therapeutic trial of some substances isolated and or combined candidates, but within ethical limits proposed by the favorable performance in the animal model of ALS, but uncertain in human form; on patient safety and real benefit on the development of ALS. Thus, a therapeutic agent candidate should be more transparent, rational and reproducible processes of clinical trials.

Since it is a seductive path to therapy with stem cells, especially in a context in which motor cells suffer irreversible and progressive damage that lead to death, there is need for understanding the many steps in this process. The cells of the organism are derived from specific progenitor cells, and this process is highly regulated, and in particular source and primordial stem cells that include migration, differentiation, proliferation and maturation cellular.

Regarding the differentiation, potential of stem cells can be totipotent, pluripotent and multipotent. Totipotent can give rise to all embryonic and extra-embryonic tissues; pluripotent can originate all cell types of the embryo; multipotent can cause various cell lines. The differentiation of stem cells into mature cells is strictly controlled, being activated or deactivated by means of gene expression, with the meaning of obtaining the properties of the tissue in its various evolutionary stages.[60]

Posteriorly neural stem cells was grafted derived from human embryonic spinal cord in the lumbar region of the spine in mice immunosuppressed SOD-G93A and that there was differentiation of stem cells into motor cells, and consequent clinical improvement.[61]

The stem cells have been employed in other neurodegenerative conditions and therefore also led to their use in ALS. Initially favorable responses were observed in terms of life expectancy when transplants of bone marrow cells were made in SOD-G93A mice.[62] There were initial doubts as to the result to be dependent neuroprotective factor released by or related to neuroregeneration stem cell itself. It was observed that neural cells derived from embryonic stem cells were more sensitive to the toxic effects caused by mutations in the *SOD1* gene glial cells.[63]

The use of mesenchymal stem cells from bone marrow was transplanted directly into the spinal cord between T7 and T9 in 7 patients with ALS and there was a slowdown in the decrease in vital capacity strength in four patients 36 months after treatment.[64] However, there are those that introduce autologous mesenchymal stem cells from bone marrow in the spinal fluid of patients with ALS without evidence of clinical improvement, nevertheless consider the procedure safe.[65] Within this line of conduct the use of stem cells in the setting of ALS has at least two well-established theoretical principles. The differentiating cells in environments in which there has been the demise of motor neurons, and also, in the protection of remaining and acting as *chaperones* to collaborate with the motor cells already affected.[8] Preclinical *in vitro* and *in vivo* evidence to support the therapeutic of stem cells. Studies demonstrated that human spinal stem cell have beneficial effects after intraspinal transplantation in G93A-SOD1 rats.[66] The Food and Drug Administration (FDA) approved, in 2009, a phase 1 clinical trial for examining the safety and feasibility of stem cell injections into the spinal cords of ALS subjects.[67] The cervical injection procedure is feasible and well tolerated.[68]

Conclusions

Despite advances in care, the evolution for patients with ALS persists the same since first description of Jean Martin Charcot. However remarkable advances in supportive therapy have altered the quality of life of ALS patient. We are gradually knowing the various mechanisms that can lead to death of motor neuron. The first genetic factor linked to ALS was reported in 1991, to lie on chromosome 21. In 1993 the alteration in SOD1 was found, a powerful antioxidant catalytic enzyme responsible for neutralizing potentially harmful free radicals. Progressively the neurodegenerative definition is changed for disturbances of the machinarium metabolism cellular. Now, many cellular metabolism disturbances are known and then with different mechanisms, we have different diseases named ALS. Recent advances in stem cell technology have allowed us to create a person's own nerve cells by taking a skin biopsy or blood sample. This study wants to use this new technology to make models for neurodegenerative diseases. We hope this will give us a better understanding of the diseases, enable us to use the cells for drug screening, and in the future, offers more specific treatment.

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