Amyotrophic lateral sclerosis: new perspectives and update

Marco Orsini,1,2 Acary Bulle Oliveira,3 Osvaldo J.M. Nascimento,1 Carlos Henrique Melo Reis,1 Marco Antonio Araujo Leite,1 Jano Alves de Souza,1 Camila Pupe,1 Olivia Gameiro de Souza,1 Victor Hugo Bastos,4 Marcos R.G. de Freitas,1 Silmar Teixeira,4 Carlos Bruno,1 Eduardo Davidovich,1 Benny Smidt3

1Neurology Department, Universidade Federal Fluminense, Rio de Janeiro; 2Programa de Mestrado em Ciências da Reabilitação – UNISUAM, Rio de Janeiro; 3Neurology Department, Universidade Federal de São Paulo – UNIFESP, São Paulo; 4Neuroscience Department, Universidade Federal do Piauí, Parnaíba, Brazil

Abstract

Amyotrophic lateral sclerosis (ALS), Charcot’s disease or Lou Gehrig’s disease, is a term used to cover the spectrum of syndromes characterized 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 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 indispen-
sable 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.8 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.5

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.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

Correspondence: Marco Orsini, Programa de Pós-Graduação em Ciências da Reabilitação, Praça das Nações, 34, Bonsucesso, Rio de Janeiro, CEP: 21041021, Brasil. E-mail: orsinimarco@hotmail.com

Key words: Amyotrophic lateral sclerosis; neurodegenerative diseases; diagnosis; treatment; rehabilitation.
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. 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. 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. 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. 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. 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. Genetic factors, changes in intracellular calcium levels in motor neurons, and programmed cell death (apoptosis) have also been linked to the development of ALS. 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. In ALS, 30% of patients begin with bulbar symptoms including dysphagia, dysarthria, dysnea 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. 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. 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. 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. 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. 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. Araújo described the clinical findings of patients with spinal muscular atrophy (SMA) with survival motor neuron (SMN) gene deletion. 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 electromyography 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 (dyssarhria 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.

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.

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 (Kendall 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.

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. The Awaji-Shima criteria was introduced in 2008, use of which improved diagnostic sensitivity without increasing false-positive rates (Table 1).

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. 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. Image evaluation is composed by: magnetic resonance investigation (brain and spine); DNA evaluation (SOD1, VAPB, Kennedy’s disease – expansion of trinucleotide 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.

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.

Differential diagnosis

In patients diagnosed with ALS, the absence 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.

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-
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. 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.

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 SpO2 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 H2O. 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.

Despite being a palliative care, the application of NIV in ALS patients can improve quality...
Dysphagia management and support in amyotrophic lateral sclerosis nutrition

Drooling, dehydration, malnutrition with weight loss and aspiration are all associated with dysphagia. 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. The loss of body weight associated with bulbar disorders (dysphagia and breathing), demonstrates the need for early assessment of 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.

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.

The guidelines for nutrition as well as the directives for implementation of enteral nutrition/parenteral follow in Table 4.

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.

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 pneumonia 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).

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).

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 hyperventila-
tention 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 serendipity 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

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 an 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 appetite, 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 (commonly triggered by contractures, immobility or associated with spasticity) | Botulinum toxin type B; Tricyclic antidepressives (Amirtipyline) |
| Pain (commonly triggered by contractures, immobility or associated with spasticity) | 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 reinervation. When the muscles become totally denervated, such mechanism does not happen. Excessive and strenuous physical activities in patients with ALS may potentiate debrigate fasciculations |
| Fatigue (several mechanisms are associated with fatigue in patients with motor neurone disease, which can be of central or peripheral origin) | Amanatadine 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 exhausting 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 contractures in 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 |

Stem cells in patients with amyotrophic lateral sclerosis

The relentless pursuit of treatment for this
inevitable 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.

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.

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. There were initial doubts as to the result to be dependent neuroprotective factor released by or related to neuregeneration 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 gial cells.

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. 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. 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. 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. 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. The cervical injection procedure is feasible and well tolerated.

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 machinaria 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.

References

1. Rowland LP, ed. Diverse forms of motor neuron diseases. In: Human motor neuron diseases. New York: Raven Press; 1982.
2. Radunovic A, Mitsumoto H, Leigh PN. Clinical care of patients with amyotrophic lateral sclerosis. Lancet Neurol 2007;6:913-25.
3. Goodall EF, Morrison KE. Amyotrophic lateral sclerosis (motor neuron disease): proposed mechanisms and pathways to treatment. Expert Rev Mol Med 2006;8:1-22.
4. Ciesler J, Sari Y. Neurotrophic peptides: potential drugs for treatment of amyotrophic lateral sclerosis and Alzheimer’s disease. Open J Neurosci 2013;3:1-13.
5. Oliveira AS, Pereira RD. Amyotrophic lateral sclerosis: three letters that change the people’s life. For ever. Arq Neuropsiquiatr 2009;67: 50-82.
6. Hirano M. Motor neuron diseases. In: Brust JCM, ed. Current: diagnosis and treatment. Philadelphia: McGraw-Hill 2011; p 574.
7. Orsini M, De Freitas MRG, Nascimento OJM, et al. Clinical and functional profile of amyotrophic lateral sclerosis patients: a one year follow up. Am J Neurosci 2007;2:28-34.
8. De Freitas MRG. Esclerose lateral amiotróficaDoenc|a de Charcot. In: Melo-Souza S, ED. Tratamento das Doencas Neurológicas. Vila Mariana; Guanabara Koogan; 2013. p 1324.
9. Sarnelli P, Brown RH. Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nat Rev 2006;7:710-23.
10. Orsini M, De Freitas MRG, Oliveira ASB, et al. Esclerosia lateral amiotrófica esporádica de inicio juvenil. Rev Neurol 2010;50:442-4.
11. Wicklund MP. Amyotrophic lateral sclerosis: possible role of environmental influences. Neurol Clin 2005;23:461-84.
12. Maarten D, Ludo VDB, Robberecht W. Microglia in amyotrophic lateral sclerosis. Acta Neurol Belg 2007;107:63-70.
13. Shaw CE, Al-Chalabi A, Leigh N. Progress in the pathogenesis of amyotrophic lateral sclerosis. Curr Neurol Neurosci Rep 2001;1:69-76.
14. Oey PL, Vos PE, Wienenke GH, ET AL. Subtle involvement of the sympathetic nervous system in amyotrophic lateral sclerosis. Muscle Nerve 2002;25:402-8.
15. Williams C, Kozlowski MA, Hinton DR, Miller CA. Degeneration of spinocerebellar neurons in amyotrophic lateral sclerosis. Ann Neurol 1990;27:215-25.
16. Lloyd CM, Richardson MP, Brooks DJ, et al. Extramotor involvement in ALS: PET studies with the GABA(A) ligand (11) C.flumazenil. Brain 2000;123:2289-96.
17. Nascimento OJM, Orsini M, Pepe C, et al. Amyotrophic lateral sclerosis with sensitive findings: A multisystem disorder? Rev Neurocienc 2010;18:320-3.
18. Nass RD, Meister IG, Haupt WF, Fink GR. ALS and frontotemporal dementia - case report and review of the literature. Fortschr Neurol Psychiatr 2012;80:711-9.

[Neurology International 2015; 7:5885]
30. Wirth B. An update of the mutation specific features of amyotrophic lateral sclerosis. N Engl J Med 2001;344:1688-700.

31. Araújo APQC, Ramos VG, Cabello PH. Chronic respiratory failure in patients with neuromuscular diseases: diagnosis and treatment. J Bras Pneumol 2007;33:81-92.

32. Lévêque N. Speech therapy guidelines in patients with amyotrophic lateral sclerosis. Rev Neurol (Paris) 2006;162:269-72.

33. Andersen PM, Nilsson P, Keranen ML, et al. Phenotypic heterogeneity in motor neuron diseases patients with Cu/Zn-superoxido dismutase in Scandinavian. Brain 1997;120:1723-37.

34. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. N Engl J Med 2001;344:1688-700.

35. Traynor BJ, Codd MB, Corr B, et al. Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Arlie house diagnostic criteria: apopulation base study. Arch Neurol 2000;57:1017-6.

36. Nodera H, Izumi Y, Kaji R. New diagnostic criteria of ALS (Awaji criteria). Brain Nerve 2007;59:1023-9.

37. Hardiman O, van den Berg LH, Kiernan MC. Clinical diagnosis and management of amyotrophic lateral sclerosis. Nat Rev Neurosci 2011;7:639-49.

38. Schroten M, Smetcorten C, Robberecht W, Van Damme, P. Benefit of the Awaji diagnostic algorithm for amyotrophic lateral sclerosis: a prospective study. Ann Neurol 2011;70:79-83.

39. Carvalho MD, Swash M. Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis. Amyotroph Lateral Scler 2009;10:53-7.

40. Daube JR. Electrodagnostic studies in amyotrophic lateral sclerosis and other motor neuron disorders. Muscle Nerve 2000;23:1488-502.

41. Chio A, Logrosino G, Hardiman O, et al. Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler 2009;10:310-23.

42. Chieia MAT. Esclerose lateral amiotrófica: considerações a respeito dos critérios diagnósticos. Thesis dissertation., Universidade Federal de São Paulo/Escola Paulista de Medicina, 2008.

43. Donaghy M. Classification and clinical features of motor neuron diseases and motor neuropathies in adults. J Neurol 1999;246:III-5.

44. Orsini M, De Freitas MRG, Silva JG, et al. Emergency guidelines for professionals on the diagnostic process and its implications in amyotrophic lateral sclerosis. J Neurol 1999;246:III-5.

45. Silani V, Borasio D. Honesty and hope: announce of diagnosis in ALS. Ned Tijdschr Geneeskd 2001;145:1252-8.

46. Yan J, Xu L, Welsh AM, et al. Combined use of motor neuron disease patients with amyotrophic lateral sclerosis: a prospective study. PLoS One 2011;6:1-11.
ing mutations. Cell Stem Cell 2008;3:637-48.
64. Mazzini J, Maresh K, Ferrero I, et al. Stem cell treatment in amyotrophic lateral sclerosis. J Neurol Sci 2008;265:78-83.
65. Dimos JT, Rodolfa KT, Niakan KK, et al. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neuron. Science 2008;321:1218-21.
66. Yan J, Xu L, Welsh AM, et al. Extensive neuronal differentiation of human neural stem cells grafts in adult rat spinal cord. PLoS Med 2007;4:318-32.
67. Feldman EV, Boulis NM, Hur J, et al. Transplantation in amyotrophic lateral sclerosis: phase 1 trial outcomes. Ann Neurol 2014;75:363-73.
68. Riley J, Federic T, Park J, et al. Cervical spinal cord therapeutics delivery: preclinical safety validation of a stabilized microinjection platform. Neurosurgery 2009;65:754-61.