Amyotrophic Lateral Sclerosis: the Current World Situation

COMMENTARY

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of unknown cause that affects mainly the motor neurons of the spinal cord, brain stem and brain. The pathogenesis is still obscure and the diagnosis is based on patient history and clinical examination. A handful of factors have been proposed to be associated with ALS; however, the only established risk factors to date are older age, male sex, and a family history of ALS. The familial cases have their historical importance in causative gene identification since through these discoveries much has been uncovered about ALS pathogenesis. The understanding of clinical and epidemiological factors associated with functional impairment is of fundamental for early adoption of measures to promote a better survival and a better quality of life. Rapid diagnosis of amyotrophic lateral sclerosis (ALS) and other neurological disorders is vital if future treatments are to be applied at an early disease stage. The current pace of discovery and identification of novel disease mechanisms in ALS is unprecedented. Advances in this area, however, have also introduced challenges in the heterogeneity of diagnostic definitions affecting this patient population.

Keywords
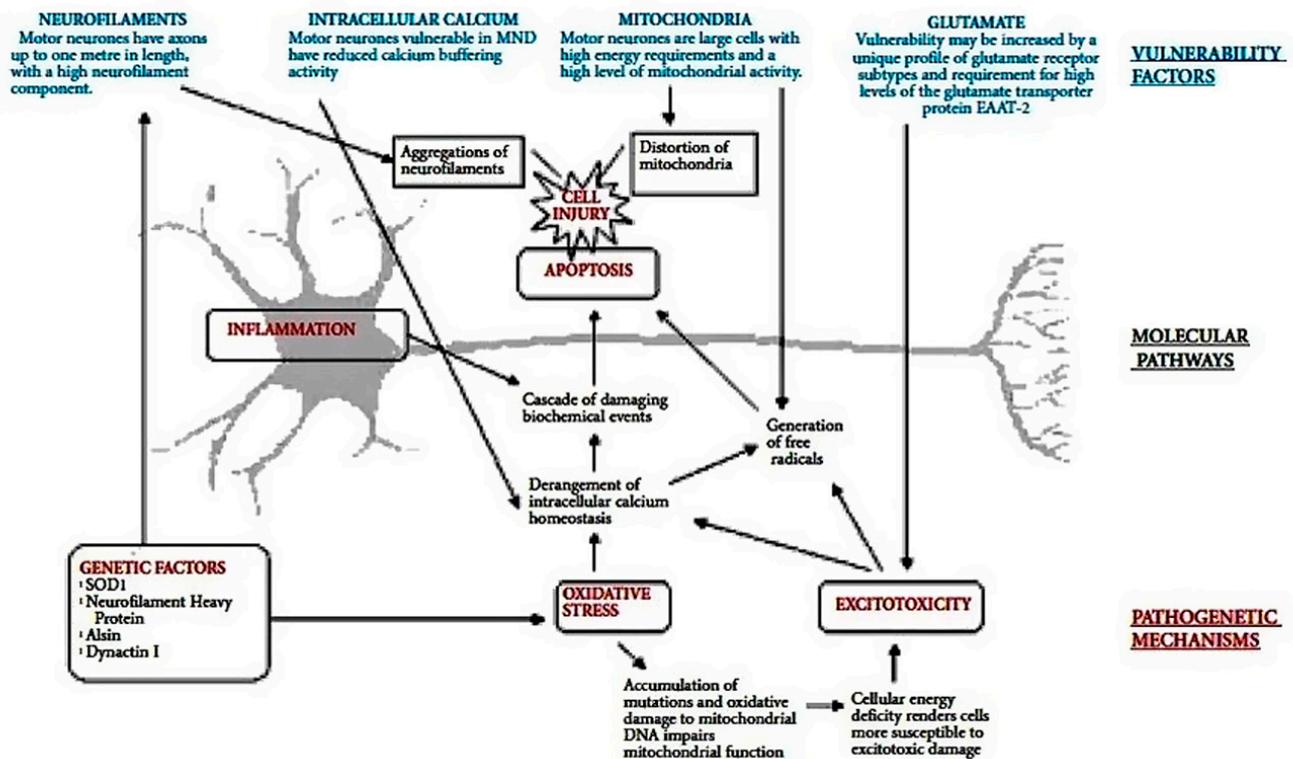Amyotrophic Lateral Sclerosis; Neurodegenerative Disease.

Motor neuron disease (MND) is a collective term for a devastating group of disorders that result in muscle paralysis through the degeneration of motor neurons. Amyotrophic lateral sclerosis (ALS) is the most common form of MND, in which affected individuals generally die from respiratory failure within 2-5 years of diagnosis. [1, 2] Also known as Charcot's disease (France) or Lou Gehrig's disease (USA) is a acquired disease and neurodegenerative of unknown cause that affects mainly the motor neurons of the spinal cord, brain stem and brain. [3]

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ALS is a devastating neurodegenerative disease, and luckily, very rare: only one to two people out of 100,000 develop ALS yearly. This fact, however, makes studies of ALS very challenging since it is very difficult to collect the representative set of clinical samples and this may take up to several years. The pathogenesis is still obscure and the diagnosis is based on patient history and clinical examination. The mechanism of disease onset in humans is not yet fully understood and no effective treatment is available at present. Several pathogenic mechanisms have been proposed to be involved in the loss of the motor neurons in ALS, including oxidative stress, excitotoxicity, protein aggregation, and mitochondrial dysfunction **(Figure 1)** [4, 5, 6]. Many efforts have been made to find biomarkers to enable earlier diagnosis, to monitor disease progression and to predict prognosis. [6] **(Figure 1)**

This disease has a global occurrence, with 120,000 new cases per year. The survival rate is on average of 3-5 years, the prognosis is worse in cases where the onset is characterized by bulbar involvement, followed by the cases where signs of involvement of the upper motor neuron (UMN) or lower motor neuron (LMN) first appear in the upper limbs (UL). Survival may be slightly higher in younger individuals and those in which the signs of ALS begin in the lower limbs (LL). [3, 7, 8, 9, 10, 11, 12, 13, 14] The understanding of clinical and epidemiological factors associated with functional impairment is of fundamental importance for early adoption of measures to promote a better survival and a better quality of life. [14]

It is believed that the incidence of Amyotrophic Lateral Sclerosis (ALS) is the same all over the world, however, there is not a well conducted and com-

Figure 1: Vulnerability factors and mechanism of injury in Motor Neuron Disease. This picture was extracted from Brockington A, Shaw P. (2003). [55, 56, 57]. This legend was modified.

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Figure 2: Countries and regions with studies about Amyotrophic Lateral Sclerosis. This picture was adapted from Pereira, RDB (2006). [8].

Regions	Incidence (per 100,000 population)	Prevalence (per 100,000 population)	Publication Year
Guam	3,9		2004
Libya	3,4		2005
Australia	2,9		2005
Ireland	2,8	4,7	1999
Japan*	2,5	11,31 - Wakayama	2005
Finland	2,4		2006
USA	2,0	3 - 8	2004
Canada*	2,0	6,7	2005
Estonia	1,9		2006
Norway	1,9		2005
England	1,7		2001
Italy	1,7	4,03	2005
Brazil	1,5		1998
France*	1,5		2000
Greece	1,3		2005
Poland	0,8		2005
Chile	0,5		2005
Mexico	0,4		2005
China	0,3		2006

*Average incidence of studies carried out in the country

parative study among different populations with ALS, among ethnic or geographical area defined outside of Europe and North America **(Figure 2)**. However, research shows that there are individual variations. SLA usually affects more men than women, although more recent studies show that both sexes are affected similarly. Reports of the increase in the ALS cases number in women may be related to the better population identification with previous studies, to the recent effects of a not identified environmental exposure, and/or to the lifestyle changes causing on them a higher exposition to the potential toxics, associated historically with men (smoking, occupational exposures). Other risk factors draw attention and specially to whom may be related to the ALS development, such as exposure to severe electrical shock, strenuous physical activity, soldiers who served in the first Gulf War and professional soccer players. [8] **(Figure 2)**

The classic disease form is insidious, characterized by asymmetric muscle weakness, limbs and tongue atrophy, in addition to fasciculations and hyperreflexia. Progressively, the reduced muscle strength becomes systemic culminating in quadriplegia. [7, 14, 15, 16, 17] The bulbar symptoms usually arise in a disease later stage, being characterized by dysphonia, dysarthria, dysphagia, weakness, atrophy and language fasciculation and later by respiratory failure, the most serious disease symptom and the major cause of death. [7, 14, 15, 18]

The Clinical ALS types are: 1. sporadic; 2. Familiar; 3. ALS plus syndrome; 4. ALS mimicking syndrome; 5. Syndrome with uncertain significance laboratory abnormalities. The diagnostic criteria used for ALS were currently established by the El Escorial World Federation of Neurology, revised in 1998. There is also a sub-classification of the diagnostic criteria El Escorial which subdivides ALS in: defined ALS (typical), probable ALS, possible ALS, suspected ALS. [3]

There are well-established criteria for patients in whom the manifestations are restricted to dysfunction solely of the upper motor neuron (primary lateral sclerosis), lower motor neuron [progressive muscular atrophy (PMA), or bulbar segment (progressive bulbar palsy). [19-23, 24] There are, however, no established criteria for a significant number of patients who present and progress with predominantly upper and only subtle lower motor pathology, or, conversely, predominantly lower motor with only subtle upper motor neuron signs. These patient groups can be further prognostically dichotomized based on the presence or absence of either bulbar or respiratory dysfunction at the time of symptom onset, thus expanding the heterogeneous nature of the disease. [19, 24, 25, 26] This variability in clinical manifestation at the time of initial assessment may be associated with significant variability in survivorship. Superimposed on this clinical variability is the presence or absence of a syndrome of frontotemporal dysfunction that may coexist with many of the motor neuron disorders and, for several, be of prognostic importance. [24, 25] Formal diagnostic criteria for ALS/MND have been developed and modified several times. [24, 27-34] In the absence of widespread acceptance of diagnostic criteria for

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specific disease subtypes, there have been a number of clinical phenotypes described. [23, 24, 35-40]
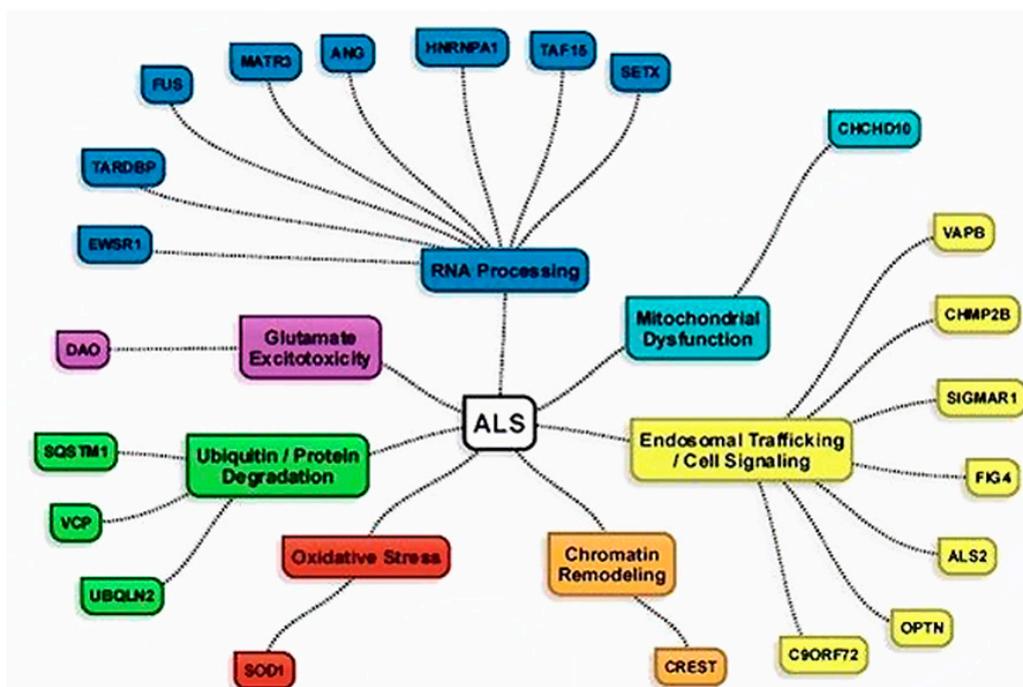
The multisystem involvement of patients affected by ALS/MND, as well as the varied mechanisms attributed to the disease has led to a multitude of clinical and biological markers proposed as indices of disease progression and/or severity **(Figures 1, 3)**. [24, 40-43] Despite this, one of the primary challenges in studying ALS/MND is the absence of an accepted marker with both the appropriate sensitivity and specificity applicable to the wide range of affected patients. The result of this void in our understanding is a lack of confidence that we can reliably measure disease progression or therapeutic efficacy in our clinical trials. [24]

Also, the potential for genetic markers as correlates of disease subtype and progression has generated much enthusiasm and promise, although remains incompletely understood. There are currently very few established relationships between a specific genetic mutation and a specific phenotype. The hope is that a potential etiology, at least for a specific phenotype, will emerge and highlight a primary disease mechanism. [24, 44, 45, 46, 47]

Rapid diagnosis of amyotrophic lateral sclerosis (ALS) and other neurologic disorders is vital if future treatments are to be applied at an early disease stage. For genetic causes of these diseases, the current technology lies with sequential Sanger sequencing. However, with an array of multiple genes causing each disease and, additionally, numerous alterations within each gene being potentially harmful, it can be time consuming and costly to diagnose a patient suspected of harboring a detrimental genetic variation **(Figure 3)**. Furthermore, the range of genetic tests at each institution can be limited. It is now plausible that next-generation sequencing (NGS) technologies will eliminate many of these issues. To test this possibility, we have developed a single comprehensive assay containing 25 genes which have, to varying degrees, been implicated in ALS. NGS technology shows promise for the diag-

Figure 3: Genes currently known as associated with ALS classified by common molecular pathways involved in the disease pathophysiology. This picture was extracted from Coatti GC et al. (2015). 50,58,59 This legend was modified.

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nosis of both familial and sporadic ALS; our rapid high-throughput method is suitable for large scale genetic studies. [48]

A handful of factors have been proposed to be associated with ALS; however, the only established risk factors to date are older age, male sex, and a family history of ALS. [49] Identification of risk factors, especially non-genetic factors, for ALS has proven difficult, and likely reflects the complexity of the disease. Over the last two decades, a great deal of new knowledge has been gathered on ALS, especially in terms of its underlying genetics and potential mechanisms implied by these genetic findings. In contrast, there is substantial impact of non-genetic factors on the etiology of ALS, so far little progress has been made in identifying these factors with some degree of certainty. An improved knowledge of non-genetic risk factors for ALS, hand-in-hand with our increasing knowledge of ALS genetics, should prove more fruitful in deciphering the causes of this devastating disease and eventually providing a cure. [49] **(Figure 3)**

ALS is mainly classified into two groups: FALS (Familial ALS), for the inherited forms of the disease, and SALS for the sporadic cases, in which there are no affected relatives and where in the majority of cases it is not possible to identify a single causative agent. The familial cases have their historical importance in causative gene identification since through these discoveries much has been uncovered about ALS pathogenesis. Around 33 genes or chromosomal regions have been linked to ALS, providing important clues on the pathophysiological mechanisms of the disease **(Figures 1, 3)**. Although, environmental conditions could play an important role for disease development. [50]

In this context, TBK1 have been implicated as an ALS gene, providing insight into disease biology and suggesting possible directions for drug screening programs. Also, evidence has been provided that OPTN plays a broader role in ALS than previously recognized. Both TBK1 and OPTN are involved in au-

tophagy, with TBK1 possibly playing a crucial role in autophagosome maturation as well as the clearance of pathological aggregates. [51, 52, 53] These observations highlight a critical role of autophagy and/or inflammation in disease predisposition. It is also noteworthy that many drugs have been developed that act on TBK1-mediated pathways owing to their role in tumor cell survival [53, 54] and can therefore be used to investigate the effects of drug-dependent loss of function of the kinase. Although, a large genetic dataset for ALS has been provided, which suggests other possible ALS genes and provides a substantial collection of pathogenic variants across ALS genes. After removing the expected number of variants to be seen based on the frequencies of rare variants in controls, we identify more than 70 distinct pathogenic mutations across SOD1, OPTN, TARDBP, VCP, SPG11, and TBK1 that can be used in future efforts to functionally characterize the role of these ALS genes. The identification of TBK1 and the expanded role for OPTN as ALS genes reinforce the growing recognition of the central role of autophagy and neuroinflammation in the pathophysiology of ALS. [53]

About 90% of cases are sporadic while about 10% are hereditary and are Caused by mutations in the Super Oxide Dismutase 1 (SOD1), TARDBP and FUS genes. [2, 8] The gene therapy attempts to ALS have had as major target the defective activity of superoxide dismutase correction. These experiments were made possible after the animal models development. These experiments still require in vivo evidence. This type of therapy for neuromuscular diseases promises great advances in the coming years, however many obstacles remain to be overcome; as the large number of vectors required for effective treatment; the vectors direction exclusively for motor neurons, the continuous expression and not just the transgene transient; the defects correction without toxic side effects and these therapies application for various forms of MND and ALS, not limited to only a few models. [8]

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Previous research has provided extensive evidence of a pivotal role for excitotoxicity in ALS pathophysiology. Investigations indicate that raised central levels of excitotoxic stimuli could be a primary mechanism involved in the degeneration of motor neurons, and therefore indicate that excitotoxicity could account for the selective motor neuron death observed in ALS. Understanding excitotoxic mechanisms of neuronal cell loss and NMJ degeneration is a vital step in the pathway to developing potential new therapeutic interventions for ALS. The data suggest that targeted interventions, directed specifically at the cell body, might be more efficacious in tackling this devastating disease. [1]

Current clinical practice for patients affected by ALS/MND includes a combination of proactive, adjunctive and symptomatic therapies. Outcome data are lacking relative to the number and variety of treatments used regularly in this population. While treatment approaches are likely more consistent today than they were a decade ago, implementation of these often efficacious treatments has introduced another source of variability in comparing groups of patients for clinical trials. Specifically, maintenance of respiratory health, nutritional stability, physical safety, and aids to improve daily function have an impact on quality of life and disease duration. While these benefits have been difficult to measure in controlled studies, multidisciplinary care has become the standard of treatment for this complex multisystem disease. [4]

The current pace of discovery and identification of novel disease mechanisms in ALS/MND is unprecedented. Despite the great expansion in our knowledge base, there remain some fundamental challenges on issues such as disease definition, appropriate biomarkers of disease progression, interpretation of the multitude of genetic mutations associated with disease, and the impact of aggressive symptomatic treatment. Identification of frontotemporal dysfunction in a majority of patients with both familial and sporadic ALS/MND has both added greatly to the potential for a common underlying mechanism between ALS and frontotemporal dysfunction, while at the same time providing an important prognostic determinant. Advances in this area, however, have also introduced challenges in the heterogeneity of diagnostic definitions affecting this patient population. Our ability to design effective clinical trials that will ultimately lead to efficacious therapies will likely depend upon resolution of some of these most basic questions of diagnosis and disease progression. [4]

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