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REVIEW PAPER

The increasing importance of environmental conditions in amyotrophic lateral sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is the most common neurodegenerative disease affecting motor neurons (MNs). Although a small percentage of ALS has a familial origin, the vast majority of cases are sporadic in which genetic factors and environment interact with each other leading to disease onset in genetically predisposed individuals. In the current model of the disease, each individual has a determined genetic load, some degree of cell degeneration related to age and several risky environmental exposures. In this scenario, MN degeneration would occur when the sum of these factors reach a certain threshold. To date, an extensive list of environmental factors has been associated to ALS, including different categories, such as exposure to heavy metals and other toxicants, cyanotoxins or infectious agents. In addition, in recent years, lifestyle and other demographic parameters are gaining relevance in the genesis of the disease. Among them, physical activity, nutrition, body mass index, cardiovascular risk factors, autoimmune diseases and cancer are some of the conditions which have been related to the disease. In this review, we will discuss the potential mechanisms of environmental conditions in motor neuron degeneration. Understanding the role of each one of these factors as well as their interactions appears as a crucial step in order to develop new preventive, diagnostic and therapeutic approaches for ALS patients.

Keywords Amyotrophic lateral sclerosis · Environment · Epidemiology · Pollution

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common neurodegenerative disease affecting motor neurons (MNs) (Zufiria et al. 2016) with an annual incidence that ranges from two to three cases per 100,000 habitants across Caucasian populations (Riancho et al. 2016d). Lower incidences rates have been reported in other populations, such as Asians and Afro-Americans (Zufiria et al. 2016). Regarding gender, the vast majority of epidemiological studies have showed a male predominance with a male/female ratio ranging from 1.2:1 to 1.5:1 (Zufiria et al. 2016).

ALS pathogenesis has not been fully elucidated yet; however, our knowledge about disease mechanisms has significantly improved (Zufiria et al. 2016). The impairment of various cellular functions has been related to MN degeneration (Zufiria et al. 2016). Among them, dysfunction of gene processing, proteostasis, axonal transport, as well as the involvement of glial cells surrounding MNs seem to be some of the most relevant mechanisms (Riancho et al. 2016c). ALS cases can be divided into

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familial (fALS) and sporadic (sALS). fALS represent a small percentage of cases. These are secondary to mutations in specific genes (Cr9orf72, SOD1, FUS, TDP43, etc.) which directly induce MN degeneration and disease onset (Table 1) (Zufiria et al. 2016). By contrast, most cases are thought to be sporadic (sALS) in which genes and environment interact with each other leading to disease onset and progression in genetically predisposed individuals (Zufiria et al. 2016). On this basis, the role of environmental factors in the pathogenesis of ALS is receiving increasing attention (Zufiria et al. 2016). Thus, without negating the role of genetic and other conditions

Table 1 Genes related to Mendelian inheritance of ALS

Gene	Chr. localization	Heredity	Protein	Main cellular function involved
ALS1/SOD 1	21q22.11	Dominant/recessive	SOD-1	- Oxidative stress - Glucose uptake and lipid/carbohydrate metabolism - Proteostasis
ALS 2	2q33.2	Recessive	Alsin	- Vesicle transport - Oxidative stress
ALS4/SETX	9q 34.13	Recessive	Senataxin	- DNA and RNA processing
ALS5	15q15.1-q21.1	Recessive	Unknown	- Unknown
ALS6/FUS	16p11.2	Dominant/recessive	FUS (Fused in sarcoma)	- DNA/ RNA processing
ALS8/VAPB	20q13.3	Dominant	VAMP (vessicle-associated membrane protein)	- Autophagy - Vesicle transport
ALS9/ANG	14q.11.1	Dominant	Angiogenin	- rRNA transcription
ALS10/TARDBP	1p 36.22	Dominant/recessive (rare)	TDP-43	- DNA/RNA proccesing - Glucose uptake and lipid/carbohydrate metabolism - Mitochondrial integrity - Apoptosis
ALS11/FIG4	6q21	Dominant	Polyphosphoinositide phosphatase	- Vesicle transport
ALS12/OPTN	10p15-p14	Dominant/recessive	Optineurin	- Autophagy - Vesicle transport - Apoptosis
ALS13/ATX2	12q23q24.1	Dominant	Ataxin-2	- Vesicle transport - Autophagy
ALS14/VCP	9p13.3	Dominant	VCP (valosin containing protein)	- Autophagy - Vesicle transport - Lipid/carbohydrate metabolism
ALS15/UBQLN2	Xp11.21	Dominant X-linked	Ubiquilin-2	- Autophagy
ALS16/SIGMAR1	9p13.3	Recessive	Sigma1R	- Autophagy - Vesicle transport
ALS 17/CHMP2B	3p11.2	Dominant	CHMP2b	- Vesicle transport
ALS18/PFN1	17p13.3	Dominant	Profilin 1	- Cytoeskeleton organisation
ALS19/ERBB4	2q34	Dominant/sporadic	ERBB4	- Glucose uptake
ALS20/HNRNPA1/A2B1	12q13.13	Dominant	hnRNPA1 hnRNPA2B1	- DNA/RNA processing
ALS21/MATR3	5q31.2	Dominant	Matrin 3	- DNA/RNA processing
FTDALS1/C9ORF72	9p21.2	Dominant	C9orf72 Uncharacterized	- DNA/RNA processing - Autophagy/ - Vesicle transport
SQSTM1	5q35.3	Dominant	P62/Sequestosome-1	- Glucose uptake and lipid/carbohydrate metabolism - Autophagy
NEFH	22q12.2	Dominant/sporadic	NF-H	- Cytoeskeleton organisation
GLE1	9q3411	Dominant?	hGLE1	- DNA/RNA processing
TAF15	17q12	Unknown	TAF15	- DNA/RNA processing
TBK1	12q14.2	Dominant	TANK-binding kinase	- Autophagy

as ageing, in this review, we will particularly focus on the evidences supporting the role of the environment in ALS.

ALS as the result of the interaction of genes, environment, age and chance

Not only ALS but also other neurodegenerative diseases are considered to be the final result of the interactions between genes, ageing, environmental conditions and a component of chance which can not be easily measured (Fig. 1) (Al Chalabi and Hardiman 2013).

In this line, each subject has a determined genetic load, some degree of cell damage according to ageing, and a variety of environmental risk exposures. The development of ALS would then occur when the sum of these factors reached a certain threshold. Upon this basis, in fALS cases, the genetic load and the MN damage related to ageing would be sufficient for developing the disease without the environmental influences. However, environment may be crucial in the genesis of the disease in an important proportion of sporadic cases (Fig. 2). It would be particularly relevant in aged subjects harbouring ALS genetic risk variants. In those cases, risky environmental factors could be determinants for developing ALS or not; thus behaving as modifiers of genetic ALS. This fact is

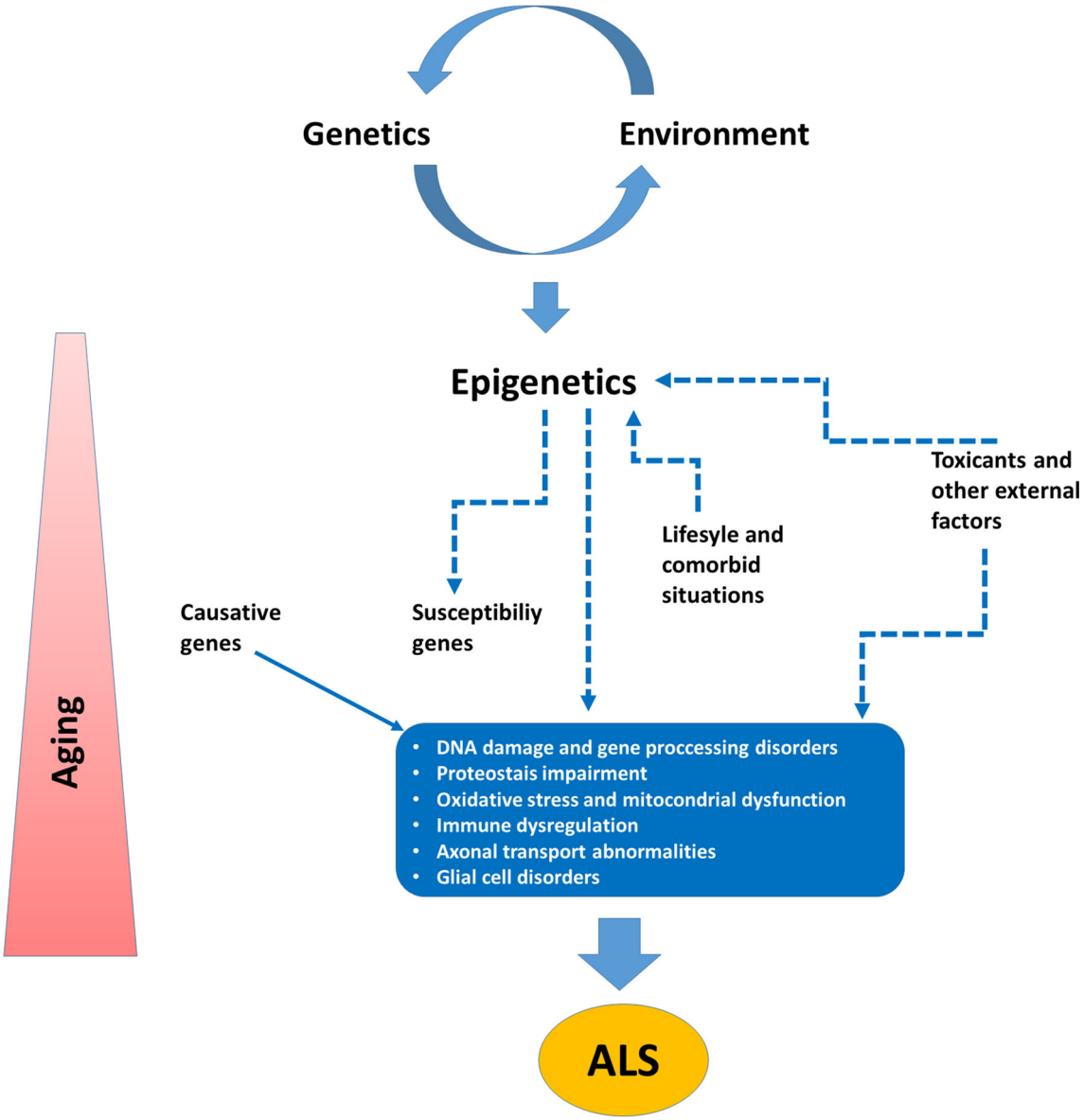

Fig. 1 Main involved components in the genesis of ALS. Each individual has a determined prenatal genetic load and during life accumulates a number of risky environmental exposures and progressive age-related cell damage. Regardless of the particular 'weight' of each of these components, ALS would develop when the sum of them reach a certain threshold. Once established, several auto-perpetuating mechanisms would occur leading to disease progression. In familiar cases of ALS, the 'genetic load' has a high relevance; however, in the vast majority of cases (sporadic ALS cases), the environmental exposures may be crucial to reach the threshold or not

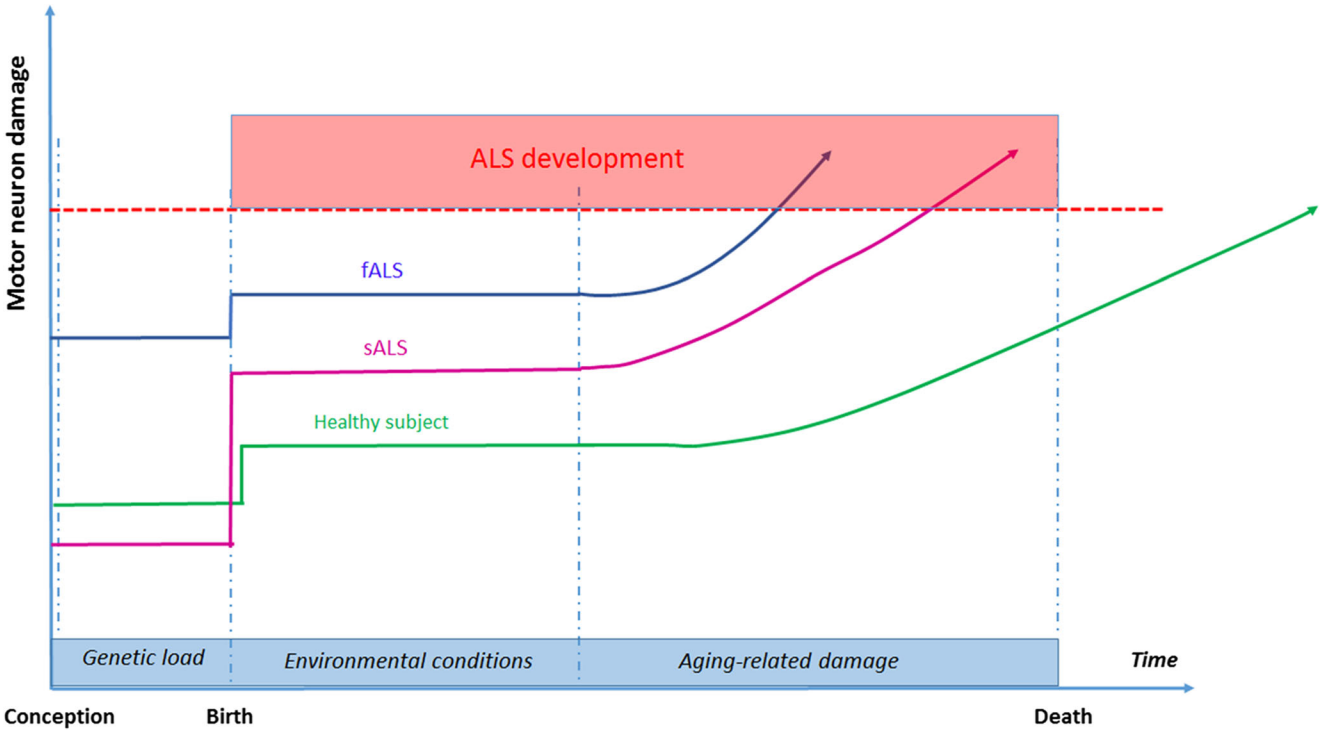

Fig. 2 Genes and environment in ALS. Genetics and environmental factors interact promoting ALS onset in predisposed individuals. The final result of such alterations induces MN degeneration through the impairment of several cellular pathways including (i) DNA damage and gene processing disorders, (ii) proteostasis impairment, (iii) oxidative stress and mitochondrial dysfunction, (iv) immune dysregulation, (v) axonal transport abnormalities, and (vi) surrounding glial cells dysfunction. In the field of genetics, a number of causative genes which directly promote MN degeneration and a group of susceptibility genes predispose to ALS. Regarding environmental factors, toxicants and other external factors, as well as several lifestyle conditions and comorbidities, are likely involved. Toxicants and other external factors could promote MN degeneration directly by impairing some crucial cellular functions or in an indirect way, by modulating gene expression throughout epigenetic modifications. By contrast, most comorbidities and lifestyles are supposed to act mainly through the latter. In this complex scenario, ageing would behave as a facilitating factor, inducing age-related degeneration and accelerating the disease in those predisposed subjects

supported by several studies performed in discordant-ALS monozygotic twins. As an example, Al Chalabi et al. studied 49 ALS twin pairs. Among them, 5 and 44 monozygotic twin pairs were concordant- and discordant-affected, respectively. After applying several statistical tests, the authors estimated the heritability of sporadic ALS around 0.60, with an unshared environmental component of 0.4 (Al Chalabi et al. 2010).

Environmental factors

There is evidence for a role of environmental conditions in ALS. A wide number of epidemiological, ecological and experimental studies have highlighted the role of the environment in ALS pathogenesis. Next, we will discuss the most relevant studies published in the literature until 31 October 2017 regarding the role of environmental factors in ALS.

2.1. Cluster studies

Cluster studies leaded to the identification of specific regions with increased ALS incidence. Interestingly, this increase of ALS cases was not only related to genetic factors, thus highlighting the importance of the environment in ALS. Some of the most representative are summarised in Table 2.

In 1945 in Guam, a disproportionate incidence of an ALS complex syndrome which also included dementia and Parkinsonian features was reported among the Chamorros population (Reed et al. 1966) Two decades later, the neurotoxin b-N-methylamino-L-alanine (BMAA) was discovered in the indigenous cycad (*Cycas micronesica*), the seeds of which were used by Chamorros to make flour (Torres et al. 1957; Reed and Brody 1975). Not long after, the causal inference was further supported when the *BMAA* was detected in brains of Guamanian patients with ALS, but not in Guamanian control brains (Murch et al. 2004a, b). Further studies demonstrated that *BMAA* in cycads came from a symbiotic cyanobacteria resident in specialised coralloid roots of this plant and that it got concentrated during the process of flour production (Murch et al. 2004a). A similar explanation was given for another cluster of ALS patients also presenting with Parkinsonism that was reported in 1962 in the Indonesian part of New Guinea, where *Cycas circinalis* seeds are also consumed by indigenous (Gajdusek and Salazar 1982). More recently, a third major cluster in the Pacific area was reported in Japan in the Kii Pensinsula of the Honshu Island (Kuzuhara and

Table 2 Representative geographic ALS clusters

Authors	Year	Location	Proposed agent	Results
Dwayne et al. Spencer et al.	1957 1987	Guam, Marianas Islands	BMAA	Annual incidence: 200 cases per 100,000 habitants (*100-fold higher than expected)
Gajdusek et al	1963	New Guinea	BMAA	Annual incidence: 100 cases per 100,000 habitants (*50-fold higher than expected)
Kusui et al	1962	Kii Peninsula, (Japan)	BMAA	Annual incidence: 6.42 cases per 100,000 habitants in K. area and 23.46 cases per 100,000 habitants in Oshima.
Taylor et al. Sienko et al.	1989 1990	Wisconsin	Contaminated fish	Crude death rate > 3/100,000 in northest Wisconsin (*US crude rate 1,12/100,000)
Gunnarson et al.	1991	Skaraborg County, (Sweden)	Agriculture - BMAA	Male farm workers (OR 1.7) Male agricultural workers (OR 1.4) Female workers (OR 1.7)
Sabel et al.	2003	Finland	Pollution	Two high-incidence clusters (RR 1791 and RR 1315)
Caller et al.	2009	Lake Macoma, (New Hampshire)	BMAA	Annual incidence: 20–50 cases per 100,000 habitants (*10–20-fold higher than expected)
Masseret et al.	2013	Thau Lagoon, (France)	Seafood - BMAA	Annual incidence: 2.5 cases per 100,000 habitants (SIR 2,18)
Torbick et al.	2014	New England	Poorer lake water	Poorer water quality is associated with higher odds of belonging to an ALS spot (not reported exact values)
Lannuzel et al.	2015	Marie-Galante, (Guadalupe Island)	Neurotoxins	Annual incidence: 3,73 cases per 100,000 habitants (*4.5-fold higher than expected)
Nicoletti et al.	2016	Mont Etna, (Sicily)	Trace metals	Annual incidence: 2.4 cases per 100,000 habitants (*RR 2,75 when compared with eastern flank)

BMAA beta-N-methylamino-L-alanine; *K. area* Koza, Kozagawa and Kushimoto; *OR* odds ratio; *RR* relative risk; *SIR* standardised incidence ratio

Kokubo 2005). Differently from previous clusters, no direct relationship with Cycas seed consumption was found, but the type of drinking water was postulated as a possible link among patients (Kuzuhara and Kokubo 2005; Kuzuhara 2011). To elucidate if these clusters were due to due genetic variants among affected subjects or not, several genetic studies were carried out. Interestingly, these studies only demonstrated mutations in several ALS-related genes in a small subset of patients (Ishiura et al. 2012), thus highlighting the role of environment. In addition, the reduction of cases among these populations after modifying dietetic habits clearly supported the role of external factors in the genesis of the disease (Spencer et al. 2005).

The role of *BMAA* in motor neuron disease has been further supported by other clusters reported in France and USA (Field et al. 2013; Caller et al. 2013; Lannuzel et al. 2015; Masseret et al. 2013). The precise mechanisms explaining *BMAA* toxicity have not been completely elucidated. It has been postulated that BMAA behaves as an endogenous neurotoxic reservoir, stored in a bound form, which would be slowly released within brain and spinal cord tissues inducing its neurotoxic effects over years (Murch et al. 2004a). Regarding histological characterisation, the vast majority of neuropathological studies were performed in Guam while other *BMAA* clusters have not been extensively characterised. It has been reported that Guamanian patients exhibited a constellation of neuropathological hallmarks which combined (i) abundant neurofibrillary tangle pathology, (ii) neuronal loss, (iii) amyloid plaques resembling those observed in Alzheimer's disease (AD) patients, (iv) alfa-sinuclein pathology in the substantia nigra and cerebellum and (v) TDP43-positive inclusions in both hippocampus and motor neurons reactive (Schmidt et al. 1998; Buee-Scherrer et al. 1995; Sebeo et al. 2004; Geser et al. 2008). Complementary experimental studies have shown that the neurotoxic effects of *BMAA* are related to the depletion of glutathione, glutamatergic toxicity, synergism with other neurotoxins, the capacity to induce protein misfolding and the accumulation of intracellular aggregates (Bradley 2015). The interindividual *BMAA* susceptibility has been assessed by several investigators without having identified any risk gene variant (Sieh et al. 2009).

Apart from the previously discussed clusters, other high-incidence clusters have been reported in the literature. As example, recently, Nicoletti et al. (2016) studied ALS patients in Catania, the Italian region of Mount Etna. During 2005 to 2010, authors identified 126 ALS cases. Remarkably, ALS incidence was almost three times higher in the population living on the eastern flank compared to the western flank of the volcano (2.4 vs 0.9 cases per 100,000, respectively). These differences were interpreted by the authors as being secondary to distinct volcanogenic trace elements spreading depending

on the mountain flank (Nicoletti et al. 2016). Importantly, some clusters of low incidence of ALS have also been reported. For example, there have been recently identified two low-incidence areas after analysing the Irish ALS register from 1995 to 2013 (Rooney et al. 2015a). Despite the potential relevance of this finding, ALS was not associated to obvious demographic nor other common environmental factors (Rooney et al. 2015b).

As a conclusion, cluster studies provided some of the earliest evidences supporting the role of the environment in ALS. They may represent a useful tool for generating new hypothesis. However, they require complementary confirmatory approaches because these studies commonly present several weaknesses and they are prone to be biased. A common drawback of cluster studies lies on the difficulty in distinguishing between fALS and sALS. Families also tend to be spatially clustered, which could lead investigators to mix up a potential environmental condition with genetic influences (Rothman et al. 2008). In addition, these approaches might frequently miss other environmental confounders which can falsify the final results. On the other hand, when considering rare diseases with low incidences such as ALS, minimal changes in the number of cases (numerator of the fraction) substantially influence the final result, thus increasing the risk of random error and subsequently resulting in wide confidence intervals of the effect estimates, which should be cautiously interpreted (Rothman et al. 2008).

2.2. Environmental factors

In the last decades, a wide number of external factors have been proposed as etiologic or underlying conditions for ALS. In this section, we will review some of the most important ones.

2.2.1. Heavy metals: lead, mercury and selenium

Heavy metals probably constitute one of the groups of external factors that has been most assessed during the last decades (Johnson and Atchison 2009; Talbott et al. 2016). Among them, lead, selenium and mercury have been the most studied ones (Sutedja et al. 2009; Johnson and Atchison 2009). Although the role of these toxicants has been widely investigated, the precise mechanisms by which these induce MN degeneration have not been fully elucidated yet.

Lead Lead is the heavy metal most studied in ALS patients. Interestingly, it has some intriguing paradoxical effects. Several studies have reported increased lead levels in both blood and cerebrospinal fluid of ALS patients (Fang et al. 2010; Kamel et al. 2005). We recently performed an ecological study to correlate ALS mortality with air lead levels across Spanish provinces during a 10-year period. In this study, we described that those provinces with higher air lead levels had up to a 25% higher rate of ALS deaths (Santurtun et al. 2016a).

However, paradoxically, basic studies in the SOD1 murine model of ALS have demonstrated that transgenic mice exposed to low doses of lead had significant longer survivals. Histological and biochemical analyses showed that lead-exposed mice had a less prominent astroglial response that seemed to be mediated through an increased expression of the vascular endothelial growth factor (VEGF) (Barbeito et al. 2010). In addition, based on the potential relationship between lead and ALS, it has been studied if there is an association between variants in genes encoding for proteins regulating lead toxico-kinetics and ALS. Kamel et al. (2005) studied whether polymorphisms in aminolevulinic acid dehydratase (ALAD) and vitamin D receptor (VDR) genes (both of them potentially modulating susceptibility to lead exposure) were associated to ALS risk. Interestingly, some variants in the ALAD gene were significantly associated to lower lead levels, concluding that genetic susceptibility conferred by polymorphisms in *ALAD* may affect ALS risk, possibly through a mechanism related to internal lead exposure. Regarding VDR, no significant associations were reported (Kamel et al. 2005).

Further studies will help to elucidate the precise role of lead in MN degeneration as well. They will eventually clarify the potential of the 'lead pathway' as a new therapeutic target.

Selenium Selenium was initially implicated in ALS after two epidemiological studies that reported an increased risk of ALS in two seleniferous regions (Kilness and Hichberg 1977; Vinceti et al. 1996). One of them included more than 5000 Italian people for an 11-year period and concluded that those subjects who drank high-selenium tap water had almost seven times higher risk of ALS than those who did not drink high-selenium tap water (Vinceti et al. 1996). Additionally, animal models have demonstrated that swine exposure to selenium is associated to anterior horn atrophy and MN degeneration at the spinal cord (Casteignau et al. 2006). The neurotoxic effects of selenium seemed to be related to selenium-induced oxidative stress, decreased cholinergic signalling, increased accumulation of mitochondrial SOD1 protein and the degeneration of cholinergic MNs (Estevez et al. 2012; Maraldi et al. 2011).

Mercury Mercury was initially thought to be implicated in the genesis of ALS due to the fact that patients with long-term accidental exposure to mercury developed a characteristic clinical syndrome that is very similar to that reported in classic ALS (Schwarz et al. 1996). Regarding epidemiological studies, although there is no full concordance, most of them showed a slight positive correlation between mercury exposure and ALS (Adams et al. 1983; Pamphlett and Waley 1998; Praline et al. 2007).

Several basic experimental studies also support the role of this metal in the genesis of ALS, particularly in those genetically predisposed individuals. Studies with ALS transgenic mice have described mice exposed to mercury exhibit a more abrupt disease course (Johnson and Atchison 2009). Complementary in vitro studies have demonstrated that mercury influenced the secretion of proinflammatory cytokines, thus impairing the interaction between microglia and astrocytes (Bassett et al. 2012). More recently, Rooney et al. postulated that mercury also interfered with normal DNA methylation (Rooney 2011).

2.2.2. Other chemical toxicants

In the evaluation of other toxicants stands out the study published by Weisskopf et al. (2009) a few years ago. In their study, they assessed the relation between self-report of regular exposure to 11 different chemical classes or x-rays and ALS mortality. More than 1 million of participants were included with a 15-year follow-up period. During that time, 1156 (617 men, 539 women) ALS deaths occurred. Among the different chemicals studied, the authors found a small and non-significant association between pesticide/herbicide exposure and ALS (Weisskopf et al. 2009). In contrast, a clear significant association was found between the exposure to formaldehyde and ALS (relative risk (RR) 2.45; 95% CI 1.58 to 3.56) (Weisskopf et al. 2009). Remarkably, they also described a strong dose-response relationship between the years of formaldehyde exposure and the risk of developing the disease (Weisskopf et al. 2009; Roberts et al. 2015). These results are concordant with other subsequent studies (Pinkerton et al. 2013). In vitro assays have shown that formaldehyde induce mitochondrial disorders and reduced SOD1 activity, thus increasing oxidative stress and inducing neurodegeneration (Nie et al. 2007; Gurel et al. 2005). Inter-individual susceptibility to formaldehyde has been suggested to be mediated by allelic variants in genes encoding paraoxonase and cytochrome P450 (Boccia et al. 2007).

Regarding pesticides, two other meta-analysis have revealed a moderate positive association between ALS risk and the use of organochlorine insecticides, pyrethroids, herbicides and fumigants (Malek et al. 2012; Kamel et al. 2012). In addition, some polymorphisms in the metallothionein family of genes have been postulated to modulate the capacity to detoxify pesticides, thus influencing the risk of MD degeneration (Morahan et al. 2007).

2.2.3. Electromagnetic fields and electrocution

During the last decades, the growth of telecommunication systems has raised the question whether electromagnetic fields increase the risk of neurodegenerative diseases. Up to date, more than 20 studies evaluating the role of electromagnetic radiation and ALS have been published. In 2012, a meta-analysis including 19 of these studies was carried out (Zhou et al. 2012). After the combined analysis, the authors concluded that exposure to extremely low frequencies-electromagnetic fields slightly increased ALS risk (relative risk 1.29; 95% CI 1.02–1.69) (Zhou et al. 2012). From a pathogenic perspective, the exposure to these fields seemed to induce increased oxidative stress, DNA damage and apoptotic-pathways activation (Falone et al. 2008), although these findings have not been replicated in murine models (Poulletier et al. 2009). Regarding electrical injury, more than 30 studies have been conducted without having demonstrated any causal relationship between this type of injury and ALS condition (Abhinav et al. 2007).

2.2.4. Infectious agents

A few studies have also highlighted the potential role of viral, bacterial and fungal infections in ALS. Although the evidences supporting the involvement of microbiological agents are not very solid yet, this is an intriguing field that will probably help us to better understand the disease in the future. Among infectious agents, viruses have been the most studied ones. Initial studies identified reverse transcriptase (RT) in serum of patients with ALS at levels comparable to those observed in human immunodeficiency virus (HIV)-infected patients (Steele et al. 2005; MacGowan et al. 2007). Subsequently, Douville et al. (2011) reported an active locus of a human endogenous retrovirus in brain neurons and described a specific pattern of HERV-K expression among ALS patients. In line with this concept, more recently, Li et al. (2015) demonstrated that expression of HERV-K or its envelope protein in human neurons induced retraction and beading of neuritis. In addition, the authors reported that transgenic animals expressing the envelope protein gene developed a progressive MN disease phenotype (Li et al. 2015).

Regarding bacterial infections, *Borrelia burgdorferi*, the agent of Lyme disease, has been the most studied one. Recently, in a large case-control study including 491 ALS patients and 982 matched controls, no significant association between these diseases was found therefore not supporting the inclusion of *Borrelia* antibodies in the diagnostic work-up in patients with classical ALS (Visser et al. 2017b).

Interestingly, as a novel line of research in this field, gut microbiota has been postulated as a promising line of research. Each individual can be considered as an ecological community composed by a large number of prokaryotic microorganisms known as microbiota (Potgieter et al. 2015). Interestingly, microbiota behaves as a dynamic agent depending on environmental conditions and other host substrates (Potgieter et al. 2015). Microbiota has been widely involved in several diseases such as diabetes, obesity and other autoimmune diseases as inflammatory bowel disease or multiple

sclerosis. In the field of neurodegenerative diseases, there are some evidences supporting its potential role in AD and Parkinson's disease (Tremlett et al. 2017). Regarding ALS, microbiota changes have been reported in ALS murine models (Fang 2016; Zhang et al. 2017) thus postulating it as both a new pathogenic issue to elucidate and at the same time as a new potential therapeutic approach.

The evidences of fungal involvement are also very limited. Recently, one study described fungal infection traces (fungal DNA and fungal antigens) in CSF and brain tissue from a limited subset of ALS patients (Alonso et al. 2015). Although these findings are doubtlessly interesting, we consider that future studies with larger cohorts of patients are needed to better clarify this potential relationship.

2.3. Lifestyle and demographic factors

Social factors, lifestyle and comorbidity During the last decade, several groups have been studying how lifestyle and comorbid situations predispose/modulate ALS development. This is a rapidly growing emerging field which will doubtlessly help us to better understand the disease and that will probably provide us both new pathogenic and preventive approaches. In this section, we will discuss the most interesting issues concerning this field.

2.3.1. Socioeconomic factors

Classically, richness has been inversely correlated to neurodegenerative diseases such as dementia (Satizabal et al. 2016). In this way, those countries or regions with lower incomes had a higher age-adjusted incidence of dementia, probably due to insufficient prevention of cardiovascular risk factors, as well as less optimal strategies for early diagnosis.

When evaluating the role of richness in a particular disease, it should be realised that richness and socioeconomic status are complex factors that are commonly associated to other than merely monetary income, such as race, education level, type of job or the access to healthcare system and preventive measures. To date, there are two studies which have addressed the association between richness or other socioeconomic parameters and ALS both with intriguing results (Roberts et al. 2016; Santurtun et al. 2016b). First, our group correlated ALS mortality and richness across Spanish provinces during an 11-year period (2000–2011). Our results demonstrated a significant positive correlation between gross domestic product (GDP) per capita and ALS mortality ($r = 0.73$; $p < 0.00003$) (Santurtun et al. 2016b). Subsequently, after performing an economic sector-stratified analysis, we observed a clear positive correlation between the degree of development of the industrial sector and ALS mortality ($r = 0.73$; $p < 0.0001$). By contrast, those regions which had a more developed primary (cattle and fishing) sector exhibited significant lower ALS mortality ($r = -0.41$; $p < 0.0001$) (Santurtun et al. 2016b). Although our results show a clear positive correlation between richness and ALS, they might be influenced by other confounding factors such as pollution or the distinct styles of life (in terms of nutrition, physical activity, social habits) which typically vary among the different activity sectors. Shortly after this study, Roberts et al. studied the association between race/ethnicity, socioeconomic status and ALS in USA (Roberts et al. 2016). They included more than 2 million of people with a follow-up period of more than 30 years. In their study, they reported lower ALS incidence in non-Hispanic blacks, Hispanics, and other non-Hispanic races when compared with white people. However, after adjusting by race and ethnicity, they did not find a significant association between income and ALS, thus highlighting race as potential confounder when evaluating socioeconomic status and welfare. Altogether, these studies bring up a new important issue to clarify, providing a starting point for future studies that will have to elucidate the precise factors and mechanisms involved in these economy-related associations.

2.3.2. Tobacco and alcohol

The role of smoking and alcohol consumption has been widely studied in many neurodegenerative diseases (Plassman et al. 2010). Regarding ALS, multiple studies have tried to elucidate if smokers were more likely to develop ALS (Gallo et al. 2009; Schmidt et al. 2010). This hypothesis lies on several facts, such as the high concentration of toxic substances in cigarettes, including lead, formaldehyde, selenium or cadmium. Recently, Alonso et al. (2010) published a meta-analysis of 18 studies previously published. They reported a pooled relative risk of 1.28 (95% CI 0.97–1.68). After gender-stratification, they described a significant increase of risk among smoker women (relative risk 1.66; 1.31–2.10), without significant differences reported in males (Alonso et al. 2010). In conclusion, although there is not an overall strong association between smoking and ALS risk, tobacco seems to be associated with increased risk of ALS in women.

Regarding alcohol consumption, epidemiological studies have not reported a clear relationship between alcoholism and ALS (Nelson et al. 2000). Importantly, in some of these studies, smoking seemed to behave as a confounding factor, suggesting a non-causal association between alcohol intake and risk of ALS development (Nelson et al. 2000).

2.3.3. Physical activity

Since the appearance of several ALS cases in professional sportsmen such as Lou Gehrig or Italian football players, many studied have tried to elucidate if exercise is associated with an increased risk of ALS (Feddermann-Demont et al. 2017; Janssen et al. 2017; Pearce et al. 2015; Kuwahara and

Sato 2013). However, there is some controversy because some of them have reported a positive association (Hamidou et al. 2014) while others did not find it. The first prospective cohort study on ALS and physical activity was recently published by Gallo et al. (2016). It was based on the EPIC cohort (European Prospective Investigation into Cancer and Nutrition) and included a total of 472,100 individuals and 219 ALS deaths. In that study, after adjusting by potential confounding factors, authors reported that physical activity was weakly inversely associated with ALS mortality with a borderline statistically significant trend ($p = 0.042$), with those physically active being 33% less likely to die from ALS compared to those inactive (HR = 0.67; 95% CI 0.42–1.06) (Gallo et al. 2016). A few months later, Eaglehouse et al. evaluated the role of exercise in a cohort of postmenopausal women aged 50 to 79 years (Eaglehouse et al. 2016). In their study, they identified 165 ALS cases among a cohort of more than 161,000 women followed up for 10 years. Interestingly, they found a positive significant association between women practising strenuous exercise and ALS (odds ratio 1.56; 95% CI, 1.02–2.37; $p = 0.04$) (Eaglehouse et al. 2016). Similar tendencies were reported in a cohort of more than 200,000 cross-country skiers in Sweden. Interestingly, long-distance cross-country skiing was associated with a higher risk of ALS, but only among the best skiers while recreational skiers appeared to have a largely reduced risk (Fang et al. 2016). In addition, other studies have directly related the gruelling exercise practice, at a professional level, with the risk of ALS (Gotkine et al. 2014).

Taken together, these seminal studies suggested that moderate physical activity was associated to a lower ALS risk, while strenuous exercise, particularly at a professional level and during early stages of life, could promote disease onset.

2.3.4. Body mass index, nutrition and diabetes

The relationship between body mass index (BMI) and ALS appeared as a tantalising question for many years. In this line, clinical case series consistently reported that patients with ALS were generally lean, with a normal or low BMI (Desport et al. 1999; Vaisman et al. 2009). On the other hand, several lines of evidence suggested that patients with ALS have an energetic imbalance (Zufiria et al. 2016; Dupuis et al. 2011).

Recently, Gallo et al. (2013) performed a cohort study to evaluate the association between BMI and ALS risk. It was also based on the EPIC cohort and included more than 518,000 subjects. During a follow-up period of 13 years, 222 ALS deaths occurred. Remarkably, a significant negative association between BMI and ALS was noted. In men, a linear decrease of risk per unit of BMI was observed (hazard ratio = 0.93, 95% confidence interval 0.86–0.99). This tendency was even more marked in the female group, in which ALS risk was more than threefold increased for those underweight compared with normal-weight women (Gallo et al. 2013).

Otherwise, nutrition seems to be important not only at presymptomatic stages but also when the disease is already established. In this line, several studies have tried to assess the role of nutrition in the progression of the disease (Okamoto et al. 2007; Fitzgerald et al. 2013). A case-control study involving 153 ALS patients and 306 matched controls evaluated pre-illness dietary patters in Japan. Interestingly, the investigators found that high intakes of carbohydrate and low intakes of fat and fatty acids (both saturated, mono and poly-unsaturated fatty acids), when combined, were linked to an increased the risk of ALS (Okamoto et al. 2007). Not long after, Nieves et al. conducted a study to evaluate the association between nutrients and ALS function in more than 300 ALS patients (178 men and 124 women) at initial stages of the disease (Nieves et al. 2016). After complex software analysis, authors concluded that those patients who regularly consumed antioxidants, carotenes, fruits and vegetables had a better preservation of several disease parameters (Nieves et al. 2016). Regarding carotene-related products, a number of studies have supported their role in ALS pathogenesis (Riancho et al. 2016b). Specifically, we have demonstrated in the SOD1 murine model of ALS that chronic treatment with the retinoid agonist bexarotene had marked neuroprotective effects throughout both proteostasis and astroglial response modulation, thus appearing as a new potential therapeutic approach (Riancho et al. 2015, 2016a).

Among metabolic and cardiovascular diseases, diabetes is probably the one harbouring the strongest association. In this line, one of the most important studied was based on the Danish National Register and performed by Kioumourtzoglou et al. (2015). They included 3650 ALS patients and 365,000 control subjects matched by gender and age between 1982 and 2009. Overall, they found that patients with diabetes had a significantly lower risk of ALS (odds ratio 0.61; 95% CI 0.46–0.80). Remarkably, this protective association was stronger in individuals with a more advanced age. In this way, the odds ratio for patients ageing 40 years or less was 1.66 (95% CI, 0.85–3.21) whereas in those subjects ageing 40 or more, the odds ratio markedly decreased to 0.52 (95% CI, 0.39–0.70) (Kioumourtzoglou et al. 2015). This intriguing finding could be related to the different pathogenic mechanisms underlying both types 1 and 2 diabetes. In this way, type 1 diabetes commonly presents at early ages, has a clear autoimmune aetiology, and is commonly associated to both low uric acid levels and hypoglycaemic states which seem to exert some degree of neurotoxic effects (Alberti and Zimmet 1998; Bjornstad et al. 2014; Leese et al. 2003). By contrast, in people over 40 years, type 2 diabetes is much more prevalent. This is commonly associated with metabolic syndrome, with increased BMI, patients commonly tends to hyperglycemia and are sometimes treated with potential neuroprotective

drugs, such as PPAR agonists (Alberti and Zimmet 1998; Hyder et al. 2006; Riancho 2016). An additional explanation for this interaction between age and diabetes on ALS risk could be related to a stronger genetic component in ALS cases appearing in younger individuals (Daneman 2006).

In addition, several reports found a protective association between other vascular risk factors, such as high cholesterol (Seelen et al. 2014) and hyperlipidemia (Dupuis et al. 2008, 2011) and ALS. According to this, a recent study has also pointed out the relationship between a favourable cardiovascular fitness profile and an increased ALS susceptibility (Visser et al. 2017a). However, in all of these situations, correlation rates seemed to be rather weak.

2.3.5. Physical trauma and cerebrovascular injury

Head injury and physical trauma in general have been reported as risk factors for other neurodegenerative disorders such as Alzheimer's (Van Den et al. 2007) and Parkinson's diseases (Goldman et al. 2006). Regarding ALS, the identification of a high incidence of ALS among American football players (Feddermann-Demont et al. 2017; Kuwahara and Sato 2013), led to hypothesise that head injury/extensive physical trauma might promote disease (Kuwahara and Sato 2013; Pearce et al. 2015). Several case-control studies in ALS patients have reported an association with physical trauma or head injury, but there exists a scientist agreement that such studies should be taken with caution because they might be influenced by recall bias. Turner et al. (2010) studied the relationship between head and non-head trauma and ALS during a 36-year period. Initially, they reported an increased risk for ALS after head injury (relative risk 1.5; 95% CI 1.1–2.1). However, after adjusting by time, the evidence for increased risk was restricted to the first year after injury, concluding that this was most likely the consequence of an incipient ALS causing a tendency to fall than a cause itself (Turner et al. 2010). In line with this concept which postulated that head injury could not be a cause but a consequence of latent ALS, Watanabe and Watanabe (2017) very recently published a meta-analyses, including 16 studies, to evaluate such a possibility of reverse causation considering time lags between the incidence of head injuries and the occurrence of ALS. As expected, the meta-analyses reported a statistically significant association between head injuries and ALS (OR 1.45, 95% CI 1.21–1.74). However, when considering the time lags between the experience of head injuries and diagnosis of ALS, the association was weaker (OR 1.21, 95% CI 1.01–1.46, time lag ≥ 1 year) or not significant (e.g. OR 1.16, 95% CI 0.84–1.59, time lag ≥ 3 years). Although these data did not exclude an association between head injuries and ALS, they suggested that the relationship between head injury and ALS might have been overestimated. Future prospective studies considering the time lags between the occurrence of head injuries and the ALS onset will be needed to clarify this issue (Tanaka et al. 2012).

The risk of ALS in patients who have suffered a non-traumatic cerebral injury also seemed to be increased. In this line, a study recently evaluated the risk of ALS in patients who had previously presented arterio-venous malformations (AVMs), stroke, transient ischaemic attack (TIA) and subarachnoid haemorrhage (SAH) (Turner et al. 2016). Remarkably, authors found a significant association among patients with previous AVMs, stroke and TIA. This risk was particularly increased in patients with prior AVM (relative risk 2.69; 95% CI 1.23 to 5.12; $p = 0.005$) (Turner et al. 2016).

2.3.6. Autoimmune diseases

Inflammation and autoimmune disorders are gaining relevance in the pathogenesis of ALS (Riancho et al. 2016c). In this way, glial cell disorders with inflammatory activation appeared as a crucial step in MN degeneration (Zufiria et al. 2016). Interestingly, this is the basis of several ongoing clinical trials with immune modulators (Trias et al. 2016). In this line, the association of ALS with autoimmunity and autoimmune disorders has received increasing attention in recent years. Turner et al. (2013) recently assessed the risk of ALS in patients with autoimmune disease. The study was based on the UK hospital record from 1999 to 2011. The authors reported a significant higher number of ALS cases among subjects with previous autoimmune disease. Remarkably, the ALS risk was specially enlarged (relative risk higher than 4) among patients with type 1 diabetes, multiple sclerosis, myasthenia gravis and polymyositis (Turner et al. 2013). Future epidemiological and pathogenic studies will help to precisely elucidate the role of inflammation in the genesis of ALS.

2.3.7. Cancer

A few studies have examined the risk of cancer in neurodegenerative diseases such as Alzheimer's and Parkinson's disease, reporting an inverse association between these entities and the overall risk of cancer (Driver et al. 2012; Lo et al. 2010). Regarding ALS, some of the ALS-causative genes, such as FUS or UBQLN play important roles in various oncogenic pathways (Dormann and Haass 2013; Shah et al. 2015). In this scenario, several epidemiologic studies have been performed without having identified an overall increase in the risk of developing ALS among cancer survivors (Freedman et al. 2013, 2014; Fang et al. 2013). Recently, Gibson et al. (2016) conducted an observational longitudinal study based on the Utah Population Dabatase including 1081 ALS patients. Overall, cancer was associated to a lower risk of ALS (hazard ratio 0.80; 95% CI 0.66–0.96; $p = 0.014$). However, an increased risk of ALS was found in those

patients with salivary (hazard ratio 5.27; 95% CI 1.09–15.40; $p = 0.041$,) and testicular (hazard ratio 3.82; 95% CI 1.06–9.62; $p = 0.042$) cancers (Gibson et al. 2016). There are also evidences supporting the association between cancer and ALS. In this line, it has recently been reported that the suppressor cancer gene BRCA1, associated with both ovarian and breast cancer, was expressed in human microglia and that it appeared dysregulated in both human and animal models of ALS (Noristani et al. 2015).

Taken together, these results open new perspectives in ALS pathogenesis, but further studies are necessary to elucidate this issue. Moreover, the potential relationship between cancer and ALS points toward novel research strategies such as investigating the role of oncogenic proteins in neurodegenerative diseases.

3. Concluding remarks

In conclusion, ALS appears as the final result of a complex interplay between genes, environment, ageing and perhaps other unidentified factors. During recent years, not only external but also internal environmental conditions have gained more relevance in the genesis of the disease and are currently providing new pathogenic clues.

Although our knowledge of the disease has substantially improved and will continue improving in the future, crucial questions such as how environment and ageing influence familiar forms of the disease or the precise mechanisms (epigenetic modifications, direct toxicity) by which each environmental condition induces motor neuron degeneration remain to be elucidated. In our opinion, investigation strategies in ALS should be reconsidered in order to reach these goals. In this line, for each individual environmental factor, a holistic approach has to be performed. This assessment should include epidemiological, genetic, animal models and other basic tools in order to assess main pathogenic issues involved in ALS. These investigation approaches will doubtlessly improve our dynamic concept of the motor neuron degeneration and also will provide novel opportunities to identify new diagnostic and therapeutic strategies.

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