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Review article

ALS: A bucket of genes, environment, metabolism and unknown ingredients

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ABSTRACT

The scientific scenario of amyotrophic lateral sclerosis (ALS) has dramatically changed since TDP-43 aggregates were discovered in 2006 as the main component of the neuronal inclusions seen in the disease, and more recently, when the implication of *C9ORF72* expansion in familial and sporadic cases of ALS and frontotemporal dementia was confirmed. These discoveries have enlarged an extense list of genes implicated in different cellular processes such as RNA processing or autophagia among others and have broaden the putative molecular targets of the disease. Some of ALS-related genes such as *TARDBP* or *SOD1* among others have important roles in the regulation of glucose and fatty acids metabolism, so that an impairment of fatty acids (FA) consumption and ketogenic deficits during exercise in ALS patients would connect the physiopathology with some of the more intriguing epidemiological traits of the disease. The current understanding of ALS as part of a *continuum* with other neurodegenerative diseases and a crossroads between genetic, neurometabolic and environmental factors represent a fascinating model of interaction that could be translated to other neurodegenerative diseases. In this review we summarize the most relevant data obtained in the ten last years and the key lines for future research in ALS.

Abbreviation: ALS, amyotrophic lateral sclerosis; ALSFRS, ALS functional rating scale; BMAA, beta-N-methylamino-L-alanine; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CSF, cerebrospinal fluid; CX3CR1, CX3C chemokine receptor 1; EAAT2, excitatory amino acid transporter 2; ELP3, elongator complex protein 3; EPHA4, ephrin type-A receptor 4; ERBB4, erb-b2 receptor tyrosine kinase 4; EWSR, ewing sarcoma breakpoint region; FIG4, polyphosphoinositide phosphatase; FUS, fused in sarcoma; GWAS, genome-wide association studies; HFE, human hemochromatosis protein; IGF, insulin-like growth factor; IRAK4, interleukin-1 receptor-associated kinase 4; KIFAP3, kinesin-associated protein 3; NEFH, heavy chain of neurofilament; PLS, primary lateral sclerosis; OPTN, optineurin; PGRN, progranulin; PMA, progressive muscle atrophy; SCA2, dominant spinocerebellar ataxia; SOD1, superoxide dismutase 1; SQSTM1, sequestosome 1; TAF15, TATA-binding protein associated factor 15; TDP-43/TARDBP, transactive response DNA binding protein 43; TMEM106B, transmembrane protein 106B; TREM2, triggering receptor expressed in myeloid cells 2; TRPM7, transient receptor potential cation channel subfamily M member 7; UBQLN2, ubiquilin 2; UNC13A, unc-13 homolog A; VAPB, vesicle-associated membrane protein; VCP, valosin-containing protein; VEGF, vascular endothelial growth factor; ZNF512B, zinc finger protein 512B.

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Contents

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that affects motor neurons in the brain, brainstem and spinal cord, resulting in progressive weakness and atrophy of voluntary skeletal muscles. As a result of the concurrent involvement of the upper and lower motor neurons, neurological examination reveals a combination of upper motor neurons signs (spasticity, hyperreflexia and extensor plantar response or Babinski sign) and lower motor neuron signs (muscle atrophy, fasciculations and cramps). The clinical phenotype is generally classified according to the site at which symptoms first emerge. *Classic* or *spinal* forms, with initial involvement of the limbs, are most common, comprising approximately 65% of cases. In *bulbar* forms, which accounts 30% of cases, the diseases starts with dysarthria, dysphagia or both. Five percent of cases begin aggressively with early respiratory failure (Gordon et al., 2006; Hardiman et al., 2011; Kiernan et al., 2011). The survival rates are variable; most of patients die within an average time that ranges from 2 to 5 years, usually due to respiratory failure (Shaw et al., 2001), but about 35% of patients will survive 5 years or more.

From the epidemiological point of view, ALS shows a stable incidence in Western European countries, with 2–3 new cases per 100,000 inhabitants/year and a prevalence of 4.6 per 100,000 (Imam et al., 2010; Logroscino et al., 2010; Joensen, 2012; Pradas et al., 2013). The peak incidence occurs between 50 and 75 years, decreasing thereafter (Chio et al., 2005; Chio et al., 2009; O'Toole et al., 2008; Joensen, 2012). It is still controversial if the incidence may be lower in non-Caucasian populations (Cronin et al., 2007; Zaldívar et al., 2009; Rojas-Garcia et al., 2012) or among American Indians and Eskimos, but most of the epidemiological studies concur of a slight male/women predominance of 1.2–1.5/1 (Logroscino et al., 2010).

Since its description by Charcot in 1874, the extensive corpus of accumulated knowledge about ALS has not been enough to enable successful therapeutic strategies against this devastating disease. Despite the extensive list of molecules tested, only riluzole, a glutamate antagonist, has been demonstrated to increase survival by few months (Bensimon et al., 1994; Lacomblez et al., 1996; Riviere et al., 1998). Trials with minocycline, lithium carbonate (Chio et al., 2010; Morrison et al., 2013) or pioglitazone (Dupuis et al., 2012) have recently failed to demonstrate efficacy and it has even been suggested that the neuroprotective effect of these molecules could be antagonized by the action of riluzole (Yañez et al., 2014).

However, this scenario could be changing due to a range of breakthroughs. First, the early discovery in 1993 that some inherited forms of ALS are caused by mutations in SOD1 have enabled the development of the transgenic mouse SOD1(G93A), which have largely stimulated basic and experimental research. Later, between 2006 and 2009, several groups discovered that TDP-43 and FUS proteins were the main components of the characteristic neuronal inclusions of TDP-43 and FUS proteins as the main components of the characteristic neuronal inclusions (Neumann et al., 2006, 2009; Vance et al., 2009). And few years later, in 2011, the genetic background of ALS forms linked to chromosome 9 was discovered (DeJesús-Hernández et al., 2011; Renton et al., 2011), bringing novel insigths into pathogenic mechanisms. These discoveries boosted the interest in disease, which is well evidenced by the number of entries in Pubmed under the term *"amyotrophic lateral sclerosis"* (5670 citations) during the last 4 years (between March 1st, 2012 and February 29th, 2016), accounting 29% of all historical entries for this disease (data reviewed on March 1st, 2016). Most people are also aware of the ice bucket challenge to obtain funding for ALS research, which has achieved global attention in 2014.

The current understanding of ALS is recognized to be part of a *continuum* that includes other nosological conditions of the central nervous system (CNS), such as frontotemporal dementia (FTD), ataxias or Parkinson's disease (PD) (Strong, 2008; Pradat et al., 2009; Mackenzie et al., 2010;). Epidemiological studies have identified genes involved not only in the inherited but also in the sporadic forms, which have contributed to this paradigm shift. Based on this scientific revolution, it has been possible to perceive a hope in the therapeutic trials that are recently ongoing or in those which are coming.