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Amyotrophic lateral sclerosis: Current perspectives from basic research to the clinic

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of upper and lower motoneurons, leading to muscle weakness and paralysis, and finally death. Considerable recent advances have been made in basic research and preclinical therapeutic attempts using experimental models, leading to increasing clinical and translational research in the context of this disease. In this review we aim to summarize the most relevant findings from a variety of aspects about ALS, including evaluation methods, animal models, pathophysiology, and clinical findings, with particular emphasis in understanding the role of every contributing mechanism to the disease for elucidating the causes underlying degeneration of motoneurons and the development of new therapeutic strategies.

Contents

Abbreviations: AAV, adeno-associated virus; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ChAT, choline acetyltransferase; CHOP, C/EBP homologous protein; CMAP, compound muscle action potential; CNTF, ciliary neurotrophic factor; EAAT, excitatory amino-acid transporter; EMG, electromyography; ER, endoplasmic reticulum; fALS, familiar ALS; FTLD, frontotemporal lobal degeneration; FUS, fused in sarcoma; GDNF, glial derived neurotrophic factor; IGF-1, insulin-like growth factor 1; iPS, induced pluripotent stem; KAP3, kinesin-associated protein 3; KCC2, potassium-chloride co-transporter 2; MN, motoneuron; MND, motoneuron diseases; MRI, magnetic resonance image; MSC, mesenchymal stem cell; MUNE, motor unit number estimation; NMDA, N-methyl-D-aspartate; NSC, neural stem cell; ROS, reactive oxygen species; sALS, sporadic ALS; SMA, spinal muscular atrophy; SOD1, superoxide dismutase 1; TDP-43, TAR-DNA binding protein 43; TMS, transcranial magnetic stimulation; UPR, unfolded protein response.

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1. Motoneuron diseases

Motoneuron diseases (MND) are progressive neurodegenerative disorders with different etiologies and clinical spectra, but a common final event: loss of lower and/or upper motoneurons (MNs). Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are the most frequent forms of MND and therefore the most studied. ALS was first described by Charcot in 1869 and is the most common form of MND (incidence of 1–5 per 100,000) affecting adults. Degeneration of both upper (corticospinal/corticobulbar) and lower (spinal/bulbar) MNs distinguishes ALS from other MND. The main neuropathological features of ALS include extensive loss of MNs in the anterior horns of the spinal cord and brainstem, degeneration of the corticospinal tract, and degeneration and loss of large pyramidal neurons in the primary motor cortex, which project their axons in the corticospinal tract. There is also reactive gliosis around the areas of degeneration. A common feature with other neurodegenerative diseases is the formation of protein aggregates in the degenerating neurons. Although the composition of these protein structures remains partly unknown, neuronal cytoplasmic inclusions predominantly comprise a nuclear RNA processing protein, TDP-43 (TAR-DNA binding protein 43) in most ALS cases (Ince et al., 2011).

Despite that most ALS cases are sporadic (sALS), 5-10% are familiar (fALS), related with several genetic mutations (summarized in Table 1) (Shaw, 2005). No matter if they are sporadic or familiar, patients develop progressive weakness and muscle atrophy, with spasticity and contractures. Progressive weakness may start distally or proximally in the upper or lower limbs and reach all muscles, including those related with breathing, speaking and swallowing. Patients die, mostly due to respiratory failure, by 2-5 years after diagnosis (Wijesekera and Leigh, 2009; Worms, 2001). No effective treatment is presently available for ALS. Patient care focuses on symptomatic treatments and physical therapy. Assisted ventilation and nutrition can transiently overcome the loss of upper airway and respiratory muscular control (Wijesekera and Leigh, 2009). A large number of therapeutic trials have been attempted, but it was not until the early 1990s that the first drug approved by the FDA for the treatment of patients with ALS reached the market: riluzole, an antiglutamatergic agent that blocks the presynaptic release of glutamate. However, the efficacy of riluzole is questionable, with minimal therapeutic benefits of about 3-4 months of survival increase (Ludolph and Jesse, 2009).

2. Frontotemporal lobal degeneration – ALS complex

Frontotemporal lobal degeneration (FTLD or FTD) is caused by a progressive neuronal atrophy and loss in the frontotemporal cortex, and is characterized by personality and behavioral changes, as well as gradual impairment of language skills. It is the second most common dementia after Alzheimer's disease (Van Langenhove et al., 2012).

Traditionally, ALS and FTLD were considered as two distinct identities. However, novel evidences suggest that both pathologies form one clinical continuum, in which pure forms are linked by overlapping syndromes. The first link established between FTLD and ALS was the identification of TDP-43 positive ubiquitinated cytoplasmic inclusions in almost all cases of ALS and more than a half of FTLD patients (Neumann et al., 2006; Van Langenhove et al., 2012). Although neuropsychological testing shows normal cognition in the majority of ALS patients, up to 50% of them may present some degree of cognitive impairment, while 15-18% meet the criteria for FTLD (Ringholz et al., 2005). On the contrary, few patients with FLTD develop ALS (Lomen-Hoerth et al., 2002). In fact, FTLD-only, ALS-only and coincident FTD-ALS cases were reported to occur inside a same family. Despite genetic alterations underlying these cases are unknown, some studies have identified a common locus on chromosome 9 (Vance et al., 2006). The recent finding of an hexanucleotide expansion in C9ORF72 constitutes a strong link between ALS and FTLD (DeJesus-Hernandez et al., 2011; Ling et al., 2013; Mori et al., 2013; Renton et al., 2011). Currently, little is known about factors that may account for the phenotypic heterogeneity detected in C9ORF72 expansion carriers. However, recent findings suggest that intermediate ATXN2 repeat lengths may render C9ORF72 expansion carriers more susceptible to the development of MND (van Blitterswijk et al., 2014).

3. Diagnostic and evaluation methods

ALS is characterized by the loss of MNs of primary motor cortex, brainstem and spinal cord. This special combination of upper and lower MNs provokes physical signs of upper or lower MN