Amyotrophic Lateral Sclerosis: Autoimmune Pathogenic Mechanisms, Clinical Features, and Therapeutic Perspectives

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ABSTRACT: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive death of motor neurons leading to fatal paralysis. The causes of ALS remain unknown; however, evidence supports the presence of autoimmune mechanisms contributing to pathogenesis. Although several environmental factors have been proposed, the only established risk factors are older age, male gender, and a family history of ALS. To date, there are no diagnostic tests for ALS, and clinicians rely on the combination of upper motor neuron and lower motor neuron signs in the same body region. The aim of this paper was to provide a comprehensive review of current clinical literature with special focus on the role of autoimmunity in ALS, differential diagnosis, and available therapeutic approaches. Current evidence suggests a contribution of the innate immune system in ALS, with a role of microglial cell activation at the sites of neurodegeneration. The median time from symptom onset to diagnosis of ALS is 14 months, and this time estimate is mainly based on specific clinical signs and exclusion of ALS-like conditions. Several therapeutic approaches have been proposed, including immunosuppressive drugs, to reduce disease progression. Riluzole has been established as the only, although modestly effective, disease modifying therapy, extending mean patient survival by 3 to 6 months. Recent advances in understanding the pathophysiology mechanisms of ALS encourage realistic hope for new treatment approaches. To date, the cornerstones of the management of patients with ALS are focused on symptom control, maintaining quality of life, and improving survival.

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KEY WORDS: amyotrophic lateral sclerosis (ALS), autoimmunity, immunology, neurodegeneration

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by the progressive death of motor neurons with fatal paralysis within a few years. ALS was first described by Jean-Martin Charcot in 1869. Since then, several genes have been identified in hereditary ALS (named familial ALS), which represents about 10% of the cases [1]. The remaining 90% of cases account for sporadic ALS, a condition that does not show any conventional hereditary pattern. To date, the pathogenic mechanisms of ALS are unknown. Similarly, many efforts have been made searching for a therapeutic strategy, without success [2]. In this article, we summarized the current evidence related to autoimmunity in the sporadic form of ALS and discuss the potential pathogenic mechanisms.

EPIDEMIOLOGY

The incidence of ALS in Europe, as shown by many population-based studies, is uniform at 2.16 per 100,000 person-years [3]. Male gender has a higher incidence of the disease compared to women, while the overall population-based lifetime risk of ALS is 1:400 for women and 1:350 for men. Peak age at onset ranges between 58 and 63 years for sporadic disease and between 47 and 52 years for familial disease. Studies have shown that after 80 years of age the incidence of ALS rapidly decreases [4].

ETIOPATHOGENESIS

Immunologic hypothesis

The causes of ALS and the specific mechanisms of neuronal death are currently unknown. However, increasing evidence supports the presence of autoimmune mechanisms that contribute to ALS pathogenesis, such as pharmacological, biochemical, and physiological studies, which have been performed in animal models and in cell cultures [5,6]. Studies have also reported typical hallmarks of autoimmunity, such as the presence of circulating immune complexes, the association with other autoimmune conditions, and the evidence of higher frequency of specific histocompatibility types [7].

An important marker of autoimmunity in patients with ALS is the degree of T-lymphocytic infiltration in the anterior horn of the spinal cord [8]. T-cells and macrophages have been shown to play a relevant role in the spinal cord and brain inflammatory mechanisms in ALS [9], and aberrant macrophage activity is believed to contribute to the pathology underlying ALS.

In a recent phase 2 clinical trial in ALS patients, the authors studied the role of NP001, a regulator of inflammatory macrophage activity [10], and reported that the administration of NP001 prevented disease progression in 27% of patients. This

result was 2.5 times greater than that obtained in the placebo group.

Demestre et al. [11] demonstrated that immunoglobulins from ALS patients causes apoptosis of motor neurons in primary spinal cord cultures and that the passive transfer of immunoglobulins to mice caused degeneration of motor neurons [12]. These findings provide further evidence of the involvement of autoimmune mechanisms in ALS and suggest that antibodies can contribute to pathogenesis of the disease. Increased levels of interleukins (IL) -17 and IL-23 have been found in serum and cerebrospinal fluid of ALS patients [13], suggesting the activation of T-helper 17 (Th17), a population of T-cells considered crucial in destructive autoimmunity. Additional support for the role of the autoimmune system in ALS is the recent inclusion of ALS in the spectrum of neurologic manifestations associated with voltage-gated potassium channel autoimmunity [14].

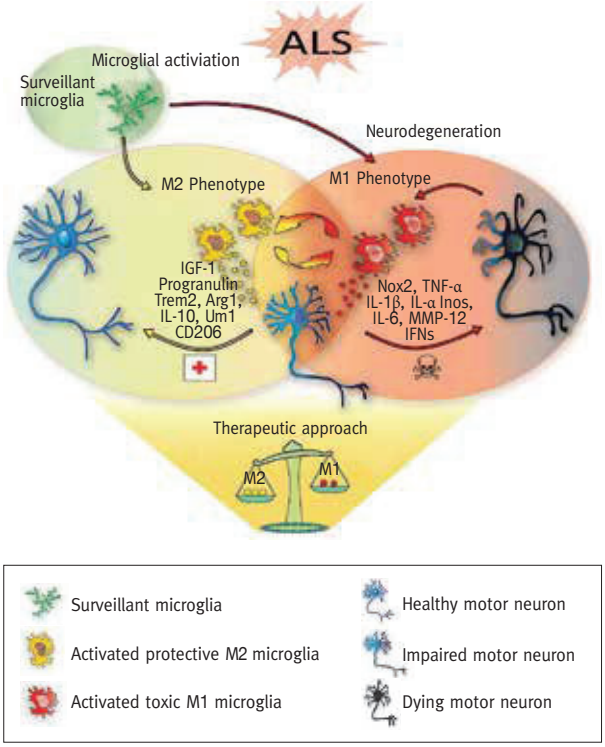
Current evidence suggests a contribution of the innate immune system in ALS. In fact, microglial cell activation has been shown at the sites of neurodegeneration. During progression of ALS, activated microglia represent a continuum between the neuroprotective M2 phenotype, which promotes tissue repair and supports neuron survival by releasing neuroprotective factors, and the toxic M1 phenotype, which produces cytokines increasing inflammation and further supporting M1 polarization, thus contributing to neuronal death [Figure 1] [15]. Frakes et al. [16] described the importance of microglia in ALS, demonstrating that classical NFκB activation is necessary to induce motor neuron death in a mutant superoxide dismutase 1 ($SOD1^{G93A}$) mouse model of ALS. These findings are also supported by positron-emission tomography (PET) imaging in patients with ALS. Researchers have found increased microglial cell activation in affected brain areas [17]. Last, the level of microglial cell activation has been shown to positively correlate with the severity of clinical symptomatology in ALS patients [18].

There are at least three mechanisms through which researchers suggest that the innate immune system affects the function and survival of motor neurons in ALS. First, aggregates of mutant SOD1 can activate neighboring microglia by binding to TLR2, TLR4, and CD14, thus inducing neuronal cell death [19]. Second, the release of pro-inflammatory cytokines has been shown to induce motor neuron damage. Last, microglial cells that express mutant SOD1 showed impaired motility and reduced capacity to clear neuronal cell debris, thus leading to the accumulation of immunostimulatory proteins at the base of disease progression [20].

Environmental factors

Several environmental factors have been proposed in ALS. They include body mass index, smoking, physical exercise, head trauma, metabolic and inflammatory states, antioxidant intake,

Figure 1. Role of microglia in ALS-induced motor neuron degeneration
During ALS progression, activated microglia represent a continuum between the neuroprotective M2 phenotype, which promotes tissue repair and supports neuron survival by releasing neuroprotective factors, and the toxic M1, which produces cytokines increasing inflammation and further supporting M1 polarization, thus contributing to neuronal death. Therapeutic approaches targeting microglia polarization and resulting in induction of the M2 phenotype are promising strategies to ameliorate local neurodegeneration and improve the clinical outcome of the disease



ALS = amyotrophic lateral sclerosis

From: Geloso MC, Corvino V, Marchese E, Serrano A, Michetti F, D'Ambrosi N. The dual role of microglia in ALS: mechanisms and therapeutic approaches. *Front Aging Neurosci* 2017; 9: 242 [16].

cancer, history of electric shock, and exposure to electromagnetic fields, heavy metals, or organic chemicals [21].

Studies have shown a significant association between head trauma and ALS susceptibility [22]. In contrast, hypercholesterolemia and the use of statins were associated with a decreased risk of development of ALS, although other studies reported either higher or unaltered lipid levels in ALS patients compared to controls [23]. Moreover, researchers reported a decreased risk of ALS development in patients using immunosuppressive drugs, although results were conflicting [24].

In a retrospective study of professional football players, higher morbidity was shown for development of ALS, especially for young-onset disease [25]. The study suggested that football players who played for more than 5 years were more at risk of

developing ALS, although the causes were unknown. To date the only established risk factors for ALS are older age, male gender, and a family history of ALS [26].

CLINICAL PHENOTYPES AND PROGNOSIS

The clinical hallmark of ALS is the combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs and symptoms, with involvement of the brainstem and of multiple spinal cord regions of innervation.

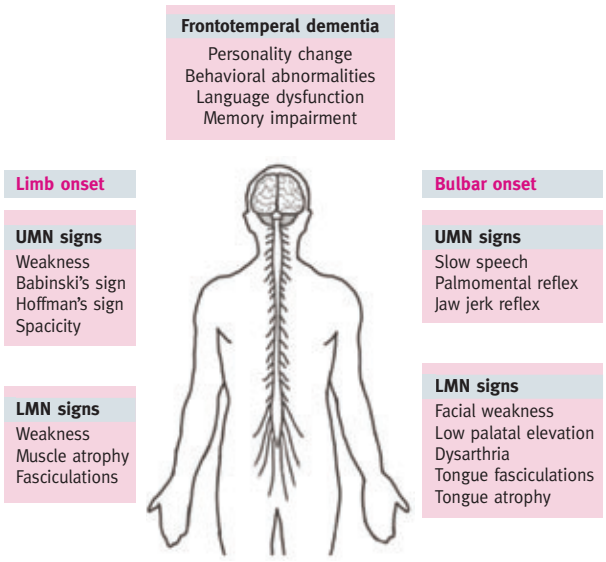
Many clinical presentations of ALS have been described. They include limb-onset ALS with a combination of UMN and LMN signs in the limbs, bulbar-onset ALS with speech, and swallowing difficulties at disease onset and later development of limb features, UMN involvement, and progressive muscular atrophy with pure LMN involvement [27]. Limb onset is found in approximately two-thirds of patients, but most will develop signs in both the bulbar region and limbs within the course of the disease. Up to 50% of ALS patients may have symptoms of frontotemporal dementia [Figure 2].

Atypical presentation of clinical symptoms and signs may include weight loss, rapid emotional changes associated with frontal lobe-type cognitive dysfunction, and muscle cramps and fasciculations without muscle weakness [28].

ALS is a progressive condition leading to death 2 to 3 years after onset of symptoms in about 70–80% of patients. Approximately 20% may survive for a time range between 5 and 10 years after initial symptom onset [29]. Therapeutic measures, comprehensive and multidisciplinary management, and palliative care may explain the increase in survival rate reported in recent studies [28-30].

Figure 2. Clinical features in patients with amyotrophic lateral sclerosis

Signs and symptoms are divided by affected motor neuron. Both UMN and LMN have to be affected for the diagnosis of ALS. Different combination of LMN and UMN signs can be observed. Limb onset is found in approximately two-thirds of patients, but most patients will develop signs in both bulbar region and limbs within the course of disease. Up to 50% of ALS patients may have symptoms of Frontotemporal dementia



ALS = amyotrophic lateral sclerosism, LMN = lower motor neurons, UMN = upper motor neurons

From: Picher-Martel V, Valdmanis PN, Gould PV, Julien JP, Dupré N. From animal models to human disease: a genetic approach for personalized medicine in ALS. *Acta Neuropathol Commun* 2016; 4 (1): 1-29 [43]

DIAGNOSIS

To date, there are no diagnostic tests for ALS. Clinical diagnosis is therefore based on the identification of the combination of UMN and LMN signs in the same body region followed by evidence of involvement of other regions. There is often a long delay before a definitive diagnosis is reached, partly because of the insidious and progressive onset of symptoms. The average time to a definitive diagnosis of ALS is between 8 and 15 months [30].

Although rare, the presence of several disorders that may mimic ALS requires a thorough diagnostic assessment to reduce the likelihood of an incorrect diagnosis. Diagnostic workup includes structural imaging as well as neurophysiological and laboratory investigations [Table 1] [31].

In cases of pure LMN syndromes, genetic testing for Kennedy's disease and spinal muscular atrophy play a relevant role. Muscle biopsy can contribute excluding unusual myopathies such as polyglucosan body disease or confirm a diagnosis of ALS by indicating atrophy of mixed-fiber types [32].

Routine neurophysiological investigations of ALS patients include nerve conduction studies, electromyography, and transcranial magnetic stimulation. Nerve conduction studies are necessary to exclude disorders that mimic ALS, such as demyelinating motor neuropathies [32]. Electromyography plays a diagnostic role for the identification of LMN loss [32].

The role of neuroimaging in the diagnostic pathway of ALS is limited to the ability of magnetic resonance imaging to exclude alternative pathological causes.

Differential diagnosis with other disorders similar to ALS, such as the ALS-like autoimmune syndromes, is important in ALS. One of the most important ALS-like autoimmune syndromes is the multifocal motor neuropathy (MFMN), a slow progressive condition that manifests as asymmetric muscular weakness affecting preferentially distal muscles, sparing upper motor neurons. Differential diagnosis is confirmed on the basis of motor nerve conduction block and on the increased levels of antibodies against ganglioside GM1, which is responsible for the typical physiological changes in MFMN [33]. Furthermore, MFMN patients have an excellent response to immunosuppressive therapy with cyclophosphamide or intravascular immunoglobulin [33].

THERAPEUTIC APPROACHES

Following the extensive evidence suggesting a neurotoxic effect of the immune response in ALS, many therapeutic trials on the autoimmune pathogenetic hypothesis of ALS have been performed. Unfortunately, these studies have failed to demonstrate an improvement in motor function. Therapeutic trials have used immunosuppressive drugs, such as corticosteroids, cyclosporine, azathioprine, and cyclophosphamide, as well as immunotherapy with plasmapheresis or intravenous immunoglobulins; however, none of these therapeutic approaches have shown evidence of being able to alter disease progression [34].

It should be noted that these studies included ALS patients with pathological and physiological evidence that the disease was well established, and with massive loss of motor neurons. Instead, such therapies could play a role in the early phase of the diseases, as little is known about the duration of any phase of motor neuronal sickness, from which motor neurons could be rescued by an effective therapy [35].

Intensive immunosuppression followed by autologous hematopoietic stem cell transplantation (AHSCT) has been used since 1996 for the treatment of severe autoimmune diseases refractory to other therapies, such as aggressive forms of multiple sclerosis (MS) [36]. A large international cohort study evaluated the long-term outcomes of these transplants in 281 MS patients [36]. The results showed a 5-year survival of 85% and a progression-free survival of 43%. This study showed that profound immunosuppression and AHSCT may induce disease remissions in patients with systemic autoimmune diseases refractory to conventional therapies, and that so-called intractable cases may improve with a more aggressive immunotherapy [36]. Hence, the failure of prior ALS therapeutic trials based on the autoimmune pathogenesis hypothesis may have reflected the inability to achieve a level of immunosuppression necessary to abolish the immune mechanisms contributing to disease progression. Stem cells have been shown to have the ability to provide numerous benefits in ALS, leading to the study of a variety of stem cell-based therapies [37]. To date, the injection of various types of stem cells into the brain or spinal cord to replace or repair damaged neurons is thought as holding the greatest potential for possible sustained results in ALS [37].

Leis and colleagues [38] proposed the use of immunoablation to reduce the neurotoxic effects of the immune response in ALS patients. In their model, reinfused stem cells were required to replenish the immune system to avoid patient undergoing immunoablation dying of opportunistic infections.

Riluzole is the only widely available drug that appears to prolong survival of patients with ALS, having been shown in clinical trials to increase the median survival time from 11.8 months to 14.8 months [39].

To date, in the absence of a cure, the cornerstones of the management of ALS patients are focused on symptom control.

Table 1. Differential diagnosis of amyotrophic lateral sclerosis and appropriate investigations

Differential diagnosis	Appropriate investigations
Disorders of motor neurons	
Spinal muscular atrophy	*SMN* gene deletion assay
X-linked spinobulbar muscular atrophy	Kennedy's disease; increased CAG repeats in DNA from blood
Poliomyelitis or post-polio syndrome	History, NCS, electromyography
Hexosaminidase A deficiency	White-cell enzyme testing
Disorders of motor nerves	
Multifocal motor neuropathy	NCS, electromyography, ganglioside GM1 antibodies
Chronic inflammatory demyelinating neuropathy	NCS, lumbar puncture
Cramp-fasciculation syndrome	NCS, electromyography
Neuromyotonia	Antibodies to voltage-gated potassium channels
Hereditary spastic paraparesis plus	Gene mutation testing
Hereditary motor neuropathy with pyramidal features	
Radiculoplexopathy	NCS, electromyography, MRI
Paraneoplastic syndrome	Serum markers, imaging, bone marrow biopsy sample
Heavy metal poisoning	Urine or blood screens
Mononeuritis multiplex	NCS, electromyography, vasculitic screen, serology
Disorders of neuromuscular junction	
Myasthenia gravis	Acetylcholine receptor antibodies, MuSK antibodies, repetitive stimulation, single-fiber electromyography
Lambert-Eaton myasthenic syndrome	Repetitive stimulation
Structural central nervous system and spinal lesions	
Syringomyelia or syringobulbia	MRI
Tabes dorsalis	Syphilis serology
Multiple sclerosis	MRI, oligoclonal bands, evoked responses
Monomelic spinal muscular atrophy	Hirayama's disease; electromyography, MRI
Lyme disease	Lyme serology
Human T-lymphotropic virus-1	HIV
Myopathy	
Inclusion body myositis	Electromyography, CK, muscle biopsy sample
Polymyositis	Electromyography, CK, muscle biopsy sample, autoimmune screens
Dermatomyositis	Electromyography, CK, skin, and muscle biopsy sample
Polyglucosan body disease	NCS, electromyography, muscle or nerve biopsy sample
Endocrine conditions	
Thyrotoxicosis	Thyroid function tests, electromyography, muscle biopsy sample
Hyperparathyroidism	Calcium ion and parathyroid testing
Subacute combined degeneration	Vitamin B_{12} concentrations
Celiac disease	Serum testing, bowel biopsy sample

ALS = amyotrophic lateral sclerosis, CK = creatine kinase, HIV = human immunodeficiency virus, MRI = magnetic resonance imaging, NCS = nerve conduction studies, MuSK = muscle-specific tyrosine kinase

Adapted and modified from Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *Lancet* 2011; 377 (9769): 942-55. [40]

These treatments may not only alleviate symptoms but also improve quality of life and survival, with greater benefits for patients treated in multidisciplinary ALS clinics [39]. Optimum care for patients with ALS is provided within a multidisciplinary

environment where neurologists, otolaryngologists, gastroenterologists, physiotherapists, respiratory physicians, and social workers collaborate to allow symptomatic management through the course of disease. Such models of care have been shown to reduce the risk of death up to 45% at 5 years [40].

Current practice guidelines recommend gastrostomy feeding for patients with severe dysphagia, since malnutrition is a negative prognostic factor and aspiration pneumonia is one of most feared causes of morbidity and mortality in ALS [41].

Respiratory failure is not only the main mortality cause but may also be the presenting symptom in patients with ALS. These cases require careful differential diagnosis to exclude other neuromuscular and non-neuromuscular disorders [39]. A recent randomized controlled trial showed that the addition of diaphragm pacing to standard care was associated with decreased survival in patients with ALS. Non-invasive ventilation (NIV) has been shown to improve quality of life and survival in patients with ALS [42]. Moreover, NIV has also been reported to significantly increase survival by 19 months in patients with ALS-bulbar onset [42]. In more advanced cases, invasive ventilation via tracheostomy is an option to increase survival [43].

CONCLUSIONS

The recent developments in understanding the pathophysiology mechanisms of ALS encourage realistic hope that new treatment approaches may be found. However, the autoantigens involved in ALS and the mechanisms that generate autoantibodies are still unknown. The possible identification of these autoantigens may play a central role in defining therapies for specific molecular targets, further characterizing the role of autoimmune mechanisms.

In addition to efforts in finding an effective therapy to interrupt the course of the disorder and alleviate ALS symptoms, researchers have also focused on identifying markers for an earlier diagnosis. Early diagnosis through the identification of biological markers, such as specific protein alterations in cerebrospinal fluid, blood, and tissues of ALS subjects, seems to be the most promising strategy in ALS research.

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Capsule

Microbiota therapy acts via a regulatory T cell MyD88/RORγt pathway to suppress food allergy

The role of dysbiosis in food allergy (FA) remains unclear. **Abdel-Gadir** and co-authors found that dysbiotic fecal microbiota in FA infants evolved compositionally over time and failed to protect against FA in mice. Infants and mice with FA had decreased IgA and increased IgE binding to fecal bacteria, indicative of a broader breakdown of oral tolerance than hitherto appreciated. Therapy with *Clostridiales* species impacted by dysbiosis, either as a consortium or as monotherapy with *Subdoligranulum variabile*, suppressed FA in mice as did a separate immunomodulatory Bacteroidales consortium. Bacteriotherapy induced expression by regulatory T (Treg) cells of the transcription factor ROR-γt in a MyD88-dependent manner, which was deficient in FA infants and mice and ineffectively induced by their microbiota. Deletion of Myd88 or Rorc in Treg cells abrogated protection by bacteriotherapy. Thus, commensals activate a MyD88/ROR-γt pathway in nascent Treg cells to protect against FA, while dysbiosis impairs this regulatory response to promote disease.

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Eitan Israeli

Capsule

Personal clinical history predicts antibiotic resistance of urinary tract infections

Antibiotic resistance is prevalent among the bacterial pathogens causing urinary tract infections. However, antimicrobial treatment is often prescribed empirically, in the absence of antibiotic susceptibility testing, risking mismatched, and therefore ineffective, treatment. Linking a 10-year longitudinal data set of over 700,000 community-acquired urinary tract infections with over 5,000,000 individually resolved records of antibiotic purchases, **Yelin** and colleagues identify strong associations of antibiotic resistance with the demographics, records of past urine cultures, and history of drug purchases of the patients. When combined together, these associations allow for machine-learning-based personalized drug-specific predictions of antibiotic resistance, thereby enabling drug-prescribing algorithms that match an antibiotic treatment recommendation to the expected resistance of each sample. Applying these algorithms retrospectively over a 1-year test period the authors found that they greatly reduced the risk of mismatched treatment compared with the current standard of care. The clinical application of such algorithms may help improve the effectiveness of antimicrobial treatments.

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Eitan Israeli

"The best way to have a good idea is to have lots of ideas"

Linus Carl Pauling (1901–1994), American chemist, biochemist, peace activist, author, educator, and husband of American human rights activist