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NEUROPATHOLOGY AND NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) disease is mainly caused by the death of motor neurons, and usually strikes in old age with a rapid course, typically resulting in fatality about 4 years after diagnosis. The death of motor neurons interrupts synapses with muscles which leads to muscle atrophy with stiffness, spasticity, and subsequent death of the patient. There are various causes of neuronal dysfunction and death, including mitochondrial malfunction, impaired axonal transport, caspase activation, and inflammatory cytokine production. In line with other neurological diseases, the immune system may be involved in ALS. Immune cells such as microglia, Treg cells, and T helper cells (TH) intervene early in the disease to defend and protect the central nervous system (CNS). Subsequently, microglia/M1, TH1, TH17, and other cells, are activated to produce inflammatory cytokines that aggravate the pathological state of ALS. In this paper, we discuss the neuropathology and neuroinflammation that occurs in ALS, a fatal disease that still needs in-depth studies.

KEYWORDS: *amyotrophic lateral sclerosis, neuroinflammation, neuropathology, neurodegeneration, immunity, CNS*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects motor neurons in the brain and medulla. The disease is late onset and involves a rapid course of progression, resulting in paralysis and eventual death (1). Affected individuals have muscle weakness which involves the diaphragm, an effect that leads to death generally after about 4 years (2). The lower motor neurons responsible for the innervation of muscles reside in the motor cortex of the brain, in the brainstem, and in the spinal cord. Motor neuron failure leads to muscle dysfunction that is characterized by stiffness and spasticity. The affected lower neurons degenerate and are no longer able to synapse with muscles, causing muscle atrophy. Muscles of the eye and the sphincter are the least affected by the disease (3). Within 30 months of the onset of symptoms, about half of the patients affected by this pathology die (4), often due to respiratory insufficiency (5).

ALS diagnosis is made through electromyography and laboratory analyses. The disease does not appear to be genetic, although some individuals do have a family history of ALS (6). Some protein-coding genes have been associated with the disease, where there is mitochondrial dysfunction, protein aggregation with dysfunction of homeostasis or protein clearance defect, impaired RNA metabolism, impaired axonal functioning, and DNA damage due to defective DNA repair mechanisms (6-8). Current therapies are not very effective, as they have undesirable side effects and improve survival by

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only a few months (9). The physiopathology of ALS is unknown, and therefore, to identify new therapeutic targets, more knowledge of this disease is needed, both at the genetic and neuroinflammatory levels.

DISCUSSION

Although significant progress has been made by studies researching the risk factors and the genetic basis of ALS in recent years, further investigation and clarification are still needed. Today, we know that the risk factors include increasing age and the male sex, and it appears that specific environmental exposure also plays a role in disease development (10). Motor neuron injury and dysfunction occur in ALS due to various possible causes, some of which are reported in the table below (Table I).

Table I. *Possible causes of motor neuron injury occurring in ALS.*

- mRNA and mitochondrial dysfunction
- Calcium toxicity
- Glutamate excitotoxicity
- Modified protein toxicity
- Impaired autophagy
- Impaired axonal transport
- Reactive oxygen species (ROS) formation
- Caspase activation with IL-1 production
- Endoplasmic reticulum (ER) stress

These malfunctions contribute to neuroinflammation in ALS and exacerbate the pathology. Some authors have found a correlation between blood lipid levels [low-density lipoprotein (LDL) cholesterol and total cholesterol] and ALS risk (11,12). In addition, it appears that exercise, type 2 diabetes, atherosclerosis, and cardiovascular disease (13-16) are linked to ALS, and it has been suggested that a favorable vascular risk profile may increase susceptibility to the disease (17).

Dysfunctional immunity may also be involved in the onset of ALS, as we know that this feature is common to neurological diseases (18). In ALS, the cooperation between motor neurons and glial cells, which is necessary to maintain the active physiological state of the brain, appears to be compromised. Microglia are macrophagic immune cells that intervene early in the disease as a neuroprotective factor which subsequently transforms into a neurotoxic factor, an effect that is counteracted by Treg and TH immune cells (19). Immune cells initially intervene in the disease by producing anti-inflammatory cytokines, such as IL-10, to protect motor neurons, but as the disease worsens, it leads to the activation of microglial/M1 cells and T cells, contributing to the pathology that occurs in ALS (20,21) (Fig.1). Dendritic cells also participate in the disease and have been found to be reduced in circulating blood (22) yet increased in the spinal cord (23) in ALS patients when compared to unaffected individuals. These cells can present harmful antigens to T lymphocytes and can contribute to the inflammatory state by producing cytokines that mediate motor neuroinflammation.

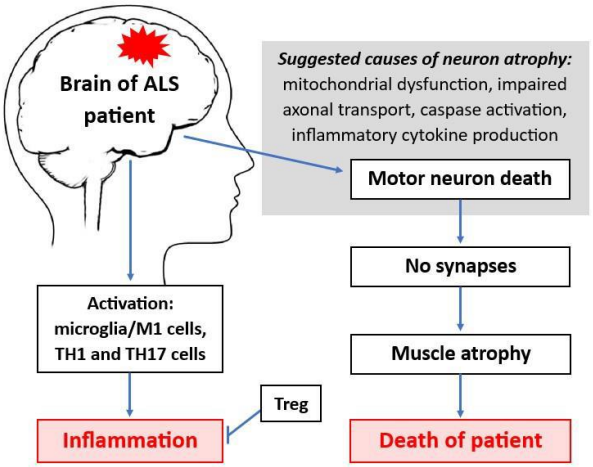

Fig. 1. *The brain of patients affected by ALS is characterized by the death of neurons which disrupts synapses and neural connections, causing muscle atrophy and the subsequential death of the patient. In addition, in ALS patients, there is activation of microglia/M1, TH1, and TH17 cells, which mediate inflammation, an effect that can be inhibited by Treg cells.*

T cells play an important role in acquired immunity and can be found in infiltrating brain tissue. They are very important in the progression of ALS. In fact, the CD4+ T helper subpopulations, together with CD8+ lymphocytes and microglia, participate in the late phase of the neuroinflammatory reaction (24). The CD4+ cells which are the most involved in ALS are Tregs, TH1, TH2, and TH17, with Tregs and TH2 cells having neuroprotective effects, and TH1 and TH17 cells mediating neuroinflammation (25,26). Since protective Treg cells are no longer effective and decrease in number in ALS, the neurotoxic phenomenon prevails with devastating motor consequences.

ALS studies have utilized transgenic mice in which the genetic composition has been modified by the insertion of exogenous DNA (27). Using SOD1G93A animals showing the loss of small cutaneous fibers, similar to that which occurs in patients with ALS, it has been noted that immune and glial cells influence the pathophysiological state of motor neurons. Transgenic mice that selectively express SOD1 in their motor neurons do not have the disease or it occurs later (28). However, microglia and astrocytes in wild mice provide a protective function by opposing the disease.

Some authors have reported that the variation in the number of leukocytes in the blood can be correlated with the onset of ALS (29). Another hypothesis correlates onset with the inflammatory response mediated by some cytokines and their receptors (30). Immunological studies of the disease have shown a correlation with an increase in white blood cells in affected patients, although the levels of inflammatory cytokines do not appear to change compared to unaffected subjects (31,32).

In an interesting article, Ching-Hua Lu, et al. (31) reported that ALS patients showed a downregulation of interferon-gamma (IFN-γ) and a nonuniform upregulation of some inflammatory cytokines in peripheral blood. These upregulated cytokines included tumor necrosis factor (TNF), IL-1β, IL-2, and IL-8, amongst others. Regarding IL-6, the authors showed that this cytokine is elevated in the advanced stage of the disease and could represent a therapeutic target (31). Elevated levels of the neuroinflammatory molecule TNF may also be associated with the disease since this cytokine is involved in motor neuron damage. However, peripheral plasma analysis demonstrated that the cytokines IL-6, TNF, and IFN-γ were the most highly regulated markers (31). The authors concluded that ALS is related to the systemic regulation of inflammatory cytokines acting on T lymphocytes that regulate the immune response (31). Treg cells play an important protective role in the neurodegeneration that occurs in ALS and many different pathologies of the central nervous system, while TH-17 mediates the neuroinflammatory process.

CONCLUSIONS

To date, studies conducted on ALS have shown that the disease pathogenesis involving motor neuron death is complex, and that gene mutation and neuroinflammation certainly play a key role. The disease initially follows a slow course neuronal injury that is mediated by different mechanisms and counteracted by immune cells including M2 microglial cells and Treg cells. Later, when M1 microglial cells and TH1 and TH17 cells are activated, ALS worsens, and degeneration follows a faster course. The cause of this disease remains unknown, although the misfolded SOD1 protein, and other abnormal proteins and peptides, can activate immune cells which leads to the production of inflammatory molecules such as cytokines and other compounds which aggravate ALS.

Conflict of interest

The author declares that they have no conflict of interest.

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