



# The Role of Neuroinflammation and Impairment of the Blood-Spinal Cord Barrier in Pathogenesis of Amyotrophic Lateral Sclerosis

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## Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting motor neurons in the brain and spinal cord. As the disease progresses, paralysis and skeletal muscle atrophy develop, ultimately leading to fatal outcomes. Investigation of ALS pathogenetic mechanisms is crucial for developing effective treatment approaches. This literature review examines the role of neuroinflammation and blood-spinal cord barrier dysfunction in disease progression. Damaged neurons release proinflammatory cytokines as the pathology advances. Neuroinflammation in ALS develops through activation of the NF- $\kappa$ B pathway and cGAS/STING pathway, RNA metabolism dysregulation, microglial and astrocyte activation/proliferation, immune cell involvement, and other processes. Activated astrocytes and microglia increase blood-spinal cord barrier permeability. Neuroinflammation induces endothelial mitochondrial dysfunction, capillary diameter reduction, and progressive loss of perivascular components. The complex of proinflammatory reactions affecting central nervous system barriers accelerates ALS symptom progression. This review presents current data and analysis of pathogenetic mechanisms underlying neuroinflammation and blood-spinal cord barrier disruption in ALS.

**Keywords:** amyotrophic lateral sclerosis; neuroinflammation; blood-spinal cord barrier

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## Роль нейровоспаления и нарушения гематоспинального барьера в патогенезе бокового амиотрофического склероза

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## Аннотация

Боковой амиотрофический склероз (БАС) является нейродегенеративным заболеванием, поражающим двигательные нейроны головного и спинного мозга. По мере прогрессирования патологии развиваются параличи и атрофия скелетных мышц, что в итоге приводит к летальному исходу. Изучение патогенетических механизмов БАС необходимо для дальнейшей разработки эффективных методов лечения. В данном обзоре литературы рассматривается роль нейровоспаления и нарушения гематоспинального барьера в развитии заболевания. По мере прогрессирования патологии повреждённые нейроны начинают выделять провоспалительные цитокины. Развитие нейровоспаления при БАС обусловлено активацией пути ядерного фактора  $\kappa$ B и пути cGAS/STING, нарушением метаболизма

РНК, активацией и пролиферацией микроглии и астроцитов, участием иммунных клеток и другими процессами. Активированные астроциты и микроглия приводят к повышению проницаемости гематоспинального барьера. Нейровоспаление приводит к развитию эндотелиальной митохондриальной дисфункции, уменьшению диаметра капилляров и прогрессирующей потере периваскулярных компонентов. Комплекс провоспалительных реакций, влияющих на барьеры центральной нервной системы, стимулирует прогрессирование симптомов БАС. В данном обзоре литературы представлены актуальные сведения и анализ патогенетических механизмов, лежащих в основе развития нейровоспаления и нарушения гематоспинального барьера при БАС.

**Ключевые слова:** боковой амиотрофический склероз; нейровоспаление; гематоспинальный барьер

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## Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive loss of motor neurons, paralysis, and atrophy of skeletal muscles. In most cases, death occurs due to respiratory muscle paralysis within 3–5 years after diagnosis [1]. Given the high mortality rate and lack of effective treatments, ALS research remains critically important [2].

According to a 2013 analysis, ALS incidence rates are 2.8 per 100,000 population in Europe and 1.8 per 100,000 in North America [3]. Epidemiological data indicate a male predominance, with a male-to-female incidence ratio of 1.4:1. The average post-onset life expectancy, regardless of gender, typically ranges from 2–4 years [4]. ALS predominantly affects elderly individuals, though some cases occur in younger populations. While the average age of symptom onset in population studies is 65 years, there is a wide variability in age at presentation. Approximately 1% of ALS cases are diagnosed in individuals under 25 years old, and up to 10% of total cases occur in patients younger than 45 years [5].

ALS is characterized by paresis, paralysis, and atrophy of skeletal muscles, painful cramps, and fasciculations. In ALS, there is often significant variability in the degree of upper and lower motor neuron involvement and progression rates depending on clinical phenotypes. This phenotypic diversity may create the impression of distinct biological underpinnings, leading researchers to question whether ALS represents a single disease with a shared pathogenesis or multiple disorders with different mechanisms. A potential answer to this question may lie somewhere along this spectrum [6].

Approximately 90% of ALS cases lack a family history of the disease and are classified as sporadic ALS. About 10% of ALS cases represent familial forms, with most familial

ALS cases involving mutations in ALS-associated genes [7]. Around 70% of familial ALS cases are linked to mutations in the *SOD1* (superoxide dismutase 1 gene), *C9ORF72* (*C9ORF72* protein gene predominantly expressed in the central nervous and immune systems), *TARDBP* (TDP-43 DNA/RNA-binding protein gene), and *FUS* (*FUS* DNA/RNA-binding protein gene). Additional gene mutations have also been identified in ALS [8–13]. Notably, approximately 15% of sporadic ALS cases exhibit mutations in ALS-associated genes.

The primary pathological processes in ALS involve RNA metabolism and autophagy dysregulation, cytoskeletal defects, mitochondrial dysfunction, impaired DNA repair, and neuroinflammation [14, 15]. Neuroinflammation is known to play a significant role in blood-spinal cord barrier (BSCB) impairment in ALS. BSCB disruption occurs even at the presymptomatic disease stage, making its study crucial for understanding ALS pathogenesis [16]. This review will examine the relationship between neuroinflammation and BSCB dysfunction in ALS.

## Pathogenetic mechanisms of neuroinflammation in ALS

Genetic analysis in ALS patients has revealed numerous alterations, some of which contribute to the neuroinflammation. Affected individuals exhibit increased production of nuclear factor kappa B (NF-κB)-associated cytokines and activation of the interferon (IFN) signaling pathway [17]. The NF-κB signaling pathway is known to be associated with inflammatory processes [18]. Normally, optineurin (OPTN) regulates NF-κB activity, but its deficiency may lead to NF-κB translocation into the nucleus, triggering inflammatory responses [19].

The TDP-43 protein, encoded by the mutant *TARDBP* gene, can form abnormal protein aggregates in neurons. Under

physiological conditions, TDP-43 is primarily localized in the nucleus where it regulates RNA metabolism, but *TARDBP* gene mutations enhance TDP-43 aggregation propensity [20]. In ALS, microglia actively engulf cytoplasmic TDP-43 aggregates, a pathological feature observed in nearly all ALS cases [21]. This process involves the triggering receptor expressed on myeloid cells 2 (TREM2) [22]. Using motor neurons derived from induced pluripotent stem cells of *TARDBP*-mutant mice, researchers demonstrated that pharmacological inhibition and genetic deletion of stimulator of interferon genes (STING) protein can mitigate TDP-43-induced neurodegeneration by suppressing NF- $\kappa$ B and type I IFN inflammatory gene expression [23].

In addition to the *TARDBP* gene, several ALS-associated genes linked to proinflammatory activity through the cyclic GMP-AMP synthase (cGAS) – STING pathway have been identified. Recent studies suggest that STING activation mechanisms may induce neuroinflammation and degeneration of dopaminergic neurons [24]. The interaction of cytoplasmic DNA with cGAS leads to the production of cyclic GMP-AMP, which activates the STING protein and subsequently initiates TBK1 protein activation for phosphorylation of interferon regulatory factor 3 (IRF3) [25–27]. Researchers have also demonstrated that TDP-43 stimulates mitochondrial toxicity, causing mitochondrial DNA release into the cytoplasm and activation of the cGAS–STING pathway, ultimately triggering type I interferon signaling [23, 28].

*C9ORF72* regulates STING degradation through autophagy and lysosomal pathways. Blood and central nervous system (CNS) tissue analysis in ALS/frontotemporal dementia patients with *C9ORF72* mutations revealed elevated type I interferon levels that could be reduced through STING inhibition [29]. Furthermore, STING interacts with hnRNP A2B1, which translocates to the cytoplasm upon detection of pathogenic DNA and activates the TBK1-IRF3 pathway to induce interferon production. These findings highlight the critical role of the cGAS–STING pathway in ALS pathogenesis [30].

Dysregulation of RNA metabolism represents a significant pathological feature of ALS, as evidenced by mutations in *C9ORF72*, *TARDBP*, and *FUS* genes. These RNA-binding proteins can specifically recognize N<sup>6</sup>-methyladenosine (m<sup>6</sup>A), regulating mRNA stability, splicing, and translation through m<sup>6</sup>A modification recognition [31–34]. Studies in ALS demonstrate increased levels of methylated mRNA forms [35]. Preliminary observations indicate similar methylation pattern alterations in peripheral blood of ALS patients. Genes undergoing methylation during differentiation influence biological processes related to immune cell migration. Co-expression network analysis and single-cell profiling of primary motor cortex in ALS revealed that several key genes are associated with m<sup>6</sup>A RNA metabolism [36]. The m<sup>6</sup>A modification, prevalent in eukaryotic mRNAs, regulates multiple biological processes including mRNA splicing, export, translation, and degradation [37–44]. This process is controlled by specialized proteins termed m<sup>6</sup>A writers, erasers, and readers that modify, remove, and recognize this epigenetic mark [45–47]. For example, hnRNP A2B1 enhances TBK1-IRF3 signaling by blocking demethylation of CGA and STING transcripts, thereby promoting increased

IFN production [30]. This RNA modification plays a significant role in regulating various biological processes [48]. Additionally, m<sup>6</sup>A modification influences macrophage polarization by promoting M1 pro-inflammatory macrophage activation through NF- $\kappa$ B and SOCS pathways [49]. Overall, dysregulation of mRNA metabolism and immune system dysfunction appear to contribute to the pathophysiology of this disease [50]. Deficiency of METTL3 methyltransferase reduces NF- $\kappa$ B activity and TNF- $\alpha$  production in macrophages, suggesting a beneficial effect of m<sup>6</sup>A hypermethylation on M1 macrophage polarization [51, 52]. Other m<sup>6</sup>A methylation regulators, such as METTL14, ALKBH5, YTHDF1, and YTHDF2, also modulate type I IFN responses. These findings highlight the importance of m<sup>6</sup>A modification in the immune system, potentially relevant to ALS [53–55].

Emerging evidence underscores the critical role of CNS immune cells in ALS initiation and progression. Activation and proliferation of microglia and astrocytes are observed in the motor cortex of ALS patients and in mice model of TDP-43 pathology [56]. Transcriptomic analysis of postmortem spinal cord tissue from ALS patients revealed increased expression of microglia- and astrocyte-associated genes alongside decreased oligodendrocyte- and neuron-related genes, further emphasizing their role in ALS-associated neuroinflammation [57].

Microglia, constituting approximately 5% of glial cells in the CNS, act as macrophages within the nervous system [58, 59]. They can activate genes in response to any disturbances in homeostasis [59, 60]. Postmortem studies have demonstrated widespread microglial activation in ALS, and PET imaging has confirmed the association between microglial activation and disease progression [61–63].

In the early presymptomatic stages in *SOD1*-mutant mice, microglia exhibit increased activity of the anti-inflammatory cytokine interleukin-10. Studies have shown that blocking interleukin-10 significantly accelerates the onset of clinical symptoms of the disease [64]. Furthermore, reactive microglia have been found to selectively remove TDP-43 aggregates and promote motor function recovery in mouse models with reversible neuronal TDP-43 aggregation [65]. Under physiological conditions, microglia typically remove TDP-43 through phagocytosis; however, in its absence, nucleocytoplasmic redistribution of TDP-43 and neurodegeneration occur, as confirmed in zebrafish models [66].

As ALS symptoms progress, damaged neurons begin releasing proinflammatory cytokines, which promote microglial stimulation and activation of gene expression associated with neurodegeneration [67]. Studies demonstrate that mutant *SOD1* protein enhances the release of free radicals and proinflammatory cytokines through Toll-like receptors (TLRs) 2, TLR4, and CD14 [68, 69]. Both mutant *SOD1* and TDP-43 can activate inflammasomes in microglia, leading to increased interleukin-1 $\beta$  expression [69]. Recent research highlights the critical role of microglial activation in neuroinflammation characteristic of ALS. However, it remains unclear whether microglial activation causes accelerated neuronal loss or a compensatory response to neurodegeneration [70–72].

Astrocytes constitute approximately 20% of glial cells in the CNS and play a crucial role in maintaining the microenvironment by providing trophic support to neurons, modulating synaptic activity, and facilitating repair processes [62, 71, 72]. Similar to microglia, astrocytes can transition to a neurotoxic A1-like reactive phenotype under conditions of CNS homeostasis disruption [73]. Early stages of ALS show no confirmed neuroprotective function of astrocytes. There is stronger evidence for intracellular interactions between astrocytes and other CNS cells, which frequently leads to astrocyte polarization toward the neurotoxic A1 phenotype. Microglia activated through this process release proinflammatory cytokines that promote the neurotoxic state of astrocytes [74]. Suppression of specific gene expression responsible for producing proinflammatory factors may reduce adverse effects on astrocytes and increase survival in ALS models. Studies demonstrate that reducing mutant SOD1 expression in astrocytes decreases their neurotoxicity, evidenced by delayed microglial activation and slower disease progression in ALS models. Transplantation of wild-type astrocytes improves microglial status and prolongs survival in ALS mice, whereas transplantation of mutant astrocytes induces neuronal degeneration [75–77].

Astrocyte neurotoxicity is likely associated with the release of soluble factors such as TGF- $\beta$ 1 and energy metabolism impairments caused by *C9ORF72* mutations [78–80]. Astrocytes with restricted TDP-43 expression demonstrate reduced neurotrophic gene expression, while mutant TDP-43 causes deficient expression of glutamate transporter genes and induces neurotoxic lipocalin 2 in astrocytes [81, 82]. *C9ORF72*-mutated astrocytes show decreased production of antioxidant proteins and increased release of oxidative stress-associated soluble components [83–85]. Thus, astrocytes contribute to ALS pathogenesis through enhanced secretion of neurotoxic factors and reduced production of neurotrophic factors. Unlike microglia, astrocytes do not acquire a neuroprotective phenotype in early disease stages. Instead, pro-inflammatory astrocyte activation depends on interactions with other CNS cells, particularly microglia, via inflammatory mediator secretion [81, 86–89].

In ALS patients, monocytes tend to develop a pro-inflammatory M1 phenotype characterized by increased interleukin-6 and tumor necrosis factor- $\alpha$  expression [90]. One study investigated peripheral macrophage role by replacing them with mutant macrophages showing reduced responsiveness to neurotoxic reactive oxygen species. This intervention suppressed microglial activation, alleviated symptoms, and improved survival in SOD1G93A mice. Interestingly, despite limited CNS infiltration, peripheral macrophages profoundly influenced microglial activation within the CNS [91].

It was also found that changes in CD4<sup>+</sup> T cells from the peripheral blood of ALS patients are closely associated with disease progression as measured by ALSFRS-R scale [92]. Infiltrating CD4<sup>+</sup> T cells exert neuroprotective effects, prolonging survival in SOD1 mice through their influence on glial cells [93, 94]. In early stages, for example, increased Treg cell counts stimulate neuroprotective M2 microglia and suppress effector T cells [76]. However, as the disease progresses, pro-inflammatory Th1 cells and M1 microglia dominate due

to Treg cell dysfunction [75]. Treg cell counts and FoxP3 expression decrease with ALS progression. Preliminary Phase I data also confirm the correlation between Treg suppression activity and slower disease progression [95–98].

Studies report increased NK cell counts in ALS patients' blood, correlating with reduced mortality risk [92, 99]. Changes in NK cell markers related to migration and cytotoxicity affect ALSFRS-R scores depending on sex and age, while NK cell reduction enhances survival in ALS mouse models [100]. Inhibition of NK cell activation promotes neuronal protection from cytotoxicity. However, decreased MHC class I expression in motor neurons under the influence of mutant astrocytes or those derived from ALS patients stimulates NK cell-mediated neurotoxicity. CCL2-induced NK cell accumulation in the motor cortex and spinal cord promotes motor neuron degeneration and impairs Treg recruitment, indicating their neurotoxic role in ALS. Further studies are required to elucidate NK cell-associated neurotoxicity mechanisms in ALS [101–103].

### **Structural and functional characteristics of the blood-spinal cord barrier and mechanisms of its damage in amyotrophic lateral sclerosis**

The blood-spinal cord barrier (BSCB) is commonly considered an extension of the blood-brain barrier (BBB). Despite their similar ultrastructural organization, there are differences in their morphology and function. The BSCB is formed by endothelial cells of capillaries accompanied by a basal membrane, pericytes, and astrocytic end-feet. The endothelium of the BSCB is characterized by the absence of fenestrations, forming tight junctions between adjacent cells [104–107].

Tight junction proteins play a crucial role in forming diffusion barriers between endothelial cells. Among these, claudins, MARVEL proteins, and immunoglobulin family membrane proteins hold particular importance. Claudin-1, claudin-5, occludin, and ZO-1 (Zonula Occludens-1 protein) are key to maintaining barrier integrity. Low concentrations of occludin and ZO-1 are associated with increased BSCB permeability compared to the BBB. Alterations in tight junction protein expression are linked to barrier dysfunction and neuroinflammation. Compared to endothelia of other tissues, it exhibits low vesicle density and a significant number of mitochondria. The basal membrane consists of laminin, collagen IV isoforms, nidogens, and heparan sulfate proteoglycans forming a three-dimensional matrix maintained by endothelial cells and embedded pericytes [108–111].

Pericytes enveloping small capillaries play a crucial role in maintaining BBB integrity. They regulate endothelial cell proliferation, migration, and differentiation by forming tight junctions and controlling soluble factor secretion. Moreover, pericytes actively interact with tight junction proteins, reducing macromolecule penetration and preserving BBB integrity. Pericytes constitute a heterogeneous cell population with no single identifying marker, though aminopeptidase-N (CD13) and platelet-derived growth factor are among the most recognized markers [112–115].

Astrocytes surround the endothelium, contributing to basal lamina formation, and ensheath neuronal synapses to establish neurovascular coupling. This structure enables neurohumoral blood flow regulation by controlling nutrient supply, energy reserves, metabolite clearance, and toxin removal within the neurovascular unit. These cells also play vital roles in neuroprotective mechanisms and demonstrate high activity in aquaporin-4 and potassium channel expression. These molecules regulate potassium ion conductance during resting state and control cerebrospinal fluid volume [116–118].

The spinal cord perivascular space connects with the subarachnoid space. At capillary levels, the endothelial basal lamina directly contacts the glial sheath. During inflammation, the basal lamina may split into two layers, forming a temporary perivascular space that facilitates leukocyte infiltration.

The permeability of the BBB and BSCB is predominantly governed by two factors: endothelial cell integrity (dependent on mitochondrial activity) and local regulatory molecules like angiogenic/anti-angiogenic polypeptides [119, 120].

Recent studies confirm that peripheral immune cells infiltrate the CNS in ALS, interacting with glial cells [121–123]. Physiological immune cell migration into CNS parenchyma is tightly regulated by CNS barriers. *SOD1* mutations induce endothelial damage, compromising BBB/BSCB integrity and triggering ALS neuroinflammation [124, 125]. *SOD1* transgenic models show vacuolated endothelial cells with mitochondrial cristae abnormalities and degenerative processes [126]. ALS patients exhibit pericyte degeneration in the medulla oblongata and spinal cord [127].

Immune cell-BSCB interactions (e.g., microglia/astrocytes) are central to ALS pathology. Astrocytic end-foot detachment from spinal endothelium correlates with BSCB dysfunction in ALS [128]. *SOD1* mice display astrocyte/endothelial mitochondrial dysfunction [116]. Activated astrocytes drive neuroinflammation in ALS [129]. Astroglial scars exhibit dual roles during disease progression. Initially, reactive astrocytes perform a protective function for the BSCB and BBB [130]. However, upon interleukin-1 $\beta$  release by activated microglia, astrocytes lose their protective properties towards CNS barriers. This occurs through suppression of astrocytic SHH protein production, which is essential for maintaining CNS barrier permeability. Additionally, reduced expression of TJ protein in endothelial cells contributes to increased barrier permeability. Interleukin-1 $\beta$  induces astrocytic release of pro-inflammatory chemokines including CXCL2, CCL2, and CCL20, which exacerbate BSCB/BBB dysfunction and neuroinflammation [131]. Based on these findings, it can be concluded that astrocytic pathology may also contribute to BSCB and BBB dysfunction observed in ALS.

It is worth mentioning the role of matrix metalloproteinases (MMPs), normally produced by glial cells, in remodeling and maintaining the integrity of CNS barrier basement membranes, as well as regulating cytokine and chemokine activity [132]. In ALS, due to inflammation, production of MMP-2 and MMP-9 increases. These changes are associated with endothelial mitochondrial dysfunction, reduced capillary diameter, and progressive loss of perivascular components including occludin and collagen IV, which enhances BSCB and BBB permeability [133].

In mice with TDP-43 overexpression, increased BBB permeability was revealed, making the frontal cortex vulnerable to systemic inflammatory response induced by lipopolysaccharide administration [134]. However, a study in ALS patients established that increased BSCB permeability and TDP-43 deposition are independent pathological processes in ALS [135].

The review by A. Mirian et al. points to evidence that BSCB integrity is impaired in animal models of ALS from presymptomatic stages to pronounced neurodegeneration; BSCB abnormalities have also been found in postmortem studies of ALS patients [136]. Several studies have demonstrated that therapeutic approaches potentially capable of restoring BSCB improve the condition of animals with ALS models [136, 137]. The review by Y. Pan et al. notes that BBB and BSCB impairments in ALS patients may modulate the effectiveness of agents intended to reach the CNS and influence the toxicity of medications that should not enter the CNS [138].

Thus, BSCB and BBB disruption in ALS depends on numerous factors. This process represents a complex network of interactions that requires further study to determine precise mechanisms and develop effective treatments.

## Conclusion

Modern research places significant emphasis on the neuroinflammation in BBB damage, which represents a key aspect in the pathogenesis of various neurological diseases. Neuroinflammation plays a critical role in disrupting BBB integrity and functionality. A crucial factor in this process is mitochondrial damage within BBB structures, leading to endothelial cell dysfunction and increased barrier permeability. Microglia and astrocyte activation accompanying neuroinflammatory responses results in the release of pro-inflammatory cytokines that further potentiate inflammatory processes in the BBB. This complex mechanism contributes to progressive deterioration of barrier integrity and increased permeability, associated with the progression of neurological pathologies such as ALS. This review presented current findings on key cellular-molecular mechanisms underlying neuroinflammation and BBB disruption in ALS. Comprehensive analysis of these processes enhances our understanding of ALS pathogenesis.

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