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The Role of Intestinal Microbiota in the Pathogenesis of Amyotrophic Lateral Sclerosis

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Abstract In recent years, increasing attention has been paid to the role of intestinal microbiota in the pathogenesis of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). The purpose of this work is to analyze modern data on the interaction of microbiota with the central nervous system through the "intestine–brain" axis and to assess its potential participation in the development of ASD. The physiological mechanisms for regulating neural inflammation, barrier function, and metabolic activity of the microbiota, as well as their potential influence on the survival of motor neurons, were considered. A review of preclinical and clinical studies confirming the link between dysbiotic changes in microflora and clinical manifestations of ALS was conducted. Particular attention was paid to microbiota metabolites (butyrate, nicotinamide, propionate) and their neuroprotective effects. The prospects of using probiotics, prebiotics, postbiotics, and fecal transplantation as supplementary therapy for ALS are being discussed. The work's conclusions emphasize the importance of further research on microbiota as a potential therapeutic target in the treatment of neurodegenerative diseases.

Keywords Intestinal microbiota, Pathogenesis, Amyotrophic lateral sclerosis (ALS), Neurodegenerative diseases, Central nervous system, Intestinal–brain axis, Neural inflammation, Barrier function, Metabolic activity, Potential influence, Neuroprotective effects, Probiotics, Dysbiotic changes, Potential therapeutic target, Clinical manifestations

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the selective degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord, leading to the loss of motor function, muscle atrophy, and ultimately, death. Despite extensive research into the etiopathogenesis of ALS, the exact mechanisms underlying the development of the disease remain unclear. Currently, ALS is believed to have a multifactorial nature, with genetic mutations, exogenous factors, and immune–inflammatory processes playing key roles.

In recent years, there has been growing interest in the role of the gut microbiota in regulating systemic inflammation, metabolism, central nervous system function, and neurodegeneration. Given the emerging evidence of the interaction between the gut microbiota and the brain, a new paradigm is forming within the scientific community, in which dysbiotic changes in the microbiome are considered a potential factor in the development of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and possibly ALS [1,2,3,4].

This study explores the hypothesis that the gut microbiota is involved in the pathogenesis of ALS, with a focus on the "gut–brain axis" as a key mechanism through which the microbiota may modulate inflammatory, metabolic, and neurotoxic processes underlying the disease.

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2. Results

Microbiota and the Brain: The Gut–Brain Axis. The gut microbiota is a highly organized ecosystem composed of trillions of microorganisms, including bacteria, archaea, viruses, and fungi. Under normal conditions, the microbiota performs a number of vital functions: it aids in digestion, synthesizes vitamins (particularly B vitamins and vitamin K), regulates immune responses, and maintains the integrity of the intestinal epithelium. In recent years, it has been established that the microbiota also plays an important role in maintaining central nervous system homeostasis, forming what is known as the "gut–brain axis".

The gut–brain axis is a bidirectional signaling system linking the gastrointestinal tract and the central nervous system via neuronal, humoral, immune, and metabolic pathways. Key components of this axis include: the vagus nerve, which provides direct neuronal communication between the gut and the brain; short–chain fatty acids (SCFA), such as butyrate, acetate, and propionate, synthesized by bacteria and affecting blood–brain barrier permeability, neuronal gene expression, and microglial activity; cytokines and chemokines, which

modulate systemic and neuronal inflammatory responses; microbial metabolites and neurotransmitters, such as γ–aminobutyric acid (GABA), serotonin, and dopamine, which can be synthesized in the gut and indirectly affect brain activity.

Dysbiosis, a disorder of the composition and function of the intestinal microbiota, can lead to disturbances in this axis and cause pathological activation of microglia, destruction of the blood–brain barrier, and increased systemic inflammation, which in turn can contribute to neurodegeneration.

In the context of ALS, it is suggested that dysbiosis can act as a trigger or modifier of the disease, increasing neuroinflammatory and metabolic disorders. Experimental data in animal models of ALS confirm that changes in the intestinal microbial composition affect the rate of disease progression, motor functions, and life expectancy. These observations open up prospects for studying the microbiota as a potential therapeutic target in ALS.

Current scientific research confirming the involvement of the intestinal microbiota in the pathogenesis of amyotrophic lateral sclerosis. In recent years, the intestinal microbiota has been increasingly considered as an important factor in the pathogenesis of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). A growing body of preclinical and clinical research supports the link between microbiome disruption and ALS progression, revealing possible mechanisms through metabolites, inflammatory cascades, and compromised intestinal barrier integrity.

Microbiota is as a modifier of the ALS phenotype. According to a review by Boddy et al., the microbiota may act as an "environmental modifier" that explains the phenotypic diversity of ALS even in patients with identical genetic mutations. Changes in the composition of the microbiome influence systemic inflammation, blood–brain barrier permeability, and the metabolism of neuroactive compounds such as short–chain fatty acids (SCFA) and nicotinamide. Through the gut–brain axis, these molecules can exert both neuroprotective and neurotoxic effects on motor neurons.

The role of nicotinamide and specific microbes: data from Blacher et al. In an experimental study by Blacher et al. (2019) on SOD1^G93A mice, the ability of certain microbiota strains to modulate the course of ALS was demonstrated. Administration of Akkermansia muciniphila alleviated symptoms by increasing nicotinamide levels in the central nervous system, while Parabacteroides distasonis and Ruminococcus torques aggravated the clinical picture. Additional administration of nicotinamide improved motor functions and slowed down neurodegeneration. Reduced plasma and cerebrospinal fluid nicotinamide levels were also detected in ALS patients, confirming the cross–validity of these findings.

Butyrate–forming bacteria and barrier function. A systematic review by Wright et al. found that ALS patients and disease models have a decreased number of butyrate–forming bacteria, which is associated with impaired intestinal epithelial integrity. Butyrate plays an important role in maintaining barrier function and modulating the immune response. Introduction of butyrates into the diet of experimental animals led to improved motor function and prolongation of lifespan, indicating an important pathophysiological role of these microbial metabolites. Probiotic therapy: preliminary clinical data. A pilot clinical trial conducted by the Russian biotechnology company Propionix confirmed the potential of microbiome–targeted therapy in ALS. Patients treated with a probiotic based on propionibacterium freudenreichii subsp. shermanii demonstrated stabilization of motor functions, reduction of inflammatory markers and improvement of general well–being after 12 weeks of therapy. Despite the limited sample, this study highlights the therapeutic potential of microbiota intervention.

Systematic review summary. Sun et al. conducted a systematic review, combining the results of both preclinical and clinical studies. The authors highlight the robust evidence for the role of microbiota in ALS models, where probiotic and prebiotic interventions demonstrate improvement in behavioral and histopathological parameters. However, human data remain fragmentary and require standardized multicenter studies with long–term follow–up.

Analysis of modern studies allows us to conclude that the intestinal microbiota plays a significant role in modulating the pathogenesis of ALS. A decrease in the level of butyrate–forming bacteria, changes in the level of neuroactive metabolites (in particular, nicotinamide), disruption of the barrier function and local inflammation form a pathological environment that promotes neurodegeneration. These data not only deepen the understanding of ALS mechanisms, but also open up prospects for the development of microbiome–oriented therapeutic approaches.

Possible mechanisms of the influence of intestinal microbiota on the pathogenesis of ALS and prospects for therapy. Modern studies increasingly demonstrate that changes in the composition and functional activity of the intestinal microbiota can contribute to the development and progression of amyotrophic lateral sclerosis (ALS). Below, we consider the key putative mechanisms of interaction between the microbiota and the nervous system in the context of ALS, as well as possible therapeutic strategies aimed at modulating the microbiome.

Impaired intestinal barrier function and systemic inflammation. One of the early manifestations of dysbiosis in ALS, described in both preclinical and clinical studies, is increased intestinal permeability. Animal models of ALS show destabilization of tight junctions and disruption of the epithelial layer, which facilitates the penetration of bacterial products (e.g., lipopolysaccharides, LPS) into the systemic circulation. This leads to activation of the innate immune response, systemic inflammation, and increased neuroinflammation via activation of microglia and astrocytes.

Microbial metabolites and neuromodulation. Some bacterial metabolites can have a direct or indirect effect on the central nervous system:

Butyrate and other short–chain fatty acids (SCFA) have anti–inflammatory effects, modulate gene expression, maintain the integrity of the BBB (blood-brain barrier), and

help regulate microglia. ALS is characterized by a deficiency of butyrate–forming bacteria, which is associated with impaired barrier function and disease progression.

Nicotinamide (vitamin B3), synthesized by certain representatives of the microbiota, in particular Akkermansia muciniphila, has a neuroprotective effect. An increase in its concentration is associated with an improvement in motor functions in mice with an ALS model.

Propionic and lactic acids, as well as tryptophan metabolites, can affect the regulation of neurotransmitters (including serotonin and GABA) and immune signaling pathways.

Attenuation of neuroinflammation and glial activation. Imbalances in the composition of the microbiota can contribute to chronic activation of microglia and astrocytes, increasing the production of proinflammatory cytokines (IL–1β, TNF–α, IL–6). Some probiotic strains (e.g., Lactobacillus rhamnosus, Bifidobacterium longum) are able to reduce the levels of these mediators. The introduction of probiotics in preclinical models of ALS was accompanied by a decrease in the expression of genes responsible for inflammation and neuronal death.

Potential therapeutic pathways targeting the microbiota. Based on the identified mechanisms, the following therapeutic approaches have been proposed:

Probiotics are live microorganisms that can have a beneficial effect on the microbial composition. The studies using Propionibacterium freudenreichii, A. muciniphila, Lactobacillus spp. have shown improvement in clinical parameters in animals and patients with ALS;

Prebiotics are dietary substrates (e.g., inulin, β–glucans) that stimulate the growth of beneficial bacteria, such as butyrate–forming species;

Postbiotics and metabiotics are biologically active bacterial metabolites (e.g., butyrate, nicotinamide) that can be used without introducing the microorganisms themselves.

Fecal Microbiota Transplantation (FMT) is a method aimed at rapidly restoring a healthy microbial balance. In early–stage trials involving ALS patients, it has shown promising results but requires further validation and standardization [1,2,3,4].

Dietary therapy–a diet rich in fiber and fermentable carbohydrates–promotes the growth of beneficial microbiota and increases the production of SCFAs.

Problems and prospects: Despite encouraging preclinical data, the implementation of microbiome–oriented therapy in clinical practice for ALS faces a number of challenges: significant individual variability of the microbiome in patients; lack of standardized diagnostic and intervention protocols; a limited number of well–designed randomized clinical trials; difficulty in long–term monitoring and evaluation of therapy effectiveness.

Nevertheless, microbiota remains one of the most promising targets for the development of personalized therapy for ALS, combining both preventive and therapeutic strategies. Available data allow us to consider the intestinal microbiota as an active participant in the pathogenesis of ALS, capable of influencing the immune response, neuroinflammation, metabolism, and the integrity of physiological barriers. The development of therapeutic approaches aimed at restoring microbial homeostasis may become an important addition to existing ALS treatments. Prospects in this area include both the use of probiotics and postbiotics, and the development of personalized microbiome interventions based on the analysis of the composition of the microflora of a particular patient.

3. Discussion

The present review highlights the growing recognition of the gut microbiota as an active participant in the pathophysiology of amyotrophic lateral sclerosis (ALS). The findings from recent studies collectively suggest that the intestinal microbiome, through its metabolic, immune, and neuroendocrine functions, plays a significant role in modulating neurodegenerative processes traditionally attributed solely to genetic and molecular factors.

Dysbiosis, or disruption in the balance and composition of the intestinal microbiota, appears to be one of the earliest systemic alterations in ALS, potentially preceding the onset of neurological symptoms. The observed reduction in butyrate-forming bacteria and Akkermansia muciniphila, together with increased intestinal permeability, indicates a disturbed gut–brain homeostasis that facilitates neuroinflammation and neuronal death. This aligns with animal model data showing that restoration of the intestinal barrier by dietary supplementation with short-chain fatty acids (SCFAs) improves motor neuron survival and motor performance [5,6,7,8].

An important finding emerging from the reviewed evidence is the dual role of microbial metabolites in either aggravating or mitigating ALS pathology. While some metabolites—such as lipopolysaccharides and ammonia—promote systemic inflammation, others, including butyrate, propionate, and nicotinamide, demonstrate strong neuroprotective properties. The modulation of nicotinamide levels by Akkermansia muciniphila, shown by Blacher et al., suggests that microbiota -derived compounds can directly influence neuronal metabolism and survival. These results also support the notion that targeted modulation of specific microbial taxa could alter the disease trajectory.

Nevertheless, the translation of preclinical evidence into clinical application remains a major challenge. Human studies are limited in number, heterogeneous in design, and often underpowered to detect significant clinical outcomes. The variability of the gut microbiome across individuals and populations further complicates the identification of universal therapeutic strategies. Moreover, the absence of standardized microbiome-based diagnostic markers prevents clear patient stratification and comparison across studies.

Despite these limitations, several pilot clinical trials have provided encouraging data on microbiota-directed therapies, including the use of probiotics containing Propionibacterium freudenreichii and Lactobacillus species. Patients receiving such interventions demonstrated improvements in inflammatory markers and stabilization of motor symptoms. Although

preliminary, these results support the feasibility of microbiome modulation as an adjunctive approach in ALS management.

Another crucial implication of current research is the potential of personalized microbiome-based medicine. Given the high inter-individual diversity of microbial communities, the effectiveness of probiotics, prebiotics, and postbiotics likely depends on baseline microbial composition, genetic predisposition, and environmental exposures. Integration of metagenomic, metabolomic, and clinical data could pave the way for tailored interventions aimed at restoring microbial equilibrium in specific patient subgroups.

In a broader context, the gut microbiota represents not only a biomarker of systemic health but also a dynamic regulator of neuroimmune interactions. Its ability to influence the integrity of the intestinal and blood–brain barriers, cytokine signaling, and neurotransmitter synthesis underlines its central role in maintaining central nervous system homeostasis. Therefore, maintaining microbial diversity and stability through dietary and lifestyle measures may have preventive as well as therapeutic significance in ALS and other neurodegenerative diseases.

In conclusion, while the causal relationship between gut dysbiosis and ALS progression has not yet been definitively established, existing data strongly support its modulatory influence on neuroinflammation, metabolic dysfunction, and neuronal survival. Future research should focus on large-scale, multicenter clinical trials with longitudinal microbiome monitoring, standardized methodologies, and mechanistic endpoints. Such studies will be essential for validating microbiota-targeted interventions as a novel and promising component of comprehensive ALS therapy.

4. Conclusions

Amyotrophic lateral sclerosis (ALS) remains one of the most severe and incurable neurodegenerative diseases characterized by progressive death of motor neurons and gradual loss of motor functions. Despite the active study of the genetic and molecular mechanisms of ALS, the etiopathogenesis of the disease remains poorly understood, and therapeutic approaches are limited. In this regard, in recent years, special attention has been paid to the role of intestinal microbiota as a potential participant and modifier of the course of ALS.

The intestinal microbiota is a highly organized ecosystem closely connected with the central nervous system through a complex network of neuroendocrine, immune and metabolic interactions–the so–called “gut–brain” axis. Disturbances in the composition of the microbiota, or dysbiosis, can contribute to disruption of the intestinal barrier function, increased systemic and neuroinflammation, changes in the level of microbial metabolites (butyrate, nicotinamide, propionate, etc.), as well as an imbalance of neurotransmitters. All these processes are potentially involved in the pathogenesis of ALS. Modern preclinical studies have demonstrated that microbiome intervention–the introduction of probiotics, metabolites, dietary changes–can favorably affect the course of ALS in animal models. The level of neuroinflammation decreased, motor function improved, and life expectancy increased. At the clinical level, data are still limited, but individual pilot studies (including the use of probiotics based on propionic acid bacteria) show promising results: stabilization of patients’ condition, reduction of inflammatory markers and improvement of quality of life.

The role of microbiota in the regulation of CNS homeostasis through several pathways has been mechanistically proven: (1) modulation of the immune response, (2) maintenance of the integrity of the intestinal and blood–brain barriers, (3) production of biologically active molecules involved in neuroprotection. Particular importance is attached to the ability of individual bacterial strains, such as Akkermansia muciniphila and butyrate–forming bacteria (Faecalibacterium prausnitzii, Roseburia spp.), to exert a protective effect on motor neurons. Thus, accumulated data indicate that the intestinal microbiota not only reflects, but also actively modulates the pathological process in ALS. This opens up broad prospects for the development of new pathogenetically substantiated therapeutic strategies. Microbiome–directed interventions can become both an additional and potentially independent element of personalized treatment [6,7,8,9,10].

However, to move from preclinical models to clinical practice, large–scale multicenter randomized studies with clearly standardized methodologies, long–term follow–up, and inclusion of microbiota biomarkers are needed. Only then will it be possible to reliably evaluate the efficacy and safety of microbiome therapy in ALS and integrate it into modern clinical guidelines.

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Authors’ Contribution

Muborak Abdullaeva conceptualized the study, conducted the literature review, and prepared the theoretical framework regarding the gut–brain axis and neurodegenerative mechanisms. She also supervised the overall research process and finalized the manuscript.

Muzaffar Abdunazarov contributed to the clinical interpretation of neurological data, analyzed relevant studies on amyotrophic lateral sclerosis (ALS), and participated in drafting and revising the sections on microbiota–based therapeutic perspectives.

Both authors discussed the results, critically reviewed the final text, and approved the manuscript for submission.

Conflicts of Interest

The authors declare that they have no known financial or personal conflicts of interest that could have appeared to influence the work reported in this paper. The research was conducted independently, without any commercial or institutional bias.

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