Intestinal dysbiosis as a modulatory factor in Amyotrophic Lateral Sclerosis (ALS)

Disbiose intestinal como fator modulador para Esclerose Lateral Amiotrófica (ELA)

Disbiosis intestinal como factor modulador en la Esclerosis Lateral Amiotrófica (ELA)

Lara Di Almeida Melo[1], Camila Machado Rizzos[2], Filipe Moreira Gomides Sardinha Carvalhedo [3], Gustavo Henrique Lopes[4], Gustavo Henrique de Oliveira Carmo Borges[5], Renata Vitorino Borges[6]

How to cite: Melo LA, Rizzos CM, Carvalho FMGS, Lopes GH, Borges GHOC, Borges RV. Intestinal dysbiosis as a modulatory factor in Amyotrophic Lateral Sclerosis (ALS). REVISA. 2026; 15 (Esp. 2): 42-47. Doi: https://doi.org/10.36239/revisa.v15 Esp.2:.p 42 a 47.

REVISA

1. Universidade Evangélica de Goiás, UniEVANGÉLICA – Anápolis, GO. https://orcid.org/0009-0003-0772-3041

2. Universidade Evangélica de Goiás, UniEVANGÉLICA – Anápolis, GO. https://orcid.org/0009-0004-6283-7620

3. Universidade Evangélica de Goiás, UniEVANGÉLICA – Anápolis, GO. https://orcid.org/0009-0004-5749-6796

4. Universidade Evangélica de Goiás, UniEVANGÉLICA – Anápolis, GO. https://orcid.org/0009-0007-4448-4595

5. Universidade Evangélica de Goiás, UniEVANGÉLICA – Anápolis, GO https://orcid.org/0009-0004-2667-860X

6. Universidade Federal de Jataí, GO. https://orcid.org/0000-0001-6724-1536

Recebido: 10/04/2026
Aprovado: 01/06/2026

RESUMO

Objetivo: A Esclerose Lateral Amiotrófica (ELA) é uma doença neurodegenerativa progressiva que afeta neurônios motores superiores e inferiores, levando à fraqueza muscular, disfagia e atrofia progressiva. Evidências recentes apontam a disbiose intestinal como potencial moduladora da evolução da doença, por meio da alteração do eixo intestino-cérebro. Foram utilizadas as plataformas de dados PubMed e LILACS, com os descritores Decs: "Dysbiosis", "Amyotrophic Lateral Sclerosis" e "Gastrointestinal Microbiome". A redução de bactérias benéficas, como *Butyrivibrio fibrisolvens* e *Firmicutes*, diminui a produção de metabólitos neuroprotetores, como o butirato, e vitaminas essenciais, como a B12, impactando a neuroinflamação, a excitotoxicidade glutamatérgica e a integridade da bainha de mielina. Estratégias terapêuticas estudadas incluem probióticos, suplementação com metilcobalamina, dietas específicas e transplante de microbiota fecal, visando restaurar a diversidade microbiana e reduzir a progressão da doença. Embora promissoras, tais intervenções ainda carecem de ensaios clínicos robustos para validação e padronização.

Descritores: Disbiose; Esclerose Lateral Amiotrófica; Microbiota Gastrointestinal

ABSTRACT

Objective: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder affecting upper and lower motor neurons, leading to muscle weakness, dysphagia, and progressive atrophy. Recent evidence highlights intestinal dysbiosis as a potential modulator of disease progression through alterations in the gut-brain axis. The PubMed and LILACS databases were used, with the DeCS descriptors: "Dysbiosis," "Amyotrophic Lateral Sclerosis," and "Gastrointestinal Microbiome". The reduction of beneficial bacteria, such as *Butyrivibrio fibrisolvens* and *Firmicutes*, decreases the production of neuroprotective metabolites like butyrate and essential vitamins, such as B12, impacting neuroinflammation, glutamatergic excitotoxicity, and myelin sheath integrity. Therapeutic strategies under investigation include probiotics, methylcobalamin supplementation, specific diets, and fecal microbiota transplantation, aiming to restore microbial diversity and slow disease progression. Although promising, these interventions still require robust clinical trials for validation and standardization.

Keywords: Dysbiosis; Amyotrophic Lateral Sclerosis; Gastrointestinal Microbiome.

RESUMEN

Objetivo: La Esclerosis Lateral Amiotrófica (ELA) es una enfermedad neurodegenerativa progresiva que afecta a las neuronas motoras superiores e inferiores, causando debilidad muscular, disfagia y atrofia progresiva. Evidencias recientes señalan la disbiosis intestinal como posible moduladora de la progresión de la enfermedad mediante la alteración del eje intestino-cerebro. Se utilizaron las bases de datos PubMed y LILACS, con los descriptores DeCS: "Dysbiosis", "Amyotrophic Lateral Sclerosis" y "Gastrointestinal Microbiome".La reducción de bacterias beneficiosas, como *Butyrivibrio fibrisolvens* y *Firmicutes*, disminuye la producción de metabolitos neuroprotectores, como el butirato, y vitaminas esenciales, como la B12, afectando la neuroinflamación, la excitotoxicidad glutamatérgica y la integridad de la vaina de mielina. Las estrategias terapéuticas en estudio incluyen probióticos, suplementación con metilcobalamina, dietas específicas y trasplante de microbiota fecal, con el objetivo de restaurar la diversidad microbiana y frenar la progresión de la enfermedad. Sin embargo, estas intervenciones aún requieren ensayos clínicos robustos para su validación y estandarización

Descriptores: Disbiosis intestinal; Esclerosis lateral amiotrófica; Microbiota intestinal

REVISÃO

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a multifactorial and neurodegenerative disease that affects upper and lower motor neurons, in a progressive and fatal manner. The disease is considered rare, with an incidence of three cases per thousand inhabitants, and although there are described genetic cases, the majority are sporadic and idiopathic. Its clinical presentation depends on the predominance of involvement (upper or lower motor neuron), but 90% of reports are of mixed symptoms—weakness, spasticity, reduced muscle tone, and fasciculations. Bulbar changes, such as dysphagia, dysarthria, and tongue fasciculations, are also frequently observed, especially in cases with a predominance of upper motor neuron compromise.[1-2]

The prognosis of ALS remains guarded, with an average course and survival of two to five years after diagnosis. Currently, therapeutic management is based on multidisciplinary care and the use of only two drugs—riluzole and edaravone. Riluzole was the first drug approved, with the effect of reducing glutamatergic transmission, slowing the rapid progression of neuronal degeneration. And edaravone acts as an antioxidant, delaying the progression of neurodegeneration in highly selected patients.[1]

In recent years, the gut microbiota has gained prominence in the scientific scenario due to its close relationship with the gut-brain axis, a bidirectional communication system between the gastrointestinal tract, the enteric nervous system, the autonomic nervous system, and the central nervous system. Thus, it is known that the gastrointestinal tract is responsible not only for food processing but also for immune regulation and the production of metabolites that modulate brain function.[2]

The vagus nerve plays a crucial role in this communication, interacting directly with the microbiota and transmitting to the central nervous system the excitatory and inhibitory neurotransmitters produced by bacteria. Examples include *Escherichia ssp.* and *Bacillus ssp.* producing norepinephrine; *Staphylococcus ssp.*, dopamine; and *Lactobacillus ssp.*, gamma-aminobutyric acid (GABA). Bacteria can also produce harmful molecules, resulting in intestinal inflammatory activity, which can cross the blood-brain barrier, activate neuroinflammatory responses, and potentially contribute to neuronal degeneration.[2]

Given this, recent investigations have pointed out that changes in the microbial profile can trigger systemic inflammatory processes and neurochemical alterations that impact the gut-brain axis, potentially influencing the course of the disease.

Objective

In this sense, the article aims to understand this relationship in order to improve therapeutics and offer a more promising perspective to patients with ALS.

Material and Methods

This is an integrative literature review, of a descriptive and qualitative nature, elaborated from the bibliographic survey on the relationship between intestinal dysbiosis and Amyotrophic Lateral Sclerosis (ALS). The Public Medicine (PubMed) and Latin American and Caribbean Health Sciences Literature (LILACS) databases were used, with the DeCS descriptors: "Dysbiosis," "Amyotrophic Lateral Sclerosis," and "Gastrointestinal Microbiome." Among the 19 articles found, 5 works were selected to compose this study.

The inclusion criteria are: articles published between 2022 and 2025, available in full, in Portuguese and English, that directly address the proposed theme. Those that did not directly address the theme, paid works, duplicates, works in a language other than Portuguese and English, and published before 2022 were excluded.

Results

All analyzed articles described the clinical and physiopathological aspects of ALS, reaffirming it as a motor neurodegenerative disease, with progressive neuron death and skeletal muscle atrophy, beginning in adulthood, presenting, associated with motor symptoms, gastrointestinal dysfunctions—gastroparesis, constipation, sialorrhea, and dysphagia. [3,4]

The genetic aspects of ALS, although less frequent, were also described, highlighting the most prevalent genes and mutations. Among them are the *SOD1* gene, the first to be related to the disease and with a predominant clinical picture of lower limb injury, mutations in *TDP-43* with 4–5% of familial cases, being responsible for the loss of nuclear function and toxic gain in the cytoplasm; and changes in the *FUS* gene, identified in juvenile and early-onset ALS.[3]

Regarding the gut-brain axis, alterations in the gut microbiota were addressed as possible potentiators of ALS symptoms and progression. The reduction of beneficial bacteria, including *Butyrivibrio fibrisolvens*, *Firmicutes peptostreptococcus*, and *Escherichia coli*, demonstrated, along with the reduction of metabolites, tryptophan, serotonin, dopamine, and butyrate, which participate in neuromodulation. The predominance of the *Bacteroidetes* and *Firmicutes* phyla was also observed, associated with shorter survival, increased homocysteine, and neuroclinical dysfunction. These two phyla establish an F/B ratio—the ratio between the quantity of *Firmicutes* and *Bacteroidetes*—capable of preceding and informing the clinical subtype: an increased F/B ratio predicts spinal-onset ALS and a decreased F/B ratio, bulbar onset.[4,5]

The main metabolite related to neuroprotection that was described as reduced or absent in patients with dysbiosis is butyrate. A short-chain fatty acid (SCFA) with anti-inflammatory effects, it modulates G protein-coupled receptors, acts in T cell differentiation, and in mitochondrial respiration. Furthermore, the alteration of the microbiota was described as impacting the prognosis of the disease due to the synthesis of essential vitamins, such as B12, which is part of the myelin sheath formation process. [6]

Therapeutic forms to improve the prognosis of ALS were also indicated in the studies, despite presenting limitations due to the absence of clinical trials. Probiotics were seen to increase the amount of butyrate and improve the intestinal

barrier; methylcobalamin (vitamin B12) demonstrated to modulate neuroprotection, inflammation, and *SOD1* gene expression; and diets were described with risk and protective factors. Red meats, processed foods, fat, and glutamate as risk factors, while coffee, tea, bread, and raw vegetables as protective factors.[6,7]

Finally, the study on fecal microbiota transplantation has a clinical trial underway, in which it is believed that the transfer of healthy microbiota to an individual with dysbiosis would correct microbial imbalances.

Discussion

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by the degeneration of motor neurons and muscle atrophy, whose pathophysiology involves multiple mechanisms, including glutamate excitotoxicity, mitochondrial dysfunction, neuroinflammation, and changes in the gut microbiota. In recent years, evidence has suggested that the gut-brain axis exerts a direct influence on modulating the progression of ALS, opening space for potential therapeutic approaches.[1,2,4]

Butyrate, identified as reduced or absent in patients with dysbiosis, was pointed out as one of the most relevant metabolites for neuroprotection. This SCFA presents anti-inflammatory properties, modulates G protein-coupled receptors, regulates T cell differentiation, and optimizes mitochondrial respiration. Its deficiency contributes to immunological dysregulation, increased intestinal permeability, and systemic inflammation, factors that potentiate glutamate excitotoxicity, one of the central mechanisms of ALS pathophysiology. Additionally, the alteration of the gut microbiota was associated with impaired synthesis of vitamin B12, essential for myelin sheath integrity and, consequently, for maintaining adequate neuronal conduction.[3,6,7]

Furthermore, according to the authors, intestinal dysbiosis alters tryptophan metabolism, diverting it to the kynurenine pathway and increasing the production of quinolinic acid, a potent NMDA receptor agonist. This alteration results in the intensification of glutamate excitotoxicity, a central mechanism in the pathogenesis of ALS. Complementarily, they demonstrated that quinolinic acid promotes excessive calcium influx into neurons, mitochondrial dysfunction, and oxidative stress, events that accelerate neuronal degeneration.[5]

On the other hand, strategies aimed at restoring intestinal homeostasis have shown promising results. There is evidence that microbiota modulation through probiotics, prebiotics, and manipulation of the kynurenine pathway can reduce quinolinic acid levels, restore microbial balance, and, consequently, decrease excitotoxicity and slow disease progression.[6,7]

Complementarily, a recent article reinforces that the reduction of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), is associated with improved intestinal barrier integrity and the attenuation of neuroinflammation. The decrease in these pro-inflammatory mediators contributes to the protection of motor neurons, suggesting that immune system modulation may be a key component in the management of ALS.[2]

Given the evidence that intestinal dysbiosis and the deficiency of neuroprotective metabolites contribute to the progression of ALS, various

therapeutic strategies have been studied with the aim of modulating the gut-brain axis and improving the prognosis of the disease. The administration of probiotics showed potential in increasing butyrate production, restoring the intestinal barrier, and reducing systemic inflammation, while supplementation with methylcobalamin (vitamin B12) can modulate neuroprotection, reduce excitotoxicity, and influence the expression of genes related to neuronal degeneration, such as *SOD1*. Dietary interventions were also highlighted, with ultra-processed foods, red meats, and glutamate associated with higher risk, while coffee, tea, raw vegetables, and fibers showed a protective effect. More recently, fecal microbiota transplantation has been evaluated in clinical trials, showing promise in restoring healthy microbial composition and correcting metabolic imbalances, which may positively reflect on the clinical progression of the disease.[6]

Despite the advances, important gaps persist. Most studies have small samples, heterogeneous methodologies, and lack of standardization in the characterization of the gut microbiota, which limits the extrapolation of results. Furthermore, the complexity of the interaction between microbiota, tryptophan metabolism, SCFA production, and glutamatergic excitotoxicity requires longitudinal clinical trials capable of establishing causal relationships and validating the efficacy of the proposed interventions.[3-7]

In summary, the findings suggest that intestinal dysbiosis plays a relevant role in the progression of ALS by modulating tryptophan metabolism, glutamate excitotoxicity, and neuroinflammation. Therapeutic strategies based on restoring microbial diversity, supplementation, and reducing neurotoxic metabolites emerge as promising to attenuate neuronal degeneration and slow the evolution of the disease. However, additional research is needed to consolidate these mechanisms and define effective and safe clinical protocols.

Final Considerations

The evidence analyzed in this study reinforces that amyotrophic lateral sclerosis is a complex neurodegenerative disease, whose progression is not limited to motor neurons but involves multifactorial interactions, including genetics, metabolism, neuroinflammation, and gut-brain axis alterations. Intestinal dysbiosis emerges as a relevant modulating factor, capable of impacting the production of neuroprotective metabolites, neurotransmitters, and essential vitamins, influencing excitotoxicity, mitochondrial function, and the inflammatory response. Future clinical research is essential to validate the efficacy of these interventions and establish safe and standardized protocols for microbiome management in ALS.

References

1. Thaler AI, Thaler MS. Neurologia Essencial. Porto Alegre-RS: Grupo A Educação S.A; 2023.

2. Cordás ATKTA. Microbiota e o eixo intestino-cérebro. Barueri-SP: Editora Manole; 2024.

3. Sun J, Zhang Y. Microbiome and micronutrient in ALS: From novel mechanisms to new treatments. Neurotherapeutics [Internet]. 2024 Aug 31;21(6):e00441.

4. Mincic AM, Antal M, Filip L, Miere D. Modulation of gut microbiome in the treatment of neurodegenerative diseases: A systematic review. Clinical Nutrition [Internet]. 2024 Jul 1;43(7):1832–49.

5. Matheson JAT, Holsinger RMD. The Role of Fecal Microbiota Transplantation in the Treatment of Neurodegenerative Diseases: A Review. International Journal of Molecular Sciences [Internet]. 2023 Jan 1;24(2):1001.

6. Sharma VK. Dysbiosis and Neurodegeneration in ALS: Unraveling the Gut–Brain Axis. NeuroMolecular Medicine. 2025 Jul 3;27(1).

7. Kaul M, Mukherjee D, Weiner HL, Cox LM. Gut microbiota immune cross-talk in amyotrophic lateral sclerosis. Neurotherapeutics [Internet]. 2024 Nov 6;21(6):e00469.

Correspondent author

Lara Di Almeida Melo
Rua Dr. Evandro Pinto,sem número,
Quadra 2, Lote 7, CEP 75083-460.
Anápolis,Goiás, Brasil.
laraalmeidamelo@gmail.com