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RELATIONSHIP BETWEEN MULTIPLE SCLEROSIS AND INTESTINAL DYSBIOSIS: AN INTEGRATIVE REVIEW

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Abstract: The aim of the present study is to provide a better understanding of the relationship between MS and intestinal dysbiosis, which may lead to new strategies for the prevention and treatment of the disease. Methodology: Integrative review on the relationship between MS and intestinal dysbiosis, PubMed and Scopus databases were used, considering articles published in the last 5 years. Nine studies were included to compose the collection. Results: The results of recent studies suggest that intestinal dysbiosis may be associated with the development of MS, since the intestinal microbiota plays an important role in modulating the immune system. They discuss possible mechanisms by which intestinal dysbiosis can lead to MS, including activation of immune cells and production of pro-inflammatory cytokines. Conclusion: It can be suggested that treatment with probiotics, prebiotics and other interventions aimed at modulating the intestinal microbiota may represent a promising approach in the treatment of multiple sclerosis.
Keywords: Multiple sclerosis, dysbiosis, microbiota.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS) and can lead to significant disability. MS is characterized by demyelinating lesions and chronic inflammation in the CNS, resulting in a variety of symptoms including muscle weakness, difficulty walking, blurred vision and cognitive problems. MS affects about 2.5 million people worldwide and is more common in women than in men, with a ratio of 3:1 (Castillo-Álvarez et al., 2017).

The clinical manifestation of MS may vary according to the location of lesions in the CNS. Symptoms can include muscle weakness, spasticity, fatigue, coordination

problems, vision problems and cognitive problems (Saresella et al., 2020). The disease is highly heterogeneous, with different types of MS including the relapsing-remitting form, the primary progressive form, the secondary progressive form, and the recurrent progressive form (Parodi & Kerlero de Rosbo, 2021).

MS is a common disease worldwide, mainly affecting young adults. The prevalence of the disease varies in different countries, with higher rates in temperate areas. It is estimated that MS affects about 35 out of every 100,000 people in Europe and 18 out of every 100,000 people in the United States (Yousefi et al., 2022). Furthermore, MS is more common in individuals of Caucasian descent than in other ethnicities, although the disease is becoming increasingly common in other ethnic groups (Moles et al., 2022).

Recent studies have pointed to the possible relationship between Multiple Sclerosis (MS) and intestinal dysbiosis, that is, the imbalance in the composition of the intestinal microbiota. The objective of this research is to investigate the possible association between MS and alterations in the intestinal microbiota, as well as to evaluate the role of diet, immunomodulatory therapies and other environmental factors in the development and progression of the disease. Previous studies suggest that alterations in the intestinal microbiota can influence the host's immune response and thus affect the progression of MS (Castillo-Álvarez et al., 2017; Zeng et al., 2019; Saresella et al., 2020). Given the context, this research seeks to provide a better understanding of the relationship between MS and intestinal dysbiosis, which may lead to new strategies for preventing and treating the disease.

METHODOLOGY

To perform the search for articles for this integrative review on the relationship between MS and intestinal dysbiosis, the PubMed and Scopus databases were used, considering articles published in the last 5 years. The search strategy was based on the PICO structure: Population: patients with multiple sclerosis; Intervention: intestinal dysbiosis; Comparison: individuals without intestinal dysbiosis; Outcome: clinical manifestations of multiple sclerosis related to intestinal dysbiosis. The guiding question of this study was: "What is the relationship between intestinal dysbiosis and the clinical manifestation of multiple sclerosis?". The keywords used in the search were "multiple sclerosis", "dysbiosis", "microbiota", "gut-brain axis" and "inflammation". The inclusion criteria for the selection of articles were: studies that addressed the relationship between intestinal dysbiosis and the clinical manifestation of multiple sclerosis in humans. Studies that did not meet the inclusion criteria, studies with animals and studies that were not available in full format were excluded. After the initial search, the titles and abstracts were evaluated independently by two reviewers, with resolution of disagreements by consensus. Then, the selected articles were evaluated in full to confirm eligibility. Studies that met the inclusion criteria and provided relevant information for the discussion of the topic were selected for this integrative review.

RESULTS

The number of articles selected in the databases is shown in Figure 1. The systematic search in the databases returned a total of 108 studies published in the last 5 years. Of these, 85 were excluded after reading the titles, leaving 23 studies for abstract evaluation. After screening titles and abstracts, 10 studies were selected and submitted to full reading. After full reading, 9 studies were included in the Systematic review table, which met the established inclusion criteria.

Nine studies with evidence available in the literature were selected. In summary, information about the studies referring to the authors/year, type of study, population and main results was listed, as shown in Table 1.

DISCUSSION

The study by F. Castillo-Álvarez and Marzo-Sola (2017) examines the relationship between MS and intestinal dysbiosis. The authors point out that MS is an autoimmune disease that affects the central nervous system, and intestinal dysbiosis is characterized by changes in the composition and function of the intestinal microbiota. The results of recent studies suggest that intestinal dysbiosis may be associated with the development of MS, since the intestinal microbiota plays an important role in modulating the immune system. They discuss possible mechanisms by which intestinal dysbiosis can lead to MS, including activation of immune cells and production of pro-inflammatory cytokines. While more studies are needed to confirm these associations, these findings suggest that promoting gut health may play an important role in the prevention and treatment of MS.

The study by Farshbafnadi and collaborators (2021) discusses the connection between the composition of the intestinal microbiota and multiple sclerosis. The authors point out that intestinal dysbiosis is an important factor in the pathogenesis of multiple sclerosis, with studies suggesting that the intestinal microbiota of patients with multiple sclerosis has significant differences in relation to the microbiota of healthy individuals. The study addresses the role of intestinal permeability in the pathogenesis of multiple sclerosis and how increased intestinal permeability can lead to the migration of bacteria and other components of the intestinal lumen into the systemic circulation, triggering a harmful immune response. The authors also discuss the influence of diet on the intestinal microbiota and on the pathogenesis of multiple sclerosis, emphasizing the importance of a balanced and personalized diet as part of the treatment and prevention of multiple sclerosis.

Castillo-Álvarez et al. (2021) verifies the relationship between interferon β-1b treatment and the composition of the intestinal microbiota in patients with MS. The authors point out that interferon β-1b is a drug widely used to treat MS, and its influence on the intestinal microbiota is still not completely understood. The results of the study showed that patients treated with interferon β-1b showed a significant change in the composition of the intestinal microbiota compared to untreated patients. They identified that treatment with interferon β-1b was associated with a reduction in the abundance of potentially harmful bacteria, as well as an increase in the abundance of bacteria with anti-inflammatory properties. These findings suggest that interferon β-1b may have beneficial effects on gut health in patients with MS, in addition to its already known immunomodulatory effect. However, further studies are needed to fully understand the relationship between interferon β-1b treatment and gut microbiota in patients with MS.

For Zeng et al. (2019) investigates the association between MS and intestinal dysbiosis in a Chinese cohort of MS patients. The authors point out that intestinal dysbiosis is characterized by alteration in the composition and function of the intestinal microbiota, and has been proposed as an important factor in the development of several diseases, including MS. Study results showed that MS patients had a significant decrease in gut microbiota diversity compared to healthy subjects. Furthermore, the authors identified a significant decrease in the production of short-chain fatty acids (SCFA) by the intestinal

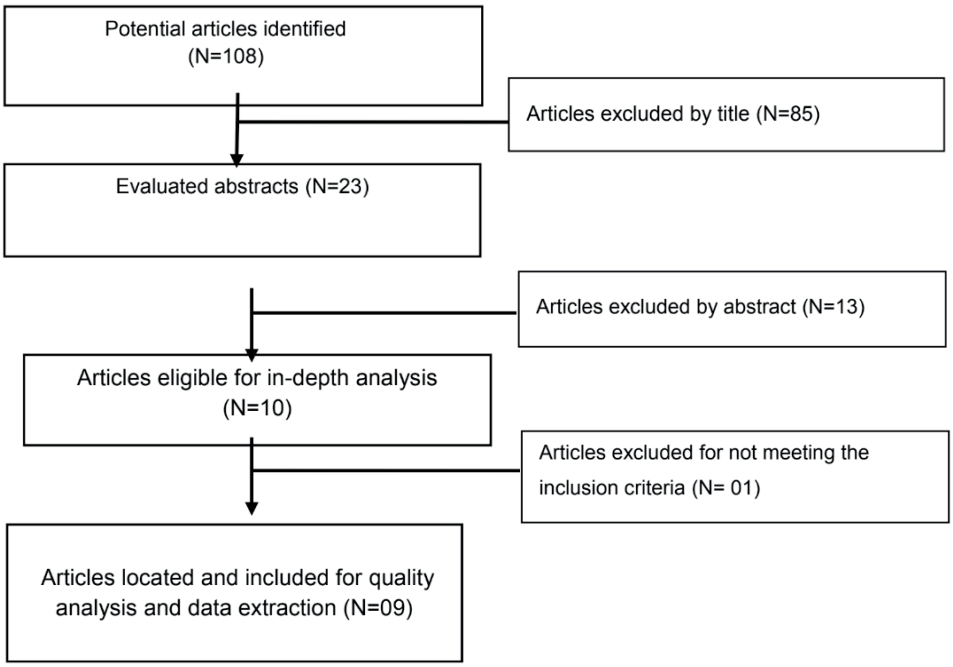

Figure 1.0 Flowchart of the distribution of articles found and selected.

Study	Type of study	Population	Main findings
Castillo-Álvarez & Marzo-Sola (2017)	Systematic review	Not specified	Intestinal microbiota may play a role in the pathogenesis of MS.
Castillo-Álvarez et al. (2021)	longitudinal study	Patients with MS	Use of interferon β-1b altered the composition of the intestinal microbiota.
Zeng et al. (2019)	case-control study	MS patients and healthy controls	Altered gut microbiota and lack of short-chain fatty acid production in patients with MS.
Saresella et al. (2020)	case-control study	MS patients and healthy controls	Patients with MS had lower levels of circulating fatty acids, correlated with gut microbiota dysbiosis and inflammation.
Moles et al. (2022)	case-control study	MS patients and healthy controls	Patients with MS showed intestinal microbiota dysbiosis and lack of production of short-chain fatty acids.
Yousefi et al. (2022)	Systematic review	Not specified	Changes in the gut microbiota have been associated with the pathogenesis of MS.
Parodi & Kerlero de Rosbo (2021)	Systematic review	Not specified	Dysfunction of the gut-brain axis can be both a cause and a consequence of MS.
Farshbafnadi et al. (2021)	Systematic review	Not specified	The composition of the gut microbiota is linked to the pathogenesis of MS.
Colpitts et al. (2017)	experimental study	animal model of MS	Intestinal microbiota showed a bidirectional association with central nervous system disease in an animal model of MS.

Table 1.0 – Distribution of scientific productions according to the following variables: authorship, year of publication, objective, methods and results (n= 09).

microbiomes of patients with MS, which may be related to intestinal dysbiosis. Decreased SCFAs can lead to reduced intestinal barrier integrity and increased intestinal permeability, which can trigger a systemic inflammatory response and affect the development and progression of MS. These findings suggest that the promotion of intestinal health and the use of therapies aimed at restoring the intestinal microbiota and the production of SCFAs can be considered as a complementary therapeutic approach in the treatment of MS.

The study by Saresella et al. (2020) investigates the relationship between intestinal dysbiosis and inflammation in patients with MS through the analysis of circulating fatty acids. The authors point out that intestinal dysbiosis can lead to chronic systemic inflammation, which is one of the main pathogenic factors of MS. Study results showed that MS patients had significantly lower levels of short-chain saturated fatty acids, such as butyric acid, which are produced by healthy gut microbiota. Furthermore, the authors identified that patients with MS also had higher levels of long-chain saturated fatty acids, which are associated with chronic inflammation. These findings suggest that intestinal dysbiosis may be related to changes in circulating fatty acid levels in patients with MS and that this may be an indicator of systemic inflammation. The study highlights the importance of promoting gut health and intestinal microbiota balance in patients with MS in order to reduce inflammation and improve the prognosis of the disease.

The study "Microbial dysbiosis and lack of SCFA production in a Spanish cohort of patients with multiple sclerosis" by Moles et al. (2022) investigates the relationship between intestinal dysbiosis and SCFA production in patients with MS in Spain. The authors point out that SCFA, such as butyric acid, are produced by the healthy intestinal microbiota and play an important role in regulating the immune response and maintaining the integrity of the intestinal barrier. The results of the study showed that patients with MS had intestinal dysbiosis, characterized by an imbalance in the composition of the intestinal microbiota and a reduction in the production of SCFA. Furthermore, patients with MS had elevated levels of inflammatory markers and a greater permeability of the gut barrier, suggesting that gut dysbiosis may be contributing to systemic inflammation and MS progression. These findings highlight the importance of promoting gut health and microbiota balance in MS patients in order to improve gut barrier function, reduce inflammation, and potentially improve disease prognosis.

The study by Yousefi et al. (2022) reviews current literature on the relationship between the gastrointestinal tract, microbiota, and MS, as well as the connection between the gut microbiota and the central nervous system. The authors point out that intestinal dysbiosis and chronic inflammation are common in patients with MS, and that this dysfunction can affect the permeability of the blood-brain barrier, allowing the entry of inflammatory molecules and causing damage to the central nervous system. The study also highlights the importance of SCFAs produced by the intestinal microbiota in regulating the immune response and maintaining the integrity of the intestinal barrier. Furthermore, the authors discuss the possibility of using probiotics and prebiotics as an adjunctive treatment in patients with MS, in order to improve the composition of the microbiota and reduce systemic inflammation. In conclusion, the study highlights the importance of gut health in the pathogenesis and progression of MS and suggests that promoting gut health may be a useful therapeutic strategy in the management of the disease.

According to the study by Parodi and Kerlero de Rosbo (2021) which reviews the current literature on the connection between the gut-brain axis and MS, investigating whether the dysfunction of this axis is a cause or a consequence of the disease. The authors point out that intestinal dysbiosis is common in patients with MS and can affect the permeability of the blood-brain barrier, allowing the entry of inflammatory molecules and causing damage to the central nervous system. Dysfunction of the gut-brain axis can also affect immune response and neuroplasticity, contributing to the progression of MS. The study also discusses the possible relationship between intestinal dysbiosis and mitochondrial dysfunction observed in patients with MS, suggesting that the intestinal microbiota can directly affect the energy metabolism of nerve cells. In addition, the authors highlight the importance of SCFAs produced by the intestinal microbiota in regulating the immune response and maintaining the integrity of the intestinal barrier. In conclusion, the study highlights the importance of the gut-brain axis in the pathogenesis and progression of MS and suggests that Dysfunction of this axis can be both a cause and a consequence of the disease. The authors suggest that promoting gut health may be a useful therapeutic strategy in the treatment of MS.

The study by Colpitts and colleagues (2017) investigated the bidirectional relationship between gut microbiota and central nervous system disease in a murine biphasic model of multiple sclerosis. The results of the study suggest that intestinal dysbiosis is associated with the pathogenesis of MS, in addition to affecting the integrity of the blood-brain barrier. The study also showed that antibiotic therapy reduced central inflammation and symptoms of MS in mice. On the other hand, the induction of an immune response in the central nervous system caused alterations in the intestinal microbiota of rats. These findings indicate that the communication between the intestinal microbiota and the central nervous system is bidirectional and that intestinal dysbiosis can be a cause or a consequence of MS. Furthermore, the results suggest that therapies aimed at restoring intestinal microbiota homeostasis may have potential for the treatment of MS.

FINAL CONSIDERATIONS

It is observed that there is a growing evidence of the influence of intestinal dysbiosis in the pathogenesis of the disease. Several studies indicate that patients with multiple sclerosis have alterations in the composition of the intestinal microbiota, as well as in the production of short-chain fatty acids and in levels of systemic inflammation. Furthermore, there is evidence that therapy with interferon beta-1b can modulate the gut microbiota in patients with multiple sclerosis, highlighting the importance of microbiota control as a potential therapeutic strategy for the disease. Although the understanding of the mechanisms involved in the relationship between intestinal microbiota and multiple sclerosis is still limited, there is increasingly robust evidence that intestinal dysbiosis plays an important role in the pathogenesis of the disease. From the evidence discussed, it can be suggested that treatment with probiotics, prebiotics and other interventions aimed at modulating the intestinal microbiota may represent a promising approach in the treatment of multiple sclerosis. However, more research is needed to elucidate the underlying mechanisms and evaluate the effectiveness of these interventions in clinical practice.

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