



Association between autism and gastrointestinal changes: a systematic review

Associação entre autismo e alterações gastrointestinais: uma revisão sistemática

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ABSTRACT

Introduction: The association between autism and gastrointestinal disorders has been increasingly investigated, with studies suggesting that children with autism may have a higher susceptibility to intestinal problems, although the nature of this relationship remains unclear.

Objective: To systematically review the most recent scientific evidence on the relationship between autism spectrum disorder and gastrointestinal disorders, aiming to clarify its implications for diagnosis and treatment.

Method: A systematic review was conducted in the BVS, Medline, and PubMed databases using the descriptors "gut microbiota" and "autism". Fifty-nine articles that met the inclusion criteria were selected.

Result: The analysis showed variations in results but indicated a possible higher predisposition of children with autism to gastrointestinal disorders, although the exact relationship remains undefined. The connection between autism and gastrointestinal problems is complex and still uncertain, highlighting the need for further research to improve understanding and treatment.

Conclusion: There is evidence of a relationship between autism and gastrointestinal disorders, but more studies are needed to clarify this association and improve the clinical management of autism spectrum disorder.

KEYWORDS: Autism. Gastrointestinal disorders. Neurology. Gastroenterology.

Central Message

The association between autism and gastrointestinal disorders has been increasingly investigated, with studies suggesting that children with autism may be more susceptible to intestinal problems, although the nature of this relationship is still unclear. Thus, there is a need to promote scientific evidence on the relationship between autism spectrum disorder and gastrointestinal disorders.

Perspective

Evidence of microbial dysbiosis in autism spectrum disorder has progressed over the past decade, and immunological and gastrointestinal dysfunction may be linked to dysbiosis. However, there is some evidence that altering the microbiota may improve behaviors, i.e., achieving a balance between beneficial commensals and potentially pathogenic microbes in the gut, with the aim of directly contributing to the quality of life of children with the disorder.

RESUMO

Introdução: A associação entre autismo e distúrbios gastrointestinais tem sido cada vez mais investigada, com estudos sugerindo que crianças com autismo podem ter maior suscetibilidade a problemas intestinais, embora a natureza dessa relação ainda não esteja clara.

Objetivo: Revisar sistematicamente as evidências científicas mais recentes sobre a relação entre transtorno do espectro autista e distúrbios gastrointestinais, visando esclarecer suas implicações para o diagnóstico e tratamento.

Método: Foi realizada uma revisão sistemática nas bases de dados BVS, Medline e PubMed, utilizando os descritores "gut microbiota" e "autismo". Cinquenta e nove artigos que atenderam aos critérios de inclusão foram selecionados.

Resultado: A análise mostrou variações nos resultados, mas indicou uma possível maior predisposição de crianças com autismo a distúrbios gastrointestinais, embora a relação exata permaneça indefinida. A conexão entre autismo e problemas gastrointestinais é complexa e ainda incerta, destacando a necessidade de mais pesquisas para melhorar a compreensão e o tratamento.

Conclusão: Há evidências de uma relação entre autismo e distúrbios gastrointestinais, mas mais estudos são necessários para esclarecer essa associação e melhorar o manejo clínico do transtorno do espectro autista.

PALAVRAS-CHAVE: Autismo. Distúrbios gastrointestinais. Neurologia. Gastroenterologia.

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INTRODUCTION

Autism spectrum disorders (ASD) are part of a series of heterogeneous neurodevelopmental disorders characterized by deficits in communication, social interaction, and cognition. ASD does not have a single defined etiology, and contemporary theories suggest a range of genetic and environmental contributions.¹ A diverse range of genetic and environmental elements has been identified as contributors to the development of ASD. These factors range from genetic predispositions to environmental influences, including nutritional deficiencies, exposure to viral agents, failures in the embryonic closure process of the neural tube, dysfunctions in the immune systems, and allergic manifestations. The convergence of these complex factors highlights the multifaceted and interdisciplinary nature of the etiology of ASD, emphasizing the importance of an integrative approach in understanding the underlying mechanisms of this neuropsychiatric disorder. Given that genetic mechanisms are responsible for approximately 10-20% of ASD cases, the etiological heterogeneity becomes even broader, promoting the study of a possible relationship between ASD and other physiological changes, such as gastrointestinal disorders, which are interconnected with an alteration of the gut-brain axis leading to intestinal dysbiosis precursors of disorders such as increased intestinal permeability, general changes in the microbiota, and the occurrence of intestinal infection and inflammation.^{2,3}

The evidence of microbial dysbiosis in ASD has progressed in the last decade, just as immune and gastrointestinal dysfunction may be linked to dysbiosis. However, there is some evidence that the alteration of the microbiota in ASD may improve behaviors, i.e., achieving a balance between beneficial commensals and potentially pathogenic microbes in the intestine, aiming to contribute directly to the quality of life of children with ASD.^{4,5} Despite its complexity in understanding the exact pathogenesis, in recent research has highlighted the relevance of the interaction between the intestinal microbiota and the brain in patients with autism and other neuropsychiatric conditions. Individuals with ASD often present notable gastrointestinal dysfunctions, such as changes in bowel habits and chronic abdominal pain, which correlate with their neurological manifestations. The microbiota, a microbial community composed of trillions of microorganisms, plays a significant role in various conditions, including those of the nervous system.⁶

The relationship between the intestinal microbiota and the central nervous system, known as the "gut-brain axis," emerges as a crucial element in neuropsychiatric disorders, including autism. This review focuses on analyzing dysbiosis in ASD, especially exploring the possible connection between gastrointestinal disorders, inflammation, and neurobehavioral symptoms in autistic children.

The objective of this review was to conduct a comprehensive systematic review of current studies to investigate the association between autism and

gastrointestinal changes, aiming to provide an in-depth understanding of contemporary knowledge on this subject. So, it proposed to identify and analyze recent studies examining the prevalence of gastrointestinal changes in individuals with autism, considering different age groups and social backgrounds; to evaluate the quality of the studies with a focus on methodology, sampling, diagnostic criteria, and statistical approaches to validate the results; to synthesize the available evidence to determine a significant association between autism and gastrointestinal changes, exploring potential risk factors and possible underlying mechanisms.

METHOD

The articles were selected through a search in the following databases: Virtual Health Library (BVS), specifically targeting works from the International Literature in Health Sciences (Medline) and PubMed. The descriptors used were "gut microbiota" and "autism," conducting an advanced search by combining the descriptors with the boolean operator AND. Inclusion criteria encompassed publications available freely in full, in English and Portuguese, published within the last 5 years, specifically addressing autism spectrum disorder and intestinal microbiota. Incomplete or repetitive articles, preliminary clinical trials in animals, or those encompassing other psychopathologies unrelated to ASD were excluded. The initial search on Pubmed yielded 444 articles, with 31 selected for analysis. On the Medline platform, 96 articles were found, with 28 selected, totaling 59 articles.

RESULT

To view the description of the summarized articles of this study use the QR Code below or click on the link below the QR Code to open the supplementary file.¹⁻⁵⁹



Supplementary file

DISCUSSION

ASD is characterized by a behavioral syndrome that affects numerous stages of normal mental development, and recently, progress in diagnosis has been reported, with an average of 1 case per 88 children. Children with ASD exhibit speech and language disorders, learning difficulties, intellectual impairment, and motor impairments. In addition to neurological impairment, current research explores the relationship between ASD and other physiological changes, such as gastrointestinal disorders, which are clearly linked to altered intestinal microbiota composition.⁷

The genetic basis of ASD is extremely complex, as more than 100 genes and genomic regions directly or indirectly related to the etiology of ASD have

been discovered. This includes genes involved in the development of the central nervous system and approximately 400 genes that may confer susceptibility to autism.^{8,9} It is understood that the effects on quality of life, in a subtle manner, vary from person to person. Thus, verbal and non-verbal intelligence quotients (IQs) and repetitive and restricted behaviors can range from stereotyped motor behaviors at a low level to a high level.¹⁰

In the last decade, there has been a growing fascination with studying the role of intestinal microbiota as a co-factor in ASD development, as numerous studies have addressed a possible bidirectional communication between the brain and the intestine, referred to as the gut-brain axis.¹¹

The communication axis between the brain and the intestine is regulated at various levels, with the nervous and endocrine systems serving as the main regulators, including the central role of the HPA axis (hypothalamus-pituitary-adrenal axis), as well as the immune pathway. Regarding the immune regulation of the HPA axis, it is predominantly mediated by changes in cytokine organization. On the other hand, nervous regulation primarily occurs through the transmission of impulses in the autonomic nervous system, including the vagus nerve, afferent and efferent fibers, and the enteric nervous system, often referred to as the "intestinal brain." This system not only directly regulates the muscles, mucosa, and blood vessels of the digestive tract but also influences their activity. Additionally, resident microorganisms in the intestine, such as certain species of bacteria and fungi, also play a role in communication with the immune system and the enteric nervous system through the synthesis and distribution of various neurotransmitters.^{12,13}

Hypothalamic hormones, such as corticotropin-releasing hormone and vasopressin, initiate a hormonal cascade along the HPA axis, stimulating the anterior pituitary gland to produce and secrete the adrenocorticotropic hormone. These hormones, in turn, stimulate the adrenal gland to secrete glucocorticoids, mainly cortisol, which plays a fundamental role in this complex interaction between the brain and the gastrointestinal system. The brain-gut axis, establishing a strong connection between the brain, intestines, and intestinal microbiota, represents a bidirectional communication pathway, where the interaction between the brain and the gastrointestinal system is mainly mediated by the nervous system, with an emphasis on the vagus nerve.^{14,15}

In individuals with ASD, food restriction, difficult eating behaviors, and gastrointestinal disorders are easily observed. This is because children with autism are predominantly selective eaters, showing aversion to colors, textures, smells, or specific characteristics of numerous foods. This directly correlates with the composition of the intestinal microbiota, nutritional deficiencies, and diet quality. Additionally, it is common for children with autism to exhibit abnormalities in gastrointestinal physiology, including increased intestinal permeability, general changes in microbiota, intestinal infections, as well as immune dysfunction and gastrointestinal inflammation.^{16,17}

Moreover, among the ASD-affected population, the relationship between gastrointestinal symptoms and behavioral abnormalities can vary according to the patient's age, implying significant clinical implications in addressing gastrointestinal disorders in children with ASD. Chronic constipation emerges as one of the most prominent gastrointestinal symptoms, often coexisting with core symptoms of ASD.^{18,19}

These changes in intestinal microbiota during early life development may influence neurodevelopment, contributing to adverse effects on mental health throughout life. Therefore, further investigation is needed to understand changes in the abundance and diversity of bacteria accompanying ASD, especially when associated with constipation, which may reveal potential effects of the interaction between ASD and gastrointestinal symptoms resulting from dysbiosis of the intestinal microbiota and fecal metabolites.^{20,21}

Despite the specific volume of studies published on dysbiosis in the intestinal microbiota of individuals with ASD, there is still no anticipated consensus regarding the precise composition of the intestinal microbiome specific to these individuals, and some studies present conflicting results. This variation in results can be attributed, in part, to the lack of uniformity in factors such as age, diet, medication, geographic location, presence of comorbidities, and severity of neurobehavioral and gastrointestinal symptoms among the patients involved in the studies. For example, the fecal microbiota of younger individuals has a lower proportion of Bacteroidetes compared to older individuals, and the microbiome profile may vary depending on the specific section of the gastrointestinal tract from which the sample was collected. Therefore, for a precise comparison and evaluation of results related to intestinal microbiota in ASD, studies with more homogeneous patient groups are necessary.²²

Despite numerous studies highlighting the potential of antibiotics in alleviating gastrointestinal and behavioral symptoms in ASD, controversies persist regarding this type of treatment. Initially, bacteria not only eradicate harmful atmospheric bacteria but also exhibit characteristics of beneficial bacteria in ASD patients, potentially increasing susceptibility to gastrointestinal issues in children with ASD. Therefore, antibiotic therapy may not be an ideal intervention to restore the balance of the intestinal microbiota.²³⁻²⁵

Recently, studies on dietary interventions for children with ASD have gained popularity. Among these, the Mediterranean diet stands out as relatively easy to introduce to children. On the other hand, the adherence to a ketogenic diet, while offering benefits, is challenging for this target population.²⁶

Furthermore, probiotics are live microorganisms that, when consumed in specific formulations, confer health benefits to the host. On the other hand, prebiotics consist of non-digestible fibers, such as oligosaccharides, which stimulate the growth and optimize the functionality of probiotics in the gastrointestinal tract, acting as specific substrates. Initial evidence suggests that supplementation of probiotics and prebiotics may have a promising

preventive effect on neurological and mental health conditions, including Alzheimer's disease, Parkinson's disease, depression, and notably, ASD.^{27,28}

However, due to the wide variation in treatments applied, the duration of therapeutic protocols, and the tools used to assess outcomes, the data obtained do not allow for a definitive decision regarding the benefits of probiotics and other interventions in relation to ASD symptoms. Given the inherent diversity in ASD, it would be advantageous to select therapeutic approaches based on the specific characteristics of each individual with ASD and their microbiota, with the ultimate goal of personalizing therapy.²⁹⁻³¹

Another significant study contributing to treatment evolution was providing additional evidence on modulating the gastrointestinal tract microbiota through fecal microbiota transplantation, probiotics, and dietary therapy. Literature from the last half-decade considers that probiotics prevent intestinal diseases by regulating and controlling the blood-brain barrier. Fecal microbiota transplantation, on the other hand, is an interventional approach where fecal microorganisms from healthy individuals are delivered to patients with a depleted microbiota, but the safety and effectiveness of this approach are still under speculation.³²⁻³⁸

In summary, therapeutic approaches for ASD centered on the intestinal microbiome include dietary therapy, antibiotic therapy, probiotic and prebiotic intervention, as well as microbial transfer therapy. Additionally, it is relevant to explore diverse perspectives among researchers regarding the relationship between the intestinal microbiome and autism, questioning whether variations in the observed microbiota in the intestines of autistic children result from their restricted dietary preferences associated with autism diagnosis characteristics or are correlated with underlying reasons for behavioral symptoms.^{39,40}

CONCLUSION

Based on the aforementioned, it is concluded that current studies on the link between autism and gastrointestinal changes emphasize the complexity of this ever-evolving relationship. Although there are indications that children with autism may be more susceptible to gastrointestinal disorders, the true nature of this connection remains elusive. This uncertainty underscores the ongoing need for more in-depth and comprehensive research efforts, not only to identify the association between these conditions but also to investigate how it may impact the diagnosis and treatment of autism. Additionally, this review highlights the importance of a multidisciplinary approach in the assessment and care of individuals with autism, integrating attention to gastrointestinal needs as an essential component of treatment. A more solid understanding of this relationship can provide valuable guidance to healthcare professionals and parents, with the potential to enhance the quality of life and overall well-being of individuals with autism. This represents a significant step toward more comprehensive and personalized care for this community.

Author's contribution

Guilherme Nobre Nogueira: Formal analysis, Methodology
 Nicole Custódio Porto Silva: Validation, Writing – review & editing
 Hugo Lorrain Souza Costa: Data curation, Writing – original draft
 Poliana Zago Perondi: Conceptualization, Investigação
 Rafaela Fernandes Gonçalves: Formal analysis, Methodology
 Gustavo Henrique Tomasi: Project administration

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