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ROLE OF MICROBIOTA-GUT-BRAIN AXIS IN AUTISM SPECTRUM DISORDER

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ABSTRACT

Background: This narrative literature review shows a close link between autism spectrum disorder and the severity of gastrointestinal symptoms, as there is a two-way communicative linking known as the gut-brain axis, and a large amount of research shows the importance of a balanced microbiota to guarantee normal development and sustainment of brain function.

Methods: A systematic review was performed utilizing the PubMed (Medline) database to explore literature published within the last 6 years, focusing on studies investigating the correlation between the gut-brain axis and autism spectrum disorder, with a specific emphasis on the gut microbiota.

Results: Some studies findings demonstrate a decrease in bacterial diversity and also the influence of microbial metabolites associated with the development of ASD and the harshness of the symptoms. An imbalance in the gut microbial flora can result in dysbiosis, leading to diseases and overproduction of proinflammatory cytokines, affecting nutrition and immune responses. Although many studies involving microbiota transfer, vitamin A, the use of probiotics, and other kinds of nourishment are being held, there are no definitive or effective therapies for ASD yet.

Conclusions: More studies are needed to understand the connection between the gut-microbiome-brain axis and ASD, as well as how dietary changes can improve ASD symptoms.

Keywords: Gut-brain Axis. Gastrointestinal tract. Microbiota. Autism.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition known for causing challenges in early social interactions, repetitive behaviors, and restricted interests. Recent data suggests that around 1 in 44 children are affected by ASD [1]. The diagnosis of ASD is entirely neurological; however, ASD is associated with several medical comorbidities. Among these comorbidities, gastrointestinal problems are the most common [2]. They can exhibit abdominal pain, gaseousness, diarrhea, constipation, and flatulence [3]. Research indicates that 17% to 86% of children with ASD experience gastrointestinal disorders, and there is a correlation between the severity of these symptoms and the severity of ASD-associated symptoms [4].

The gut-brain axis (GBA) serves as a two-way communication link, connecting the gut to the brain by involving the gastrointestinal system (GIS) and the central nervous system (CNS) [5]. The gut harbors a diverse community of microorganisms, encompassing bacteria, fungi, viruses, and other life forms, collectively known as the microbiome. Their interaction includes three major pathways, the immune, neural and endocrine/systemic pathway [6]. The gut microbiota influences the production of neurotrophic factors, regulates inflammation, and controls the production of proinflammatory cytokines, T cells, and B cells [5]. A huge body of basic investigation demonstrates that the microbiota is linked to the normal development and maintenance of brain function. Some cross-sectional studies and animals' studies provide mechanistic understanding of the role that the microbiota may play in ASD [7].

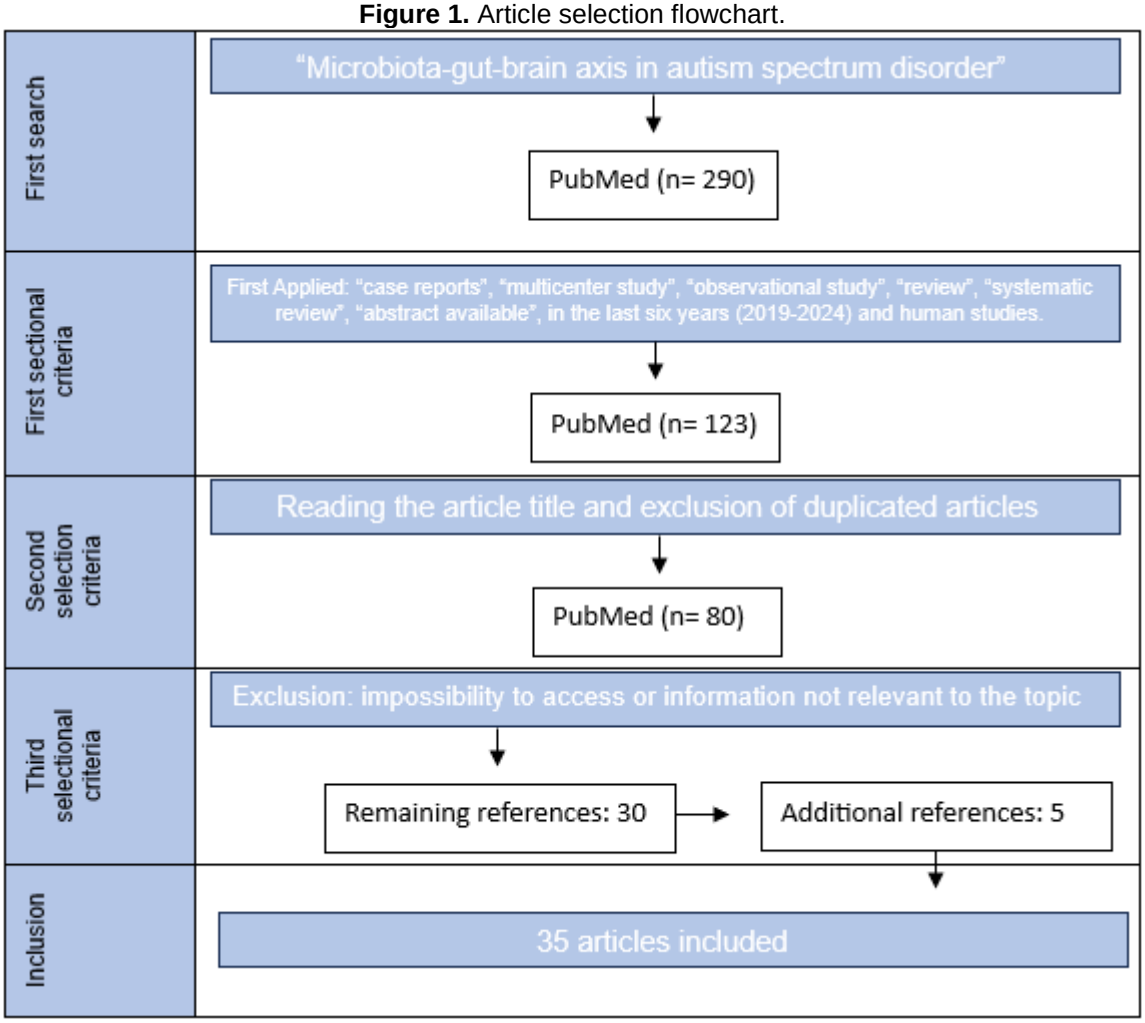
Some studies suggest that the decrease of bacterial diversity and the shift from beneficial microorganisms were presented in individuals with ASD. Perhaps the most important are decreased levels of Prevotella spp., Coprococcus, Veilonellaceae, Bacteroidetes, Actinobacteria, and Proteobacteria, and increased levels of Desulfovibrio spp., Sutterella spp., and Ruminococcus torque. Metabolites produced by the gut microbiota are abnormally abundant in autism patients, implying that certain microbial metabolites can be related with the severity and development of ASD [4].

There is expanding attestation showing how microorganisms regulate neuronal activity, making the brain-gut-microbiome axis a key focus in autism research [2]. Our evaluation focuses on the clinical and preclinical studies that highlight the involvement of gut-related processes in the onset, advancement, and management of autism.

METHODS

A systematic review approach was utilized to conduct a narrative literature review based on the PubMed (Medline) database, focusing on English-language studies. The search used the following medical subject headings (MeSH): “autism spectrum disorder” AND “gut microbiota” AND “gut-brain axis”. The authors systematically searched for studies in PubMed/Medline with an impact factor greater than or equal to two, published from 2019 to 2024. Only studies specifically examining the role of the gut-brain axis in individuals with autism and emphasizing the gut microbiota were considered. Review studies, commentaries, viewpoints, editorials, and any studies lacking original or unpublished results were excluded from this review (Figure 1).

Figure 1. Article selection flowchart.



RESULTS

An imbalance in the gut microbiome can lead to dysbiosis, which in turn can contribute to the development of diseases [8]. Dysbiosis disrupts the function of tight

junction proteins, leading to increased permeability of the intestinal wall and the overproduction of proinflammatory cytokines. This condition is linked to impaired nutrition and immune responses [5].

The gut microbiota plays a vital role in influencing the onset and progression of certain neurological and neuropsychiatric conditions, such as Alzheimer's disease (AD), anxiety, depression and autism spectrum disorder (ASD) [9].

Recent research has brought attention to alterations in the gut microbiota among individuals with ASD. Some studies have found distinct Clostridial species in the stool of individuals with ASD, particularly Clostridium bolteae, which is relevant to those experiencing gastrointestinal issues. Additionally, elevated levels of certain metabolites with chemical properties similar to p-cresols (e.g., 4-Ethylphenyl sulfate) and neurotoxins produced by Clostridiales, as well as proinflammatory cytokines (e.g., IL-6, IL-1, IL-17, and IFN-gamma), tryptophan, and serotonin, have been observed in the blood samples of some ASD patients. However, additional studies are required to further investigate these findings [2].

An animal study involving germ-free mice has revealed deficits in social behavior and increased repetitive behavior after receiving gut microbiota from human donors with ASD, indicating a potential link between gut microbiota and autistic behaviors [7].

DISCUSSION

HOW THE MICROBIOTA-GUT-BRAIN AXIS AFFECTS AUTISM SPECTRUM DISORDER

The intestine hosts a complex community of microorganisms with a high level of diversity, crucial for maintaining the health and balance of the host through a delicate interplay between beneficial and harmful bacteria associated with the enteric nervous system [10].

The gut microbiota has an enzymatic and metabolic activity, producing a large quantity of active metabolites, like folate and vitamins [11]. In addition, intestinal microorganisms form an intestinal barrier, thereby safeguarding the microorganisms against the penetration of pathogenic factors [12].

In humans, the initial colonization of the gut occurs well before birth, as there is a continuum of microbiota between mother and fetus, and the microbiota is transmitted from mother to fetus during pregnancy. The presence of commensal microorganisms in

the womb can trigger fetal colonization, and the transfer of bacteria across the placental barrier is a natural part of the developmental process [13].

Exposure to antibiotics by mothers and infants, especially intrapartum prophylaxis, can impact the early-life microbiota, leading to decreased diversity and abundance of maternal gut microorganisms and hindering their transmission to the newborn. Some evidence indicates that reduced levels of Bifidobacterium and Bacteroidetes, along with increased levels of Clostridium and Lactobacillus in infants due to perinatal antibiotic administration, contribute to gut dysbiosis [13]. Furthermore, studies suggest that antibiotic-induced changes in the microbiome may also play a role in the development of ASD [2,4].

It has been suggested that dysfunction in the intestines may contribute to central nervous system disorders. Animal studies have demonstrated that increased intestinal permeability can lead to the entry of pro-inflammatory mediators and/or hormones into the circulation, potentially affecting neurodevelopment and/or central nervous system function [4]. Additionally, the severity of autism symptoms appears to correspond to increased plasma concentration of zonulin, a protein that regulates intestinal permeability [2].

The process of storing and mentally processing information, known as working memory (WM), plays a crucial role in various daily activities such as planning, organization, cognitive flexibility, and the acquisition of skills like reading, comprehension, arithmetic, and problem-solving. In individuals with ASD, deficits in working memory can lead to various challenges in behavior regulation, cognitive flexibility, abstract thinking, and the ability to focus and sustain attention [14].

In their study, Fatturusso and colleagues have demonstrated that lower levels of Firmicutes, Bifidobacterium (known for its protective role in autism due to its anti-inflammatory properties), Pretovotella, Coprococcus, and Veillonellaceae, alongside a higher abundance of Bacteroidetes, Clostridium, Enterobacteriaceae, and Desulfovibrio, can influence the central nervous system and autism behavior. The study postulates that glyphosate (GLY), an environmental pesticide, may play a role in the pathogenesis of autism due to the promotion of toxin-producing Clostridia and change in the microbiome [15] (Figure 2).

Certain microbial families within Firmicutes, such as Gemellaceae and Clostridiaceae, have been associated with enhanced concentration, quicker memory

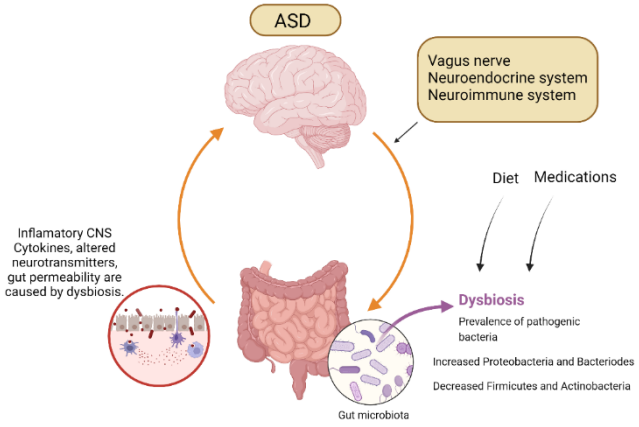
recall, improved attention, and better quality of working memory [16]. Furthermore, elevated levels of Desulfovibrio and *Bacteroides vulgatus* have been found in children with ASD, and these are linked to the severity of autism symptoms. Notably, in rodent studies, the presence of Desulfovibrio resulted in reduced working memory [17].

Moreover, neurodevelopmental disorders linked to cerebellar irregularities often coincide with impairments in working memory. For instance, reduced cerebellar vermis volumes, diminished cerebellar Purkinje cell density, and significant working memory deficits are frequently observed in ASD [18].

Literature also describes the involvement of the serotonin pathway in ASD. Elevated 5'HT levels may result from excessive secretion of 5'HT from the gastrointestinal tract, which is produced by enterochromaffin cells in the intestine and is involved in functions such as motility and secretion. Certain bacterial species affecting 5'-HT metabolism (e.g., Clostridium spp, Lactobacillus spp) have been found to be increased in stool samples from children with ASD. The increased 5′-HT production may decrease peripheral tryptophan availability, potentially contributing to the exacerbation of repetitive behaviors in ASD patients following tryptophan depletion [19].

Vagus nerve pathways have been shown to mediate gut microbial connectivity to the central nervous system. Cholinergic anti-inflammatory pathways via the vagus nerve have been identified to reduce peripheral inflammation and intestinal permeability and may alter microbiota composition [5]. Furthermore, research has demonstrated that vagus nerve stimulation can lead to behavioral improvements in individuals with ASD [3].

Figure 2 - Significant modifications observed in the gut microbiota in individuals with autism spectrum disorder [15].



Several processes may contribute to ASD: environmental influences, immune interactions, genetic predisposition, microbiota-gut-brain axis. Environmental and genetic factors interact, although the exact role of each remains nuclear (adapted by Zeidan *et al.* [20]). ASD: Autism Spectrum Disorder. Created using BioRender.com.

THERAPEUTIC PERSPECTIVES

At present, there is a lack of clear and effective treatment for ASD. Some studies, without solid scientific evidence, show that vitamin A supplementation can have a positive effect on the gut microbiota. The use of antibiotics during pregnancy might pose a risk factor for autism, and certain clinical trials indicate that autistic behavior can improve following a short course of oral vancomycin [19].

Microbiota transfer therapy (MTT) has recently attracted interest among researchers. A small-scale pilot study on microbiota transfer therapy has demonstrated promising results in ASD patients. The study revealed that children with ASD experienced significantly reduced abdominal pain, indigestion, diarrhea, and constipation, along with marked improvements in ASD-related behavior compared to their condition prior to MTT. These positive changes persisted for at least two years following microbial transmission and led to increased levels of Bifidobacterium, Prevotella, and Desulfovibrio [21].

Probiotics, which are live microorganisms, work to stabilize the mucosal barrier through increased mucin expression, stimulation of mucosal immunity, synthesis of antioxidants, and antiproliferative effects on Clostridium species [22].

Numerous studies have explored the potential use of probiotics as a treatment. A systematic review by Tan and colleagues found that while probiotic studies have not conclusively confirmed the purported positive effects of probiotics on ASD, prebiotic and synbiotic combinations seem to be effective against certain behavioral symptoms [23]. Another systematic-narrative review suggests that probiotic supplementation can reduce oxidative stress in simulated intestinal models, though direct studies on the antioxidant effects of probiotics on intestinal oxidative stress in patients with ASD are lacking [24].

Individuals diagnosed with ASD are often placed on a gluten- and casein-free diet. However, a study concluded that nutritional challenges did not have a statistically significant effect on ASD symptoms [25]. On the other hand, a randomized study involving children and adults with ASD demonstrated significant improvements in core

ASD symptoms and developmental age through the use of vitamin/mineral supplements, essential fatty acids, Epsom salt baths, carnitine, digestive enzymes, and a healthy gluten-free, casein-free, soy-free (HGCSF) diet [26].

Furthermore, minocycline may serve as a safe and effective supplement to risperidone in managing irritability and hyperactivity/noncompliance in children with ASD, although additional research is warranted [27].

The transcranial direct-current stimulation (tDCS) can influence synaptic plasticity in the brain by changing the underlying plasticity of the tissue, suggesting that tDCS modulates the balance between excitatory and inhibitory neurotransmitters [28]. Some studies suggest that tDCS may induce a significant change in the composition of the gut microbiome, with a decrease in the bacteroidetes/firmicutes ratio, and an increase in *Roseburia intestinalis* and *Faecalibacterium prausnitzii* [29]. The potential significance of transcranial direct current stimulation (tDCS) on the gut-brain axis as a treatment for ASD is an intriguing area that merits deeper investigation. Given the complex interplay between neurological functions and gastrointestinal health, exploring how tDCS may influence this connection could lead to innovative therapeutic approaches.

In their study, Feng and colleagues have demonstrated that the repetitive transcranial magnetic stimulation (rTMS) can have a positive impact on neural activity, thereby influencing behaviors and symptoms associated with ASD, such as social interaction difficulties and repetitive behaviors. Although further research is needed [30].

CONCLUSION

Research indicates that the gut microbiota significantly influences health, as an imbalance can lead to increased intestinal permeability, inflammation, neuroinflammation, and reduced production of neurotransmitters in the central nervous system. Imbalances in the gut microbiota have been suggested to contribute to ASD symptoms, but interventions such as dietary changes, probiotic supplementation, and microbiota transfer therapy may help improve these symptoms. However, the connection between gut microbiota and ASD requires further investigation as it remains unclear.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

FUNDING

Not applicable.

LIST OF ABBREVIATIONS

AD: Alzheimer's disease

ASD: Autism spectrum disorder

CNS: Central nervous system

GI: Gastrointestinal

GIS: Gastrointestinal system

MTT: Microbiota transfer therapy

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