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INTESTINAL DYSBIOSIS AND ITS RELATIONSHIP WITH AUTISTIC SPECTRUM DISORDER IN KIDS

RELACIÓN ENTRE LA DISBIOSIS INTESTINAL Y EL ESPECTRO AUTISTA EN NIÑOS

Laura Bejarano Loor [1] **0009-0000-7975-0194**
Rafaela Castro Ampuero[1] **0009-0002-9492-971X**
Andres Pazos Altamirano[1] **0009-0006-3335-8879**
Yolanda Valdés Rodríguez[1] **0009-0003-0173-9632**

[1] Facultad de Ciencias de la Salud, Universidad de Especialidades Espíritu Santo

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Correspondencia · Corresponding Author
Laura Bejarano Loor
Facultad de Ciencias de la Salud, Universidad de Especialidades Espíritu Santo
laurabejarano@uees.edu.ec

Abstract

This systematic review analyses the possible association between the intestinal microbiota and Autism Spectrum Disorder (ASD). It delves into the involvement of the gut-brain-microbiota axis and other factors implicated in maintaining a healthy microbiota. The brain and the gastrointestinal tract (GIT) exchange information with a bidirectional pathway. Multiple neurodegenerative diseases such as Parkinson's and Alzheimer's are linked to dysbiosis, an alteration in the gut microbiota. However, there is evidence supporting the association between dysbiosis and the neurodevelopment of ASD. Therefore, current treatment options

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focus on patient nutrition and diet. In this review, the best evidence regarding the effect of nutrition on children with ASD.

Keywords: Autism spectrum; genetics; gut- brain axis; metabolic stress; prebiotics; probiotics.

Resumen

Esta revisión sistemática analiza la posible relación de asociación entre la microbiota intestinal y el Trastorno del Espectro Autista (TEA). Profundizando en la participación del eje microbiota-intestino-cerebro y otros factores implicados en el mantenimiento de una microbiota saludable. El cerebro y el tracto gastrointestinal intercambian, señales de información mediante vías bidireccionales. La disbiosis, o alteraciones de la microbiota intestinal, se relaciona con múltiples enfermedades neurodegenerativas como el Parkinson y el Alzheimer. Sin embargo, existen evidencias que sustentan la relación de asociación de la disbiosis con el neurodesarrollo del TEA. Por lo que, las opciones de tratamiento de los casos con TEA se centran en su nutrición. En esta revisión, se expone las mejores evidencias sobre el efecto de la nutrición en niños con TEA.

Palabras clave: eje microbiota-intestino-cerebro; espectro autista; estrés oxidativo; genética; prebióticos; probióticos.

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that compromises an individual's social behavior and communication. Approximately 1 in 58 individuals, primarily males, are affected by this condition (Arberas & Ruggieri, 2019). The etiology of autism is unknown and has puzzled experts for hundreds of years. However, both researchers and experts agree on the multifactorial origin of ASD, which results from the interaction between genetic and environmental factors(Arberas & Ruggieri, 2019). Recent studies show that 91% of people who develop ASD present dysbiosis (Wang et al., 2024), especially in cases where individuals exhibit significant aggressive behaviors.

The classic symptoms of ASD appear in the first years of life, affecting the infant's language and social relationships with the family and other children. It is often followed, in some cases, by possible intellectual deterioration, motor dysfunctions, and learning difficulties (Ristori et al., 2019). However, autism can vary in presentation depending on the social and family environment, as well as the therapeutic management provided to individuals developing ASD.

Therefore, each person has different treatment options and therapies. Usually, specialists diagnose autism at 3 or 4 years. The success of the treatment depends on early diagnosis, which will allow adapting the environment and therapeutic strategies to the individual ASD characteristics and behavior (Clearly et al., 2023), improving the patient's well-being.

The gut-brain microbiota axis represents an intricate immuno-neuro-endocrine-metabolic connection, facilitating the exchange of signals between the intestinal microbiota and brain regions responsible for regulating intestinal functions' homeostasis (Iglesias-Vázquez et al., 2020). This connection operates bidirectionally. However, its various properties and functions in the development of neurological and psychiatric disorders, including autism, remain unknown. (Shrikantha & Mohajeri, 2019).

In the intestinal mucosa, millions of microorganisms reside, producing essential metabolites for the body while also forming a barrier that prevents the colonization and passage into the bloodstream of pathogenic microorganisms. Mutualistic and commensal relationships exist between microglia and other body systems, but disruptions in these relationships can lead to pathogenic interactions (Martínez Velasco et al., 2023).

There is evidence suggesting that intestinal dysbiosis contributes to the neurodegenerative progression of Alzheimer's disease (AD) and Parkinson's disease (PD). In PD, dysbiosis heightens the permeability to bacterial toxins, like lipopolysaccharides (LPS), triggering a neuroinflammatory response (Hirayama & Ohno, 2021). In turn, this results in abnormal accumulation of synuclein, ultimately leading to the loss of substantia nigra. The induction of the neuroinflammatory response by LPS, coupled with the reduction in the production of short-chain fatty acids (SCFAs), affects the regulatory function of T cells (Hirayama & Ohno, 2021), thereby promoting the neuroinflammation underlying PD.

In recent years, researchers have observed an increase in the number of registered cases diagnosed with ASD (Hu et al., 2020), prompting an investigation into the etiopathogenesis and triggering risk factors of ASD. Among the various hypotheses, researchers have proposed, those based on linking intestinal dysbiosis with central nervous system (CNS) diseases stand out. Therefore, the presented study focused on reviewing the best available evidence linking intestinal dysbiosis with the development of ASD in children and exploring treatment options.

Materials and Methods

Study area:

Human Health

Field sampling:

Not applicable

A systematic review was conducted on the electronic databases Science Direct, NCBI, MDPI, Scopus and Hindawi

The gut-brain microbiota axis

a. Nervous System

Between the nervous system (NS) and the gastrointestinal tract (GIT) exists many means of communication or signaling. Among these, the innervation of the GIT by the vagus nerve, endocrine secretions, and immunological components, the production of SCFAs by the microbiota, and the blood-brain barrier stand out;

see mechanisms in Fig. 1 (Carabotti et al., 2025; Splittgerber R, 2019; Cryan JF et al., 2019). When changes occur at the level of the intestinal microbiota, it affects the functional structure of the gut-brain microbiota axis. Causing epigenetic changes and increased the number of methyltransferases (Cuomo et al., 2023). However, it is not proven whether intestinal dysbiosis can affect our genome.

On the other hand, the autonomic nervous system (ANS) with neurogenic and neuroendocrine signals can produce changes in intestinal motility by modulating the CNS (Splittgerber R, 2019), which can cause malabsorption and imbalance of the microbiota. A crucial component of the relationship between the ANS and intestinal dysbiosis is the connection with the enteric nervous system (ENS). The ENS comprises a series of plexuses over a large extent of the gastrointestinal tract (GIT): the submucosal plexus of Meissner (controls mucous glands) and the myenteric plexus of Auerbach (controls peristalsis). These plexus networks are involved in microbiota changes and their direct connection with the CNS.

The ENS includes a diversity of neurons and glia in the intestinal wall that control the digestive and defense functions of the GIT through interaction with the immune system (IS). The ENS is composed of primary intrinsic afferent neurons (PIANs) that coordinate peristalsis by sensing distension in the lumen, interneurons, motor neurons, and enteric glial cells (EGCs). However, EGCs participate in the IS and ENS, expressing receptors for different components besides their supporting function (Giuffrè et al., 2020). The toll-like receptor (TLR) pathway is activated by various pathogens, explaining its involvement in the pathophysiology of different diseases (Frosali et al., 2015), inducing dysbiosis due to disruption of homeostasis. Under these conditions, susceptibility to inflammatory bowel diseases increases (Frosali et al., 2015). Another communication pathway of the ENS and CNS is through the enteric nervous system (EIN) via afferent fibers to the sympathetic ganglion and higher brain centers.

The mechanism by which the microbiota affects ENS neurons is through the activation of pattern recognition receptors (PRRs) such as TLRs, which can respond to viral RNA and bacterial lipopolysaccharides (Erny et al., 2017) and promote aberrant signals in dysbiosis conditions. An imbalance in the information connections between the GIT and the brain contributes to acute or chronic intestinal inflammatory processes (Frosali et al., 2015), which are common in individuals with ASD.

b. Vagus Nerve

Much of the connection between the brain and the intestine is through the vagus nerve (X), whose parasympathetic activity receives input from the hypothalamus or the glossopharyngeal nerve (Cryan et al., 2019). The X nerve also receives afferent information from interganglionic laminar endings which are in contact with the myenteric plexus and mucosal afferent neurons (Cook & Mansuy-Aubert, 2022) (see Fig. 1).
Additionally, the vagus nerve has 80% afferent fibers and 20% efferent fibers (Cryan et al., 2019), allowing it to participate in bidirectional interaction. Its inappropriate and excessive activation can elevate neurotransmitters that affect gastric motility (Splittgerber R, 2019). Furthermore, the vagus nerve plays a role in the immune system, activating macrophages and increasing the production of pro-inflammatory cytokines.

A decrease in vagus nerve activity correlates with bacterial overgrowth and their translocation to hematopoietic tissue.

c. Enterocytes

The gastrointestinal tract possesses a mucosal layer, secreted by goblet cells, facilitating colonization and interaction with the microbiota. Among the different types of intestinal epithelial cells, enterocytes participate in innate immunity mechanisms, by expressing receptors on their membranes and releasing cytokines. Epithelial PRRs recognize these patterns presented by bacterial polysaccharides, thus inducing the release of mediators of the inflammatory response. The microbiota is essential for the plasticity of the individual's innate immune system as it participates in the maturation and functions of microglia. Neurological disorders like ASD challenge the immune system, leading to observed dysregulations of immune-related genes and elevated inflammatory markers (Andersen-Civil et al., 2023).

Research in mice shows that a healthy microbiota exhibits a higher expression of colony-stimulating factor-1 (CSF-1), involved in the proliferation and maturation of microglia (Erny et al., 2017), suggesting the effect of the microbiota acquired at birth on microglial proliferation during the first weeks of life. Contrasting these results with information on hematopoietic cell counts led to the conclusion that a reduced number of blood cells corresponds to greater diversity in the intestinal microbiota (Erny et al., 2017).

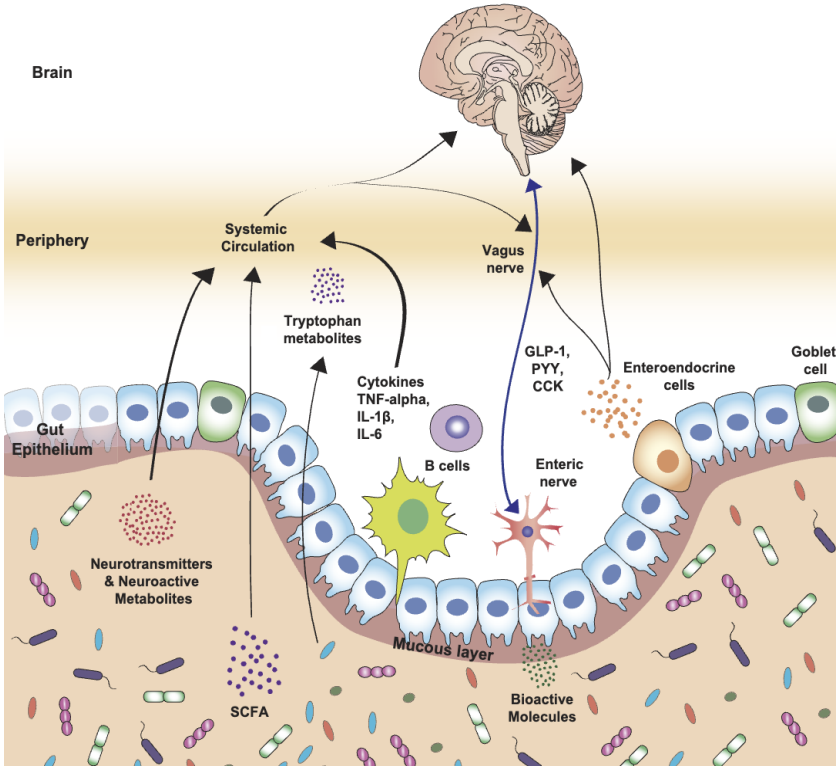
Therefore, alterations in microglial function are related to various neurodevelopmental disorders (Andersen-Civil et al., 2023). Brain inflammation is usual in ASD, with active microglia and astrocytes affecting neuronal connectivity (Andersen-Civil et al., 2023), which can lead to neuronal death.

The microbiota relies on enteroendocrine cells (EECs) as a nexus for interaction with afferent fibers of the vagus nerve through the release of serotonin, which activates 5-hydroxytryptamine-3 receptors on vagal afferent fibers, or via intestinal hormones, such as gastrin and cholecystokinin (Margolis et al., 2021; Rutsch et al., 2020; Ma et al., 2019). Although EECs comprise less than 1%, they can detect bacterial compounds and have an indirect effect on vagal afferent fibers by regulating gastrointestinal motility, secretion, and food intake and digestion. Additionally, oral administration of Campylobacter promotes the active state of neurons in the nucleus of the solitary tract as the first intracranial entry of vagal afferents (Margolis et al., 2021; Ma et al., 2019).

EECs secrete the anorexigenic hormones: glucagon-like peptide 1 (GLP-) and peptide YY (fig. 1). Whose receptors are located in enteric neurons and vagal afferent pathways (Ma et al., 2019). Activation of these L cells can be exclusively through bacterial metabolites. In contrast, enterochromaffin cells produce most of the 5-HT from tryptophan metabolism, which activates nerve afferent fibers through its binding to chemoreceptors (Ma et al., 2019).

Figure 1

Gut-brain communication pathways



There are multiple pathways connecting the nervous system and the gastrointestinal tract: endocrine (cortisol and intestinal hormones), immune (cytokines), and nervous (vagus nerve and enteric nervous system) pathways. Much of the connection is provided by the vagus nerve which has 80% afferent fibers and 20% efferent fibers. Another connection is through enteroendocrine signals which coordinate the exchange of metabolites. Glucagon-like hormone-1 (GLP-1), cholecystokinin, and peptide YY, secreted when food is ingested, are considered predictive indicators of appetite response. These have receptors on enteric neurons and vagal afferent pathways. L-cell activation depends on bacterial metabolites such as cholecystokinin. Additionally, enteroendocrine cells can detect bacterial compounds and have an indirect effect on vagal afferent fibers by regulating gastrointestinal motility, secretion, and food intake and digestion.

d. Neuroinflammation

Neuroinflammation occurs in various CNS diseases, including ASD. In this context, the protein complex known as the inflammasome stands out, composed of a receptor with oligomerization and nucleotide-binding domain (NLR) or AIM2, ASC protein, and caspase-1. Caspase-1 catalytically activates the cytokines IL-1β and IL-18, implicated in diverse inflammatory processes (Kelley et al., 2019). Demonstrating that suppressing caspase-1 helps improve symptoms related to neurological disorders due to reduced systemic inflammation (Li et al., 2023).

Inflammasomes play a significant role in neurodevelopment. It was thought that IL-1β, a crucial molecule for learning and memory in the hippocampus, was overexpressed during neuronal activity. Years later, it revealed that the AIM2 inflammasome was activated in response to DNA damage (DAMP) and promoted neurodevelopment by modulating Gasdermin-D, rather not cytokine synthesis (Lammert et al., 2020). Gasdermin-D is an executor protein of pyroptosis, forming membrane pores that induce inflammasome-driven programmed cell death.

The intestinal microbiota can be affected by intrinsic and extrinsic factors, with diet having the greatest impact on its composition (Generoso et al., 2021; Murguiondo-Pérez et al., 2022). Short-chain fatty acids (SCFAs) are bacterial metabolic products implicated in modulating the inflammatory response and CNS plasticity (Rutsch et al., 2020; Generoso et al., 2021). SCFAs induce the transcription of various molecules that enhance epithelial membrane protection.

Consequently, by reducing bacterial translocation, PAMPS/DAMPS cannot be recognized by toll receptors, nor will the synthesis of inflammasome components be initiated (Margolis et al., 2021). One reason for the loss of epithelial barrier integrity is the increase in oxidative stress in the epithelium. The importance of SCFAs in regulating the Keap1-Nrf2 signaling pathway is noteworthy, as they are major regulators of homeostasis. This pathway is responsible for metabolic resilience, and oxidative stress, and encodes several cytoprotective enzymes (Clinicaltrials, nd). Additionally, the blood-brain barrier is permeable to SCFAs, facilitating their interaction with microglia (Song et al., 2021). This means that cytokines produced due to bacterial translocation from epithelial barrier dysfunction confer no positive effects on neuropsychiatric diseases.

Previous studies have observed an association between the microbiota and the development of the hippocampus and limbic system (Margolis et al., 2021), brain areas related to memory and cognition. This could explain the relationship between dysbiosis and cognitive and memory disorders in patients with neurodegenerative diseases and other conditions.

Development of microbiota

The microbiota contains microbial communities, primarily composed of bacteria and a lower amount of viruses, archaea, and protozoa (Rutsch et al., 2020; Ma et al., 2019; Liu et al., 2023). Among the various biological functions, it assumes, fermentation of fibers, synthesis of vitamins, short-chain fatty acids, tryptophan, and defense against pathogens stand out (Liu et al., 2023).

Typically, the intestinal microbiota establishes its composition by the age of 2-3 years. However, it can be modified according to exposure to environmental and nutritional factors (Generoso et al., 2021). Given that nutrition significantly contributes to the composition of the microbiota, providing balanced diets from the early months of life is necessary.

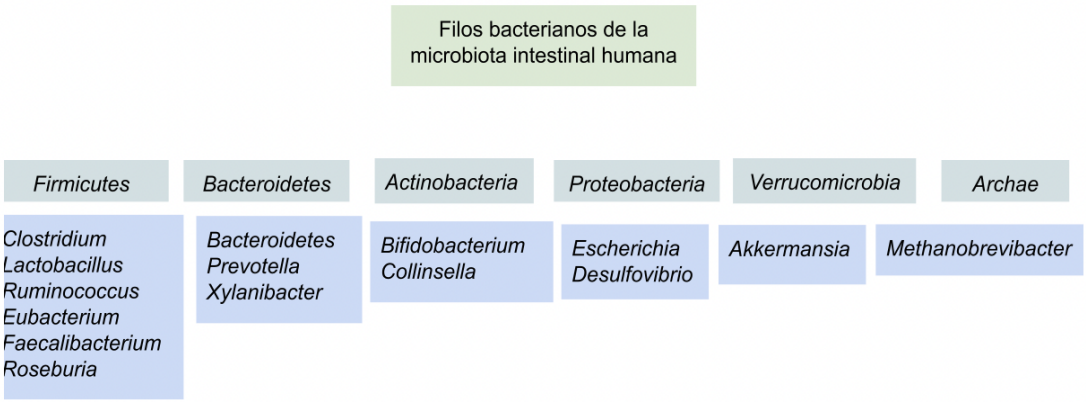
There is evidence that the consumption of diets high in fructose causes changes in the microbiota associated with prolonged inflammatory response affecting the hippocampus (Rutsch et al., 2020; Generoso et al., 2021; Murguiondo-Pérez et al., 2022), and thus the memory and cognitive abilities of patients. Therefore, professionals involved in human alimentation recommend consumption of plant-based diets, rich in fiber that can only be digested and metabolized by the microbiota. Products derived from the metabolism of these fibers have a positive effect on the normal structural and functional development of the CNS. In particular, it has been shown that SCFAs, produced by the microbiota, are neuroactive components that regulate the metabolism and activity of the body's immune system (Murguiondo-Pérez et al., 2022).

During the prenatal and postnatal stages, the composition and development of the microbiota depend on the maternal condition, such as various environmental factors, the mode of delivery, and her own diet (Melo & Reis, 2020; Barber, 2021). It has been demonstrated that neonates born vaginally present high levels of intestinal bacteria such as *Bifidobacterium* and *Lactobacillu*s (Lee, 2019), in the composition of the intestinal microbiota (fig. 2). Conversely, babies born by cesarean section have elevated levels of *Clostridium* and *Enterococcus* in their mouth and skin (Lee, 2019).

Some studies have found an increase in the density of proinflammatory bacterial strains and alterations in SCFAs in fecal samples of children with ASD, which could be associated with alterations in the gut-brain microbiota axis in these children. In this study, evidence is presented regarding the presence of epigenetic modifications of DNA from proinflammatory genes associated with ASD in fecal samples (Cuomo et al., 2023), such as methylation of CD34+ hematopoietic cell bases, affecting neuronal synapses. The risk of immunological alterations, asthma, and obesity in children born by cesarean section is also documented (Paoli et al., 2019). However, these effects are transient and can be resolved during childhood (Sassin et al., 2022) with healthy balanced diets.

Figure 2

The Predominant Bacterial Phyla in the Human Intestinal Microbiota



The human microbiota is home to different types of beneficial bacteria for our system. Our body is home to approximately 100 trillion different microorganisms. The figure shows different types of bacteria present in the intestine, which are divided into groups according to their function and family. Regarding the composition of the intestinal microbiota, at an early age, the digestive tract will contain bacteria such as Escherichia coli, which has the function of breaking down and digesting food. Additionally, the microbiota is composed of multiple species of Lactobacillus, Bacteroides, Clostridium, Eubacterium, and Bifidobacteria. The intestinal microbiota is led by anaerobic bacteria (Ballesteros & Gonzalez, 2018; Martinez & Andreo, 2020).

Children born by cesarean section show significantly higher levels of DNA methylation in leukocytes and CD34+ cells compared to those born vaginally (Guarner & Malagelada, 2003). Additionally, most children with ASD tend to have various dietary restrictions and feeding problems leading to nutritional deficiencies and alterations in microbiota composition (Wang et al., 2024). The brain undergoes rapid development in the first three years of life, concurrently with microbiota development, suggesting a relationship between microbiota and neurodevelopment (Liu et al., 2023; Grimaldi et al., 2018). It may explain the potential association between early-life intestinal dysbiosis and neurodevelopmental deficits.

Dysbiosis Prevention and its Relationship with ASD

The microorganisms that inhabit the intestine will be determined and controlled by each mouthful of food ingested. When the patient presents discomfort in the gastrointestinal tract, such as constipation, abdominal pain, irritable bowel syndrome, and diarrhea (classic symptoms of 70% of autistic patients) (Real et al., 2021; Herrera et al., 2022). Their intensity is usually associated with the severity of autistic symptoms (Real et al., 2021) such as anxiety and hypersensitivity to stimuli. Findings suggest that alterations in the microbiota are

involved in the etiopathogenesis of ASD (Real et al., 2021), therefore some therapeutic strategies are to regulate the microbiota by a balanced alimentation.

Normally there is a tendency to recommend diets without gluten or casein, and the administration of prebiotics and probiotics (Castañeda, 2019). Gluten is a protein that can be found in wheat, rye, and barley, extremely complicated to digest. If the patient is sensitive to it, it can cause irreversible damage to the villi of the small intestine mucosa.

On the other hand, casein is a phosphoprotein present in milk and its derivatives, which is only 40% digestible, and it favors gas, constipation, and intestinal permeability (Herrera et al., 2022). This intolerance to gluten and casein is due to the presence of metabolic alterations in methylation, sulfation, oxidative stress, amino acid excretion, and glutamate and glutamine levels. This causes constant inflammation of the gastrointestinal tract, increasing its permeability, and thus predisposing the patient to present sensitivity to gluten and casein (Herrera et al., 2022; Collantes et al., 2021).

Prebiotics are non-digestible foods, with high fiber content, which act as food for the microorganisms that form the intestinal microbiota, stimulating their proliferation. The main prebiotics are oligofructose, inulin, and galacto-oligosaccharides. On the other hand, probiotics are supplements or foods containing live microorganisms (bacteria and yeasts), which are implanted and colonize the intestine, favoring the intestinal microbiota. The prescription of both prebiotics and probiotics promotes the proliferation and survival of previously existing microorganisms, and the colonization of microorganisms absent in the intestine. This allows for promoting healthy digestion (Ballesteros & González, 2018; Martínez & Andreo, 2020).

The microbiota develops simultaneously with the brain (Grimaldi et al., 2018). Therefore, the diet must be balanced. The microbiota of people with ASD presents a reduction of beneficial bacterial genera such as Bifidobacterium, and an increase of pathogenic bacteria such as Clostridium (Grimaldi et al., 2018). The nutritional imbalance that occurs at early ages affects both the development of a healthy microbiota and brain mass, emphasizing the microbiota-gut-brain axis. (Song et al., 2022).

The resulting intestinal dysbiosis has been related to the pathogenesis of ASD. This is characterized by changes in the composition of the microbiota that alter the metabolism of aromatic substances such as the amino acid tryptophan; this is converted by microorganisms into biologically active molecules such as indole, essential for neurological homeostasis. Decreased plasma tryptophan levels are associated with the development of ASD. In addition, a meta-analysis of 9 studies showed that children with ASD have less amount of *Akkermansia*, *Bacteroides, Bifidobacterium*, and *Parabacteroides* colonies and an increased *Faecalibacterium* colony (Taniya et al., 2022).

In a study published in the journal BMC, the impact of exclusion diets and administration of galacto-oligosaccharide prebiotics in autistic children was evaluated. The results showed improvements in the behavior and a decrease in gastrointestinal tract problems. Food exclusion is closely related to the decrease in gastrointestinal symptomatology, and probiotic administration with improvements in antisocial behavior and changes in fecal and urinary metabolites. (Milani et al., 2017).

Food exclusion and administration of prebiotics and probiotics may be the least invasive alternatives to address dysbiosis. However, there is another slightly more invasive, yet more direct option, which is fecal

transplantation or microbiota transfer therapy, where feces are collected from a healthy donor, and fecal material is infused into the patient through a nasogastric, nasoduodenal or nasojejunal tube, or by a retention enema or colonoscopy (Feng et al., 2023). In a systematic review of 4 papers on fecal transplantation in patients with ASD, it was concluded that patients who underwent transplantation improved 80% of gastrointestinal symptoms(Ohio State University, 2020). The symptoms include abdominal pain and diarrhea; also, clinical assessments showed significant behavioral improvements and continued to improve for the next 8 weeks of treatment (He et al., 2023).

Discussion

The relevance of neurophysiological dysfunctions in the gut-brain-microbiota axis concerning ASD is acknowledged. Data supports a direct connection between neuroinflammation and the immune system, primarily affecting microglia. Through various connections, the central nervous system (CNS) and the gastrointestinal tract (GIT) communicate, explaining how poor nutrition can impact the development of microbiota and brain mass. However, ASD is a multifactorial condition, preventing dysbiosis from being classified as a direct cause of ASD development in children. This review demonstrates the importance of establishing a healthy microbiota and its effects on ASD, not as a causal agent but as an influential factor. Therefore, healthcare professionals advise children with ASD and their families to adhere to a balanced, nutritious, and high-fiber diet.

The intestinal microbiota is an underdeveloped area of study. Therefore, conducting a cohort study to analyze the specific composition of the microbiota in each child with ASD would be highly valuable, correlating whether the absence or presence of particular microorganisms affects the development and exacerbation of ASD symptoms in children.

Finance

There was no funding for this systematic review

Conflict of de interest

There was no conflict of interest on the part of the authors.

Key messages

There is a need for a case-control study to investigate the effect of dysbiosis on the development of the autism spectrum.

References

Andersen-Civil, A. I. S., Sawale, R. A., & Vanwalleghem, G. C. (2023). Zebrafish (Danio rerio) as a translational model for neuro-immune interactions in the enteric nervous system in autism spectrum disorders. *Brain, Behavior, and Immunity*, *112*, 254–266. doi: 10.1016/j.bbi.2023.06.001

Arberas, C., & Ruggieri, V. (2019). Autismo: Aspectos genéticos y biológicos. *Medicina*, *79*(1), 16–21. Retrieved from http://www.scielo.org.ar/scielo.php?script=sci_arttext&pid=S0025-76802019000200005

Ballesteros Pomar, M. (2018). Papel de los prebióticos y los probióticos en la funcionalidad de la microbiota del paciente con nutrición enteral. *Nutrición Hospitalaria: Organo Oficial de La Sociedad Española de Nutrición Parenteral y Enteral*, *35*(SPE2), 18–26. doi:10.20960/nh.1956

Barber, T. M., Valsamakis, G., Mastorakos, G., Hanson, P., Kyrou, I., Randeva, H. S., & Weickert, M. O. (2021). Dietary influences on the Microbiota–gut–brain axis. *International Journal of Molecular Sciences*, *22*(7), 3502. doi:10.3390/ijms22073502

Barbosa, P. M., & Barbosa, E. R. (2020). The gut brain-axis in neurological diseases. *International Journal of Cardiovascular Sciences*. doi:10.36660/ijcs.20200039

Castañeda Guillot, C. (2019). Trasplante de microbiota fecal. *Revista Cubana de Pediatría*, *91*(3). Retrieved from http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0034-75312019000300010

Cleary, D. B., Maybery, M. T., Green, C., & Whitehouse, A. J. O. (2023). The first six months of life: A systematic review of early markers associated with later autism. *Neuroscience and Biobehavioral Reviews*, *152*(105304), 105304. doi: 10.1016/j.neubiorev.2023.105304

Collantes, Z., Patricia, A., Tapay, M., & Isaías, R. (2021). *BENEFICIOS DE UNA DIETA LIBRE DE GLUTEN Y CASEINA EN LA DISMINUCIÓN DE LOS SÌNTOMAS PROPIOS DEL AUTISMO*. UNIVERSIDAD ESTATAL DE MILAGRO FACULTAD DE SALUD Y SERVICIOS SOCIALES.

Cook, T. M., & Mansuy-Aubert, V. (2022). Communication between the gut microbiota and peripheral nervous system in health and chronic disease. *Gut Microbes*, *14*(1). doi:10.1080/19490976.2022.2068365

Clinicaltrials.gov. (n.d.). Retrieved February 5, 2024, from Clinicaltrials.gov website: https://clinicaltrials.gov/study/NCT02903030

Cryan, J. F., O'Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., … Dinan, T. G. (2019). The Microbiota-gut-brain axis. *Physiological Reviews*, *99*(4), 1877–2013. doi:10.1152/physrev.00018.2018

Cuomo, M., Coretti, L., Costabile, D., Della Mónica, R., De Riso, G., Buonaiuto, M., … Lembo, F. (2023). Host fecal DNA specific methylation signatures mark gut dysbiosis and inflammation in children

affected by autism spectrum disorder. *Scientific Reports*, *13*(1), 1–9. doi:10.1038/s41598-023-45132-0

Erny, D., Hrabě de Angelis, A. L., & Prinz, M. (2017). Communicating systems in the body: how microbiota and microglia cooperate. *Immunology*, *150*(1), 7–15. doi:10.1111/imm.12645

Feng, P., Zhao, S., Zhang, Y., & Li, E. (2023). A review of probiotics in the treatment of autism spectrum disorders: Perspectives from the gut–brain axis. *Frontiers in Microbiology*, *14*. doi:10.3389/fmicb.2023.1123462

Frosali, S., Pagliari, D., Gambassi, G., Landolfi, R., Pandolfi, F., & Cianci, R. (2015). How the intricate interaction among Toll-like receptors, Microbiota, and intestinal immunity can influence gastrointestinal pathology. *Journal of Immunology Research*, *2015*, 1–12. doi:10.1155/2015/489821

Generoso, J. S., Giridharan, V. V., Lee, J., Macedo, D., & Barichello, T. (2021). The role of the microbiota-gut-brain axis in neuropsychiatric disorders. *Revista Brasileira de Psiquiatria (Sao Paulo, Brasil: 1999)*, *43*(3), 293–305. doi:10.1590/1516-4446-2020-0987

Giuffrè, M., Moretti, R., Campisciano, G., da Silveira, A. B. M., Monda, V. M., Comar, M., … Crocè, L. S. (2020). You talking to me? Says the Enteric nervous system (ENS) to the microbe. How intestinal microbes interact with the ENS. *Journal of Clinical Medicine*, *9*(11), 3705. doi:10.3390/jcm9113705

González-Bosch, C., Boorman, E., Zunszain, P. A., & Mann, G. E. (2021). Short-chain fatty acids as modulators of redox signaling in health and disease. *Redox Biology*, *47*(102165), 102165. doi: 10.1016/j.redox.2021.102165

Grimaldi, R., Gibson, G. R., Vulevic, J., Giallourou, N., Castro-Mejia, J. L., Hansen, L. H., … Costabile, A. (2018). A prebiotic intervention study in children with autism spectrum disorders (ASDs). *Microbiome*, *6*(1). doi:10.1186/s40168-018-0523-3

Guarner, F., & Malagelada, J. R. (2003). La flora bacteriana del tracto digestivo. *Gastroenterología y hepatología*, *26*, 1–5. Retrived from https://www.elsevier.es/es-revista-gastroenterologia-hepatologia-14-articulo-la-flora-bacteriana-del-tracto-13043240

He, X., Liu, W., Tang, F., Chen, X., & Song, G. (2023). Effects of probiotics on autism spectrum disorder in children: A systematic review and meta-analysis of clinical trials. *Nutrients*, *15*(6), 1415. doi:10.3390/nu15061415

Herrera Mejía, J., Ramos-Jiménez, A., Jiménez Vega, F., Campos Vega, R., González Córdova, A. F., & Wall-Medrano, A. (2022). Functional feeding to alleviate gastrointestinal disorders associated with autism spectrum disorders: A systematic review. *Nutrición Hospitalaria: Organo Oficial de La Sociedad Española de Nutrición Parenteral y Enteral*. doi:10.20960/nh.03898

Hirayama, M., & Ohno, K. (2021). Parkinson's disease and gut Microbiota. *Annals of Nutrition & Metabolism*, *77*(Suppl. 2), 28–35. doi:10.1159/000518147

Hu, T., Dong, Y., He, C., Zhao, M., & He, Q. (2020). The gut Microbiota and oxidative stress in autism spectrum disorders (ASD). *Oxidative Medicine and Cellular Longevity*, *2020*, 1–13. doi:10.1155/2020/8396708

Humphreys, C. (2020). Intestinal Permeability. In J. E. Pizzorno & M. T. Murray (Eds.), *Textbook of Natural Medicine* (pp. 166-177.e4). London, England: Elsevier.

Iglesias-Vázquez, L., Van Ginkel Riba, G., Arija, V., & Canals, J. (2020). Composition of gut Microbiota in children with autism spectrum disorder: A systematic review and meta-analysis. *Nutrients*, *12*(3), 792. doi:10.3390/nu12030792

Kelley, N., Jeltema, D., Duan, Y., & He, Y. (2019). The NLRP3 inflammasome: An overview of mechanisms of activation and regulation. *International Journal of Molecular Sciences*, *20*(13), 3328. doi:10.3390/ijms20133328

Lammert, C. R., Frost, E. L., Bellinger, C. E., Bolte, A. C., McKee, C. A., Hurt, M. E., … Lukens, J. R. (2020). AIM2 inflammasome surveillance of DNA damage shapes neurodevelopment. *Nature*, *580*(7805), 647–652. doi:10.1038/s41586-020-2174-3

Lee, H.-S. (2019). The interaction between gut microbiome and nutrients on development of human disease through epigenetic mechanisms. *Genomics & Informatics*, *17*(3), e24. doi:10.5808/gi.2019.17.3.e24

Li, M., Sun, X., Wang, Z., & Li, Y. (2023). Caspase-1 affects chronic restraint stress-induced depression-like behaviors by modifying GABAergic dysfunction in the hippocampus. *Translational Psychiatry*, *13*(1). doi:10.1038/s41398-023-02527-x

Liu, L., Wang, H., Chen, X., & Xie, P. (2023). Gut microbiota: a new insight into neurological diseases. *Chinese Medical Journal*, *136*(11), 1261–1277. doi:10.1097/cm9.0000000000002212

Ma, Q., Xing, C., Long, W., Wang, H. Y., Liu, Q., & Wang, R.-F. (2019). Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *Journal of Neuroinflammation*, *16*(1). doi:10.1186/s12974-019-1434-3

Margolis, K. G., Cryan, J. F., & Mayer, E. A. (2021). The Microbiota-gut-brain axis: From motility to mood. *Gastroenterology*, *160*(5), 1486–1501. doi:10.1053/j.gastro.2020.10.066

Martínez-González, A. E., & Andreo-Martínez, P. (2020). Prebióticos, probióticos y trasplante de microbiota fecal en el autismo: una revisión sistemática. *Revista de psiquiatría y salud mental*, *13*(3), 150–164. doi:10.1016/j.rpsm.2020.06.002

Mayer, E. A., Nance, K., & Chen, S. (2022). The gut–brain axis. *Annual Review of Medicine*, *73*(1), 439–453. doi:10.1146/annurev-med-042320-014032

Milani, C., Duranti, S., Bottacini, F., Casey, E., Turroni, F., Mahony, J., … Ventura, M. (2017). The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut Microbiota. *Microbiology and Molecular Biology Reviews: MMBR*, *81*(4). doi:10.1128/mmbr.00036-17

Murguiondo-Pérez, R., Alcántar-Garibay, Ó. V., Ben-Zión, E. W., Blancarte-Hernández, E., Tejerina-Marion, E., Loza-López, E. C., … Rivera-Monroy, G. (2022). The influence of gut brain axis in neurodegenerative diseases: short review. *Revista Mexicana de Neurociencia*, *23*(5). doi:10.24875/rmn.210000821

Paoli, A., Mancin, L., Bianco, A., Thomas, E., Mota, J. F., & Piccini, F. (2019). Ketogenic diet and Microbiota: Friends or enemies? *Genes*, *10*(7), 534. doi:10.3390/genes10070534

Real López, M., Peraire, M., Ramos Vidal, C., Nath, D., Hervás Zúñiga, A., & Cortés, X. (2021). Implicación de la disbiosis intestinal en la etiopatogenia y el tratamiento del trastorno del espectro autista: una revisión bibliográfica. *Revista de neurología*, *73*(08), 282. doi:10.33588/rn.7308.2021189

Ristori, M. V., Quagliariello, A., Reddel, S., Ianiro, G., Vicari, S., Gasbarrini, A., & Putignani, L. (2019). Autism, gastrointestinal symptoms and modulation of gut Microbiota by nutritional interventions. *Nutrients*, *11*(11), 2812. doi:10.3390/nu11112812

Rutsch, A., Kantsjö, J. B., & Ronchi, F. (2020). The gut-brain axis: How Microbiota and host inflammasome influence brain physiology and pathology. *Frontiers in Immunology*, *11*. doi:10.3389/fimmu.2020.604179

Sassin, A. M., Johnson, G. J., Goulding, A. N., & Aagaard, K. M. (2022). Crucial nuances in understanding (mis)associations between the neonatal microbiome and Cesarean delivery. *Trends in Molecular Medicine*, *28*(10), 806–822. doi:10.1016/j.molmed.2022.07.005

Song, M.-Y., Lee, D.-Y., Chun, K.-S., & Kim, E.-H. (2021). The role of NRF2/KEAP1 signaling pathway in cancer metabolism. *International Journal of Molecular Sciences*, *22*(9), 4376. doi:10.3390/ijms22094376

Song, W., Zhang, M., Teng, L., Wang, Y., & Zhu, L. (2022). Prebiotics and probiotics for autism spectrum disorder: a systematic review and meta-analysis of controlled clinical trials. *Journal of Medical Microbiology*, *71*(4). doi:10.1099/jmm.0.001510

Splittgerber, R. (2019). *Snell. Neuroanatomía clínica* (8th ed.). Barcelona, Spain: Lippincott Williams & Wilkins.

Srikantha, P., & Mohajeri, M. H. (2019). The possible role of the Microbiota-gut-brain-axis in autism spectrum disorder. *International Journal of Molecular Sciences*, *20*(9), 2115. doi:10.3390/ijms20092115

Taniya, M. A., Chung, H.-J., Al Mamun, A., Alam, S., Aziz, M. A., Emon, N. U., … Xiao, J. (2022). Role of gut microbiome in autism spectrum disorder and its therapeutic regulation. *Frontiers in Cellular and Infection Microbiology*, *12*. doi:10.3389/fcimb.2022.915701

Wang, H., Zhang, Q., Chen, Y., Hou, F., Zhu, K., Jiang, Q., … Song, R. (2024). Interaction between XRN2 mutation and gut microbiota on the risks of autism spectrum disorder. *Research in Autism Spectrum Disorders*, *110*(102297), 102297. doi:10.1016/j.rasd.2023.102297