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REVIEW

Relationship of dysbiosis with autism spectrum Disorder

Relación de la disbiosis con el trastorno del espectro autista

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ABSTRACT

Introduction: Autism Spectrum Disorder (ASD) encompasses neurological development disorders present from birth. According to the Diagnostic and Statistical Manual of Mental Disorders DSM-5, this neuropsychiatric condition manifests itself in two main areas, persistent deficits in social communication and interaction in multiple contexts (verbal or non-verbal languages and socio- emotional reciprocity) as well as restrictive patterns and repetitive behavior, interests or activities. A recent line of research on autism has focused on the microbiota-gut-brain axis. Alteration of the gut microbiota or Dysbiosis has been implicated in neurodevelopmental behavioral changes and gastrointestinal problems in patients with autism spectrum disorder (ASD).
Method: to carry out this review, a bibliographic search of scientific articles in computerized databases such as Pubmed and Scielo was used.
Conclusion: various studies have found that children with ASD present significant differences in the intestinal microbiota compared to neurotypical children. These differences not only seem to influence gastrointestinal symptoms, common in people with ASD, but also behavioral ones.

Keywords: Intestinal Dysbiosis; Gut-Brain-Microbiota Axis; Autism Spectrum Disorder; Social Brain; Alterations in Neurodevelopment.

RESUMEN

Introducción: el Trastorno del Espectro Autista (TEA) engloba trastornos del desarrollo neurológico presentes desde el nacimiento. Según el Manual Diagnóstico y Estadístico de Trastornos Mentales DSM-5, esta condición neuropsiquiátrica se manifiesta en dos áreas principales, déficits persistentes en la comunicación y la interacción sociales en múltiples contextos (lenguajes verbales o no verbales y reciprocidad socioemocional) así como en patrones restrictivos y repetitivos de comportamiento, intereses o actividades. Una línea de investigación reciente sobre el autismo se ha centrado en el eje microbiota-intestino-cerebro. La alteración de la microbiota intestinal o Disbiosis ha sido implicada en los cambios de comportamiento del neurodesarrollo y problemas gastrointestinales en pacientes con trastorno del espectro autista (TEA).
Método: para la realización de esta revisión se empleó una búsqueda bibliográfica de artículos científicos en base de datos informatizadas como Pubmed y Scielo.
Conclusión: diversos estudios han encontrado que los niños con TEA presentan diferencias significativas en la microbiota intestinal en comparación con niños neurotípicos. Estas diferencias no solo parecen influir en los síntomas gastrointestinales, comunes en personas con TEA, sino también en los comportamentales.

Palabras clave: Disbiosis Intestinal; Eje Intestino- Cerebro- Microbiota; Trastorno del Espectro Autista; Cerebro Social; Alteraciones en el Neurodesarrollo.

INTRODUCTION

Autism Spectrum Disorder (ASD) encompasses a group of neurodevelopmental conditions that typically appear in early childhood. This classification includes diagnoses such as Childhood autism, classic autism (formerly known as Kanner autism), Asperger syndrome, pervasive developmental disorder not otherwise specified, and childhood disintegrative disorder. According to the Diagnostic and Statistical Manual of Mental Disorders DSM-5 (the global reference for diagnostic criteria), people on the spectrum may have deficits in social communication or social interaction (such as verbal or nonverbal languages and socioemotional reciprocity) and restricted patterns and repetitive behaviors, such as continuous movements, highly restricted interests that are abnormal in intensity or focus, and unusual reactions to sensory stimuli, such as hypersensitivity to specific sounds or textures. Each patient will be affected in a particular way in some of these areas to varying degrees and intensities. Although it is still called childhood autism, as the diagnosis is common in children and even infants, autism spectrum disorder (ASD) is a permanent condition that accompanies the person throughout all stages of life. Throughout this paper, the terms "autism" and "ASD" will be used interchangeably.[1,2]

Worldwide, it is estimated that there is approximately one case of autism for every 100 people, according to recent data from the WHO (World Health Organization). We recognize that the diagnosis of ASD has grown exponentially in the last decade, with a higher prevalence among boys under the age of 6. There is evidence that this increase in diagnosis is partly associated with greater access to health services and awareness in high socioeconomic settings.

It should be noted that the prevalence of autism appears to depend on the country in which the study is conducted, demographics, the year in which the data is collected, and the diagnostic criteria used.

Risk factors and causes of autism

The World Health Organization classifies autism as a developmental disorder. It proposes studying it in three dimensions that provide a broad view of the factors that may explain the presence of the disorder. First, it mentions a group of diseases called genetic conditions due to delays in developing processes, skills, and behaviors. In its second category, the WHO mentions the so-called group of metabolic diseases, which are behavioral disorders caused by biochemical alterations in the body of genetic origin that affect cellular metabolism. Thirdly, it mentions autism spectrum disorder secondary to prenatal, perinatal, or postnatal injuries or when there are pathological conditions that interfere with the acquisition and refinement of skills during normal development.[2]

The study of autism raises the coherence of various methodological approaches. It adopts a stance on life from different sciences, biological, medical, psychological, social, and educational, to clarify the complex reciprocal relationships between the constitutional-genetic, organic, environmental, educational, and emotional factors that make up the totality of the human being. However, the issue of the causes of autism remains complex and incomplete. The conditions underlying autism are incredibly diverse. Although no absolute risk factor is known, autism is likely multifactorial.

Clinical manifestations of autism

These patients generally exhibit repetitive behavior that can be obsessive, incessant, perfectionist, always the same, and rigid. At times, they may display resistant behaviors. They also tend to be shy and have difficulty interacting with others.

The clinical manifestations and symptoms within the autism spectrum vary significantly from one person to another, reaching extreme levels of disability in communication, in the ability to understand the society around them, or in repetitive behaviors that seriously disrupt their lives and those of the people around them. There may also be some limitations (blocking, impaired intuitive abilities, and difficulty going beyond the literal) in imagining things, events, possible ways of acting, sensations, etc.

The relationship between microbiota and ASD

The brain-gut-microbiota axis has been identified as a key mechanism in regulating various physiological and psychological functions. This axis establishes two-way communication between the gut and the brain, influenced by the gut microbiota, which plays a crucial role in the homeostasis of the central nervous system (CNS). Recent research has begun to explore how intestinal dysbiosis—an imbalance in microbial composition—may be involved in the pathogenesis of neuropsychiatric disorders, including autism spectrum disorders (ASD).

Studies show that children with ASD have a higher prevalence of intestinal dysbiosis compared to neurotypical children. This alteration in the microbiota appears to correlate with the severity of gastrointestinal and behavioral symptoms associated with ASD.[3,4] Furthermore, modulation of the microbiota through probiotics or specialized diets has shown promise to improve the quality of life of children with ASD by reducing gastrointestinal and neurological symptoms.[5,6]

There is a significant correlation between intestinal dysbiosis and the severity of autistic symptoms.

Interventions that modify the microbiota can improve both gastrointestinal and behavioral symptoms.

Dysbiosis

Dysbiosis is an imbalance that disrupts the normal state of symbiosis, evidenced by both qualitative and quantitative changes in the composition and functions of the microbiota.[3] Defining what constitutes a normal microbiota, in terms of its composition and functions, is complicated due to the influence of various factors and considerable variability between individuals and physiological conditions. Dysbiosis states are often characterized by a decrease or lack of beneficial species that are typically predominant and an increase in the presence of minority species that may include opportunistic pathogens. They may lead to an overall alteration in the structure of the microbiota, as well as the loss or acquisition of particular species.

In ASD, it is recognized that there is bidirectional communication between the central nervous system (CNS) and the immune system through noradrenergic lymph nodes, entero-intestinal circulation, and parasympathetic innervation of the intestine.[4] Consequently, the immune and neuroendocrine microenvironment of the intestine can influence brain functions that are highly dependent on neurochemical conditions such as mood, alertness, and cognitive and behavioral functioning. On the other hand, the brain can influence the physiology and pathophysiology of the gastrointestinal system, its immune function, and microbiota.

In a randomized pilot study[5] on the use of probiotics in children with autism spectrum disorders and gastrointestinal symptoms, the aim was to evaluate the impact of probiotics on the quality of life in children with ASD and gastrointestinal symptoms. Thirteen children (aged 3-12 years) were randomly assigned to an 8-week crossover trial with VISBIOME (probiotic) and placebo, separated by a 3-week washout period. The results showed a 77 % retention rate (10 children completed the study), high treatment adherence (96 %), and no serious adverse events. It was concluded that there was a significant improvement in gastrointestinal symptoms with VISBIOME compared to placebo.

In the clinical trial by Niu et al.[6] differences between children with autism spectrum disorder (ASD) and neurotypicals (NT) were explored, as well as the impact of applied behavior analysis (ABA) training combined with probiotics versus ABA alone. Significant differences were found in the gut microbiota between the ASD and NT groups, including a lower abundance of Bacteroides and several bacterial genera in the ASD group. These findings suggest that the gut microbiota differs between children with ASD and NT, highlighting the potential usefulness of probiotics as an adjunct to ABA treatment to improve outcomes in ASD.

In a randomized controlled trial conducted by Sanctuary et al.[7] with children with ASD and gastrointestinal problems, the tolerability of a combined treatment of

probiotic (Bifidobacterium infantis) and prebiotic (bovine colostrum) was evaluated. The results indicated the treatment was well tolerated, with mild flatulence as the most common side effect. Some participants showed reduced gastrointestinal symptoms and atypical behavior, possibly related to decreased IL-13 and TNF-alpha. The study concluded that these findings suggest potential benefits of combined treatment in this population.

Advanced microbiome sequencing to compare the gut microbiota composition between children with ASD and neurotypical children was evaluated in the study by Plaza-Díaz et al.[8] children with ASD were found to have elevated levels of specific bacterial groups such as Acinetobacter, Proteobacteria, Bacillus, and Gammaproteobacteria compared to the control group. In addition, a specific increase in Proteobacteria was identified in children with ASD who experienced mental regression. These findings suggest that intestinal dysbiosis may be related to ASD, highlighting the importance of further research in larger cohorts and consideration of clinical subtypes within ASD.

METHOD

The search for articles for this review was conducted using the PubMed search engine. The search included the terms (axis gut-brain microbiota) OR (intestinal dysbiosis) AND (autism) OR (autism spectrum disorder). Some filters were applied: articles published in recent years (2010-2024), and according to the type of publication, cross-sectional studies, case-control studies, intervention studies, and literature reviews were selected.

The following eligibility criteria were established:

- Research articles that include patients diagnosed with ASD associated with gastrointestinal disorders.
- Articles published in English, Spanish, and Portuguese.
- Studies on the brain-gut-microbiota axis and psychoneuroimmunology.
- Observational and quasi-experimental studies.
- Clinical studies comparing the microbiota of children with ASD and neurotypical children.
- Research on probiotic interventions, gluten/casein-free diets, and other approaches to microbiota modulation.

The following exclusion criteria were stipulated:

- Open or crossover clinical trials.
- Studies that included patients hospitalized for chronic gastrointestinal diseases.
- Patients diagnosed with intestinal dysbiosis unrelated to ASD.
- Studies with incomplete data or without control groups.
- Observational research without an in-depth analysis of the gut microbiota.

Finally, 51 articles were found. After an initial reading of the titles, 26 publications were excluded because they focused on other neurodegenerative or psychiatric diseases, focused on epigenetic alterations, or did not meet the criteria, and duplicates were eliminated. This left 25 articles eligible for the review.

RESULTS

Microbiota and ASD

The link between the gut microbiota and autism spectrum disorder (ASD) has been the subject of a growing number of studies, which suggest that alterations in the microbial composition of the gut (dysbiosis) could play an important role in the onset and exacerbation of ASD symptoms. Several studies have found that children with ASD have significant differences in their gut microbiota compared to neurotypical children. These differences appear to influence not only gastrointestinal symptoms, which are common in people with ASD but also behavioral symptoms.[9,10]

Reduction in bacterial diversity

One of the most relevant studies on dysbiosis in ASD was conducted by Kang et al.[4], who found a significant decrease in bacterial diversity in children with ASD and an increase in

pro-inflammatory bacteria such as Clostridia. This study evaluated fecal samples from children with ASD and observed a high prevalence of bacteria of the Clostridium genus, known for their ability to produce neurotoxic metabolites such as propionic acid. These metabolites can potentially damage the intestinal barrier, increasing its permeability and facilitating the passage of toxic substances into the bloodstream. This phenomenon, commonly referred to as "leaky gut," has been associated with increased chronic inflammation and could contribute to the deterioration of brain processes, exacerbating the symptoms of ASD.[10]

Alteration of beneficial bacteria

A study conducted by Moreno et al.[11] found a higher prevalence of pathogenic bacteria such as Klebsiella pneumoniae and Proteus mirabilis in children with ASD compared to neurotypical children. These bacteria are linked to intestinal inflammatory processes, suggesting a connection between dysbiosis and the gastrointestinal symptoms frequently observed in people with ASD. In addition, children with ASD had significantly lower concentrations of beneficial bacteria such as Bifidobacterium and Prevotella, which play a key role in producing short-chain fatty acids (SCFAs), such as butyric acid. This SCFA is key to maintaining the integrity of the intestinal barrier and preventing chronic inflammation.[12]

Increased Bacteroidetes/Firmicutes ratio

Another important aspect of dysbiosis in ASD is the alteration in the proportion of specific bacterial phyla. Fattorusso et al.[12] documented an increase in the Bacteroidetes/Firmicutes ratio in children with ASD compared to neurotypical children. This elevated ratio is associated with an increase in the production of lipopolysaccharides (LPS), molecules that activate the immune system and promote systemic inflammation. The study also suggested that LPS may exacerbate behavioral symptoms of ASD, such as irritability, repetitive behaviors, and social interaction problems.

Studies in animal models

Animal models have also shed light on the role of dysbiosis in ASD. Hsiao et al. (2013) demonstrated that mice inoculated with dysbiotic microbiota from children with ASD exhibited altered behaviors, including reduced social interaction and increased repetitive behaviors. This finding supports the hypothesis that the gut microbiota may influence the central nervous system and play a role in the onset of behavioral symptoms of ASD. Research suggests that dysbiosis may alter the production of key neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin, which are involved in behavior regulation.[13]

Gastrointestinal Symptoms

Gastrointestinal symptoms are a relevant and often underestimated aspect in children with autism spectrum disorder (ASD). Numerous studies have shown that gastrointestinal conditions such as diarrhea, constipation, and abdominal pain are much more common in children with ASD than in those with neurotypical development.

This intestinal dysfunction appears to be directly related to alterations in the gut microbiota, which affect the integrity of the intestinal barrier and its interaction with the central nervous system (CNS) through the gut-brain axis.[12]

Prevalence of gastrointestinal problems in children with ASD

Gastrointestinal problems in children with ASD have been documented with a considerably high prevalence. A study by Marler et al.[14] estimated that between 46 % and 84 % of children diagnosed with ASD experience recurrent gastrointestinal symptoms, with constipation and diarrhea being the most common. In addition, intestinal inflammation, accompanied by abdominal pain, has been widely reported. In comparison, neurotypical children have a much lower prevalence of these conditions, suggesting that gastrointestinal dysfunction maybe associated with the behavioral disorders that characterize ASD. Relationship between intestinal dysbiosis and gastrointestinal symptoms

The alteration of the intestinal microbiota in children with ASD, known as dysbiosis, is a key factor in understanding the prevalence of gastrointestinal problems in this group. Fattorusso et al. (2019) highlighted that children with ASD have a higher incidence of pathogenic bacteria such as Clostridium and Desulfovibrio, which produce toxic metabolites that alter the function of the intestinal barrier, promoting its permeability. This condition, known as "leaky gut," facilitates the passage of inflammatory molecules into the bloodstream, which can trigger immune responses and influence the bidirectional connection between the gut and the brain. This contributes not only to gastrointestinal symptoms but also to the exacerbation of autistic behaviors such as irritability, social isolation, and repetitive behaviors.[10]

An imbalance in bacterial species characterizes the intestinal dysbiosis observed in children with ASD. While beneficial bacteria such as Bifidobacterium and Lactobacillus, which are responsible for maintaining intestinal health, are significantly reduced, pro-inflammatory bacteria increase. These pathogenic bacteria not only disrupt digestion but also trigger chronic inflammation, which can exacerbate both digestive and neurological symptoms associated with ASD.[11]

Influence of the microbiota on interaction with the CNS

The microbiota-gut-brain axis is crucial for regulating behavior and emotional state. It has been proposed that disruption of this axis due to intestinal dysbiosis in children with ASD could alter the production of neurotransmitters, such as gamma-aminobutyric acid (GABA) and serotonin, which play important roles in mood and behavior regulation. Animal models of mice with intestinal dysbiosis have shown behaviors similar to those observed in ASD, suggesting that gut microbiota may play a causal role in the onset of behavioral and digestive symptoms.[10]

Impact of Microbiological Interventions on Children with Autism Spectrum Disorder (ASD)

Interventions that seek to modulate the gut microbiota have shown promising results in improving both gastrointestinal (GI) and behavioral symptoms in children with autism spectrum disorder (ASD). Among these interventions, probiotics, prebiotics, specialized diets, and fecal microbiota transplantation (FMT) have been investigated, with some studies reporting notable improvements in patients' symptoms.[4,15] However, although initial findings are encouraging, evidence is still limited, and large-scale controlled clinical trials are needed to confirm the effectiveness and generalizability of these treatments.

Use of probiotics in the treatment of ASD

The use of probiotics has been one of the most studied therapeutic approaches to modify the gut microbiota in children with ASD. Probiotics, which are live microorganisms that benefit intestinal health, have shown the potential to improve GI and behavioral symptoms. A study by Shaaban et al.[15] evaluated the administration of a combination of Lactobacillus acidophilus, Bifidobacterium longum, and Streptococcus thermophilus in children with ASD over a four-month period. The results revealed a significant improvement in intestinal function, with a reduction in episodes of diarrhea and constipation, as well as improvements in behavioral symptoms, such as increased sociability and a decrease in repetitive behaviors. These results suggest that modulation of the microbiota through probiotics could be a viable therapeutic tool for alleviating symptoms associated with ASD.

Gluten- and casein-free diet: a focus on the microbiota

Another widely explored intervention is the gluten- and casein-free diet, which has shown benefits in some children with ASD. Several studies suggest that this diet may favorably modify the composition of the gut microbiota by reducing the presence of pathogenic bacteria and promoting the growth of beneficial bacteria. A clinical study showed that children on this diet experienced a reduction in gastrointestinal symptoms, such as abdominal pain and diarrhea, improved sociability, and reduced repetitive behaviors. Although this approach has shown positive effects in some instances, the effectiveness of the diet varies among individuals, and more

controlled studies are needed to understand its impact [12] better.

Fecal microbiota transplantation (FMT): promising results

One of the most innovative approaches to treating ASD is fecal microbiota transplantation (FMT), which involves transferring microbiota from a healthy donor to the patient's gut to restore microbial balance. An open-label study conducted by Kang et al.[4] investigated the effects of FMT in a group of children with ASD. The results showed notable improvements in gastrointestinal function, with a significant reduction in symptoms of diarrhea and constipation. More importantly, the study also observed improvements in the severity of behavioral symptoms, as measured by autism scales. Children treated with FMT showed increased social interaction and a decrease in repetitive behaviors, supporting the hypothesis that intestinal dysbiosis may influence ASD symptoms.

However, despite FMT's positive results, studies in this area are still in the preliminary stages and have several limitations. First, the sample sizes of these studies are often small, making it difficult to generalize the findings. In addition, the microbiota composition varies considerably between individuals, which may affect the treatment response. To validate these results, larger-scale controlled clinical trials are needed to explore individual variables that may influence the effectiveness of FMT.[16]

DISCUSSION

Despite growing interest in studying the relationship between gut microbiota and autism spectrum disorder (ASD), studies conducted to date have significant limitations that should be considered when evaluating the findings. One of the main barriers is the lack of long-term controlled studies. Most available studies have short-term designs, and although they have shown promising results, they do not allow for the evaluation of the sustained impact of interventions on the microbiota over time.[17] This is particularly relevant for using probiotics and fecal microbiota transplants (FMT), interventions that may require prolonged monitoring to determine their long-term effectiveness and safety.

Sample size and heterogeneity of interventions

One of the most frequently cited limitations in the literature is the small size of the samples studied. Many studies investigating the relationship between microbiota and ASD have few participants, which reduces statistical power and limits the generalizability of the results. In addition, heterogeneity in the interventions studied, ranging from the administration of different combinations of probiotics to specialized diets and FMT makes direct comparisons between studies difficult.[18] This lack of uniformity in interventions and protocols limits the ability to perform conclusive meta-analyses that integrate the results of different studies.

For example, the study by Shaaban et al.[15] which showed improvements in gastrointestinal and behavioral symptoms after the administration of probiotics, used a specific combination of Lactobacillus acidophilus, Bifidobacterium longum, and Streptococcus thermophilus. In contrast, other studies have used different strains or doses, making replicating and comparing findings difficult. Similarly, differences in the methodologies used to assess microbiota composition, such as fecal analysis, which may not accurately reflect the small intestine microbiota, add another complexity to interpreting results.[12]

Individual variability and confounding factors

Another significant limitation is the variability in microbiota composition between individuals. The gut microbiota is influenced by several factors, including diet, antibiotic use, environmental conditions, and genetic differences. This means that results obtained in one study group may not be applicable to others due to these individual variations. In addition, many studies do not adequately control for these confounding factors, which can influence results and lead to misinterpretations.[13]

Causality: Is dysbiosis a cause or a consequence?

Another key challenge is the lack of clarity regarding causality. It is not entirely clear whether gut dysbiosis is a cause of ASD symptoms or whether, conversely, the behavioral and dietary alterations typical of children with ASD cause changes in the gut microbiota. Some studies suggest that dysbiosis may contribute to the exacerbation of ASD symptoms, such as gastrointestinal and behavioral problems.[18] In contrast, others argue that these changes in the microbiota result from characteristics specific to ASD, such as dietary restrictions or frequent use of antibiotics in some cases.

This ambiguity about the relationship's direction underscores the need for further research to explore the underlying mechanisms of this interaction.

Need for longitudinal studies and large-scale clinical trials.

To overcome these limitations, future studies on the microbiota in ASD must include larger sample sizes

and more standardized intervention approaches. In addition, longitudinal studies are needed to assess the long-term effects of interventions on the microbiota, and large-scale controlled clinical trials are needed to better evaluate the safety and effectiveness of therapies such as probiotics and FMT. This research is essential to determine whether microbiota modulation can be a viable and sustained therapeutic strategy for managing ASD symptoms.[17]

CONCLUSIONS

Intestinal dysbiosis is associated with greater severity of gastrointestinal and behavioral symptoms in children with autism spectrum disorder (ASD). Alterations in the microbiota, such as an increase in pathogenic bacteria and a decrease in beneficial bacteria, are linked to common symptoms in these patients, such as diarrhea, constipation, intestinal inflammation, repetitive behaviors, and social interaction difficulties.

Interventions based on modulating the gut microbiota, such as the use of probiotics and specific diets, have shown a positive impact on these symptoms. In a study by Shaaban et al. the administration of probiotics (Lactobacillus acidophilus, Bifidobacterium longum, Streptococcus thermophilus) for four months resulted in significant improvements in both gastrointestinal and behavioral symptoms in children with ASD. In addition, fecal microbiota transplantation (FMT), according to the study by Kang et al. produced positive results in improving intestinal function and reducing the severity of ASD symptoms.

However, these studies have methodological limitations. Most of them have small samples, which limits the ability to generalize the results. Furthermore, many studies do not control for external factors such as diet or antibiotic use, which can significantly influence the microbiota. On the other hand, the available studies are mainly short-term, which does not allow for adequate assessment of the long-term effects of interventions on the microbiota. Therefore, more longitudinal studies and large-scale clinical trials are needed to validate these findings.

Another challenge is establishing whether gut dysbiosis is a cause or a consequence of ASD symptoms. Although some studies suggest that dysbiosis may be contributing to the onset of ASD symptoms, others indicate that behaviors and diets typical of ASD may be responsible for alterations in the microbiota. This ambiguity in the direction of causality underscores the need for further research to clarify the role of the microbiota in the pathogenesis of ASD.

In conclusion, although interventions focused on modulating the microbiota have shown promising results in improving gastrointestinal and behavioral symptoms in children with ASD, more rigorous and larger studies are needed to confirm the effectiveness and safety of these treatments. As knowledge about the microbiota-gut-brain axis advances, new therapeutic strategies for managing ASD symptoms may emerge

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