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THE INFLUENCE OF GUT MICROBIOTA ON NEURODEVELOPMENT IN CHILDREN WITH AUTISM SPECTRUM DISORDER (AUTISM SPECTRUM DISORDER): A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairments linked to deficits in social interaction and verbal or non-verbal communication, as well as restricted and repetitive patterns of behaviour, interests or activities. The initial phase of the disorder is usually noticed early in life. ASD always begins before the age of three and is usually noticed by parents between 12 and 18 months, when they notice a delay in speech development and the child's lack of interest in maintaining social relationships. According to Ângelo et al (2021), there are an estimated 2 million Brazilians with ASD, and more than 100 genes have the ability to trigger autism and worsen it according to exposure to pollutants and pesticides, from the gestational period of the fetus and lasting for the first thousand days of the child's life. Studies indicate that the intestinal microbiota can influence the neurodevelopment and behavior of autistic individuals, since individuals with ASD have a higher elevation of pathogenic bacteria in the intestine compared to neurotypical individuals. The aim of this study is to analyze the relationship between autism and the intestinal microbiota in neurodevelopment in children with ASD. This systematic review used the main databases Google Scholar, PubMED and Scielo. Through the analysis of various studies and scientific evidence, we concluded that. However, it is important to note that the influence of gut microbiota on neurodevelopment in children with ASD is still a developing field of research. Further studies are needed to elucidate cause and effect relationships and determine the most effective therapeutic strategies. Despite this, the findings to date suggest a promising approach to the treatment and management of ASD.
Keywords: Gut-brain axis, intestinal microbiota, nutritional therapy.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairments linked to deficits in social interaction and verbal or non-verbal communication, as well as restricted and repetitive patterns of behaviour, interests or activities. However, diagnosing what causes this disorder is one of the most difficult medical challenges, as it encompasses a wide range of complex variables relating the genetic aspect of neurodevelopment to environmental factors (ÂNGELO et al, 2021).

The initial phase of the disorder is usually noticed early in life. ASD always begins before the age of three, and is usually noticed by parents between 12 and 18 months, when they notice a delay in speech development and also the child's lack of interest in maintaining social relationships (ARAÚJO, 2019).

It is possible to consider that the journey to understanding this disorder has been a long one, with its first case diagnosed in the 1930s by the Austrian psychiatrist Leo Kanner, who examined a boy called Donald Grey Triplett who, despite his incredible capacity for memorization, tended to remain isolated from human contact (QUEIROZ, 2019).

According to Ângelo et al (2021), there are an estimated 2 million Brazilians with ASD, and more than 100 genes have the ability to trigger autism and worsen it according to exposure to pollutants and pesticides, from the gestational period of the fetus and lasting for the first thousand days of the child's life, therefore, the impact of nutritional alterations during this period can be seen as a possible ally in increasing the likelihood of alterations in the neurodevelopment of children with ASD. Observing this factor is of great importance, since there are several studies that demonstrate the influence of the microbiota on the development of cognitive capacity (SILVA et al, 2022).

Moving on to the present day and considering the developments that have already taken place on the subject, it can be said that ASD is a health condition characterized by impairment in neurological development, leading to consequences for cognitive functions, impacting the socialization, communication and behaviour of those affected by this disorder, with its level of severity varying: mild, moderate or severe (MAGAGNIN et al.,2021).

Studies indicate that the intestinal microbiota can influence the neurodevelopment and behavior of autistic individuals, since individuals with ASD have a higher elevation of pathogenic bacteria in the intestine compared to neurotypical individuals (CHEN; XU; YOU CHEN, *et al.*, 2021). Through the gut-brain axis there is communication between the gut microbiota and the brain through some signaling molecules, so children with autism are more affected by gastrointestinal problems such as dysbiosis, which is the most common, proposing clarification and nutritional guidelines, aiming at a significant improvement in the quality of life in individuals with ASD in an individual and methodologically appropriate way (YAG; TIAN; BO, 2018; KANG et al., 2019).

Therefore, this study aims to analyze the relationship between autism and the intestinal microbiota in the neurodevelopment of children with ASD through a systematic review of the literature.

OBJECTIVES

GENERAL OBJECTIVE

A systematic review of the literature analyzed the relationship between autism and the intestinal microbiota in the neurodevelopment of children with ASD.

SPECIFIC OBJECTIVES

- Distinguish the role of the microbiota between healthy children and children with ASD.
- Describe the environmental and biological risk factors in autism.
- Report on the importance of nutritional therapy in Autism Spectrum Disorder.

THEORETICAL REFERENCIAL

HISTORY OF AUTISM SPECTRUM DISORDER (ASD)

Considering that around 1% of the world's population is currently diagnosed with Autism Spectrum Disorder (ASD) , it can be seen that the diagnosis occurs in the first years of the child's life (MONTEIRO *et al*, 2020). It is therefore important to consider the reasons why it is possible to reach a diagnosis, bearing in mind that this is a disorder with as yet unknown causes. Despite this, it is also important to review the history of research into ASD, since it was through this research that the relationship between genetic defects and various environmental and biological factors was discovered (MONTEIRO *et al*, 2020).

In this sense, it was in the 1940s that this term became better known, when Leo Kanner appropriated it to speculate on a behavioral disorder that preceded schizophrenia (JUTLA; FOSS-FEIG, 2022). His research, carried out with around 11 children, presents "innate autistic disorders of affective contact", which means that ASD, at the time, was characterized by serious problems in social interaction and connection from the beginning of life and by resistance to change (*ROSEN et al*, 2021). It is interesting to note that at the time Kanner was conducting his studies, many children were enrolled in training schools for the intellectually disabled and, because of their unique and sometimes violent behavior, especially to maintain the sameness of their own world, many of them were abandoned by their parents in these places.

At the same time, Hans Asperger carried out studies aimed at the same clinical correlation; however, his research revealed behavioral aspects that more closely resembled personality disorders, unlike the developmental aspect analyzed by Kanner, whose research contributed to greater discussions about neurodiversity and the limits of autism (HOSSEINI; MOLLA, 2023).

Years later, Rimland created the first list to evaluate the symptoms that are suggestive of ASD, with this, several studies emerged that sought to refute Kanner's assertion that autism was a factor prior to schizophrenia, and therefore proposed to consider the disorder with the delay of social and linguistic skills as well as the general development of the individual, their interests and repetitive behaviors, emphasizing hypo and hypersensitivity to the environment (ROSEN *et al*, 2021).

However, ASD continues to present itself through a variability of symptoms and they are not always related to genetic and environmental aspects that can be systematized, so despite the advances in research, the different subtypes in which ASD presents itself remain an open question for researchers (CRESPI, 2022). However, thanks to all the research carried out since Leo Kanner's first discussions, ASD was validated as a diagnostic concept in the Diagnostic and Statistical Manual (JUTLA; FOSS-FEIG, 2022). This was of great importance, as it differentiated the concepts of autism and schizophrenia in early childhood from a clinical phenomenology (HOSSEINI; MOLLA, 2023).

Although the problem with this manual was that it was inflexible, since for diagnostic purposes all the characteristics had to be marked, as well as the very problem that surrounded the first term with which ASD was

categorized for early childhood, they do not take credit for this achievement, because in the following years, the research that began to be developed mentioned ASD in more and more particular terms involving its diagnosis (CRESPI, 2022).

With regard to advances in research, the study based on the genetic aspect is considered, in which, in recent decades, it has been observed that a range of genes are associated with the symptoms of ASD while it has two striking characteristics: poor social communication and repetitive behaviors (LI; POZZO-MILLER, 2020). For Li and Pozzo-Miller (2020), the genes related to ASD have altered axonal growth and, among others, impaired synaptic plasticity in the corticostriatal pathway. Among the related genes is SYNGAP1, which provides instructions for the production of a protein that is related to the synaptic functions of the brain and when there is a mutation in this gene it is possible to observe an interference in the synaptic function causing alterations in the structure and function of the brain and may present symptoms characteristic of ASD such as difficulty communicating and interacting socially (LI; POZZO-MILLER, 2020).

Part of this obstacle to communication and social interaction has been proven by recent studies to be related to the neurobiological differences associated with ASD (JUTLA; FOSS-FEIG, 2022). This is because some dysfunctions in the circuits that involve social cognition lead to difficulties in recognizing emotions and interacting socially, as well as responding appropriately to social cues. These alterations are often diagnosed early when patients are still in childhood, usually by associating the presence or severity of the disorder with biomarkers, such as neuroimaging (JUTLA; FOSS-FEIG, 2022).

These show a decrease in metabolic activity in the primary motor and somatosensory cortexes, in divergence with the signs presented by patients with schizophrenia, which are just one of the methods used to assess the particularities of ASD, as well as proving that there is an unequal distribution based on gender (WIEBE *et al*, 2022).

Men are more likely to develop ASD both because of their genetic condition (women have greater genetic protection because of their X chromosomes) and because they use their brains in a more focused way, suffering from changes in neuronal development, this factor being related to levels of testosterone (MASINI *et al*, 2020).

Despite the advances and studies in the field of neurobiology, there is evidence that environmental factors also contribute to its development, in this sense, the mother's health conditions have a great impact even in the formation of the fetus, therefore, diets lacking specific nutrients even at short intervals can have an adverse effect on fetal development (MASINI *et al*, 2020). Another important point that has gained the attention of researchers in recent years is the relationship between the environment and pregnancy and the prenatal period for the development of autism (RITZ, 2018).

The research by Ritz (2018) highlights the influence of air pollution on the increased risk of developing ASD in the first years of a child's life, with higher incidence rates in male children and the author also warns of prolonged exposure to air pollutants such as nitrogen dioxide, even during pregnancy and the first years of a child's life, explaining the increased risk of developing not only ASD but also Asperger's and other disorders.

In this sense, observing all the advances in research related to the causes for the development and diagnosis of ASD, it is also possible to consider how the first treatment since Leo Kanner's Patient Zero has received innovations influenced by all the studies that

have been conducted in the following years, so therapeutic interventions have undergone improvements, especially with a focus on reducing communication and social interaction difficulties, where, in the case of the use of virtual reality associated with cognitive therapy for the treatment of social communication difficulties, its first steps do not yet seem to be viable for clinical use, but it is already a promising field (WIEBE *et al*, 2022).

This research provides a safe and controlled environment for exposure to situations that can be stressful triggers for individuals with ASD, and augmented reality can allow interaction with virtual objects and people in a real environment in a way that improves attention and social skills as well as communication skills (WIEBE *et al*, 2022).

Therefore, it is possible to note that recent advances have increased the understanding of ASD at various levels, whether genetic, neurobiological, environmental and/or therapeutic, and thus, in recent years the research developed has contributed to bringing a significant improvement in the quality of life of individuals with ASD considering the profile of gender differences to propose appropriate methodological alternatives (THAPAR; RUTHER, 2021).

NEURODEVELOPMENT

The brain development of people with ASD has been monitored for more than two decades using magnetic resonance imaging, which has proved capable of showing brain overgrowth in the first year of life (GIRAULT; PIVEN, 2020). Understanding this is of great importance because it hints at the relationship between neurobiology and the development of ASD, especially considering that the development of ASD is non-linear and dynamic (GIRAULT; PIVEN, 2020).

From the moment the fetus is conceived, neurogenesis begins with the formation of the first neural stem cells which, when they proliferate, end up producing the progenitor cells of neurons. These, in turn, lead to the development of dendrites and axons which, when they connect, begin the synaptic process (SAAD *et al*, 2022). This process depends on neurotransmitters stored in presynaptic compartments until their release to interact with postsynaptic dendritic receptors, inducing excitation, inhibition or modulation of postsynaptic neurons (KAWANO *et al*, 2022).

During development, a large number of cells are mobilized to guard and protect developing neuronal cells, including mast cells, astrocytes and microglia. However, severe inflammation or infection can trigger abnormal immune activation that can progress throughout life, as is the case with the imbalance between anti- and pro-inflammatory cytokines triggered by ASD and which favors pathogenic neuroinflammation in which it is possible to observe increased levels of neurotensin, which is a neuromodulator well known for activating mast cells and releasing pro-inflammatory mediators (COWAN; PETRI, 2018).

In the development process, the inflammatory response and the neurotransmitters that act in the processes of excitation and inhibition must be taken into account in order to regulate and balance the synaptic levels of homeostasis and brain function, especially GABA, whose function in the adult brain is inhibitory, while in the developing brain it has an excitatory effect (ZHAO *et al*, 2022). This neurotransmitter appears early in the development of the fetus, indicating its importance for cell proliferation, however, studies show that exposure to drugs and medications, such as benzodiazepines or valproate, which affect the GABA receptor during pregnancy, interfere with brain maturation, increasing the risk of ASD.

Therefore, Cowan and Petri (2018) specify that disorders and deficiencies in neuromodulators can be responsible for interfering with brain maturation in both prenatal and postnatal development and throughout life these deficiencies can be attributed to genetic mutations and/or environmental aspects (such as medications or drugs) during pregnancy.

In relation to brain structure, the work by Girault and Piven (2020) shows, based on analysis of MRI scans, a growth rate in the total volume of the brain in children between 12 and 24 months of age with ASD, as well as greater cortical thickness in various regions of the brain in infancy with a subsequent reduction in early adulthood, However, there is still no consensus on this relationship with ASD, and the authors still discuss the development of white matter, whose local and global efficiency is reduced in children with ASD as early as 6 months of age, especially in sensory processing regions in the occipital and temporal lobes.

With regard to neurodevelopment, Girault and Piven (2020, p. 9) argue that

> "with the growing evidence of brain alterations in ASD preceding the emergence of the defining features of the disorder, it becomes critical to place these prodromal phenotypes in the context of early emerging behaviors associated with ASD and ASD risk."

This implies that alterations in both brain volume and functions coincide with delays in motor development, atypical visual development and attention to social stimuli, all of which are brain and behavioral phenotypes that begin to appear even before the diagnostic symptoms are consolidated, In this sense, it is valid to state that the hyperexpansion of the cortical surface area with this period of motor, sensory and visual orientation deficits that follow brain overgrowth anticipates autistic social deficits as early as the second year of life (SAAD *et al*, 2022).

In this case, it is likely that the development of ASD occurs through multiple pathogenic mechanisms (KAWANO *et al*, 2022; ZHAO *et al*, 2022), the risk of a person developing ASD depends on the level of polygenic load of thousands of common variants, and many genes associated with ASD are pleiotropic in nature indicating a fragility in neuroimaging studies suggesting an emerging vulnerability already in the first year of life whose effects implicate brain development.

GUT-BRAIN AXIS: HEALTHY GUT MICROBIOTA

There is bidirectional communication between the intestine and the brain, which exert a mutual influence, as they are connected by the vagus nerve, and during evolution, as the role of the intestine was of vital importance to our survival, nature chose to leave it on its own, today it is possible to understand this functioning as the enteric nervous system, also known as the "brain of the intestine" or "second brain" (SAVIOLI, 2021).

The first thousand days of an individual's life are essential for their health. They are a significant period of opportunity for the formation of a healthier society, since adequate nutrition during this period can affect growth and neurocognitive development, as well as reducing the risk of diseases and comorbidities throughout life. This period is made up of the 270 days of pregnancy plus the 730 days corresponding to the first two years of life. (ALMEIDA; NADER; MALLET, 2021)

The intestinal microbiota is the sum of various microorganisms that coexist in a symbiotic relationship with the human host and are capable of stimulating the immune system, positively influencing immune responses to pathogens in organs outside the intestine. In healthy people, the intestine maintains a balance, in which bacteria related to intestinal health outnumber those that cause disea-

se (**Figure 3**). When dysbiosis occurs, which is the deregulation of this balance, the body becomes prone to the appearance of diseases (NESI et al., 2020).

The Gastrointestinal Tract (GIT) is made up of microorganisms contained in the microbiota that have a mutual and harmonious relationship with the human being, in which the host receives protection against pathogens, aid in the digestion and absorption of nutrients and vitamins, as well as the metabolization of toxic substances, while the microorganisms establish themselves in an environment with ideal conditions for survival (DE OLIVEIRA et al., 2020).

The intestinal microbiota is, by definition, a grouping of trillions of microorganisms including bacteria, viruses, archaea and fungi, in which these microorganisms populate the gastrointestinal tract and have the power to live in symbiosis with the human being, favoring a healthy environment when it is in balance, enriching the defense mechanisms against possible pathogens, thus improving intestinal immunity (GOMES et al.,2020) (Figure 3). The development of the gut microbiota is regulated by a complex interaction between the host and environmental factors, including diet and lifestyle (ROTHSCHILD, 2018).

In the intestinal compartment of the human body there is a complex community of microbial cells (commensal and symbiotic) that form the intestinal microbiota, where the composition of these microbial cells is made up of living beings such as bacteria, fungi and viruses and depending on the bacteria present in the microbiota there is a relationship of beneficial commensality with the host (ANGELUCCI et al., 2019).

According to Sacramento, (2020), the intestinal microbiota plays a fundamental role in the relationship between the intestine and the brain, and can influence cognitive capacity, memory, learning, mood and the behavior of human beings, through neurotransmitters (acetylcholine (Ach), catecholamines, gamma-aminobutyric acid (GABA), histamine, melatonin and serotonin), capable of crossing the blood-brain barrier (BBB) and reaching the brain (**Figure 1**).

The healthy maintenance of the intestinal microbiota is still not well defined, what is known is that it is not static and is modified during adulthood, with diet being one of the means that most contributes to this dynamic, in which the type of food can shape the microbial composition, as well as the intestinal microbiota can modify the nutritional value of food (ILLIANO et al., 2020).

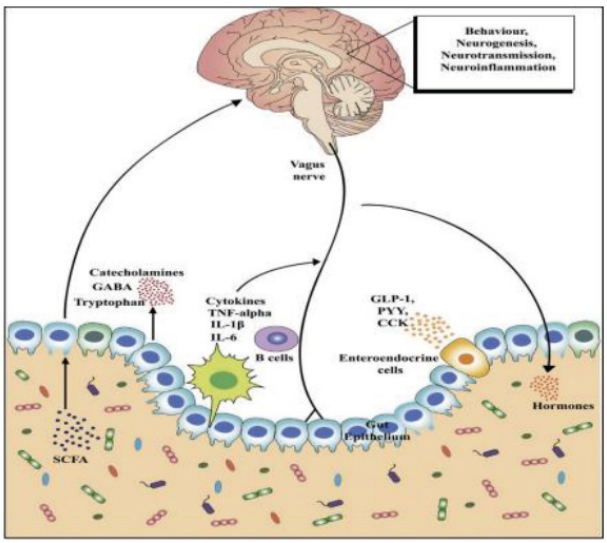

FIGURE 1. Gut-brain axis - main communication pathways.

SOURCE: CRYAN, J.F. et al. 2019

GUT-BRAIN AXIS: GUT MICROBIOTA IN TEA

The first elucidation regarding digestive system dysfunctions in autistic people was proven by Goodwin, Cowen, Goodwin in 1971, where they evaluated a group of autistic children with gastrointestinal symptoms, among them: altered stool consistency, abdominal discomfort, vomiting, among others, which could prove intestinal malabsorption (DE OLIVEIRA et al.,2019).

Intestinal health is based on a balance between beneficial and pathogenic bacteria that maintain intestinal homeostasis. Inadequate nutrition leads to a greater proliferation of pathogenic bacteria and the development of dysbiosis, resulting in gastrointestinal (GI) symptoms (REIS et al., 2022). These bacteria are classified as gram-negative and have toxins such as lipopolysaccharide (LPS) in their membrane, which are released and damage the tights junctions causing greater permeability in the intestine (RICCIO, 2019).

Stool or intestinal biopsy samples have shown that ASD patients have a higher amount of pathogens such as *Clostridium bolteae*, *C. hystoliticum*, *C. perfringens* or *Sutterella sp*, where the presence of *Sutterella sp* causes the Bifidobacterium bacteria to be in a significantly lower amount (LEFTER et al., 2020). Children with ASD have altered gut microbiota profiles compared to neurotypical children, and have a reduction in Prevotella, Coprococcus, Enterococcus, Lactobacillus, Streptococcus, Lactococcus, Staphylococcus, Ruminococcus, Sutterella and Bifidobacterium type bacteria and an increase in Clostridia and Desulfovibrio type bacteria and a lower proportion of Bacterioidetes and Firmicutes (RISTORI et al., 2019).

According to recent studies, ASD coexists with alterations in the gastrointestinal tract, immune-inflammatory pathways and the nervous system (AZHARI; AZIZAN; ESPOSITO, 2019). Symptoms such as gastrointestinal inflammation and altered immune function also frequently affect individuals with ASD and corroborate the worsening of the behavioral disorder (CHIDAMBARAM et al., 2020 ; RISTORI et al., 2019).

More than half of all children with autism spectrum disorders (ASD) have gastrointestinal (GI) comorbidities, with dysbiosis being a common feature, which results in increased intestinal permeability, allowing toxins and bacterial metabolites to enter the bloodstream, which when they reach the brain, cause a set of behavioral disorders, such as hyperactivity, anxiety, depression and mood disorders (SANCTUARY, 2019).

Anxiety disorder, gastrointestinal problems and autonomic dysfunction are common characteristics of a subgroup of children with ASD and according to recent studies ASD coexists with alterations in the gastrointestinal tract, in the immunoinflammation pathways of the nervous system (AZHARI; AZIZAN; ESPOSITO, 2019). Symptoms such as gastrointestinal inflammation and altered immune function also frequently affect individuals with ASD and corroborate the worsening of the behavioral disorder (CHIDAMBARAM et al., 2020; RISTORI et al., 2019).

Changes in intestinal bacterial composition, overproduction of bacterial metabolites as well as increased permeability of the gastrointestinal mucosa is common in people with autism leading to poor digestive health (CHIDAMBARAM et al., 2020; RISTORI et al., 2019).

Dysbiosis is an increase in harmful bacteria in relation to beneficial bacteria, caused by various factors, both endogenous and exogenous, and profoundly interferes with the integrity of the intestine, as well as overall health, influencing and causing diseases such as diarrhea, fatigue, obesity and depression, among others: diarrhea, fatigue, obesity, depression, among others, as a consequence, this high number of harmful bacteria starts to produce a greater amount of toxins, favors the permeability of the intestinal barrier and the emergence of chronic non-communicable diseases (NCDs) and inflammatory processes (ALMEIDA; NADER; MALLET, 2021) (Figure 3).

Intestinal dysbiosis favors the imbalance of the intestinal microbiota, promoting significant changes in the immune, metabolic, neurological and microbiotic functions that lead to the worsening of Autism Spectrum Disorder (DIAS PAR et al.,2021).

The imbalance of the microbiota characterized by an increase in Clostridia, Bacteroidetes, Firmicutes and Lactobacilli type bacteria is present in children with autism spectrum disorder (AZHARI; AZIZAN; ESPOSITO, 2019) (CHIDAMBARAM et al., 2020).

Unfavorable conditions for intestinal dysbiosis can also be seen in food refusal, nutritional deficiencies and/or deficiencies, metabolic alterations, food selectivity and nutritional intolerances, such as casein and gluten (LAZÁRO; SIQUARA; PODÉ, 2019).

Due to food rejection and selectivity, these children have an aversion to colors, textures and smells, causing a loss in diet quality, nutritional deficiency and consequently leading to a change in the intestinal microbiota that ends up aggravating ASD symptoms (RISTORI et al., 2019).

Other gastrointestinal disorders report gastroesophageal reflux disease, selectivity, food rejection and difficulty swallowing, where cognitive deficits are clearly related to gastrointestinal disorders in some groups of autistic individuals (LEFTER et al., 2020).

On a global scale, there is growing interest in the gut-brain axis, which is characterized by a reciprocal communication between the Enteric Nervous System (ENS) and the Central Nervous System (CNS), based on which it is noticeable how gastrointestinal alterations correlate with alterations in neurological patterns, studies have concluded that the intestinal microbiota plays a relevant role in autism spectrum disorders, and may also be modulating the immune system and gastrointestinal functions, thus generating greater caution when observing the interaction between the intestine and the brain and the impacts they may cause. (DO CARMO CUPERTINO et al.,2019)

Given that the connection between the functioning of the gut and the brain already has a lot of scientific evidence showing that the gut-brain axis depends on the microbiota and that this axis uses neural, hormonal, immunological and metabolic pathways that can contribute to the manifestations of ASD (SRIKANTHA; HASAN MOHAJERI, 2019) .

There is a growing body of evidence indicating that the intestinal microbiota can influence the neurodevelopment and behavior of the individual due to the microbiota-intestine-brain axis, which refers to the interactions between the central nervous system, the gastrointestinal system and the microorganisms that live in the gastrointestinal tract, the microbiota is able to communicate with the brain through signaling molecules, immune mediators, intestinal hormones and neurotransmitters, so children with neurodevelopmental disorders, including ASD, are regularly affected by these gastrointestinal problems and dysbiosis of the intestinal microbiota (YANG; TIAN; BO YANG, 2018). (**Figure 2**)

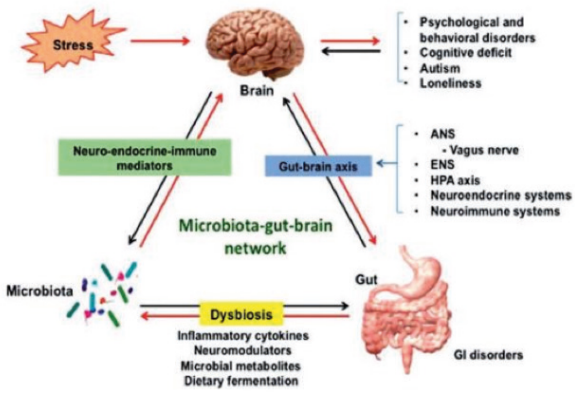

Figure 2. Altered gut-brain axis in autism

SOURCE: reproduced from CHIDAMBARAM et al.,2020

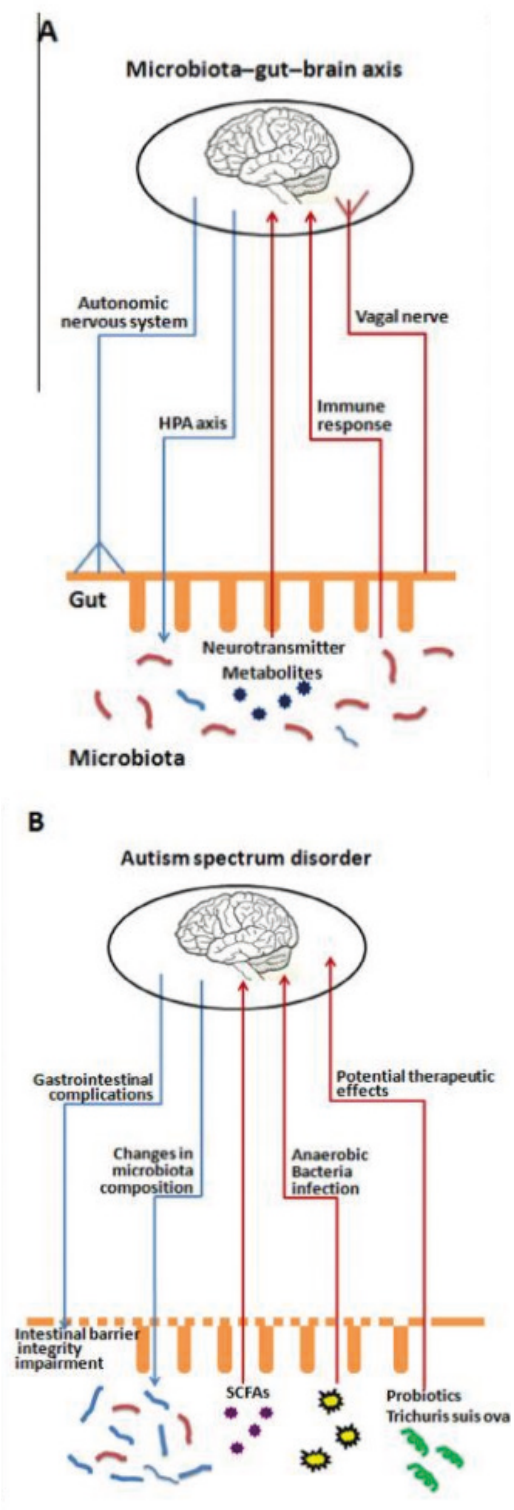

Figure 3. Healthy microbiota x microbiota in individuals with TEA.

SOURCE: Reproduced from Li; ZHOU (2016).

ENVIRONMENTAL RISK FACTORS IN NEURODEVELOPMENT

Environmental risk factors refer to elements present in the environment that can affect human health or the environment, these factors can be natural or anthropogenic and can include chemical products, basic health neglect, food insecurity, exposure to ionizing or non-ionizing radiation, contamination by biological agents, especially due to their nature, concentration, intensity or exposure time (CRESTANI, 2022).

APAE (Association of Parents and Friends of the Exceptional) published an article in the magazine SACT Redação explaining that autism is not just about the parents' genetics, but also about environmental factors such as climate change, pollution, pesticides, infections, medicines used during pregnancy and states that all of these cause gene alterations, in addition to immune dysfunction, prenatal and perinatal factors, socioeconomic status, exposure of the pregnant woman to chemicals, drugs and toxic exposures, physical or verbal/emotional violence. (EDITORIAL STAFF, 2023).

Climate change can be linked to neglect of basic health, food insecurity and pollution for the following reason: climate change is about heat waves, cyclones, winds and heavy rains and floods that cause high water levels in rivers and lakes, interfering not only with the health of children living in these conditions, but also with education, protection and access to food supplies, these children are exposed and extremely vulnerable due to the lack of drinking water, clean air, basic sanitation and care services, as well as the risk of being exploited (UNICEF, 2021).

UNICEF (United Nations Children's Fund) states that around 1 billion children live in situations of high levels of air pollution, 920 million in water scarcity, 820 million exposed to heat waves, 815 million in lead pollution,

600 million with vector-borne diseases, 400 million exposed to cyclones and 240 million exposed to coastal flooding, so compared to adults it is known that children are less likely to survive or develop in a completely healthy way in the face of these conditions (UNICEF, 2021).

When it comes to pesticides, we can highlight the exposure of pregnant women to chemicals, drugs and toxic exposures that are factors directly linked to autism, since studies show that the exposure of pregnant women to these products is not only harmful to their health, but can also influence the neurodevelopment and behavior of the growing fetus and future generations, leading us to believe that this exposure is a major risk factor for the development of autism (KONKEL, 2019).

Among the chemicals that most affect children's health are pesticides, for example, which are a huge risk factor.

> Organophosphate pesticides (OP) have been identified as potential environmental risk factors. Epidemiological studies suggest that children exposed prenatally to the OP pesticide chlorpyrifos (CPF) have significant mental and motor delays and strong positive associations for developing a clinical diagnosis of intellectual delay or disability, ADHD or ASD (BERG et al. 2020).

Matsuzaki H. and Fukunaga K (2022), also state that prenatal exposure to picrotoxin, a GABA receptor antagonist, reduces social interaction and its enrichment. The authors also suggest that exposure to GABA receptor inhibitors during the prenatal period, in addition to inducing behaviors similar to ASD, contributes to deficiencies in odor function and social deficits in the offspring, prenatal and perinatal factors are also associated with some pathologies developed during this period, such as diabetes and gestational viral infections, intrauterine bleeding and infections, which are associated with a significant increase in the risk of autism.

Neglect of basic health and food insecurity are totally linked to the child's first 1,000 days, which is also known as the "golden interval" or "window of opportunity", where these first 1,000 days range from the day of conception to the child's second birthday.It is considered a crucial time not only for health, but also for development, learning, emotional and social well-being, so from the moment of conception it is important that the child receives the prenatal nutrition necessary for its development, in the postpartum period exclusive breastfeeding until six months of age and the introduction of complementary healthy food after the breastfeeding period according to age, in addition to being in a peaceful and welcoming environment (TRAEBERT, 2018).

Knowing that, during the first 1,000 days of life, brain development occurs at an incredible and once-in-a-lifetime speed, these new neural connections form the main axis of the structures that support learning for the rest of life, and during this period emotional, cognitive and social skills, intellectual capacity, aptitudes and competences will also be formed, so it is also important that the child is in a welcoming home that receives the necessary attention and affection, love and protection (DERBYSHIRE and OBEID, 2020).

Author TRAEBERT (2018) suggests that nutritional deficits during this period can have serious consequences for cognitive and motor development, as well as causing an absurd loss of performance and productivity, and increasing the risk of chronic diseases.

Another environmental risk factor that has also greatly affected children is physical and verbal/emotional intrafamily or community violence, where during childhood, parents are the main socializing pivots that will be in direct contact with them, teaching them how to function effectively in the social environment in the most different scenarios where

they live and grow up, that is, it is at home that the child learns to live together and maintain relationships with others (ANUNCIAÇÃO, 2022).

Intrafamily violence can be classified as domestic violence that happens to children, parents and others who make up family relationships where most of the time this is the way that is found to resolve conflicts and, incredible as it may seem, in an "educational" way, it usually happens in families with low income and low schooling, where life prospects are also scarce and in this scenario the lack of protection and basic care for children is also noticed (SILVA et al., 2018).

When children grow up in contact with intra-family violence, they can automatically develop aggressive behavior, becoming child offenders and later problematic, totally unstructured adults. Community violence, on the other hand, is practiced by individuals who have no ties with each other, who may or may not be living with the victims, and this type of violence occurs in a wide variety of public or private places, such as schools. Children who suffer bullying or even physical aggression at school tend to develop low self-esteem and lack psychosocial autonomy, which can lead to problems such as depression, suicide or even violent reactions and social maladjustment. However, the Health at School Program (PSE) was created in order to act in the prevention of injuries and promotion of health and learning and training of this population, it is important that the type of violence is identified, so that this child has the appropriate treatment (SOUZA, 2021).

Therefore, it is necessary for these children to be in a safe environment from the moment they are conceived, away from any and all environmental risk factors that interfere with their motor, psychological and especially neurological and social development, where they do not have their rights invalidated, being protected by the family and also in the social sphere, enabling them to grow up in the healthiest way possible, where they can receive love and affection and can transmit it to others as well (SILVA et al., 2018).

BIOLOGICAL RISK FACTORS IN NEURODEVELOPMENT

Biological risk factors are those related to the characteristics of the organism that increase the likelihood of developing a certain disease, regardless of whether they cause mild, moderate or severe damage; they are known as fungi, bacilli, protozoa, bacteria, viruses or parasites (STOCKLER; WERNECK, 2018).

According to KATTAB et al. (2020) the biological risk factors related to the development of autism are comorbid conditions and mainly the epigenetic contribution, comorbidities deal with the existence of two or more diseases in a single person, and there is a possibility that these pathologies intensify each other, however, the epigenetic contribution is the transcription of genetic material without altering the underlying nucleotide sequence, if there is any type of alteration of this sequence it will generate imperfection in embryofetal development.

The comorbid conditions are multiple psychiatric disorders, anxiety, depression, attention deficit/hyperactivity disorder, epilepsy, gastrointestinal symptoms, sleep disorders, learning difficulties, obsessive/compulsive disorder, intellectual disability, sensory and immunological problems. All these comorbid conditions that the pregnant woman has can be passed on to the fetus through epigenetic contribution, where the multiple psychiatric disorders present in the pregnant woman can be transmitted to the fetus and cause deficiencies in synaptic function (communication between neurons), knowing that autism occurs from changes in the signaling of the synapses, because, Once the pregnant woman

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has anxiety, depression or schizophrenia and other comorbid conditions, the fetus begins to suffer interference in the formation of its personality and emotions, leading it to probably develop mental disorders such as autism, schizophrenia in particular triples the chances of ASD (KATTAB et al. 2020).

The epigenetic contribution is classified in two ways: rare genetic contributions (Tourette's syndrome, tuberous sclerosis, fragile X, FOXP1 gene, Rett syndrome), and genetic contributions (pre-eclampsia, gestational diabetes, metabolic conditions, advanced parental age, gestational hemorrhage, prenatal stress, maternal mental illness, prematurity, fetal respiratory distress, among others) (MACIEL et al., 2021).

Rare genetic variants play a significant role in autism, contributing to the manifestation of symptoms and the heterogeneity of the condition. Tourette's syndrome is a neuropsychiatric disorder characterized by involuntary motor or sound tics, in which a child who has Tourette's syndrome after birth has an 85% chance of having or developing obsessive compulsive disorder (OCD) or autistic spectrum disorder (ASD) (SILVA, 2022).

According to APAE (Association of Parents and Friends of the Exceptional), tuberous sclerosis is a rare genetic disease that affects one in every six thousand people, and it is thought that 50% of people with this condition also have autism, because sclerosis causes tumors that affect parts of the brain responsible for communication, social interaction and behavior (STOCKLER; WERNECK, 2023).

Fragile X Syndrome is an inherited genetic neurodevelopmental condition that causes intellectual disability, anxiety, delayed neuropsychomotor development, impaired communication and social interaction, among others, is associated with invasive developmental disorders such as autism spectrum disorder, this condition is caused by an alteration in the Fragile Mental Retardation-1 (FMR1) gene located on the X chromosome (KERCHES, 2020).

The FOXP1 gene (Forkhead Box Protein P1) is a human gene that is located on chromosome 3 (region 3p13), and it encodes a protein called FOXP1, which belongs to the family of forkhead box proteins and plays a crucial role in embryonic development and the regulation of gene expression, This gene has been the subject of extensive studies due to its involvement in a variety of biological processes, including the formation of the central nervous system, heart development, lung development and lymphocyte maturation. In addition, mutations or deregulation of the FOXP1 gene have been associated with various human diseases, including autism spectrum disorders, neurodevelopmental disorders, speech and language development disorders, motor development disorders and certain types of cancer, this gene has currently been the most important in the development of ASD, and children who have it in altered form usually have eating problems, sleep disorders, seizures, irritability, excessive crying and autism spectrum disorder (JÚNIOR, 2020).

Rett syndrome is a neurodevelopmental disorder that usually affects girls, 1 in 10.000 live births, with boys normally not being compatible with life because it is a dominant mutation related to the X chromosome and as girls have two X chromosomes, they can survive with one mutated X and one unmutated X. This disorder is associated with a mutation in the MECP2 gene that codes for protein 2, which is located on the X chromosome, and can lead to loss of speech, motor skills and the occurrence of stereotyped hand movements (TONINI et al. 2019).

According to Russo (2018), children with Rett syndrome, Down syndrome, Tuberous Sclerosis and Fragile X syndrome have an increased likelihood of developing ASD due to genetic conditions.

The genetic contribution to the development of autism is widely recognized in the scientific community and studies have shown that genetic factors also play a significant role in susceptibility to ASD. Genetic inheritance is believed to account for around 90% of the risk of developing autism, and one of the main pieces of evidence for this genetic contribution comes from studies with twin families, for example, research with identical (monozygotic) twins, who share 100% of their genetic material, shows that when one twin is diagnosed with autism, there is a high probability that the other will also be affected, these studies indicate a concordance rate of around 70-90% for ASD in monozygotic twins, compared to approximately 0-10% in dizygotic (non-identical) twins, who share around 50% of their genetic material (PIGNATARI, 2019).

Pre-eclampsia is a medical condition that affects about 3-5% of women during pregnancy, characterized by increased blood pressure and the presence of protein in the urine, this condition can have several consequences for the health of the mother and the fetus, such as maternal and neonatal mortality and morbidity, where studies carried out in recent years prove that there is scientific evidence that in utero exposure to PE acts as a risk factor for numerous neurodevelopmental disorders, among them ASD (BARRON et al. 2021)

Gestational diabetes is a condition in which a pregnant woman's blood sugar levels are elevated, but do not yet reach the threshold for a diagnosis of type 2 diabetes and in a study by AL-DBASS et al. (2021), suggests that neonates of mothers with diabetes can develop significant autistic features.

Metabolic conditions are also factors that influence the development of ASD, as recent studies highlight several metabolic conditions that may be related to autism, including mitochondrial disorders, vitamin and mineral deficiencies, abnormal cholesterol metabolism, alterations in serotonin metabolism and others (ROSSIGNOL *et al.* 2018).

Advanced parental age has been consistently identified as a significant risk factor for autism. When we talk about advanced maternal age in particular, we immediately associate the risk of autism mainly with the first-born child, due to the increase in chromosomal abnormalities in eggs of advanced age. On the other hand, the effect of the father's advanced age can influence gene expression in paternal germ cells, as the viability of these mutations only increases further as the man ages, thus increasing the risk of autism in children and has important implications for understanding the biological mechanisms underlying the disorder (NEWSCHAFFER et al., 2020).

Gestational bleeding refers to any type of bleeding during pregnancy and can occur at different times, such as in the first trimester (implantation bleeding) or in the third trimester (placental bleeding), gestational bleeding that can cause fetal hypoxia, thus offering a risk for the development of ASD (KATTAB, 2020).

Prenatal stress can also have irremediable effects on the formation and development of the fetus in the 21st week of gestation up to the 32nd week, because epigenetic mechanisms and all the genes involved in metabolism, neurodevelopment and physiology will subsist for its entire life (BERGH et al. 2020).

In epidemiological studies, maternal mental illnesses such as depression, bipolar disorder and anxiety have shown a significant association with contributing to the manifestation of autism, knowing that these illnesses can affect the uterine environment and fetal development, causing epigenetic programming to be excessively affected, causing stress to the fetus that will persist throughout life (REICHENBERG et al. 2021).

According to studies, prematurity and the increased risk of developing autism spectrum disorder have a significant association, although most children with ASD have a genetic origin, premature children are also more likely to have autistic characteristics, such as difficulties in social communication, repetitive behaviors, low IQ and smaller head circumference observed in a study through neonatal cranial ultrasound that detected abnormalities due to cognitive impairment (CRUMP et al. 2021). Premature births usually happen when the mother is very young due to the lack of physical maturity and consequently the lack of intrauterine growth of the fetus, thus causing premature birth and the risk of autism (SEDICIAS, 2021).

Fetal respiratory distress, in turn, can be caused by the umbilical cord moving around the fetus' neck, which can then be called fetal nuchal cord, causing hypoxia (low oxygen), increasing the risk of autism by at least 26%, with around 23.2% of children diagnosed with autism having suffered from fetal nuchal cord, In addition to respiratory failure, hypoxia also causes a lack of fetal nutrition and blood, causing damage to brain development, especially in the basal ganglia, hippocampus and lateral ventricles, hence the reason for larger lateral ventricles and hippocampus abnormalities in autistic children (CHENGZHONG et al. 2017).

DIAGNOSIS OF AUTISM SPECTRUM DISORDER

ASD is characterized by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) as a neurodevelopmental disorder with two very particular characteristics, such as difficulty in social communication and restrictive and repetitive interests, especially in the field of food (AMERICAN PSYCHIATRIC ASSOCIATION, 2023). Also according to the DSM-5-TR Manual, the symptoms cause significant impairment in the social, professional or other areas of the individual's life and are presented in at least three levels of severity and should be recorded with the level of support required for each of the two corresponding psychopathological characteristics (AMERICAN PSYCHIATRIC ASSOCIATION, 2023).

Certain specifiers can be used to describe the symptomatology according to severity, separating social communication difficulties from restricted and repetitive behaviors. The specifiers, according to the DSM-5-TR Manual, are (AMERICAN PSYCHIATRIC ASSOCIATION, 2023, p. 59):

> With or without concomitant intellectual impairment
>
> With or without concomitant language impairment
>
> Associated with a known medical or genetic condition or environmental factor [...]
>
> Associated with another neurodevelopmental, mental or behavioral disorder [...]
>
> With catatonia [...].

These specifiers should be used by understanding the intellectual profile of the child or adult, as well as the current level of verbal functioning in conjunction with the presence of any genetic disease or known medical condition (STYLES *et* al, 2020).

The characteristics of ASD are configured as evident impairment manifesting itself according to the characteristics of the individual and the environment in which they are inserted, in this regard, it is possible to consider that ASD encompasses disorders previously called early infantile autism, infantile autism, Kanner's autism, high-functioning autism, atypical autism, global developmental disorder without other specification, childhood disintegrative disorder and Asperger's disorder (AMERICAN PSYCHIATRIC ASSOCIATION, 2023). As for the use of the term "Spectrum", this is because the manifestation

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of the disorder varies according to the severity of the autistic condition, level of development and chronological age of the individual (ROSEN *et al*, 2021).

Diagnoses regarding social interaction can be more accurate when based on various sources of information, such as the clinician's observation, the caregiver's history and even self-report, also considering that many individuals have language deficits such as total absence of speech, language delays, echoic speech and literal language (AMERICAN PSYCHIATRIC ASSOCIATION, 2023).

With regard to deficits in socio-emotional reciprocity, language is used in a more unilateral way, focusing on requests rather than dialogue or talking about feelings, as well as processing responses to complex social cues, requiring support to develop strategies that compensate for social challenges (THAPAR *et al*, 2021).

As for relationships, young children may show absent or reduced social interest usually associated with rejection of others, while older individuals may have a preference for solitary activities (AMERICAN PSYCHIATRIC ASSOCIATION, 2023).

All these patterns and behaviors mentioned above relate to criterion A, which is the difficulty of communication and social interaction, while criterion B, defined by restricted and repetitive patterns of behavior, presents stereotyped behaviors or behaviors that include simple motor stereotypes with repetitive use of objects and repetitive speech, another characteristic is adherence to routines in resistance to change (ROSEN *et al*, 2021).

According to the DSM-5-TR manual, these reactions can be related to hyper or hypoactivity to sensory stimuli that is manifested by extreme reactions to sounds, textures, smells, among others (AMERICAN PSYCHIATRIC ASSOCIATION, 2023). There are other diagnostic criteria, such as criterion D, which requires that the characteristics cause clinically significant impairment in the social or professional context and criterion E which specifies that social communication deficits are not at the same level of individual development with impairments according to this level (HAYES *et al*, 2022).

Symptomatology can be well recognized in the child's second year of life (12 to 24 months), but can be seen before this period in the case of more severe delays and after 24 months if the delays are more subtle, causing impairment in social, professional or other areas of functioning (HAYES *et al*, 2022).

To diagnose the symptoms, in addition to the social impairment observed in the DSM-5-TR, it is possible to use the Scoring Scale for Autism in Childhood, which covers a series of social, emotional, adaptive, communicative and cognitive functions and evaluates them based on 12 descriptors, dividing the results into three different levels: mild (asymptomatic), moderate and severe (MOON *et al*, 2019).

This tool has a diagnostic score for general severity that varies between 0 and 60 points, with 0 being the absence of ASD characteristics and 60 being the fulfillment of all the characteristics on the scale, where the equivalences are: 0-29 points configure the absence of ASD or its presence, but at a mild level, which does not require support, like the DSM-5-TR; 30-35 already indicates a moderate degree, and therefore the damage is more visible although not as severe; finally, 36-60 which characterizes the most severe level, in which there is quite marked damage in the social, professional or other fields in which the individual is inserted. It should be noted that this tool for assessing and diagnosing ASD has proven effective in making an accurate diagnosis in the countries where it is used (MOON *et* al, 2019).

THE IMPORTANCE OF NUTRITION BETWEEN TEA AND THE INTESTINAL MICROBIOTA

Autistic children have ritualistic, repetitive, routine behaviors and many of them end up choosing or demanding specific diets, usually avoiding various foods, textures and flavors, ingesting little fiber or liquids, so gastroesophageal reflux is very common in children with ASD and causes food that is poorly digested together with gastric juice to return to the esophagus causing heartburn and discomfort in the affected region, which can lead to regurgitation (FETISSOV; AVERINA; DANILENKO, 2019).

ASD patients can present gastrointestinal disorders such as: abdominal pain, heartburn, bruxism, weight loss, irritability, constipation, excess brain opioids due to high intestinal absorption, changes in the permeability of the gastric mucosa and enzyme defects, which can be the cause of the so-called artistic enteropathy, these clinical presentations, often unknown by their guardians, impact on the feeding of children with ASD (ARÉVALO, 2018).

People with ASD present with gastrointestinal problems including intestinal motility problems, autoimmune and/or other adverse responses to certain foods and lack of nutrient absorption, where these problems can be caused or worsened by restrictive behavioral patterns (preference for sweet and salty foods and/or refusal of healthy foods), salty foods and/or refusal of healthy foods). Thus, individuals with gastrointestinal problems tend to show more behavioral deficits (irritability, agitation, hyperactivity) and tend to have an imbalance in the overall composition of the intestinal microbiome, corroborating several studies that have implicated brain-intestinal pathways as potential mediators of behavioral dysfunction (ESSA et al., 2020).

Some food compounds such as gluten, casein, dyes, monosodium glutamate, aspartame and other types of sugar are considered harmful to children with ASD (DIAS, 2018).

The nutritional treatment suggested for ASD patients is based on controlling the symptoms of the gastrointestinal tract (GIT) and implementing a gluten and casein exclusion diet associated with individualized supplementation with micronutrients that will help improve signs and symptoms (ADAMS et al., 2018; CARREIRO, 2018).

Due to several factors involved, children with autism become prone to gastrointestinal disorders, including abdominal pain, which is related to behavioral eating problems, such as food refusal and sensory selectivity in intake that contribute to the development of clinical symptoms (HUGHES et al., 2018).

Food is essential for the proper physical and psychological development of patients with ASD (FARIA et al., 2021). However, it is understood that each child diagnosed with ASD has different needs, which is why it is important to have an individualized diet based on the different needs of each individual (MOURA et al., 2021).

Eating problems are a reality among autistic people, which negatively affects the quality of life of children with autism, thus the importance of nutritional monitoring from an early age, so that a nutritious and balanced diet plan can be drawn up (BOTTAN et al., 2020).

Clinical assessment is nutritional semiology, i.e. the observation of signs and symptoms, which are indicators of dehydration, lack or excess of nutrients, metabolic alterations, among others. However, it must always be correlated with other assessments in order to complete the diagnosis and draw up nutritional guidelines. In this physical examination, the skin, face, nails, hair, mucous membranes of the eyes and mouth should be assessed (DUARTE, 2018).

Diet has been shown to be one of the most influential environmental factors modulating gut microbiota composition, brain and behavior. Clinical and preclinical data have shown how different dietary sources significantly affect gut microbiota composition and mood in individuals diagnosed with disorders such as ASD (CRYAN, 2019).

It is also worth noting that intestinal dysbiosis reflects changes in the microbiota, where a healthy intestinal microbiome has several bacteria, mainly bifidobacteria and lactobacilli, which are responsible for strengthening the immune system, however, in the body of individuals with autism, there is an imbalance of these beneficial bacteria and the consequent abnormal growth of pathogenic bacteria, resulting in a decrease in the immune system, inflammatory processes and increased changes in intestinal permeability, which leads to a significant increase in behavioral changes in these individuals (DO CARMO CUPERTINO, 2019).

Nutrition plays an important role in the treatment and progress of these children, as nutritional intervention can treat and reduce symptoms (LIMA, 2018).

METHODOLOGY

SAMPLE

The sample comprises 41 articles and academic papers on the subject selected from a search of the databases. Forty-one papers were selected, including literature reviews and clinical studies, in order to carry out the discussion. This systematic literature review seeks to consolidate information that has already been studied regarding the consequences of adequate nutrition for the neurodevelopment of children with ASD, based on research and discussions carried out in the specified time frame, 2018 to 2023.

ELIGIBILITY CRITERIA

Inclusion criteria

The inclusion criteria were scientific articles, where the title and abstract were initially evaluated according to the theme between 2018 and 2023 in English, Portuguese and Spanish.

Exclusion criteria

The exclusion criteria were editorials, abstracts/commentaries, newspaper articles, articles that were not related to the topic and that were published before 2018.

Systematic literature review

This study proposes a systematic review of the literature to investigate the influence of gut microbiota on neurodevelopment in children with Autism Spectrum Disorder. In order to carry out this research, it was necessary to follow a series of steps which are standard for methodological rigor: 1) define the subject of the study; 2) review the literature; 3) analyze and organize the available data; 4) elucidate and qualify the results of the study; 5) present and publish the qualified and selected literature review in a clear and succinct manner, mentioning the particularities of the studies used to compose the discussion of the same (ALBUQUERQUE; AVILA; BARROS, 2022).

The research subject was constructed using a qualitative and quantitative approach in secondary sources, based on the answers to the following question: what is the relationship between autism and the intestinal microbiota in neurodevelopment?

This systematic review followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The electronic search was carried out in the main academic databases, including PubMed, Scielo and Google Scholar, using a combination of relevant keywords, such as "gut-brain axis

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AND gut microbiota", "neurodevelopment", "Autism Spectrum Disorder" and their synonyms. Studies published between 2018 and 2023 and written in English, Spanish or Portuguese were included. Experimental studies, cohort studies and case-control studies were considered.

It is hoped that this systematic review will provide a comprehensive overview of the influence of gut microbiota on neurodevelopment in children with ASD, as it is a promising field that is still evolving. Studies investigating the composition of the gut microbiota and the functional and metabolic changes associated with the gut microbiota of children with autism spectrum disorder were examined. Understanding the mechanisms involved and developing interventions targeting the gut microbiota could have important implications for clinical management and contribute to the advancement of more effective complementary therapeutic and nutritional strategies for this population.

The process of selecting publications, the number of publications included and excluded, as well as the reasons for exclusion, are shown in the flowchart (**Figure 4**) (ALBUQUERQUE; AVILA; BARROS, 2022). This type of research focuses on a well-defined question and aims to identify, select, evaluate and summarize the relevant evidence available.

Once the final sample of publications to be reviewed had been selected, the results related to the study's guiding question were organized and categorized. The extracted results were presented in a summary table (X1, X2, X3, X4, X5, X6, X7, X8, X9, X10, X11) and identified according to title, authors and year of publication. The interpretation of the results was based on a comparison of the data obtained and its connection with other scientific productions related to the topic of interest.

RESULTS AND DISCUSSION

We analyzed 11 studies consulted through the databases and which met the eligibility criteria. All the studies were qualitative literature reviews, narrative literature reviews, integrative literature reviews, systematic literature reviews, systematic literature reviews and review articles, which were identified by title, abstract and year of publication. The analysis of the texts sought answers to the guiding question, which led to the creation of a synthesized table presented below:

Considering the difficulty of diagnosing ASD in childhood, given the lack of knowledge of a specific etiology, many studies have been carried out in order to identify biological, genetic and environmental aspects that act as determining factors in the development of ASD. It is worth considering that the progress of these studies has made it possible to include ASD in the DSM-5 as a neurodevelopmental disorder, according to X6.

From a historical perspective, from the first study led by Leo Kanner to the DSM-5, many advances have been made, especially in the approach to ASD, including a new dimensional approach that is able to provide more effective clinical information by capturing the phenotypic profiles of individuals with ASD with greater heterogeneity presented in X6. Among the symptom specifiers listed are cognitive functioning (from intellectual disability to superior intelligence), language impairment and concomitant psychological and medical conditions. With regard to symptomatology, the X6 study considers that there is a better understanding of the importance of correctly diagnosing ASD while there are more tools capable of verifying the developmental nature of its main characteristics.

With regard to these characteristics, X7 discusses the relationship that has long been established between ASD and schizophrenia, disorders that, despite sharing several charac-

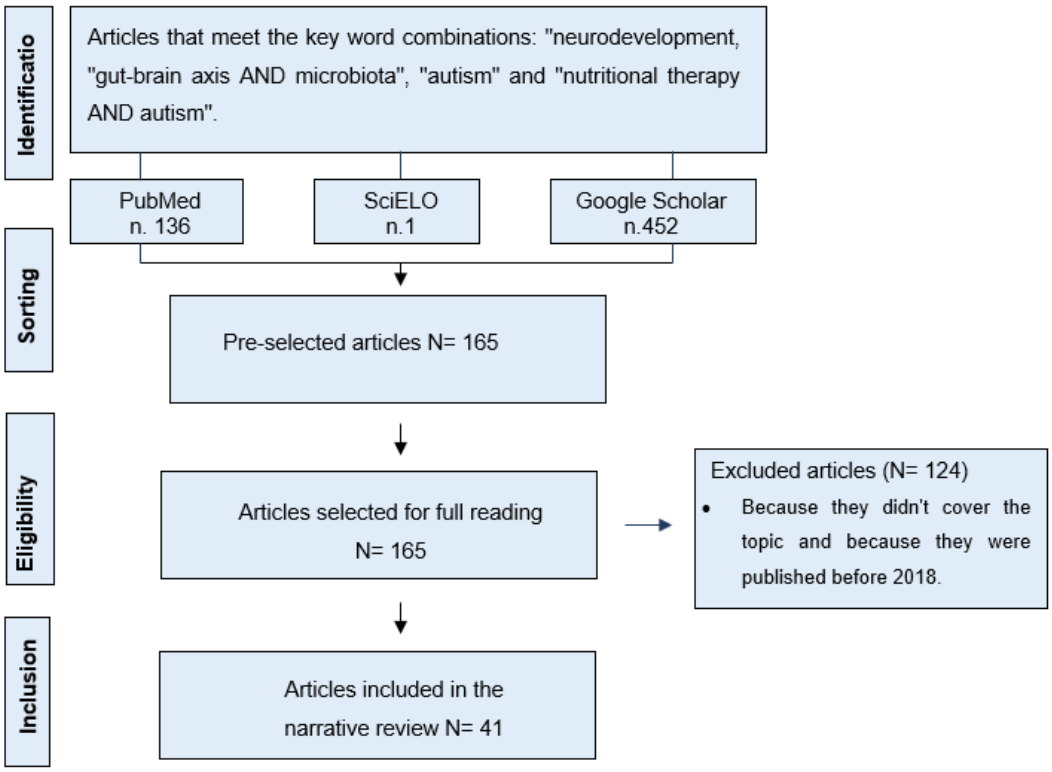

FIGURE 4. FLOWCHART OF THE SAMPLE SELECTION OF ARTICLES FOR THE REVIEW

SOURCE: Own elaboration, 2023

AUTHOR (S) YEAR	ARTICLE TITLE	TYPE OF STUDY	OBJECTIVE	MAIN RESULTS
X1Silva; Araújo; Vasconcelos, 2020	Nutritional intervention in the treatment of intestinal dysbiosis in children with autism spectrum disorder: a literature review	This is a narrative literature review carried out in September 2020.	Literature review on the impact of nutritional intervention in the treatment of intestinal dysbiosis in children with ASD	Studies indicate that nutritional intervention has shown effective results in the treatment of dysbiosis, resulting in significant improvements in the behavior of children with autism.
X2Fonseca; Piedade; Silva, 2022X 3Sabino; Belém, 2022	The study of the gut-brain axis and its influence on neurodegenerative diseases - a literature reviewThe relationship between autism spectrum disorder and intestinal dysbiosis: an integrative review	This is a qualitative narrative review of the literature from the last eleven years. This was an integrative literature review	To highlight the influence of the intestinal microbiota on neurodegenerative diseases, emphasizing the importance of maintaining good eating habits from childhood.To relate the existence of the worsening of Autism Spectrum Disorder due to intestinal dysbiosis, contributing to the identification of relevant aspects that can accentuate the clinical picture, and to highlight the relationships and the existence of the worsening of Autism Spectrum Disorder due to intestinal dysbiosis.	Based on the 40 studies analyzed over the last eleven years, it was found that the intestinal microbiota has an influence on the gut-brain relationship, the association that exists between neurodegenerative diseases and the imbalance of the intestinal microbiota; and how nutritional strategies help in the management of these diseases.Fifty-two manuscripts were identified and, after applying the inclusion and exclusion criteria, 11 articles were considered which showed that ASD is aggravated by factors intrinsic to the intestinal microbiota.

X 4Gomes et al., 2022	The importance of proper nutrition for children with autism spectrum disorder and improving their lives.	The study is classified as a systematic literature review (Lopes et al., 2008).	The overall aim of this research is to assess the importance of healthy eating for children with Autism Spectrum Disorder.	The narratives show that the studies carried out prove a significant improvement in the intake of vitamins and minerals, resulting in an improvement in the children's quality of life. In this sense, it is necessary to expand the studies focused on the characteristics and eating patterns of children with ASD, with a view to discovering new studies that can help parents and/or guardians to conduct the nutritional process in terms of acceptability.
X 5 Bruni et al., n.d.	Intestinal microbiota and the factors that influence its formation.	Literature review.	The aim of this work is to analyze the determining aspects for establishing a healthy ICM in early life.	
X 6ROSEN, N. E. *et al.* (2021)	The Diagnosis of Autism: From Kanner to DSM-III to DSM-5 and Beyond	Literature review article	Analyze the impact of DSM-III and its successors on the field of autism - both in terms of clinical work and research.	It is possible to observe the categorization of ASD since Leo Kanner and how studies have included dimensional approaches in the diagnosis, conceptualizing the advances from the first study to the production of the DSM-5, suggesting future approaches.
X 7JUTLA, A.; FOSS--FEIG, V. J. (2022).	Autism spectrum disorder and schizophrenia: an updated conceptual review.	Systematic literature review article	To analyze, from a review of studies since 2013, the convergence between autism and schizophrenia, categorizing into: symptoms and behavior, perception and cognition, biomarkers, and genetic and environmental risk.	It was noted that there are few studies in the area that evaluate clear diagnostic methodologies for ASD and SCZ and that, although many clinical studies consider the characteristics of ASD in adults with schizophrenia, the reverse has not been done much. It is clear that ASD is increasingly being diagnosed in adulthood and that it is possible to detect and distinguish between the two disorders.
X 8SAAD, A.K. *et al.* (2022)	Role of Brain Modulators in Neurodevelopment: Focus on Autism Spectrum Disorder and Associated Comorbidities	Review article.	Discuss the impact of various endogenous neuromodulators and pharmacological agents on the fetus during pregnancy, manifested in various aspects of neurodevelopment.	It has been found that neurodevelopmental disorders, including ASD, incorporate deficiencies in various neuromodulators, interfering with the proper maturation and vital functions of the brain. Among the causes attributed to this are: genetic mutations, environmental insults, including pharmacological agents used during pregnancy.
X 9GIRAULT, J. B., PIVEN, J. (2020)	The Neurodevelopment of Autism from Infancy Through Toddlerhood.	Review article	To review neuroimaging studies of brain development in ASD from birth to childhood, relating them to neurobiological mechanisms.	The brain phenotypes observed led to the discovery of brain overgrowth, increased extra-axial fluid volumes, altered white matter development and structural connectivity patterns in individuals with ASD

X 10MASINI, E. *et al.* (2020)	An Overview of the Main Genetic, Epigenetic and Environmental Factors Involved in Autism Spectrum Disorder Focusing on Synaptic Activity.	Review article	It provides an overview of the genetic, epigenetic and environmental factors that contribute to the pathogenesis of ASD.	Considering synaptic activity, it was possible to observe several candidate genes for ASD, such as CAPG, which codes for actin architecture, as well as epigenetic aberrations such as altered DNA methylation and microRNA for the etiology of ASD. Environmental factors included the age of the parents, fetal exposure to sex steroids and micronutrient deficiency.
X 11KATTAB et al. 2020	Risk Factors Diagnosis Prognosis and Treatment of Autism	This is a discursive review carried out in March 2020.	Provide practical steps that can be used to reduce the incidence and severity of ASD, as well as the prognosis and treatment of autism.	Prenatal and pre-pregnancy awareness of environmental factors, including recommendations against consanguineous marriage, information on optimal maternal nutrition and the importance of limiting exposure to toxins and pollutants are essential. In addition, with regard to biological risk factors, genetic screening and early postnatal monitoring of infant feeding, nutrition and eye contact will help provide the earliest possible treatment.

TABLE 1. ORGANIZATION OF THE REFERENCES INCLUDED IN THE LITERATURE REVIEW ACCORDING TO AUTHOR, YEAR OF PUBLICATION, ARTICLE TITLE, TYPE OF STUDY, OBJECTIVE AND MAIN RESULTS ACCORDING TO THE INCLUSION AND EXCLUSION CRITERIA.

SOURCE: Own elaboration, 2023

teristics, have different diagnoses. There are differences both in the time of diagnosis (ASD during childhood while SCZ occurs in adolescence and as an adult), as well as brain growth in individuals with ASD in relation to the reduction in cortical thickness in pre-adolescence as a symptomatic factor in schizophrenia. There are points of convergence between the two disorders, however, the characteristics of ASD in SCZ have been understood more than individuals with ASD and SCZ, above all because, despite being diagnosed in childhood, ASD in adults has been increasingly recognized on the basis of both genetic and neurobiological tests.

On the other hand, but still in relation to the diagnosis of ASD, X8 questions and discusses synaptogenesis as a factor that interferes with ASD starting in neurodevelopment during pregnancy. This is because, as a large number of cells are mobilized to assist in the synaptic process, when exposed to inflammation, they can trigger abnormal immune activation, interfering with the proper maturation and vital functions of the brain. Among the reasons for this interference have been genetic mutations (especially in the GABA receptor) and environmental insults such as the use of drugs and benzodiazepines or valproate during pregnancy, even though these drugs can be used later to correct diseases in the neuromodulatory systems.

X9 notices, from the analysis of early ASD neuroimaging, including structural, diffusion and functional MRI scans from postnatal to preschool, characteristic changes in brain structure and function that are indicative of ASD in addition to changes in neuromodulators. That said, brain overgrowth, increased extra-axial fluid volumes, altered white matter development and aberrant structural and functional connectivity patterns in individuals with ASD were found to be related to mechanisms governing synaptic pruning, cor-

roborating X8's study. This demonstrates the importance of neuroimaging in identifying the risk of ASD and proposing effective pre--symptomatic interventions.

Another point to take into consideration is the relationship between the gut microbiota and the brain. This is because it influences the brain to the extent that neurodegenerative diseases are linked to an imbalance in the intestinal microbiota, as listed by X2 and X3, discussing, above all, the worsening of ASD related to this imbalance in intestinal functioning.

The development of the intestinal microbiota in the first months of life is a determining factor in the child's current and future health, as discussed in X5, and when the initial diet, with breast milk, is deficient in HMO with a higher amount of protein, this leads to a more diverse microbiota, which is used by various opportunistic pathogens. Therefore, nutritional interventions are needed that take into account the individual's needs, such as vitamin insufficiency, increased oxidative stress and reduced energy transport capacity.

X10 seeks to list some other factors responsible for epigenetic aberrations in the etiology of ASD, including DNA methylation and microRNA deregulation in various matrices, such as saliva, blood and brain tissue. Another point discussed is environmental factors that interfere in the etiology of ASD, reinforcing what has already been discussed, especially drug use during pregnancy, and relating it to the age of the parents and some micronutrient deficiency during pregnancy.

Therefore, X11 corroborates the importance of prenatal care and correct maternal diet and nutrition, since these can become environmental factors for the development of ASD, especially when there is consanguineous marriage, so it is necessary to limit exposure to toxins and pollutants. X11 also emphasizes the importance of monitoring children's nutrition early on, right from the post-natal period, in order to propose the best possible treatment.

With regard to the importance of proper nutrition, X1 points out that when this is carried out in an interventional way, with the help of professionals, it has guaranteed very effective results, including improvements in behavior through the treatment of dysbiosis. X4 confirms that nutritional interventions in children with ASD have had an impact on improving methionine metabolism, cell methylation capacity, reducing ASD symptoms and hyperactivity, as well as improving communication and social interaction.

FINAL CONSIDERATIONS

Through the analysis of various studies and scientific evidence, we have concluded that the intestinal microbiota has a significant influence on the neurodevelopment of children with autism spectrum disorder. ASD is a complex condition characterized by deficits in social communication, restricted social interactions and repetitive patterns of behaviour. Although the exact cause of ASD is still unknown, recent research has pointed to the importance of the gut microbiota in its etiology.

The gut microbiota, made up of trillions of microorganisms that reside in the gastrointestinal tract, plays a fundamental role in regulating the immune system, producing neurotransmitters and modulating inflammation. Studies have shown that children with ASD have alterations in the composition and diversity of their gut microbiota compared to neurotypical children. These alterations may contribute to the manifestation of ASD symptoms.

The interaction between the gut microbiota and the brain occurs through complex and multifactorial pathways, including neuroendocrine communication, the immune system and the vagus nerve. The gut microbiota can affect brain function and neurodevelopment through the production of metabolites, such as short--chain fatty acids (SCFA), which have anti-inflammatory and neuroprotective properties.

In addition, the gut microbiota is involved in regulating the gut-brain axis, which plays an important role in regulating mood, behavior and cognitive function. Dysfunctions in this axis have been associated with neuropsychiatric disorders, including ASD. It is believed that modulating the gut microbiota through dietary interventions, probiotics or fecal transplantation may have beneficial effects on neurodevelopment and ASD symptoms.

However, it is important to note that the influence of gut microbiota on neurodevelopment in children with ASD is still a developing field of research. Further studies are needed to elucidate cause and effect relationships and determine the most effective therapeutic strategies. Despite this, the findings to date suggest a promising approach to the treatment and management of ASD.

In summary, the gut microbiota plays a fundamental role in the neurodevelopment of children with ASD. Alterations in the composition and function of the gut microbiota may contribute to the manifestation of ASD symptoms, and interventions aimed at modulating the gut microbiota may have beneficial effects on the neurodevelopment and quality of life of these children.

It is suggested that further research be carried out to fully understand these mechanisms and to develop specific therapies based on the intestinal microbiota.

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