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Role of Gut-Brain Axis in Autism Spectrum Disorder: a Focus on the Neuroinflammation and Microglial Polarization

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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition that affects communication, social behavior and gives rise to repetitive behaviors and restricted interests. The complexity of ASD suggests the influence of multiple etiological factors, including genetic, environmental, and immunological elements. Recently, the gut-brain axis has emerged as a significant field of interest, proposing an intriguing connection between the composition of the gut microbiota and the neurobehavioral manifestations of ASD. This narrative review explores the current evidence linking the gut-brain axis to neuroinflammation and microglial polarization in the context of ASD. This review highlights the importance of integrated approaches to understanding the complexity of ASD, pointing to the need for further research exploring the role of the gut-brain axis as a potential therapeutic target. We conclude that a deeper understanding of the interactions between gut microbiota, neuroinflammation and microglial activity may reveal new avenues for more effective interventions in ASD.

Keywords: Autism; Microglia; Gut-Brain axis.

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1. Introduction

Autism or Autistic Spectrum Disorder (ASD) is a chronic neurodevelopmental disorder, prevalent in both sexes [1]. According to more recent studies, autism is a multifactorial condition, resulting from genetic and biological interactions in interaction with the environment [2]. According to epidemiological data, about 1 in every 100 children are diagnosed with autism in the world, with men being 4 times more affected than women [3]. The diagnosis is made around 18 to 24 months, using the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) tool. As much as there is evidence of the involvement of genetics in autism, there is still no laboratory test that confirms the diagnosis [2]. Signs and symptoms are usually presented by food neophobia (selection and difficulty accepting food), hyperreaction or hyporeaction to sensory stimuli, difficulty and failures in social interactions and communication, lack of social, emotional, and verbal interest, inflexible routine, in addition to others [2].

There is a neural, metabolic, endocrine, and immunological communication, which takes place through the gut microbiota and the brain itself, being called the gut-brain axis (GBA). This pathway contributes to neurodevelopment, in addition to processes such as microglial maturation, myelinating action, and neurogenetics. It also affects mood, cognition, behavior, social skills, and anxiety [4]. The enteric nervous system (ENS) transmits

sensory information from the periphery to the central nervous system (CNS), this occurs through the ganglia of the plexus of Auerbach, intestinal flux cells and through the ganglia of the submucosal plexus. Finally, the afferent fibers reach the subcortical and cortical centers, crossing the limbic system, thalamus, and vagus nerve, which ensures fluidity in gastrointestinal activity, thus being a two-dimensional dynamic communication between intestine and brain [5].

The intestinal microbiome has a very important role that goes beyond its action in the digestive system. Organisms such as Enterococcus spp., Escherichia coli, Candida spp., sporogenic bacteria, and streptococcus spp. have because of their metabolism the production of serotonin, playing key roles in enteric motility, pain perception, secretion, thus acting in the serotoninergic modulation of the ANS, which controls the production of intestinal mucus, and thus is crucial in shaping the environment in which the GM resides. At the central level, this serotonin even acts on mood by regulating the cognitive functions of the CNS [4]. Added to this, the gut microbiome (GM) acts as a mediator between the enteric nervous system and the CNS, due to the transmissions of information concerning the intestinal lumen by means of neuroendocrine substances [4].

Neuroinflammation is a chronic or acute immune response of the central or peripheral nervous system, characterized by the proliferation of glial cells (microglial and astrocytes), activated by circulating immune cells, usually mast cells, and reactive oxygen species (ROS), chemokines, and inflammatory cytokines in response to infections, injuries, and pathogens in general [6]. Furthermore, studies show that the interaction between lifestyle, environment, and genetics result in neuroinflammation and neurodegenerative disorders [7]. The microglia (non-neural cells) play a key role in maintenance, protection, neuronal function, and in neurogenesis, through secretion of neurotrophic substances, control of the balance of the basal neurogenic cascade, added to inflammatory activation through cytokines such as IL-1β, IL-18 and CD68 [8]. If the mycroglia do not fulfill their role in modulating neuroinflammation, this can be a worsening factor in various pathologies, and lead to neurodegeneration [9].

Carriers of autistic spectrum disorder (ASD) constantly present clinical manifestations such as food neophobia, which is usually associated with chronic abdominal pain, altered bowel habits, probably because of gastrointestinal dysbiosis [10]. In a neurotypical individual, the autonomic nervous system (ANS) acts in the production of intestinal mucus and intestinal peptides that will affect the microbiome and the intestinal innate immunity through Goblet and Paneth cells, mediating the production of macrophages and mast cells, which alters intestinal epithelial permeability [4]. As such, Paneth cells produce and secrete antimicrobial peptides known as AMPs, which are lysoenzymes, phospholipases.

After the ANS stimulates the Paneth cells, the antimicrobial granules produced by them accumulate in the mucus layer of the GIT, then act so that there is no bacterial invasion and attachment. When in non-neurotypical individuals, such as those with TEA, the ANS may be altered, and thus not send the cholinergic inputs that trigger the antimicrobial reactions, unbalancing the commensalism relationship between the microbiome and the host [10]. The imbalance of the microbiome also affects the activity of short head fatty acids (SCFAs), which would normally be products of food fiber fermentation, absorbed by the enteric mucosa, acting on the microglia and counteracting neuroinflammation by stimulating the sympathetic branch of the PNS. If SCFAs levels are low, immune responses, CNS and PNS functions, and gut epithelial cell turnover are impaired. This is due to SCFAs being a source of ketone bodies, which are a source of ATP at the central level [4].

In addition to the alteration of SCFAs, the imbalance of the microbiome also affects the production of serotonin, since serotonin is a product of the metabolism of various microorganisms that convert dietary tryptophan into 5-hydroxytryptophan, preventing activation of the microglia, and thus brain neuroinflammation, since the metabolization of tryptophan into serotonin prevents the neurotrophic tryptophan molecule from

crossing the blood-brain barrier and being modified into quinolinic acid [4]. In this sense, knowing the importance and the correlation between the brain-intestine axis in autism spectrum disorder, we conducted this review with the purpose of updating the literature about this topic.

2. Material and methods

A narrative literature review was conducted according to a systematic review method based on Pubmed (Medline) Database. The English-language-based studies were retrieved using the following medical subject headings (MeSH): "autism spectrum disorders" AND "gut-brain axis" OR "autism spectrum disorders" AND "neuroinflammation" OR "autism spectrum disorders" AND "microglial polarization" OR "autism spectrum disorders" AND "neuroinflammation" AND "microglial polarization". The authors undertook a systematic search of PubMed/Medline peer-reviewed studies (impact factor greater than or equal to two) published in the last ten years (2020 to 2023). Only studies that exclusively evaluated the role of gut-brain axis in autism spectrum disorder with a focus on the neuroinflammation and microglial polarization were included in this review. Review studies, comments, perspectives, editorials, or other research that did not provide original or unpublished results were excluded.

3. Brain-Brain Axis in Autism

The gut-brain axis (GBA) features a variety of interconnected body structures, such as the central nervous system (CNS), autonomic nervous system (ANS), and enteric nervous system (ENS), and failures in this axis can lead to various health disorders, from inflammation to neurodevelopmental problems, including autism spectrum disorder (ASD) [11]. The gut microbiota is influenced by several factors, including genetics, environment, and/or immune status [12]. The microbiome ends up interacting not only with the immune system, but also with the nervous system to modulate, in addition to gut function, mood and behavior [12] through the regulation of various neurotransmitters such as, for example, GABA, glutamate, serotonin, and dopamine, which were altered in people with ASD [11].

Individuals with ASD often have comorbidities and are thus at higher risk for gastrointestinal symptoms (GI symptoms), among them diarrhea, constipation, and abdominal pain [13, 14]. Furthermore, the composition of the gut microbiota is closely linked to the colon transit time, i.e., if the time is fast, it ends up selecting fast-growing bacteria and if the time is slower, it ends up selecting slower-growing bacteria [14]. Concomitantly, SGI can cause pain and distress when these are abdominal pain and constipation, and in individuals who have little or no communication skills it can be a problem as they are unable to tell their caregivers that they are in pain, leaving them more hyperactive, withdrawn, or irritable when compared to those who do not have SGI [13]. When this symptom is diarrhea, individuals with ASD may exhibit tantrum behavior, and when the symptom is nausea, individuals with ASD may exhibit worry/depression behaviors as well as avoidant behavior [13].

Although the normal intestinal microbiota presents a natural defense against pathogenic species, the increase in these, generated by dysbiosis, can promote an alteration in intestinal permeability, where metabolites associated with intestinal microbes (LPS and proinflammatory cytokines), mainly gram negative bacteria (GBN), leave the gut and enter the bloodstream and thus end up reaching the brain through the GBA, and may affect brain functions, the integrity of the BHE, and development, besides being more present in children with autistic phenotypes [11, 12, 14].

4. Neuroinflammation in Autism

Neuroinflammation, physiologically, aims to establish homeostasis, in addition to enabling the body to adapt to exogenous and endogenous stimuli, in order to protect the

body. However, it has been evidenced that autistic patients have neuroinflammatory dysfunctions, which are strongly associated with symptom intensity [9]. Neuroinflammatory processes were first identified in patients with autism in the cerebellum, cerebral cortex and white matter, but there is evidence that neuroinflammation exists in other brain areas, as shown by elevated levels of pro-inflammatory cytokines in cerebrospinal fluid and increased autoantibodies.

The pro-inflammatory cytokine found highest in autistic patients is IL-17, very present in systemic neuroimmune cells, which are in imbalance in these patients, this causes the brain-peripheral inflammatory axis to be the link between other immune cells, so signaling by IL-17 in monocytes, activates these other immune cells and thus, aggravate neuroinflammation [15]. Added to this, the high concentration of IL-17 leads to alterations in Nuclear Factor Kappaβ (NF-kβ), an important regulator of the inflammatory response, which has been found elevated in the plasma of autistic patients. The elevation of NF-kβ causes overexpression of pro-inflammatory genes, again contributing to the whole neuroinflammatory process.

Postmortem studies carried out in autistic patients in search of neuroinflammation showed that in these patients there is a great activation of astrocytes, as well as of the microglia itself, associated with levels of IL-6, IL-12p40, and IFNγ, besides the decrease of cytokines that do the negative regulation of inflammatory processes, such as TGFβ1 [16]. Another form of neuroinflammation in autistic patients is by interaction of mast cells with microglia and neurons, where mediators such as reactive oxygen species, hydrolases, cytokines, histamine, and especially TNFα are released, which at high levels in the cerebrospinal fluid and brain of autism patients, is related to the severity of symptoms.

3.3 Microglia and Autism

ASD is a condition characterized by restricted and/or repetitive behavior of the individual, as well as persistent deficits in communication and social interaction. Although it has a genetic origin, environmental factors can lead to the potentiation of symptoms and worsening of the disorder [17-19]. In turn, microglia are composed of immune cells in the central nervous system, and its dysregulation is present in several psychiatric disorders, among them, TEA [18, 20].

That is, the association between microglia and the pathophysiology of ASD is supported by evidence of increased microglial density in the cerebral cortex and increased levels of pro-inflammatory molecules, creating a link between microglial activation and neuronal dysfunction [21]. Given this, microglia act by monitoring the microenvironment and their activation occurs when infection, injury, disease or high-risk environmental factors occur, when this activation occurs chronically during the early stages of neurodevelopment changes can be seen in assignments, length and orientation of dendritic spines of neurons. Mainly, in the functionality of excitatory and inhibitory neurons which will eventually compromise cognitive, behavioral and/or social communication example of what occurs in the brains of individuals with ASD [22]. In other words, microglial inflammation plays an important role as a negative regulator of the neurogenic microenvironment and can interfere with and support synaptic processes in neurons [23].

With a still poorly explored pathophysiology, it is worth noting the presence of obvious abnormalities both morphologically and functionally in brains of patients with ASD, especially demonstrating consistent and frequent microglial activation throughout the brain especially in the cerebellum [22]. In view of this, a large part of the findings made were made in brains after death of people with ASD, among them we can mention signs of microglial activation involving increased cell number or cell density, morphological changes and phenotypes, a significant increase in the somal volume of mycroglia in the white matter and a significant increase in cell density of the gray matter. Furthermore, the branching that occurs in the microglia in TEA may be behind the deficits in synaptic monitoring that lead to increased local connectivity and shorter, overconnected cortical networks [4, 16].

Added to this is the presence of several genes that are predominantly expressed in glial pathways such as: ABAT, MAOA, and MAOB, genes involved with neurotransmitter metabolism, as well as genes that encode scaffolding proteins, transcription regulators, NMDA coding, enrichers of calcium signaling pathways, and metabotropic glutamate receptors. Thus, their occurrence in TEA demonstrates that altered gliotransmitter pathway plasticity and synaptic modulation may also be present [21]. Considering this, a model already validated for research, induces the onset of SAD through the use of propionic acid in rodents, in which abnormal histology of the hippocampus, abnormal neuronal cellular organization, secretion of neurotoxic cytokines, and increased microglia activity were found in the rodents' brains [18, 24].

Likewise, antibody activation against the HLA-DR antigen, a subset of MHC II proteins, is seen concomitant with microglia activation. In an analysis of areas of neuropathological changes in brain tissues of individuals with ASD it was possible to identify increased immunocytochemical staining for the marker HLA-DR when compared to neurotypical brains demonstrating extensive microglial activity. Furthermore, increased expression of the markers TREM2, DAP12, CX3CR1, AIF1, PFC was found in TEA carriers. Furthermore, gene expression corresponding to M2 activation states was found in microglia which implies a dysregulated response that corresponds to the neuronal activity of TEA, these findings demonstrate the close association between TEA and microglial alterations [16].

Finally, aberrant activation of microglia associated with genetic and environmental factors may influence neurodevelopment by alterations in synaptic functions and structures and even without a fully described mechanism it is valid to associate constant microglial activation during early developmental periods to TEA [22].

3.4 Role of the brain-gut axis on neuroinflammation and microglia in autism

The brain-intestine axis, formed by parasympathetic and sympathetic pathways that make the connection between the Central Nervous System and the Enteric Nervous System, and through this communication, the Autonomic Nervous System acts together with immune cells, causing the release of neurotransmitters, regulating gastrointestinal activity. Patients with ASD present as one of the symptoms, an abnormality in the functioning of the ANS. Such abnormality causes the sympathetic branch of the ANS to be hyperactivated, and antagonizes the parasympathetic branch, so there is a decrease in exosomal secretion by the gastrointestinal mucosa, more specifically, colonics, associated with a decrease in lectin secretion, and consequently a decrease in bactericidal metabolites and peptides from Paneth cells, also decreasing phagocytosis of the intestinal mucosal surface coexisting with the microbiome. Thus, commensal bacteria have their population reduced, in addition to dysregulation of the luminal osmotic, water, and ionic balance, generating dysbiosis.

Similarly, gastrointestinal dysbiosis is common in the clinical practice of patients with ASD; symptoms such as chronic abdominal pain and dysregulated bowel habits are strongly associated with the severity of the syndrome. Bacterial populations in saliva, oral cavity and feces of autistic children were analyzed, and it was found that there was a major decrease in bacterial diversification, but an increase in non-spore-producing anaerobic gram negatives, unbalanced ratio between these gram negatives and aerobic gram positives. Therefore, abnormal activation of the sympathetic branch of the ANS decreases the host's ability to contain commensals within the gut lumen, which then affect gut metabolism and generate metabolic stress, producing reactive oxygen species, pro-inflammatory molecules, and other cytokines such as IL-17.

4. Conclusion

Through the increased number of studies about the gut-brain and how it can affect/contribute to some diseases, mainly neurodegenerative such as autism, there has

been an increase in curiosity about the axis in this disorder. In this review, we discuss how the gut-brain axis acts in ASD from neuroinflammation, mainly by microglial polarization. Thus, this study will contribute to a better understanding of how this axis can cause/alter behaviors of ASD and contribute to a better management of this disorder in the future.

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