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THE POTENTIAL ROLE OF THE INTESTINAL MICROBIOTA IN THE MANIFESTATION OF ALZHEIMER'S DISEASE: A LITERATURE REVIEW

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Abstract: Goal: To discuss, through the scientific literature, the association between the balance of the intestinal microbiota and the emergence of neurodegenerative disorders, especially Alzheimer's disease (AD). **Methods:** Literature review carried out from October to November 2022 through searches in the following PubMed database. 248 articles were selected and, after inclusion criteria, 17 studies were selected to compose this review. **Review**: The different studies analyzed indicate that the microbiota-intestine-brain axis is closely interconnected and involved in neural and brain functioning. Its participation consists of processes of cognitive regulation and aging processes, which are directly related to intestinal dysbiosis and its repercussions at the level of the central nervous system (CNS). Intestinal dysbiosis may be in the process of biological senescence and culminate in chronic systemic inflammation, with the potential for brain beta-amyloid aggregation. **Final Considerations**: There is an imbalance of the intestinal microbiota that is related to neurodegenerative diseases. As the pathophysiology of AD is multifactorial, it is still necessary to deepen studies on this relationship to aid in early diagnosis and treatment.

Keywords: Microbiota-gut-brain axis; Alzheimer's disease; Neurodegenerative Disorders; intestinal dysbiosis.

INTRODUCTION

Understanding the influence of the intestinal microbiota on brain functioning has recently been the subject of research due to new discoveries. It is known that the intestine has a diverse population of microorganisms, such as bacteria, fungi, protozoa and viruses, collectively called the microbiota, which represent most of the microbial population of the human body. Such beings are influenced by several external factors, such as the use

of antibiotics and diet, and also by intrinsic factors, such as genetics. In view of this, each individual has a unique variability of their microbiota (LIU S. et al., 2020). Intestinal metabolites, neurotransmitters and hormones derived directly or indirectly from the intestinal microbiota, together with immunological signals, can reach the brain and an adequate balance between these factors is important for the functioning of the entire body (LIU S. et al., 2020; DE LA FUENTE M., 2021).

The microbiota-gut-brain axis is closely linked with interactions between the CNS, immunological and endocrine systems, and in cases of dysbiosis, characterized by alteration or imbalance of the intestinal microbiota, its functioning can be compromised, leading to manifestations of different disorders. With aging and consequent deterioration of the intestinal microbiota, recent evidence suggests that such conditions could favor beta-amyloid aggregation, neuroinflammation, inflammatory oxidative stress and insulin resistance (CHEN C. et al., 2020). Factors which are directly related to the pathogenesis of Alzheimer's disease, which will be the focus of this review, in particular Alzheimer's disease (AD) (LIU S. et al., 2020; DE LA FUENTE M., 2021).

AD is known to be the leading cause of dementia worldwide, seen mainly in the elderly, representing approximately 60 to 70% of all cases of dementia (EKUNDAYO T.C. et al., 2021). It is a progressive neurological condition associated with neurodegeneration, memory loss, learning, disability, and significant changes in character and behavior (VARESI A. et al., 2022). Even with more than 100 years of research into the possible pathological mechanisms of the disease, there are currently no effective drugs (MEGUR A. et al., 2020).

The United States Food and Drug Administration (FDA) has approved in recent years only a few compounds for use in people with AD and most of them are based on the older hypothesis of the pathophysiology of the disease with cholinesterase inhibitor active principles (MEGUR A. et al., 2020). Currently, several studies demonstrate that probiotic therapies can positively affect neural and cognitive functions, reinforcing the potential relationship between the gut microbiota-brain axis in the manifestation of AD. (DE LA FUENTE M., 2021; WIATRAK B. et al., 2022). Given such evidence, the aim of this study is to discuss the association between the balance of the intestinal microbiota and the emergence of neurodegenerative disorders, especially Alzheimer's disease.

METHODOLOGY

The present study is a bibliographic review carried out from October to November 2022. It was developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. In this sense, according to the parameters mentioned above, the population or problem of this research refers to the population of patients of advanced age, with possible cases of intestinal dysbiosis, and how such conditions can be related to the manifestation or worsening of neurodegenerative disorders, particularly Alzheimer's disease. The guiding question was adopted for the elaboration of the research: "What is the relationship between intestinal dysbiosis and the appearance of neurodegenerative disorders, mainly Alzheimer's disease, in elderly patients?". The searches were carried out through searches in the PubMed database. The following descriptors were used: Neurodegenerative Disorders; Dysbiosis; Alzheimer's Disease;

Microbiota-Gut-Brain-Axis, in English and associated through the Boolean operators AND and OR according to the following string: (neurodegenerative disorders) AND ((dysbioses) OR (Microbiota-Gut-Brain)) AND (Alzheimer's disease). 248 articles published in the last 5 years were found. The inclusion criteria were: articles published in the period from 2017 to 2022 and that address the theme proposed for the research, studies of the review type, systematic review, meta-analysis, clinical trial and papers, available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, 17 articles were selected to compose the collection of this present study.

REVIEW

The intestinal tract is considered the largest microecosystem present in the human body, containing approximately 1014 bacteria from more than 2000 known species, and which collectively have 100 times the genomic DNA of humans. The gastrointestinal microbiota, in a healthy state, has a very delicate balance. Minimal changes due to internal and external factors can easily affect this microecological balance, affecting the functioning of various apparatuses and systems of the body. The microbiota-gut-brain axis is involved in neuronal and brain functioning, and also in cognitive regulation and aging processes. This axis, which includes the CNS, endocrine and immune systems, has an information exchange network that connects the intestine and the brain, with a bidirectional transmission of information through two systems: "top-down" or efferent, from the brain to the brain. the intestine, and "bottom-up" or afferent, from the intestine to the brain (CHEN Y. et al., 2021).

There is evidence that different metabolites produced by intestinal bacteria, such as short-chain fatty acids and their respective precursors, as well as different substances with neurotransmitter action, directly and indirectly influence brain functioning via blood circulation, can thus also act on the regulation of different cognitive functions. Added to this, the intestinal microbiota also has action locally in the nervous system through enteric nerves and the vagus nerve, quickly transmitting signals to the brain through the "bottom-up" system (CHEN Y. et al., 2021).

The constitution of the intestinal microbiota varies between individuals and may change due to a diet with excess protein, fat or carbohydrates. In addition, changes in intestinal bacteria may result from factors such as: excessive use of antibiotics, poor immune system and alteration of gastrointestinal barriers (TREJO-CASTRO A. et al., 2022; HUNG C.C. et al., 2022; MEGUR A. et al., 2020). Commensal and pathogenic bacteria can also, through the production of lipopolysaccharides and amyloids, lead to immunological changes that affect the activity of the central nervous system (CHEN C. et al., 2020). Such dysbiosis locally and, as a consequence, systematically induces immune-mediated inflammation, and generates the production of pro-inflammatory cytokines, which also lead to neuroinflammation, possibly associated with the neurodegeneration process (LEBLHUBER F. et al., 2021).

Furthermore, the influence of the gut microbiota specifically on neuropsychiatric disorders can be partially attributed to the modulation of the availability of circulating tryptophan, serotonin, kynurenine and short-chain fatty acids, as well as the permeability of the blood-brain barrier and activation of peripheral immune cells and brain cells of

the glia. Compromising the structure of the gastrointestinal tract leads to changes in its mucosal barrier with a consequent increase in intestinal permeability and absorption of potentially harmful substances to the body. Such events lead to the activation of immune responses with chronic elevation of levels of inflammatory mediators, which are known triggers for a wide spectrum of neuropsychiatric disorders (GENEROSO J.S. et al., 2020).

In the elderly, due to a multitude of conditions common to the normal aging process, the intestinal microbiota presents changes that may facilitate the manifestation of dysbiosis and the consequent appearance of systemic inflammation, resulting from the damage to the permeability of the gastrointestinal tract already mentioned. Changes in the oxidative framework of the central nervous system may increase the likelihood of developing different neurodegenerative disorders, especially Alzheimer's disease. Studies demonstrate that the intrinsic relationship of the afferent branch or "bottom-up" of the microbiota-gut-brain axis and the onset of Alzheimer's Disease (AD) occurs through the regulation of neurotransmitters, such as acetylcholine, dopamine, glutamate, serotonin, GABA and norepinephrine, produced by commensal microorganisms in the intestine (CHEN Y. et al., 2021). Low levels of butyrate have also been shown to favor the formation of reactive oxygen species, enhancing the organism's oxidative stress. Dysbiosis in the elderly can influence the decrease in cognitive function through increased deposition of amyloid protein in the brain, a common and determinant condition for the diagnosis of Alzheimer's disease (SHABBIR U. et al., 2021; GOYAL D. et al, 2021; CHEN C. et al., 2020).

A recent survey of elderly people with cognitive impairment (without a diagnosis of AD) reported an increase in the abundance of pro-inflammatory bacteria:Escherichia/ Shigella and a decrease in the abundance of anti-inflammatory bacteria, such as: *Eubacterium rectale*, in subjects with evidence of amyloid deposition on PET imaging compared to subjects who were amyloid negative. Another study carried out with animals analyzed the behavior of rats with AD induced by the administration of D-galactose and β-amyloid, exposed to fructooligosaccharides from *Morinda Officinalis* for 4 weeks and a greater synthesis and secretion of neurotransmitters was observed (CHEN Y. et al., 2021; GENEROSO S.J. et al., 2021).

In line with these results, studies have also shown significant changes in the microbiota of elderly people diagnosed with AD compared to elderly people without the disease. A greater amount of pro-inflammatory bacteria was identified, such as: *Gammaproteobacteria*, *Enterobacteriales* and *Enterobacteriaceae* of phylum in elderly people with AD and a decrease in the amount of anti-inflammatory bacteria, thus supporting the hypothesis that there is an association between dysbiosis and the manifestation of Alzheimer's disease (LEBLHUBER F. et al., 2021; CHEN Y. et al., 2021).

According to Tan L.Y. et al. (2021), hypercaloric diets, with a high content of lipids and simple carbohydrates, result in a decrease in the diversity of the microbiota and an excess of microbes related to intestinal inflammation. On the other hand, strict calorie-restricted diets, vegetarian and ketogenic diets have been found to cause reduced microbiota and intestinal dysbiosis in the long term. Normocaloric diets with higher amounts of fiber, more antioxidant substances and amino acids (BCAA) do not alter the general diversity

of the intestinal microbiota, but provide an increase (growth/prevalence) of probiotic strains, which are beneficial for the patient's secondary prevention; help slow disease progression, minimize risk, and improve neurodegenerative conditions. These data indicate that, in general, a nutrient-balanced diet is the best option for the adjuvant therapeutic management of AD. It is noteworthy that the constant practice of physical exercise increases levels of brain-derived neuroprotective neurotrophic factor (BDNF) (TAN L.Y. et al., 2021). Accumulating evidence also suggests that improvements in degenerative symptoms have been reported following probiotic supplementation. A double-blind randomized clinical trial investigated the behavior of elderly people supplemented with probiotics containing: *B. longum* and *Lactobacillus spp* for 12 weeks, and improvement in cognition was demonstrated, as assessed by cognition tests such as the Mini Mental State Examination (GENEROSO J.S. et al., 2020; VARESI A. et al., 2022).

Probiotics are living microorganisms, grouped into defined strains, whose effects benefit the host organism. In the studies carried out by Tanja J. et al. (2022), male mice with AD (n=9) were submitted to supplementation with specific probiotics, in order to demonstrate the influence of different probiotics on the composition of the intestinal microbiota and identify how this could affect the pathogenesis of neurodegeneration. Among the selected genres: *Lactobacillus* and *Bifidobacterium were the most used, while:B. longum* (NK46), *C. butyricum* and the SLAB51 blend stood out as the most effective probiotics, as most results showed improvement. In summary, the administration of probiotics in this animal population diversified the gut microbiota (n = 13 studies), meaning that it was possible to maintain a healthy microbiome. There was also an increase in the levels of short-chain fatty acids (n = 4 studies), which are known to be important for neurogenesis, learning and memory. There was a reduction in inflammatory markers (n = 7 studies) and improvement in cognitive function between groups (n = 12 studies). What still remains uncertain is the effect of probiotics on beta-amyloid peptides, since both positive effects (n = 10 studies) and insignificant effects were found, compared to the control group of animals with Alzheimer's (n = 5 studies) (TANJA J. et al., 2022).

In this sense, it must be noted that Peterson C. T. (2020) evidenced through a double-blind, randomized and placebo-controlled study in 30 people with Alzheimer's, in which the use of probiotics (with: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidume* and *Lactobacillus fermentum*) for 12 weeks demonstrated a positive outcome similar to that previously described. The Mini-Mental State Examination (MMSE) test demonstrated improvements in learning and memory. Additionally, a probiotic has been found to:multi-estirpe *(Bifidobacterium lactis, Lactobacillus bulgaricus, Streptococcus thermophilus* e *Lactobacillus lactis),* it is effective in regulating mood, due to its action on brain regions associated with the insula. It is important to know that the intestinal microbiota sometimes modulates the expression of BDNF, the main neuroprotective factor related to neurogenesis, memory, learning and cognitive processes (PETERSON C. T., 2020).

Studies have also proposed to evaluate kefir, a specific probiotic composed of symbiotic bacteria and yeast. According to Batista L.L. et al. (2021), the kefir microbiota and metabolome were determined using specific and appropriate scientific methods. Having done this, they used flies of the species: *Drosophila melanogaster* – model for

AD -, which have a simple nervous system, but similar to that of mammals. After treatment, the following criteria were analyzed: survival, vascular injuries and climbing ability. As a result, flies treated with kefir in natura and fractions improved in all those criteria, including the neurodegeneration index. Thus, such a compound can be considered promising regarding the control of amyloidogenic pathways (BATISTA L.L. et al., 2021). In line with this study, Peterson C. T. (2020) evaluated 13 patients during 12 weeks of kefir use. And, at the end of that period, it was possible to state that there was considerable cognitive rehabilitation, a decrease in oxidative stress and inflammatory markers (PETERSON C. T., 2020).

Prebiotics are substrates, usually carbohydrates, selectively fermented by intestinal microorganisms that are beneficial to health. Despite few studies regarding prebiotics, clinical trial data shown by Peterson C. T. (2020) bring good results. B-GOS (beta-galactooligosaccharides), FOS (fructooligosaccharides) or placebo were offered to healthy subjects in order to assess the emotional and psychophysiological response secondary to their use. At the end of the study, participants who consumed B-GOS were observed to have an optimized waking cortisol response, whereas vigilance was minimized, suggesting reduced reaction to negative events. Thus, the use of this prebiotic proved to be advantageous to regulate mood disorders and anxiety disorders. In addition, another substrate was also researched: inulin enriched with oligofructose. This compound administered in another clinical trial obtained good results compared to the placebo group, as there was an improvement in mood, recall and recognition memory. This implies reinforcing that prebiotics can be used in a personalized way to improve mood and neurological functioning. However, there is a lack of research on the effect of prebiotics in populations diagnosed with neurocognitive disorders, mainly different manifestations of dementia and AD (PETERSON C. T., 2020).

However, even with the development of several studies on the subject, there is still no possibility of curing or interrupting the worsening of AD, due to the complex pathophysiology of the disease. Added to this, there is still little public knowledge about therapeutic approaches aimed at preserving the intestinal microbiota with the use of probiotics and prebiotics. There are also indications that biomarkers derived from the intestinal microbiota can even be used for the early detection of AD. Such factors provide not only the manipulation of probiotics, prebiotics and dietary control, but also the possibility of fecal microbiota transplantation as possible and plausible complementary therapeutic options for AD (EKUNDAYO T.C. et al., 2021).

FINAL CONSIDERATIONS

It was found that there is a close relationship between the microbiota-gut-brain axis and the development of neurodegenerative diseases, especially AD. Intestinal dysbiosis that occur through the natural process of biological senescence culminate in chronic systemic inflammation, with the potential for aggregation of cerebral beta-amyloid, although the pathophysiology of AD is still mysterious and requires further investigation. Finally, there is a need to carry out further studies that explore the early screening of intestinal biomarkers for the early diagnosis of AD, in addition to the use of prebiotics and probiotics in the prevention and/or treatment of the disease.

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