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RELATIONSHIP BETWEEN ALZHEIMER'S DISEASE AND CHANGES IN THE INTESTINAL MICROBIOTA: LITERATURE REVIEW

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ABSTRACT

The relationship between changes in the intestinal microbiota and the increased risk of Alzheimer's disease (AD) is an area of rich scientific interest. According to Alkasir *et al* (2017), there is strong physiological evidence that strengthens the theory that both events may be related. The objective of this work was to review the knowledge obtained until now by researchers on the subject. For this, the platforms Pubmed, Scielo and Google Scholar were used. As a result, it was found that changes in the microbiota may be strongly related to the structural changes present in AD. In conclusion, it was noticed that new studies on the subject are needed, since understanding this relationship may clarify mechanisms underlying the events and lead to the development of new drugs for the treatment of AD.

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INTRODUCTION

According to Harrison (2017), Alzheimer's disease (AD) is the most prevalent cause of dementia syndrome in the elderly. In it, the presence of neuritic plaques containing beta amyloid, neurofibrillary tangles (NFT) composed of tau filaments that have undergone hyperphosphorylation and accumulation of amyloid in the walls of blood vessels in the cortex and leptomeninges are observed. In addition, Harrison states that the disease is associated with reduced levels of acetylcholine, the enzyme choline acetyltransferase and nicotinic cholinergic receptors, correlating this reduction with the involvement of neurons in the basal nucleus of Meynert. According to Alterthum and Trabulsi (2015, p.101), the concept of the organism's microbiota is "the presence of microorganisms that establish permanent residence or not, without causing infections or any other damage to the host in normal conditions. They report that "the microbial population of the Gastrointestinal Tract (GI tract) would be in the range of 1011 to 1012 CFU / ml of intestinal content, being composed of about 700 different species of microorganisms, with a predominance of bacteria. They also state that the intestinal mucosa is of great importance in the relationship between the body's immune system and the external environment, since the intestine is responsible for housing about 80% of human immune cells. According to Alkasir *et al*. (2017), new research has indicated that the microbiota of the gastrointestinal tract is directly related to the pathogenesis of dementia syndrome through the onset of metabolic diseases and mild inflammation. According to the authors, the analysis of the intestinal microbiota can lead to new views regarding the biology of AD, collaborating with the early diagnosis, prevention, identification of new therapeutic targets and development of new drugs for its treatment. For this reason, it is necessary to review the knowledge obtained so far with research to try to elucidate the mechanisms underlying this theme.

Literature Review

Li *et al*. (2016) define AD as a neurodegenerative condition characterized by a deficiency in synaptic plasticity, dramatic neuronal dysfunction and massive neuronal loss. According to the authors, several hypotheses suggest the cause of the disease, such as the hypothesis of amyloid deposition and the hypothesis of changes in the tau protein. According to the

Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (2013), the central characteristics of Neurocognitive Disorder (CNT) caused by AD include an insidious onset and gradual progression of cognitive and behavioral symptoms. In the mild stage of the disorder, Alzheimer's usually manifests itself with impaired memory and learning. In the larger phase of the cognitive impairment caused by AD, on the other hand, there is a disturbance in the visuoconstructive / perceptomotor capacity and in the language. According to Harrison (2017), in the most advanced stages of the disease there is a loss of discernment and cognitive reasoning, in addition to the presence of delusions. It also states that, in advanced AD, patients become rigid, mute, incontinent and confined to bed, being more susceptible to death from malnutrition, secondary infections, pulmonary embolism, heart disease and aspiration. There are certain authors, such as Itzhaki *et al*. (2017), who bring the theory that AD is, in fact, an infectious / immunological disorder. As arguments to support their theory, they claim that viral infectious agents manage to regulate genes that regulate the encoding of the cholesterol 25-hydroxylase enzyme (CH25H), whose polymorphisms are related to AD and susceptibility to amyloid deposition. In addition, Itzhaki *et al*. (2017) also show that the disease would appear with age due to the immunosenescence mechanism, which would reactivate viruses and other latent microbes in the brain. Xu *et al*. (2016) elucidate that the intestinal microbiota contributes to brain function not only through neural, humoral and immune pathways, but also through the cumulative effects of microbial metabolites. They bring undigested diet components that are fermented by the microbiota to produce a large array of metabolites such as bile acid, choline and short chain fatty acids (SCFAs), which are essential for health. He reports that changes in the microbiota are also related to other neurological diseases, such as autism, depression and multiple sclerosis.

METHODOLOGY

For this review, the works "Diagnostical and Statistical Manual of Mental Disorders" (DSM-V) of the American Psychiatric Association, the eighteenth edition of Harrison's Manual of Internal Medicine and the book Microbiology by Trabulsi-Alterthum were used. In addition, Pubmed, Google Scholar and Scielo were searched using the keywords "Alzheimer", "Microbiota", "Probiotics", "Dementia", "Brain", "Gut", "Microbiome" and "Microbiology". Only articles in English published in the last seven years were used. In all, fourteen articles were collected, among which twelve were used for this review.

RESULTS AND DISCUSSION

Wu *et al*. (2017), in their study of *Drosophila* flies with Alzheimer's disease, demonstrated that enteric infections exacerbated Alzheimer's progression by promoting the recruitment of hemocytes to the brain, causing TNF-JNK-mediated neurodegeneration. In their article, they stated that the presence of reactive oxygen species (ROS) and the chemokine CCL2 in the brain were necessary for the recruitment of immune cells and that the genetic manipulation of ROS levels reduced the effects of enteric infection on the progression of AD. They also elucidated that the recruitment of immune cells to the brain, initially, can be beneficial by cleaning incorrectly folded proteins, but when this recruitment occurs in an excessive or chronic way, it can lead to overproduction of pro-inflammatory and oxidizing cytokines that damage the cells of the central nervous system. Park *et al*. (2017), in turn, use Tg-APP / PS1 rat models, more susceptible to beta amyloid deposition, to investigate whether the extracellular vesicles secreted by the microbiota in the blood are useful for the metagenomic analysis in these rats. In the study, they showed that the microbiota of these rats was altered in relation to the control rats, with a greater number of bacteria from the phylum *Firmicutes* and from the genera *Aerococcus*, *Jeotgalicoccus*, *Costridales* and *Blautia*. On the other hand, they noticed that there was a decrease in bacteria of the genus *Lactobacillus*. They also theorize that, with further studies and advances, microbiota analysis can be used as a marker for the diagnosis of Alzheimer's disease. Zhao *et al*. (2017) detected in their studies the presence of bacterial LPS in brain lysates of hippocampi of patients with Alzheimer's disease, the anatomical region where the initial and deepest phase of neuropathology occurs. They showed that the hippocampus of patients with the most advanced stage of the disease exhibited an increase of up to twenty six times in LPS compared with the control group. Bearing in mind that the intestinal microbiota is an important source of neurotoxic species secreted by Gram Negative bacilli and that the transit of pro-inflammatory neurotoxins through the compromised gastrointestinal tract and the blood-brain barrier has an important role in the cell adhesion structures, allowing the passage of harmful TGI molecules to the central nervous system, Zhou *et al*. stated that further studies on the interaction between intestinal microbiota and its host can lead to a potential contribution to the understanding of human aging and the pathophysiology of neurodegeneration, amyloidogenesis and Alzheimer's disease.

In a population-based study, Chen *et al*. (2016) aimed to observe the importance of gut-brain interaction and correlate intestinal changes with a higher risk of dementia. For this, they collected data from about thirty thousand patients with Irritable Bowel Syndrome, comparing them with a control group of about one hundred and thirty thousand patients. In the study, excluding confounding factors and analyzing the data, they found that patients with Irritable Bowel Syndrome had a higher risk of dementia when compared to those without the syndrome, with an adjusted risk rate of 1.26. Thus, they demonstrated the close relationship between gastrointestinal disorders and the risk of developing dementia. Noble *et al*. (2014) correlate oral dysbiosis with the highest risk of developing Alzheimer's. In their cohort study, they state that the presence of IgG antibodies to high *A. naeslundii* bacteria in the serum, present in periodontal infections, increased the risk of developing Alzheimer's disease, with a risk rate of 1.9. As an explanation for the fact, they raised that it could be due to subclinical cerebrovascular damage and inflammatory processes, which directly influence neurodegenerative diseases. According to Alterthum and Trabulsi (2015), probiotics are defined as living organisms that provide benefits to the host, when inoculated in adequate quantities. For this, they must not show virulent activity and must be able to survive in the TGI environment, adhering to the mucosal surface and epithelial cells and inhibiting pathogens. According to Martínez *et al*. (2014), the use of probiotics causes a decrease in the synthesis of pro-inflammatory cytokines that are unbalanced in the older population, such as IL-8, IL-6 and TNF-alpha, in addition to causing an increase in the levels of lymphocytes, natural killer cells (NK cells) and

phagocyte activity. With this, they are able to reduce neuroinflammation. Akbari *et al*. (2016) demonstrate, through a clinical trial, that the use of probiotics for twelve weeks increases the score of patients with Alzheimer's in the Minimental exam in relation to the control group that had not ingested probiotics. In addition, its use has positive effects on the levels of Malondialdehyde (MDA), C-reactive protein of high sensitivity (hs-CRP), markers of insulin metabolism and levels of triglycerides in the blood of patients with the disease. Pistollato *et al*. (2016) highlight that certain substances in the diet can also reduce the risk of dementia and neuroinflammation by mechanisms that affect the production of amyloid in the brain. Among them are "oleuropeína aglicona" and "oleocantal", present in olive oil. These substances act by promoting amyloid beta clearance and autophagy, as well as inhibition, aggregation of tau proteins and neuroinflammation. According to them, the oleocantal regulates two amyloid beta transporters in the brain expressed in the blood-brain barrier, increasing its efflux out of the brain.

Conclusion

Based on the physiological and epidemiological data collected in the analyzed articles, it is concluded that there is a great chance that, in fact, abnormalities in the intestinal microbiota may influence the development of Alzheimer's disease. It is also concluded that a greater number of studies on the subject is necessary, since advances in this area can elucidate the pathophysiological mechanism adjacent to Alzheimer's disease, identify biomarkers for its early diagnosis and enable alternative pharmacological therapies for the treatment of this disease, improving the quality of life of those affected.

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