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The role of the gut microbiota in the pathogenesis and treatment of Alzheimer disease – review

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Summary

Introduction and purpose:

Currently, the role of the gut microbiota in the pathogenesis of different diseases is being widely researched, the understanding of whether the dysbiosis of the gut flora demonstrates the significant role in Alzheimer disease (AD) is accentuated. The aim of this paper is to summarize the existing paper about the role of the gut microbiota - its diversity, stability and composition in this condition. The search was conducted using PubMed and Google Scholarship databases.

Brief description of the state of knowledge:

It is still uncertain if alteration in gut microbiome is a consequence of AD or its risk factor, but some findings suggest that the intestinal flora is able to influence the activity of the brain and lead to its dysfunctions. There is also the association between composition of the gut microbiome and AD. Results indicate that affected patients had less heterogeneity in their microbiome and the progression of AD led to alterations in the bacterial flora. Introducing modifications of the gut microbiota is considered as a therapeutic option for AD. Following personalized diet, probiotics, prebiotics and synbiotics administration or fecal microbiota transplantation (FMT) may be beneficial for affected patients.

Conclusions:

The subject of the role of the gut microbiota merits further research as foregoing results of conducted studies are pointing to its possibly meaningful role. Presently, still more data is needed as most of the research was collected on animal models and the analysis conducted on humans remains insufficient. We conclude that further studies are warranted in order to fully understand the pathophysiology of the disease and the possible usefulness of microbiome therapy.

Key words: Alzheimer disease; gut microbiota; neurodegenerative disorders; fecal transplantation; health

1.Introduction

Alzheimer disease (AD) is a neurodegenerative disease and the most common form of dementia. Among the elderly AD is the fifth leading cause of death. Epidemiological studies indicate that over 50 million people worldwide have been affected by AD [1] and according to the World Alzheimer's Disease Report it is expected that by 2050 the number of people with dementia will increase to 139 million (60-80% due to AD) [2].

This disease starts slowly and worsens progressively. The accumulation of amyloid- β ($A\beta$) and downstream pathological events including tau proteins hyperphosphorylation, neuroinflammation and synaptic loss, eventually cause in a progressive memory loss,

impaired language skills and cognitive thinking. That interrupts the patient's daily activities. It is well known that AD is associated with interaction of multiple factors such as aging, bad dietary habits and genetic factors [3]. Recent studies indicate that also alteration in the gut microbiota composition may play a role in the pathogenesis of AD [4]. The brain-gut axis, which consists of bidirectional communication between the central and the enteric nervous system, is responsible for linking emotional and cognitive centers of the brain with peripheral intestinal functions [5]. The association between the gut microbiota imbalance and AD still remain difficult to determine, but it has been suggested that dysbiosis can lead to higher secretion of lipopolysaccharides and amyloid, which may impair the permeability of the intestine and the blood-brain barrier [3].

Although changes in gut microbiota may play an important role in the pathophysiology of AD, they might also serve as a treatment strategy. Dysbiosis reduction and restoring gut microbiota composition seem to be an effective approach for this neurological disease. Microbiota-targeted interventions including personalized diet, probiotics, prebiotics and synbiotics administration or fecal microbiota transplantation (FMT) might be a potent treatment for AD.

2. Gut microbiota in Alzheimer disease

In a comprehensive meta-analysis conducted by Jemimah et al., published in 2023 and encompassing studies conducted between 2010 and 2022, the relationships between gut microbiota and AD and mild cognitive impairment (MCI) were examined. The meta-analysis, comprising 17 studies, revealed significant alterations in the composition of gut microbiota in individuals with the disease. It was observed that the progression of AD led to a differentiation in the bacterial flora present in the gut microbiome compared to healthy individuals, with a particular emphasis on a decrease in the abundance of certain species. In individuals with MCI preceding the onset of Alzheimer disease, an increase in the abundance of *Phascolarctobacterium* genus was noted. The authors particularly highlight a decrease in the abundance of the *Bacteroidetes* phylum in Alzheimer disease patients. However, it is important to note that these results may vary depending on factors such as chronic diseases or geographical location [6].

Additionally, in 2023, a meta-analysis was published by Cammann et al. describing the correlation between AD and gut microbiome genera. The study investigated the association between the presence of APOE (a risk factor for AD) and gut microbiota. The meta-analysis

demonstrated that four genera were associated with an increased risk of developing AD (Collinsella, Bacteroides, Lachnospira and Veillonella). It was also shown that six genera were associated with a protective effect (Adlercreutzia, Eubacterium nodatum group, Eisenbergiella, Eubacterium fissicatena group, Gordonibacter and Prevotella9). Furthermore, three genera were highlighted as potentially useful in diagnosing AD (Intestinibacter, Candidatus Soleaferrea, and Roseburia). The authors then examined the association between these identified bacteria and AD risk factors, taking into account genetic factors. It was found that there was an association between the presence of Collinsella and the APOE risk allele C at rs429358, which is a risk factor. Additionally, a negative correlation was identified between this APOE allele and three genera (Eubacterium nodatum group, Adlercreutzia and Prevotella9), suggesting a potential protective effect [7].

It is noteworthy that there are reports suggesting that in patients with MCI, the intake of probiotics may bring health benefits, such as improvement in sleep quality or cognitive abilities. These conclusions were drawn from a randomized controlled trial where improvements were observed after 12 weeks [8].

In a study from 2019, it was observed that patients with AD experience disturbances in the occurrence of D-amino acids in the blood. According to the authors, one of the markers of AD could be D-glutamate, the reduced levels of which are found in AD patients. This was measured using the Alzheimer Disease Assessment Scale-cognitive Subscale (ADAS-cog) [9]. In a 2020 publication, the authors indicate that bacteria constituting the gut microbiota may influence their role in the gut-brain axis by transforming chemical compounds. For example, Corynebacterium glutamicum, Brevibacterium lactofermentum and Brevibacterium avium can convert L-glutamate to D-glutamate. On the other hand, Bacteroides vulgatus and Campylobacter jejuni may reduce glutamate metabolites such as 2-keto-glutaramic acid. However, it is still unknown how these changes in substance metabolism may affect the development and course of AD [10].

Metaanalysis conducted by Hung et al. which took into account 11 studies with 378 healthy examiners and 427 patients with AD concluded that patients affected with the disease had less heterogeneity in their microbiome. They also had bigger presence of Proteobacteria, Bifidobacterium and Phascolarctobacterium, but their flora was less abundant in the inherence of Firmicutes, Clostridiaceae, Lachnospiraceae and Rikenellaceae. Authors also noted that the presence of Alistipes and Bacteroides were distinct dependly of the country of the patient - Americans had higher levels of Alistipes while Chinese had it decreased. This paper also

analyzed α and β diversity in patients with AD disease and stated that alpha diversity is significantly reduced in patients with AD [11].

Another metaanalysis investigated the efficacy of probiotic therapy in the course of Alzheimer disease treatment. Authors took under consideration 5 randomized controlled trials which included 386 samples in total and their conclusion stated that the obliged therapy led to improvement of the cognitive function and the patient's quality of life [12].

It is still unclear how the brain-gut-microbiota axis should be understood and whether certain changes in the gut microbiota in individuals with AD should be perceived as a consequence of the disease or an independent factor influencing the development of disease. It is asserted that connections between the brain and the gut microbiome can occur not only through hormones and proinflammatory cytokines but also through signaling via the vagus nerve [13].

However, in a 2021 meta-analysis, the impact of probiotic supplementation on AD patients was investigated. The analysis included three randomized controlled trials, encompassing a total of 161 AD patients. The authors demonstrated that supplementation with *Lactobacillus* and *Bifidobacterium* did not lead to an improvement in cognitive function in these patients, although some parameters related to cholesterol and sugar metabolism showed improvement (plasma triglycerides, very-low-density lipoprotein cholesterol, insulin resistance and plasma malondialdehyde) [14].

3. Fecal microbiota transplantation in the treatment of Alzheimer disease

Fecal microbiota transplantation (FMT) is a method transferring fecal material from a fit donor to a receiver, which directly changes the recipient's gut microbiota. This method leads to normalizing the composition and gaining a therapeutic benefit. In 2013 United States Food and Drug Administration approved FTM as a therapeutic option for treating recurrent and refractory *Clostridium difficile* infection and since then this method is used not only in gastrointestinal disorders, but also in extra-gastrointestinal diseases such as AD [15].

Fecal donors could be either close relatives, family members or unrelated, healthy volunteers, however it is beneficial to use fecal material from unrelated donors, from a centralized stool bank. In order to reduce and prevent occurrence of any adverse events and infections, donors should be strictly selected and screened with questionnaires, interviews, blood tests and stool examinations [16]. There are some conditions generally considered to prevent donor recruitment [3] (table 1).

Table 1: Donor exclusion criteria

antibiotic treatment during the 3 months preceding donation
ongoing immunosuppressive treatment or chemotherapy or a history of malignant illness
inflammatory bowel disease (IBD) or irritable bowel syndrome
acquiring HIV or hepatitis B or C recently
underlying infection
Obesity
Polyposis
history of travel to areas with endemic diarrhea
high-risk sexual behaviors
use of illicit drugs

Then comes to the stool preparation and administration of received material to the upper gastrointestinal tract or the distal colon, or a combined approach [16]. This process should result in restoring phylogenetic diversity and microbiota to be more typical. This gut microbiota modification can positively affect patients with AD and play a key role in combating this disease.

Its possible efficacy in the treatment of AD was investigated firstly on animal models in order to decide if it could be applied for humans. Zhan et al. transplanted fecal bacteria from senescence-accelerated mouse prone 8 - SAMP8 or senescence-accelerated mouse resistant 1-SAMR1 mice into pseudo germ-free mice which at the beginning had significantly lower cognitive function. Pseudo germ-free mice that received fecal bacteria transfer from SAMR1 mice marked positive changes in the way of acting of the floral microbiota and also in α -diversity and β -diversity. Completely, 14 bacteria from six different phylogenetic levels were changed as a result of this procedure [17]. Yu et al. performed the procedure of fecal bacteria transplantation from mice without cognitive dysfunction to the mice that had cognitive abnormalities. The recipients also marked positive results which were thought to be associated with the change in β -diversity [18]. In another study Dodiya et al. showed that fecal

microbiota transplantation from male mice with AD that were not treated with antibiotics into the ones with AD that were antibiotic-treated improved the microbiome composition with subsequently reduced expression of pro-inflammatory cytokines [19]. Fuji et al. observed the changes in a microbiota of a humanized mice model after the procedure of fecal transplantation from both a healthy person and an AD patient. Mice that had transferred fecal microbiota from an AD patient showed significant deterioration in the functioning [20]. Sun et al. in their study on mouse models sought to investigate the changes caused by the transplantation of the fecal sample. They noticed the decrease in the levels of A β 40 and A β 42 and in the phosphorylation of tau proteins while the cognitive functions were boosted [21]. This result is also supported by the paper published by Kim et al. - authors highlighted that the transplantation of the fecal microbiota allied the development of amyloid β plaques, neurofibrillary tangles and glial reactivity. It is worth mentioning that the setback of cognitive function was lessened [22]. The crucial role of the gut microbiota in this neurological disease was also brought out in another paper - scientists that transplanted the gut microbiota from AD-mouse into non-AD-mouse observed the impairment in cognitive functions of the recipients [23]. Considering the positive results on animal models a fecal microbiota transplantation on a human was performed. The patient was an 82 year old man with Alzheimer disease that received the sample from his non-AD wife. After two months of fecal microbiota transplantation, the patient took the Mini-Mental State Examination and his result - 26 points - was six points higher than previously and it classified him as a person with normal cognitive function. Patient was under observation during the four-months follow up and his results continued to improve [24].

4. Conclusion

As more research is being gained on the role of the composition of the gut microbiota the foregoing data brings to a conclusion that this topic should be in the spotlight as a possible treatment for Alzheimer disease and also a way of preventing it from happening.

However, the results of the conducted studies are promising and encouraging, the data is still insufficient as most of the research is based on the animal models and there is the lack of data on how it applies to humans.

Specific understanding of the role of the gut microbiome and its dysbiosis in the pathogenesis of this neurodegenerative disease could create noteworthy opportunities for higher life standards of patients affected with the disease.

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