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Association between Alzheimer's disease and gut microbiota, and potential therapeutic benefits

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Abstract. Alzheimer's disease (AD), or a type of dementia., represents a neurological condition that poses significant threats to individuals' well-being and overall quality of life. In turn, numerous research has been undertaken to investigate the therapy of AD with the aim of improving the quality of life for affected individuals and overcoming the limitations of human epidemiology. Recent studies have provided evidence of a correlation between AD behaviour and the microbial composition of the gut microbiome. Probiotics, antibiotics, and faecal transplantation have been extensively examined in lots of research, and there is evidence to suggest that these interventions may contribute to the enhancement of gut microbiota and the reduction of symptoms associated with AD. The unique bacterial activity within gut microbiota exerts an apparent effect on the frequency of symptoms associated with AD. The deliberate manipulation of gut microbiome bacteria has provided evidence that some bacteria have a role in the manifestation of symptoms associated with AD, and that there exists a close correlation between the gut microbiome and cognitive processes. This review summarizes the significance of certain bacteria in impacting AD and explores the impact of altered norms on AD behaviour. Additionally, discusses potential treatments for AD that are associated with the gut microbiome.

Keywords: Alzheimer's Disease, Gut Microbiota, Potential Treatments.

1. Introduction

Based on epidemiological studies, it is projected that the global prevalence of Alzheimer's disease (AD) will affect around 55 million individuals in the year 2020. According to estimates, it is anticipated that the population of individuals affected by AD will experience a quadruple rise every two decades, resulting in an estimated total of 139 million AD patients by the year 2050 [1]. The symptoms of AD exhibit variability, with notable symptoms including mild impairments in memory, delusions, inappropriate behaviours, and abnormal social behaviour [2]. These symptoms impose significant burdens not only on the affected individuals but also on their family members and friends. The occurrence of symptoms across different age groups and individuals gives cause for a multitude of significant concerns. Unfortunately, there has been a recent increase in the prevalence of individuals diagnosed with AD, which is a significant concern for human well-being. A variety of therapeutic interventions are available for the treatment of AD, encompassing pharmacological approaches as well as psychological counselling. Consequently, there exists significant variation in the elements that can contribute to the progression of the disease. The reasons that have been extensively discussed include the ageing process, the influence of dietary patterns and malnutrition, and the impact of severe brain

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injuries [3]. Recent study has revealed a notable difference between the gut microbiota of individuals with good health and those diagnosed with AD, as well as corresponding differences observed in experimental animal models. This finding posits that the configuration of the gut microbiota bacteria would potentially have a substantial role in the development of AD.

The human gastrointestinal tract holds an estimated 1000 distinct gut microbiota, with a collective population of around 10^14 bacteria. This microbial community surpasses eukaryotic cell numbers by 10-100 times [4]. The gut microbiota is critical to both human health and the development of illnesses. It facilitates the maturation of the immune system, contributes enzymes in metabolic processes, is critical to the production of vital vitamins inside the human body, and fulfills other additional tasks [5]. Consequently, dysregulation of gut microbiota may cause various diseases development. One illustrative instance pertains to obesity, as research has indicated that mice exhibiting the 'obese microbiota phenotype' possess a diminished abundance of Bacteroides, a prominent bacterial phylum in organisms. This observation suggests a plausible association between Bacteroides and the development of obesity [5]. However, the disorders associated with gut microbiota are not just limited to obesity. Recent research has indicated that there exists a correlation between it and metabolic syndrome, autoimmune pathologies, allergies, certain forms of cancer, and neurological disorders including AD [5]. Several studies have revealed that when comparing individuals with AD to a control group of healthy individuals, there is an apparent alteration in the abundance of specific genera in those with AD. Research investigations that choose to conduct experiments on individuals by administering targeted probiotics to modify the diversity of gut microbiota have revealed a reduction in behaviors associated with AD in participants. Proposing that probiotics justify further investigation as a potential therapeutic intervention for individuals with AD.

This review provides a comprehensive overview of the clinical observations about the changes in gut microbiota in both human subjects and experimental animals. Furthermore, intentional altering of the gut microbiota through interventions such as probiotics, faecal transplants, and antibiotics has been suggested as a potential therapeutic approach for addressing AD.

2. Gut microbiota in humans and animal models

2.1. Gut microbiota and AD, in humans

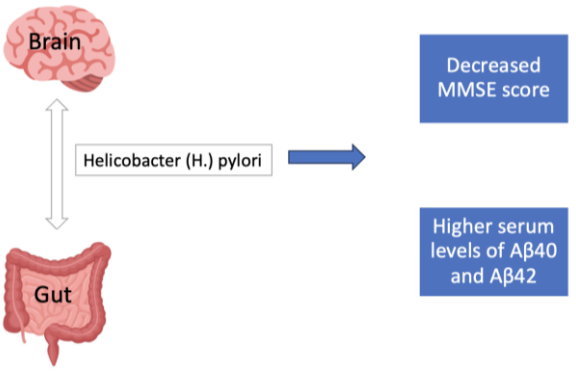

Figure 1. Effect of Helicobacter (H.) pylori on the Alzheimer's disease (AD) patients compared to healthy control group. MMSE score: Mini-Mental State Examination score. Information from [8,9]. Picture credit: original.

Comparing the serum levels for individuals with AD and healthy control group, there are more proinflammatory cytokines, such as interleukin (IL)-1, IL-6, TNF-α and TGFβ [6]. Cytokines are known to have a significant impact on neuroinflammation, and a growing amount of information that substantiates the concept that gut microbiota can regulate astrocytic processes within the brain [7]. Cytokines are secreted by microglia and astrocytes, and the persistent release of cytokines by these cells

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indicates a disruption in the interplay between the gut microbiome and the functioning of the central nervous system [7]. Recent research findings have indicated that individuals diagnosed with AD who have a chronic infection caused by Helicobacter (H.) pylori exhibit a notable decline in their Mini-Mental State Examination (MMSE) score when contrasted to a control group of individuals who are in good health, as shown in figure 1 [8]. Furthermore, it has been observed that individuals with AD who are also infected with Helicobacter pylori and other bacteria (i.e Borrelia burgdorferi and Chlamydia pneumoniae) exhibit increased concentrations of Aβ40 and Aβ42 in the blood, also shown in Figure 1 [9]. These bacteria are crucial to the modulation of neurotransmitters, hence exerting a direct influence on the functioning of the central nervous system. Furthermore, several research have provided evidence that the gut microbiota has the ability to modify proteins and receptors that play a role in synaptic plasticity. These include serotonin receptors, N-methyl-D-aspartate (NMDA) receptors and brain-derived neurotrophic factor (BDNF) [10]. In a study undertaken by other researchers, a total of 30 individuals diagnosed with AD, 30 with amnestic mild cognitive impairment (aMCI), and 30 healthy controls without any known AD conditions were chosen. The demographic parameters of the participants, including age, gender, educational attainment, body mass index (BMI), and presence or absence of constipation, were found to be comparable among the three groups [11]. The findings indicated that individuals diagnosed with AD exhibit comparable composition of gut microbiota to those diagnosed with MCI. The faecal samples of patients with AD exhibited a decrease in the abundance of Bacteroide, Alistipes, Sutter Ella, Paraprevotella, and Parabacteroides , as compared to the control group [11].

2.2. In vivo studies of relationship between AD and gut microbiota

Numerous research found notable modifications in the composition of gut microbiota in mice with AD in comparison to mice that are in a healthy state. As an example, a comparative investigation was conducted to assess the composition of intestinal flora in AD model SAMP8 mice and control SAMR1 mice [12]. The findings indicated a notable disparity in the intestinal microbiome composition between SAMP8 mice and SAMR1 mice. Significantly, the researchers noted a heightened prevalence of norank f Lachnospiraceae and unclassified f Lachnospiraceae in SAMP8 mice [12]. Multiple studies have provided evidence suggesting a potential association between Lachnospiraceae and AD in the human population. Furthermore, there was a notable rise in the prevalence of Alistipes in SAMP8 mice, a strain that has been observed to have higher levels of this bacterium, similar to what has been observed in individuals diagnosed with AD [12]. These investigations have consistently shown a similar pattern in both animal and human models, indicating a significant association with AD. Researchers have discovered that there is a distinct variation in the composition of 27 intestinal bacteria across six phylogenetic levels between SAMP8 mice and the control group of SAMR1 mice [12]. The pseudo germ-free mice had a notable decline in cognitive performance, which was subsequently reduced following the transplantation of faecal bacteria from SAMR1 mice as opposed to SAMP8 animals [12]. This finding indicates that the aberrant symptoms and cognitive dysfunction observed in SAMP8 mice can be attributed to alterations in their gut flora. Researchers conducted a comparative analysis of the gut microbiota in APP/PS1 mice and their C57BL/6 wild-type sisters (Table 1) [13]. The researchers observed that the bacterial profiles had a statistically significant similarity at the 3-month mark, but underwent alterations by the 6-month mark. As the subjects getting older, the abundance of Turicibacteriaceae and Rikenellaceae across all groups was found to be increased. However, the overall abundance of Bacteroidetes remained constant [13]. Proteobacteria, particularly those belonging to the Sutter Ella genus, exhibited a notable rise at the 6-month mark in APP/PS1 mice, a phenomenon that has also been observed in human models (Table 1) [13]. Additionally, it was shown that the Erysipelotrichaceae family, which is associated with inflammation, had higher levels of content in 24-month-old APP/PS1 mice [13]. This finding suggests that the development of AD in mice is accompanied by alterations in the gut microbiota, leading to characteristics of an inflammatory disorder [13].

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Table 1. Models of Alzheimer's disease (AD).

Models	Results	References
Male senescence-accelerated mouse prone 8 (SAMP8) mice, aged seven months, and control senescence-accelerated mouse resistant 1 (SAMR1) animals.	27 gut bacteria across 6 phylogenetic levels were found to have been modified. The faecal bacteria derived from SAMR1 mice exhibited advantageous effects for AD, no benefits were shown in the case of SAMP8 mice.	[11,12]
Transgenic APP/PS1 mice, samples were taken at 3, 6 and 24 months	As the age of subjects progressed, there was an observed increase in the abundance of Turicibacteriaceae and Rikenellaceae, overall abundance Bacteroidetes remained constant, specific increase of Proteobacteria of genus Sutter Ella at 6 months mark.	[12,13]

3. AD treatment

3.1. Probiotics in AD treatment

The study observed a notable inhibition of intestinal microbial endotoxin production, as well as the stimulation of NF-B in BV-2 cells upon treated with lipopolysaccharide (LPS) when exposed to Bifidobacterium Iongum, a probiotic strain derived from the intestinal microbiota of humans [14]. The researchers identified that administration of NK46 orally has the potential to modify the gut microbiota composition, specifically affecting the abundance of Proteobacteria. Additionally, this treatment was found to decrease the concentration of LPS in both faecal and blood samples, while also promoting the expression of tight junction proteins in the colon [14]. They employed 5xFAD-Tg mice, which are recognised as an AD model, to carry out this experiment. Furthermore, administration of NK46 resulted in the downregulation of amyloid-, /-secretase, and caspase-3in the hippocampus, leading to a reduction in cognitive decline [10]. Scientists conducted an investigation to examine the impact of orally administering Bifidobacterium breve strain A1 on the behavioural and pathophysiological processes that were administered A25-35 injections in the lateral ventricle [14]. They made the observation that the administration of B. breve A1 resulted in a decrease in the time interval before a response in a passive avoidance experiment, as well as a restoration of normal performance in an alternate behaviour task conducted in a Y maze trial [14].

Oligosaccharides have demonstrated potential in modulating the gut microbiota, hence suggesting their potential utility in the development of a therapeutic intervention for AD. The impact of fructooligosaccharides (FOS) on AD was explored by researchers using APP/PS1 mice as test subjects [10]. The researchers made the observation that a six-week therapy involving FOS was able to reverse the changes in the composition of gut microbes, resulting in a reduction of cognitive impairment and pathological abnormalities [15]. The use of FOS resulted in a notable decrease in the phosphorylation level of JNK, accompanied by a large increase in the synapsin 1 and PSD-95 expression [15]. Oligosaccharide (OMO) is an oligosaccharide that is obtained from the plant species Morinda officinalis [10]. The administration of OMO was observed to facilitate memory performance, decrease neuronal cell death, as well as decrease the formation of A1-42 in both APP/PS1 transgenic mice and A1-42-induced faulty rats [10]. Previous studies have provided evidence that the CA-30, which is derived from the oligosaccharide portion of Liuwei Dihuang decoction [16], possesses the ability to modulate the composition of the intestinal microbiota. Furthermore, it has been seen that this modulation leads to the restoration of the equilibrium within the gut microbe-neuroendocrine immune regulatory network [17]. Additionally, CA-30 administration has been found to reduce cognitive deterioration in SAMP8 mice [10]. Hence, probiotics may emerge as a prominent therapeutic approach for AD in the future.

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3.2. Antibiotics in AD treatment

The impact of a substance's capacity to change the composition of the gut microbiota, for example, antibiotic medications, on AD can be either beneficial or detrimental, dependent upon its considerable involvement in the pathogenesis of the disease. Multiple studies demonstrated that various antibiotic treatments have an impact on the composition of the intestinal microbiota in both animal and human subjects, either in the short-term, long-term, or both.

Research has demonstrated that the utilisation of antibiotics as a combined therapeutic approach in individuals elevates their vulnerability to neurological disorders, such as anxiety and panic attacks, notable depressive symptoms, psychosis, as well as delirium [18]. Nevertheless, the occurrence of neuropsychiatric side effects is not commonly associated with the regular application of antibiotics among the general population. Prior research has indicated that the administration of a combination of antibiotics (ABX) to APP/PS1 transgenic mice may exacerbate the neuroinflammatory state, leading to increased levels of cytokines and ultimately triggering the development of AD [13].

Upon treatment of ampicillin to rats, notable outcomes were seen, including an elevation in serum corticosterone levels, an augmentation in anxiety-like behaviour, and a deterioration in spatial memory [18]. There exists a correlation between heightened levels of glucocorticoids and cognitive impairments, as well as a reduction in brain-derived neurotrophic factor (BDNF) in the hippocampus [19]. These two phenomena are commonly observed in the pathological manifestations of AD . It is noteworthy that the physiological and psychological abnormalities caused by ampicillin in rats can be improved with probiotics treatment, specifically the strain NS9 of Lactobacillus fermentum [18].

The idea is strengthened by the utilisation of antibiotics such as streptozotocin in animal models that cause sporadic forms of AD, resulting in observable effects on their cognitive abilities, namely in the domains of learning and memory [20]. Animals have been exposed to the administration of a single antibiotic, resulting in the development of diabetes mellitus, a prevalent comorbidity of AD characterised by cognitive decline [20]. Furthermore, it has been observed that streptozocin-induced diabetes rat models exhibit enhanced synaptic activity and cognitive function upon the use of probiotic substances as a dietary supplement [20].

The findings of the study indicated that the application of antibiotic combinations to adolescent mice would lead to enduring changes in the gut microbiota and an elevation in proinflammatory cytokines. These changes have been observed to affect cognitive function in adulthood and align with the hygiene hypothesis[11]. In the absence of gut flora, certain antibiotics, such as cefepime, have the ability to traverse the blood-brain barrier in humans, leading to changes in cognitive function, such as reduced consciousness, myoclonus, and disorientation [11]. Antibiotics, nonetheless, have the potential of providing benefits for AD. The previously mentioned consequences arise from alterations in the gut microbiota, a phenomenon that is not exclusively attributed to the administration of antibiotics and has the potential to foster the proliferation of bacteria that may have detrimental effects on the brain [11]. Patients diagnosed with AD have exhibited enhancements in their cognitive and functional indicators subsequent to the elimination of detrimental microorganisms, for instance, Helicobacter pylori by the implementation of a triple elimination antibiotic regimen consisting of omeprazole, clarithromycin, and amoxicillin [11].

4. Conclusion

Prior research has demonstrated that AD exerts a substantial influence on human development and is a tough challenge for affected individuals. Multiple studies, including those discussed in this publication, have provided evidence that the gut microbiota exerts substantial and direct impacts on symptoms associated with AD. Numerous investigations conducted on both human subjects and animal models have provided empirical evidence supporting the efficacy of manipulating the intestinal composition by the administration of probiotics and antibiotics in improving the symptoms associated with AD. Consequently, investigations conducted in this particular domain possess the potential to eventually contribute to therapeutic interventions for a significant number of individuals suffering from AD.

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Despite the ongoing expansion of research in this field, there remain certain domains where the preservation of accuracy poses significant challenges.

The gut microbiota exhibits a significant level of complexity and reflects interindividual variability. The control of complexity and variation is influenced by factors such as food patterns, lifestyle choices, and other relevant variables. Due to this phenomenon, it is possible that the healthy control group used in experimental trials may possess a distinct composition of gut microbiota, hence exerting a substantial influence on the extent to which the control group and the experimental group can be considered similar. Furthermore, the complex interaction between the gut microbiota and the brain is comprised of several pathways, encompassing the neurological, immunological, metabolic, and endocrine systems, among others. As a result, the effort of discovering the specific method employed by a singular strain of bacteria to exert behavioural effect might be a highly challenging effort. The current research mostly centres on investigating the relationship between modifications in the microbiome and their impact on the behavioural manifestations of AD. In future investigations, it is suggested that academic research should prioritize efforts towards enhancing the dependability of clinical assessments, with the goal of attaining the mechanisms underlying the utilization of gut microbiota as a potential therapeutic intervention for AD.

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