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Mini Review

The Relationship between the Composition of Intestinal Flora and Dementia

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Abstract

With the aging process of society, the incidence of dementia is increasing year by year and has become a common disease among the elderly which is prognosed to affect approximately 131 million individuals by 2050. The gut microbiome, as a diverse community of microorganisms, plays a crucial role in maintaining health and well-being. Recent research suggests that the gut microbiome significantly influences the development and progression of Alzheimer's Disease (AD) and other neurodegenerative dementias in the elderly. Interventions targeting the gut microbiome through diet, probiotics, and lifestyle changes may offer promising avenues for preventing these conditions. Aging is associated with specific changes in the gut microbiome composition, including the loss of certain beneficial bacteria at the expense of other potentially pathological microorganisms like Akkermansia and Butyricimonas, which may lead to dysbiosis, which was implicated in various aging-related diseases, including AD. Despite advancements in identifying pathobionts associated with unhealthy aging and disease progression, more research is needed to delineate changes attributable to aging from those due to independent disease processes, nevertheless, some studies suggest that modulating the gut microbiome through diet and probiotic supplementation may have potential in improving health status and reducing rate of neurodegeneration. Especially maintaining a healthy, diverse gut flora through diet and lifestyle may be an important factor in preventing dementia and delaying the progression of aging. Further research is needed to fully elucidate the causal mechanisms linking the gut and brain in neurodegenerative diseases. Therefore, this paper aims to present the latest knowledge on gut microbiota changes and their contribution to dementia, proposing strategies for prevention and delaying neurodegenerative processes.

Introduction

With the aging process of society, the incidence of dementia is increasing year by year and has become a common disease among the elderly. It is reported that by 2015, the number of global dementia patients was about 47 million and is expected to reach 131 million by 2050 [1], which is bound to place a heavy burden on families and society [2].

The gut microbiome, as a compositionally and functionally diverse community of microorganisms that influences health and well-being, is an important factor in the development and progression of Alzheimer's disease and other neurodegenerative dementias in the elderly population. Targeting the gut microbiome through dietary, probiotic, and lifestyle interventions may offer new avenues for the prevention and potentially even treatment of these devastating conditions [3].

During aging, specific changes in gut microbiome composition, such as the loss of certain commensal bacteria, including *Prevotella*, *Faecalibacterium*, and *Bifidobacterium*, and the species *Eubacterium rectale* may lead to increased risk of allowing replacement with other commensal organisms, such as *Akkermansia*, and also *Butyricimonas* and *Odoribacter*, which presence was linked with mucin degradation in the intestines and changes in the gut permeability and inflammation [4]. Interestingly, gut microbiome dysbiosis, characterized by pathological imbalances in microbial community and function, has been implicated in various diseases, also those related

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to aging, including Alzheimer's Disease (AD) and potentially other neurodegenerative diseases [5].

Although the results of current research allowed for the identification of several pathobionts, or conditionally pathogenic microorganisms, that are increased in "unhealthy" aging, characterized by rapid physical and mental decline and associated with disease progression, the more studies need to be done to understand how these changes can be attributable solely to age and which due to independent disease development [5]. Therefore, the main aim of this paper is to present the most recent knowledge on changes in the gut microbiota and their contribution to dementia, while proposing certain strategies to aid prevention and delay neurodegenerative processes.

Changes in the gut microbiota composition and risk of dementia and neurodegenerative diseases

There is a strong relationship between the composition of the intestinal microbiome and the development of dementia. The presence of certain imbalances in gut microbiota composition was associated with an increased risk of neurological diseases, such as Parkinson's disease, AD, Amyotrophic Lateral Sclerosis (ALS), and multiple sclerosis. Separately, these conditions were also linked with functional gastrointestinal disturbances which may occur at all stages of the neurodegenerative pathology, with studies showing that changes in gut microbiota and enteric neuro-immune system alterations could contribute to gastrointestinal dysfunctions as well as initiation and upward spreading of the neurologic disorder [5]. In addition, a growing number of studies report associations between specific bacteria species with dementia risk. For example, a lower abundance of microorganisms with anti-inflammatory properties, such as Lactobacillus, Bifidobacterium, and Ruminococcus, have been demonstrated in Alzheimer's patients, whereas the increase in pro-inflammatory species, including Escherichia and Enterococcus seemed to be common [2]. Changes in the gut composition were also reflected in the different concentrations of microbial-produced metabolites, like ammonia, which may additionally contribute to cognitive decline [6].

Although the exact mechanism of how changes in the intestinal community can impact neurodegeneration is an area of intense research, one of the proposed explanations suggests that gut microbiota dysbiosis may play an important role. For example, a higher abundance of *Bacteroides* and associated with their presence increased levels of Lipopolysaccharide (LPS), a component of the outer leaflet of the outer membrane of these bacteria with capabilities to potentiate systemic inflammation and amyloid fibrillogenesis, can result in amyloid deposition in the brain [7]. Therefore, the overgrowth of pro-inflammatory bacteria may contribute to increased levels of pro-inflammatory mediators, such as TNF-α and IL-6 in the systemic circulation [2], which then cross the blood-brain barrier, may lead to neuroinflammation and development of amyloid plaques, a feature of AD [6].

Analysis of the gut microflora and its relationship with dementia, evaluated in patients with AD have found significant changes in the characteristics of the intestinal flora structure showing that the significantly increased abundance of *Bacteroides*, *Firmicutes*, and *Proteobacteria* accompanied by reduced abundance of anti-inflammatory species of *Lactobacillus*, *Bifidobacterium*, and *Ruminococcus* in expense of pro-inflammatory bacteria such as *Escherichia* and *Enterococcus* raises among AD patients. Interestingly, these changes were reflected in the inflammatory profile, as a comparative analysis of inflammatory cytokines between AD and controls has shown elevated TNF-α and IL-6. Therefore, these observations may indicate that an increased abundance of pro-inflammatory bacteria in the intestinal flora may lead to or aggravate neuroinflammation through the release of inflammatory factors, thus further leading to the occurrence and development of AD [2]. In this context, reduced frequencies of *Lactobacillus* may be of great importance, as this bacteria has also been reported to have a protective effect against dementia via system activity and neurotransmitter release [8].

A case study 1

Changes in gut microbiota may serve as an early diagnostic biomarker for AD: The results of a recent cross-sectional study conducted in the cohort of cognitively normal individuals, with certain groups showing evidence of early preclinical AD, indicated that reported changes in the gut microbiota composition, in those with preclinical AD were correlated with pathological biomarkers, including β-amyloid (Aβ) and tau protein, thus suggesting that the gut microbiome may change early in the development of AD. Interestingly, these differences in the microbial community were not related to biomarkers of neurodegeneration [9].

Dysregulation of the gut microbiome is associated with dementia, and microbiome-associated metabolites, such as ammonia and lactic acid can be considered independent from other risk factors indicators for dementia and dysregulation of the gut microbiome. A cross-sectional study conducted on individuals with dementia identified that concentrations of microbial metabolites differ significantly between subjects with and those without dementia. For example, for 1 standard deviation increment in faecal ammonia concentration was associated with around a 1.6-fold risk for the presence of dementia; whereas a higher faecal lactic acid concentration was linked with a reduced risk of dementia by around 60%. Based on the presented findings authors proposed, that using a combination of higher faecal ammonia and lactic acid concentrations might be indicative of the presence of dementia, as it has a similar predictive value as traditional biomarkers used in the diagnosis.

Proposed strategies restoring gut balance and delaying neurodegeneration

The research indicates the gut microbiome is an important factor in the development and progression of AD and other neurodegenerative dementias in the elderly population. Targeting the gut microbiome through dietary, probiotic, and lifestyle interventions may offer new avenues for the prevention and potentially even treatment of these devastating conditions.

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Diet: A component of age-related changes in the microbiome seems to be highly attributable to dietary habits, which is of great importance for the elderly, as these individuals are at increased risk for poor dental health associated with difficulties with chewing, as well as decreased appetite, and lack of social support in obtaining nutritious foods. Many studies have shown that regardless of age, specific diets can cause unique alterations in the microbiome that can influence the mental and physical condition. In particular, the transition from a high-fiber, low-fat diet to a low-fiber, high-fat diet, has been associated with a shift to a lower diversity microbiome in long-term [10], which was followed by a change in the benefits for health microbial-derived metabolites, like Short-Chain Fatty Acids (SCFAs), which benefits to the gut health and also serves as an energy source for probiotic microbiota with anti-inflammatory properties [11].

The research suggests these dietary patterns, rich in antioxidants, anti-inflammatory compounds, and nutrients important for brain health, may help prevent or delay the onset of dementia by reducing inflammation, oxidative stress, and vascular risk factors.

Interestingly, intervention with the Mediterranean diet, consisting of plant-based foods, whole grains, and healthy fats, has been shown to promote a healthy gut microbiome, while supporting overall health including improved cognitive function and reducing inflammation. In addition adherence to the Mediterranean dietary pattern for at least one year induced favourable changes in the intestinal community, characterized by an increase in the relative abundance of protective bacteria, including *F. prausnitzii*, *R. hominis*, *E. rectale*, *E. eligens*, *E. xylanophilum*, *B. thetaiotaomicron*, *P. copri* and *A. hadrus* [12].

Similarly, intervention with the MIND diet, which is a hybrid of the Mediterranean diet and the DASH (Dietary Approaches to Stop Hypertension) diet, with a proven ability to reduce high blood pressure, may also be beneficial for delaying dementia. This diet is based on plant foods, such as vegetables like green leafy ones, as well as berries, whole grains, beans, nuts, fish, and olive oil. It limits high-fat foods, like red meat, butter, cheese, pastries, and fried/fast food, which are believed to protect the brain from inflammation and oxidative stress, which are key contributors to neurodegeneration.

Strict adherence to the MIND diet has been shown to reduce the risk of AD by 53%, whereas more freely applying recommendations of this eating style may also bring benefits and reduce the risk of this disease by 35% [13].

Probiotic supplementation: Probiotic interventions have been intensively studied in the context of delaying aging, nevertheless, the great heterogeneity of available products does not allow for the proposal of a single strain or their combinations that would definitively improve or reverse signs of aging [14]. Nevertheless, some studies indicate that microbiome-based interventions may have a positive impact on cognitive function, and memory, and therefore delay neurodegeneration attributed to the modulatory role of the probiotic on the gut microbiome, reduced inflammation, and oxidative stress. Emerging clinical trials have investigated the efficacy of interventions modulating the GM in alleviating or reversing disease progression. Despite inconsistent changes in effects on the gut microbiota composition, the majority of clinical studies have shown that microbiome-modulating interventions improved disease burden and improved constipation [15].

To date, research has proposed some of the most effective probiotic strains. Among single strains of *Lactobcillus* and *Bifidobacterium* as well as used in combination, like *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* have shown cognitive improvements in Alzheimer's disease patients. *Lactobacillus rhamnosus* GG and *Lactobacillus plantarum* DR7 appear to be beneficial for improving cognitive function in adults with certain levels of neurodegeneration while enhancing serotonin pathways and supporting memory recall, mood regulation, and sleep quality after 12 weeks of supplementation. Similar benefits were demonstrated for bifidobacteria, especially *Bifidobacterium breve* and *Bifidobacterium longum* whose anti-inflammatory and antioxidant properties may help in AD management [15].

A case study 2

Probiotic intervention to aid cognitive function in AD: An intervention with multi-strain probiotic supplements, including *Bifidobacterium longum* subsp. *infantis* BLI-02, *B. breve* Bv-889, *B. animalis* subsp. *lactis* CP-9, *B. bifidum* VDD088, and *Lactobacillus plantarum* PL-02 with a daily dose of 5×10^7 - 1×10^{10} colony-forming units per day, CFU) in patients with AD with dementia, after 12 weeks lead to a 36% increase in serum brain-derived neurotrophic factor (BDNF) and reduced inflammatory markers, such as IL-1β. In addition, probiotic supplementation increased antioxidant ability which was demonstrated as an increase in antioxidant Superoxide Dismutase (SOD). Interestingly, individuals given probiotics have shown a trend towards less cognitive deterioration suggesting the benefits of multi-strain probiotics in ameliorating inflammation and oxidative stress in AD patients [16].

Conclusion

The evidence underscores the critical role of the gut microbiome in the development and progression of AD and other neurodegenerative dementias. Aging-related changes in the gut microbiota, characterized by the loss of beneficial bacteria and an increase in pro-inflammatory species, contribute to systemic inflammation and neuroinflammation, potentially accelerating cognitive decline.

This study underscores the critical importance of the gut microbiome in the development and progression of AD and other neurodegenerative dementias. The key findings of this work reveal that age-related changes in gut microbiota, such as the reduction of beneficial bacteria and the increase in pro-inflammatory species, contribute significantly to systemic and neuroinflammation, accelerating cognitive decline. Interventions targeting the gut microbiome, including dietary

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modifications and probiotic supplementation, show promise in promoting a healthier gut microbiome and potentially reducing the risk of dementia.

Interventions targeting the gut microbiome, including dietary modifications and probiotic supplementation, hold promise for mitigating the risk and progression of dementia. Diets rich in anti-inflammatory and antioxidant compounds, such as Mediterranean and MIND diets, have been shown to support a healthier gut microbiome and may reduce the incidence of neurodegenerative diseases. Probiotic interventions have also demonstrated potential benefits, including improvements in cognitive function and reductions in inflammatory markers.

Despite the promising evidence, there remains a need for further research to elucidate the exact mechanisms by which gut microbiota dysbiosis influences neurodegeneration. Future studies, particularly longitudinal analyses and randomized controlled trials are essential to establish causal relationships and optimize intervention strategies. Personalized approaches, considering individual microbiome profiles, may further enhance the efficacy of these interventions. Therefore, future research should focus on understanding the precise mechanisms through which gut microbiota dysbiosis impacts neurodegeneration. Longitudinal studies and randomized controlled trials are necessary to establish causal relationships and identify the most effective interventions. Additionally, personalized approaches considering individual microbiome profiles could enhance the efficacy of prevention and treatment strategies.

In conclusion, maintaining a balanced gut microbiome through diet and probiotics represents a promising avenue for preventing and potentially treating neurodegenerative dementias. This approach not only addresses the microbial imbalances associated with aging but also offers a holistic strategy to support overall brain health.

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Although AI-generated tools were used to generate this eBook/ Article, the concepts and central ideas it contains were entirely original and devised by a human writer. The AI merely assisted in the writing process, but the creative vision and intellectual property belong to the human author.

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