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Does gut microbiota have an impact on the origin of Alzheimer's and Parkinson's disease? – literature review

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ABSTRACT

Keywords: Alzheimer’s disease; Parkinson’s disease; gut microbiota; neurodegenerative diseases, neurodegenerative diseases treatment.

Introduction and purpose:

Among neurodegenerative disorders, Alzheimer's disease (AD) and Parkinson's disease (PD) are the most prevalent. It has been observed recently that alterations in the gut microbiota are associated with the onset of neurodegenerative disorders. This research aims to estimate the pathomechanisms and disease courses associated with the gut microbiota that lead to AD and PD development.

Material and methods

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included Alzheimer’s disease; Parkinson’s disease; gut microbiota; neurodegenerative diseases.

State of knowledge

The advancement of neurodegenerative processes is linked to the varying progressive course of both disorders. There are numerous likely reasons that connect the development of AD and PD and the gut microbiome. These include the hypotheses on inflammation, the decrease in the quantity of bacteria that produce short-chain fatty acids, and hygiene. The researchers' suggested treatment plans for the two illnesses are comparable.

Conclusions

A major influence on the development of neurodegenerative disorders is the gut microbiome. To clarify the precise connections between the gut microbiota and the development of AD and PD, further thorough research is required. More human research is required. Furthermore, it's possible that early interventions, such switching to a Mediterranean diet, are anticipated to lower the risk of AD or PD.

Keywords: neurodegenerative diseases, Alzheimer disease, Parkinson's disease, gut microbiota

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease, and it is the most common type of dementia (60-70% of cases of dementia). It is a multifactor disease that includes environmental and genetic risk factors [1,2]. AD usually starts slowly, and the first symptoms are mistakenly attributed to aging. The most common symptoms are short-term memory loss, apathy, problems with planning and abstract thinking. As the disease progresses, common manifestations are disorientation of place and time, wandering, or change of mood, such as

irritability, aggression, or depression. There is a severe accumulation of neuritic plaques in the cortex area that may cause difficulties in swallowing and urination. Patients cannot recognize even their family members. The research focuses on abnormal tau protein metabolism and amyloid B-protein production, which could be caused by an inflammatory response, improper diet, obesity, and vascular disease [1]. AD can only be definitively confirmed by an autopsy of the patient's brain tissue [3]. The first pharmacologic intervention should include cholinesterase inhibitors (donepezil, rivastigmine patch, or galantamine). Memantine, NMDA receptor antagonists, and SSRIs are also used for treatment [1,4].

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. PD diagnosis is based on the presence of symptoms such as bradykinesia, cogwheel rigidity, resting tremor, slow shuffling gait, and imbalance. In PD, alpha-synuclein becomes clumped together and causes degeneration of dopaminergic neurons in the substantia nigra of the midbrain. These clumps are Lewy bodies and can be seen during autopsy [5]. When making a diagnosis, other causes, such as drug-induced or multiple system atrophy (MSA), have to be ruled out. The main medical treatment for PD is the use of levodopa, often combined with MAO inhibitors, directly acting dopamine agonists, amantadine, or deep brain stimulation [5,6]. The cause of PD is still mostly unknown. PD results from a complex interaction between genetic and environmental risk factors. Recent studies demonstrate that intestinal bacteria are likely to be involved in producing intestinal alpha-synuclein fibrils. Enteroendocrine cells have a synapse with the vagus nerve, and the vagus nerve has a synapse with the substantia nigra [7].

The gut microbiota greatly influences human health and is the subject of intense research. The gut microbiota is associated not only with gastroenterological diseases but also with diseases of the central nervous system, such as neurodegenerative diseases or behavioral disorders. The link between the intestinal microbiota and the brain is described as „gut-brain-axis" [8,9]. The leveraging of animal models shows that bacteria in the gastrointestinal tract are able to produce and consume a range of significant neurotransmitters, including dopamine, serotonin, norepinephrine, or gamma-aminobutyric acid (GABA).

In this review, we discuss the link between the gut microbiome and its influence on the development of AD and PD.

2. Methodology

The following review was based on articles from the PubMed and Google Scholar databases. Key search terms included Alzheimer's disease; Parkinson's disease; gut microbiota; neurodegenerative diseases.

3. State of knowledge

3.1 Neurodegenerative diseases

AD and PD are, respectively, the first and second most common neurodegenerative diseases [10]. For each one, age is the most critical risk factor; however, the average time of becoming sick slightly differs – for PD, it is 60 years, and for AD, it is above 65 years. Furthermore, in PD, the prevalence is higher in men, and in AD, women are more likely to suffer from it. [11,12] Another difference reveals itself in pathology: AD is caused by accumulation of amyloid-β plaques and or tau aggregates, whereas PD develops as a result of losing dopaminergic neurons in the substantia nigra pars compacta. Interestingly, tauopathy is also the base of the Parkinsonism-dementia complex of Guam. [11,12,13,14] As for symptoms in AD, they are most commonly pronounced in the decrease of language skills (e.g., repetition of long sentences, incorrect wording, difficulty recalling words) and memory flexibility. [11] On the other hand, PD is more associated with motor dysfunction: bradykinesia, resting tremor, rigidity, postural instability, etc. However, it is worth mentioning that with the progression of PD, dementia is becoming notably more prevalent. [12] Although those diseases have been known to scientists for many years, their diagnosis has long remained a nuisance. Clinical criteria have been developed, but a certain confirmation could be provided only by a post-mortem examination of brain tissue [13]. In recent years, there has been a tendency to seek new diagnostic tools such as biomarkers, cerebrospinal fluid (CSF), and positron emission tomography (PET), which, in combination with clinical evaluation, could lead to a more precise AD diagnosis. [12,13,15] Concerning PD, there is still no strong evidence of specific CSF markers or blood tests existing that could enhance the probability of a correct diagnosis. However, MRI has been shown to be a helpful tool to exclude conditions other than PD. [12] Interestingly, both AD and PD share an early preclinical symptom – hyposmia. Studies presented multiple explanations of that state, including the accretion of pathological aggregates in the olfactory system. It was implied that hyposmia may be a better marker of neuronal damage in AD than amyloid pathology. In addition, olfactory dysfunction

is also an indication of incoming decades-later motor symptoms of PD.[16] To make matters more complex, there has been an emergence of a new theory that drives scientists' attention in a different direction. Recent studies suggest the existence of a specific microbiota that creates a pro-inflammatory environment in the GI tract of patients with neurodegenerative diseases, including AD and PD.[17]

3.2 Gut microbiota in Alzheimer's disease

One hypothesis for the origins of AD is that the gut microbiota produces substances that may contribute to the development of the disease. These include the microbial metabolite trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFA). TMAO's myogenesis of action is the secretion of β-secretase, which increases amyloid-beta accumulation in the brain. In addition, TMAO increases platelet reactivity and the production of amyloid-beta in platelets, causing more of this substance to enter the brain, thereby contributing to the onset and worsening of AD. [18,19]

Moreover, another hypothesis implies that in Alzheimer's patients, there is an increase in the ratio of intestinal *Firmicutes* bacteria to those of the genus *Bacteroidetes* in the intestinal microbiota, leading to the accumulation of amyloid protein precursors in the gut. With dysbiosis and inflammation of the gut, extracellular amyloid-beta penetrates the brain, resulting in AD. [18,19]

Reduced diversity of the gut microflora may contribute to AD. During experiments conducted on GF and SPF mice with reduced gut microbiota diversity, they were shown to develop immature microglia, which, when functioning properly, reduce the amount of accumulated amyloid-beta in nerve cells. It is interesting to note that according to Erna et al. introducing SCFAs and a normal, diverse gut microbiota can help repair microglia defects. [18,19,20,21]

The inflammatory hypothesis complements numerous ideas of the AD formation. It has recently been demonstrated that amyloid-beta is an antimicrobial protein, which implies that it is involved in microbial control. For example, in mouse studies, amyloid-beta is deposited in the brain parenchyma of mice infected with HSV-1 virus. In addition, bacterial endotoxin lipopolysaccharide of gram-negative bacteria can penetrate the blood-brain barrier, causing activation of pro-inflammatory cytokines and thus contributing to AD formation. Additional factor confirming the involvement of the intestinal microbiota in the pathogenesis of AD is

that the intestinal dysbiosis results in an increase in intestinal wall permeability by microorganisms, thereby causing systemic inflammation, which promotes the formation and progression of AD. [18,21,22,23,24]

It is interesting to note that gut microbiota may influence not only the onset of AD but also psychiatric diseases such as depression and schizophrenia. A meta-analysis by Zhuang et al. showed that a decrease in the number of bacteria of the genus *Blautia* causes a decrease in the neurotransmitter GABA, which contributes to AD. Moreover, changes in the intestinal microflora in people with AD lead to a marked decrease in plasma glutamate levels, which can be considered as one of the pathomechanisms of the disease's onset. In addition, reduced glutamate levels can be linked to depression and obesity. [25,26,27]

The hygiene hypothesis is the next theory regarding the onset of AD. Excessive hygiene at an early age can lead to later immune dysfunction. In consequence, the body is exposed to fewer microorganisms, which results in inadequate function of regulatory T cells and increases the risk of AD. In addition, microglia in mice with less germ exposure react less to microorganisms. [20,22,28,29]

Antibiotics are another factor that disrupts the gut microbiota in patients undergoing therapy. Clinical studies have illustrated that through the use of antibiotics, gut dysbiosis occurs, which can result in a change of the brain chemistry and behavioral disorders such as psychosis, anxiety attacks, and depression. Antibiotics that particularly disrupt the gut microbiota include ampicillin and streptozotocin. Ampicillin administered in animals is associated with an increase in anxiety disorders through an increase in serum cortisol. In contrast, streptozotocin decreases memory and learning ability. However, it is interesting to note that if *Helicobacter pylori* is eradicated with antibiotics, it leads to improved cognitive processes in AD patients. In addition, antibiotics reduce systemic inflammation that can contribute to AD. Probiotics are essential in antibiotic treatment, as they can reverse the intestinal dysbiosis caused by antibiotics. In addition, the use of probiotics in people with AD has been shown to increase their learning and cognitive abilities. [22,30]

Potential treatments for disruption of the gut-brain microbiota axis in AD:

- Adequate diet - studies indicate that people who follow a Mediterranean diet are less likely to develop AD; moreover, following such a diet can slow the progression of the disease,

- Probiotics and prebiotics - studies carefully suggest that probiotics and prebiotics can prevent AD. In addition, foods rich in prebiotic-resistant starch increase the diversity of intestinal microflora

- Fecal microbial transplantation - animal studies have shown that fecal microbial transplantation can improve cognitive abilities in AD patients. Research with human participants is needed. [1, 31,32,33]

3.3 **Gut microbiota in Parkinson's disease**

According to Hirayama et al., two hypotheses explain the involvement of the gut microbiota in the pathogenesis of PD. The first one regards reducing the number of bacteria in the gut microbiota that produce SCFAs. Reduced amounts of SCFAs are associated with people suffering from PD, with less of their effect on GPR41 receptors that are widely expressed in the peripheral nervous system, which may act on microglia and exacerbate PD symptoms. A second hypothesis is about an increase in *Akkermansia* bacteria, which degrade mucin, and a decrease in the microflora bacterias producing SCFA, which increases the permeability of the intestinal wall and exposes the enteric nervous system (ENS) to substances such as pesticides and bacterial lipopolysaccharides, which contributes to abnormal aggregation of α-synuclein in the ENS. In addition, according to Zhang et al. *Akkermansia* bacteria produce a protein that contributes to the production of oxygen free radicals in mitochondria, which results in an increased aggregation of α-synuclein in enteroendocrine cells in mice- the outcome of those events could be the development of PD. [34,35, 36]

Another reason may be the disruption of *Prevotella* bacteria, which may be associated with decreased SCFA, mucin, and reduced levels of vitamin B1, hydrogen sulfide, and thiamine, which have neuroprotective effects. In addition, a case-control study by Aho et al. found that people with PD had significantly reduced amounts of *Prevotella* bacteria compared to the healthy subjects. In addition, reduced bacterial counts were associated with faster disease progression. [36,37,38]

Patients with PD have been observed to have higher levels of bacteria from the genera *Lactobacillus* and *Bifidobacterium*. However, it is possible that they are not a cause for the severity of PD, but levodopa used to treat PD may increase their numbers. A study in patients with newly diagnosed PD showed no particular increase in these types of bacteria. [36,37,39]

Another abnormality in the gut microbiota noted in PD patients is Small Intestinal Bacterial Overgrowth (SIBO). According to Li et al., about 46% of PD patients also suffer from SIBO; interestingly, a geographic correlation has been shown in Western countries that 52% of PD patients have SIBO, while in Eastern countries, 32% have SIBO. In addition, osteoporosis and malnutrition have been observed in patients with PD and SIBO. The pathomechanism underlying the co-occurrence of SIBO and PD likely is that SIBO results in an increased intestinal permeability, which causes a systemic inflammatory response and contributes to an increased α-synuclein in the ENS and worse motor function in PD patients. [38,40,41]

Helicobacter Pylori infection may be considered a cause of PD. Long-standing studies show a positive correlation between the above; in a study conducted on the Danish population by Nielsen et al. it is illustrated that patients who have had *H.pylori* eradicated about five years earlier have an increased risk of PD of about 45%. On the other hand, they showed no link between colonization with the bacterium and PD.A meta-analysis by Dardiotis et al. showed that the presence of *H.pylori* in a PD patient influences a higher score on the Unified Parkinson's Disease Rating Scale, associated with increased disease symptoms, than in patients without H. Pylori or after eradication. [38,42,43]

In addition, patients with PD can be expected to have more pro-inflammatory gut bacteria. In PD patients, increased amounts of *Enterobacteriaceae* in the intestinal microflora have been associated with impaired motor function. [36,43]

Possible treatments for intestinal dysbiosis in PD:

- Diet - a Mediterranean diet improves cognitive and motor function in PD patients.

- Probiotics - can significantly help patients with PD and constipation and have a positive effect on the gut microbiota

- Fecal microbial transplantation - in a study on mice by Zhao et al. it was noted that mice with PD after transplantation have reduced levels of lipopolysaccharides and reduced systemic inflammation, which inhibits the progression of PD. [45,46, 47]

Disease	Alzheimer's disease	Parkinson's disease
Factors that may affect the disease	TMAO and SCFAs produced by the gut microbiota.	Reduction in the number of SCFAs-producing bacteria.
	Increase in the ratio of intestinal *Firmicutes* to *Bacteroidetes* bacteria.	Increase in *Akkermansia* bacteria, wchich degrading mucins
	Intestinal dysbiosis, which causes systemic inflammation.	*Provotella* bacterial disorders, which lead to decreased level of vitamin B1
	Blautia decrease, which lead to GABA neurotransmitter decrease.	Small intestinal bacterial overgrowth (SIBO)
		Helicobacter Pylori infection
Examples of therapeutic options for the disease	Proper diet, probiotics, fecal microbial transplantation.	

Table 1. Gut microbiota in PD and AD

4. Conclusions

The gut microbiota has a huge impact on the formation of neurodegenerative diseases. The number of possible pathomechanisms influencing the formation of the aforementioned diseases is extremely large. There are some linking between AD and PD gut microbiota, like decreasing number bacteria producing SCFAs and some differences, like SIBO and H. pylori infections. Detailed studies are needed to elucidate the exact relationships between the gut microbiota and the formation of AD and PD. It is worth noting that most of the studies cited above were conducted on laboratory animals. More human research is required.. In addition, it is worth noting that it is likely that an early intervention, such as changing to a Mediterranean diet, can reduce the risk of stunting.

Author's contribution

Conceptualization, Iwona Welian-Polus, Michał Leśniewski; methodology, Michał Leśniewski; software, Karolina Maliszewska; check, Iwona Welian-Polus, Karolina Maliszewska, Joanna Ziółkowska; formal analysis, Izabela Oleksak, Michał Leśniewski; investigation, Iwona Welian-Polus, Joanna Ziółkowska; resources, Karolina Maliszewska, Izabela Oleksak; data curation, Joanna Ziółkowska, writing – rough preparation, Michał Leśniewski; writing – review and editing, Iwona Welian-Polus, Izabela Oleksak; visualization, Michał Leśniewski, supervision, Izabela Oleksak; project administration, Karolina Maliszewska; receiving funding, Joanna Ziółkowska.

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Supplementary materials

Table 1: Gut microbiota in PD and AD

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