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The Link Between Periodontal Disease and Alzheimer's Disease: a narrative review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder influenced by a range of factors, including chronic inflammation and microbial infections. Recent research highlights a potential link between AD and periodontal disease — a chronic inflammatory condition caused by dysbiotic oral bacteria such as *Porphyromonas gingivalis*. These pathogens may reach the brain via the bloodstream or trigeminal nerve, triggering neuroinflammation through microglial activation and promoting pathological changes, including amyloid-β accumulation and Tau hyperphosphorylation. *P. gingivalis* secretes virulence factors like gingipains and lipopolysaccharides (LPS), which disrupt immune responses and contribute to neuronal damage. Genetic predispositions, such as mutations in microglia-regulating genes (e.g., *TREM2*, *CD33*, *CLU*), further impair immune function and exacerbate AD pathology. Aging, a common risk factor for both diseases, weakens immune defenses and the blood-brain barrier, facilitating bacterial entry into the brain. As no cure

currently exists for AD, preventing and managing periodontal disease could be a promising strategy to reduce the risk and progression of AD. This review underscores the need for interdisciplinary approaches and further research into the oral-systemic connection to better understand, prevent, and treat neurodegenerative diseases like Alzheimer's.

Keywords: Alzheimer's disease, periodontitis, inflammation, microglia, dementia

Introduction

Alzheimer and periodontal disease are increasingly recognized as interconnected health issues. In many countries, the prevalence of Alzheimer's is on the rise, particularly as populations age. At the same time, periodontal disease, which affects a significant part of the global population, is often overlooked in discussions about systemic health.

Aim of the work

The purpose of this study is to explore the potential link between periodontal disease and Alzheimer's disease (AD) by analyzing the underlying biological mechanisms, including microbial infection, neuroinflammation, and genetic susceptibility.

Methods

A literature review was made using the databases Scielo, PubMed, EBSCO and key words: "Periodontitis", "Periodontal disease", "Alzheimer disease", "Inflammation mediators", "Neurodegeneration", "Elderly", "LPS", "dementia", "microglia".

Conclusions

Given the growing evidence linking periodontal disease to Alzheimer's disease, this connection remains underexplored in clinical settings. Further research employing diverse

theoretical and methodological frameworks is needed to understand the full impact of periodontal health on neurodegenerative diseases, enabling the development of targeted interventions to reduce the risk of Alzheimer's across various populations.

1. Introduction

Alzheimer's disease is a neurodegenerative brain disorder in which the patient gradually loses the ability to live independently due to progressive impairments in memory, cognitive functions, speech, and motor coordination, ultimately leading to a fatal outcome in its most severe stage. It is projected that as people live longer, the number of Alzheimer's patients will increase to 152 million by 2050, posing a serious challenge to healthcare systems [1]. The causes of the disease are still not fully understood. It is suspected that physical inactivity, mood disorders, hypertension, diabetes mellitus, and obesity [2], systemic inflammation [3,4,5], HSV viruses [6,7,8], and genetic factors [9] may play a role.

Periodontal disease is a chronic inflammatory condition affecting the tissues surrounding and supporting the teeth, including the gums, periodontal ligament, alveolar bone, and root cementum. Two stages leading to the disease are distinguished: gingivitis, which, if untreated, progresses to second stage: periodontitis. According to data, it affects between 20% and 50% of the population and is the sixth most common disease worldwide [10, 11]. Evidence of the inflammatory nature of the disease is the elevated CRP level in patients diagnosed with periodontitis [12]. Moreover, the components of a dysbiotic oral biofilm may impair brain function, potentially contributing to the onset of depression and dementia [13]. Among the predisposing factors for periodontal disease, systemic diseases such as type 2 diabetes, insulin resistance, and even Alzheimer's disease are mentioned.

The relationship between Alzheimer's disease and periodontal disease is the subject of research by many scientists, and shared risk factors have been identified. These include oral hygiene practices, tobacco use, dietary habits, systemic inflammation, diabetes, and stress exposure [14], but studies also show that polymorphisms in genes encoding pro-inflammatory cytokines, such as TNF-α, IL-1α, IL-1β, and IL-6, may act as risk factors for both periodontitis and Alzheimer's disease [15].

2. Mechanisms of the potential link between periodontal disease and Alzheimer's disease

2.1. Microbes and Microglia

Numerous bacteria have been linked to the development of Alzheimer's disease (AD), including *Chlamydia pneumoniae, Borrelia burgdorferi*, and *Treponema denticola*. Similarly, studies indicate that periodontal bacteria such as *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Tannerella forsythia, Eikenella corrodens,* and *T. denticola* are also implicated. Two primary pathways through which these bacteria and their products can spread to the brain have been identified: via the bloodstream and through peripheral nerves, particularly the trigeminal nerve [16, 17, 18]. These substances may trigger an inflammatory response in the nervous system, and prolonged neuroinflammation promotes the activation of microglia into the pro-inflammatory M1 phenotype [16]. Microglia in the state of health serve a neuroprotective function, but under inflammatory conditions, they contribute to neuroinflammation, making them a key factor in the early stages of Alzheimer's disease [19].

2.2. *Immunomodulatory and Inflammatory Effects of Porphyromonas gingivalis*

Porphyromonas gingivalis, through the secretion of specific peptidases (gingipains) can dysregulate the immune–inflammatory response by degrading important immunological factors like IgG, IgA, complement components, and defensins. It activates matrix metalloproteinases (MMPs), promotes the release of pro-inflammatory mediators and prostaglandins, inhibits protease inhibitors, reduces receptor expression, suppresses the respiratory burst of phagocytes, and uses membrane proteins like RagA and RagB, which could potentially be associated with antibiotic resistance and are involved in bacterial growth and the activation of proinflammatory mediators. Additionally, it inhibits the biosynthesis of IL-8, which impairs chemotaxis [20, 21].

Research on mice has shown that *P. gingivalis* can migrate from the mouth to the brain, leading to increased Aβ42 levels and neurotoxic effects, which can be reduced through the use of gingipain inhibitors [22, 23]. Additionally, the presence of *P. gingivalis* DNA in the brains of ApoE-null mice indicates that the ApoE genotype may contribute to neuroinflammation and support the colonization of *P. gingivalis* in the brain [24].

2.3. *LPS*

Lipopolysaccharide (LPS) is a major component of the surface of Gram-negative bacteria. When LPS enters the human body or brain, it can induce inflammation and act as an endotoxin [25]. It has been proven that patients with Alzheimer's disease have higher levels of LPS in their blood [26, 27, 28, 29], as well as higher levels of gingipain [30]. The role of LPS produced by *P. gingivalis* in periodontal disease (there are two forms of LPS secreted by *P. gingivalis*: O-LPS and A-LPS [31]) and its involvement in the development of AD has been

established in animal models. It was either injected or introduced through inoculation, and it was observed that it causes an increase in the production of pro-inflammatory cytokines and mediators, leading to Tau protein hyperphosphorylation and elevated Aβ levels, which contribute to neuronal damage [32, 33].

Moreover, it has been proven that prolonged exposure to LPS leads not only to AD but also to other dementia-related diseases [34], such as neuroinflammation driven by microglia, intracellular beta-amyloid accumulation in neurons, and cognitive decline, including learning and memory impairments in middle-aged mice [35].

2.4. Genetic factors, P. gingivalis periodontal infection and microglia interaction

Genetic predisposition and chronic periodontal infection by *Porphyromonas gingivalis* play a crucial role in microglial dysfunction and the progression of Alzheimer's disease (AD). Interestingly, research on twins has demonstrated that genetic factors account for approximately 60–80% of the risk of developing Alzheimer's disease [36]. Genome-wide association studies (GWAS) have identified key microglia-related genes, such as TREM-2, TYR-OBP [37], CD33, CLU, and CR1 [38], which regulate microglial activation, complement signaling, and Aβ clearance. Mutations in these genes impair microglial response, leading to inefficient Aβ removal and increased inflammation. P. gingivalis produces virulence factors like LPS and gingipains, which activate microglia through the TLR4 pathway. In the study by Henry et al. [39], it was found that peripheral LPS challenge in aged mice induced a hyperactive microglial response along with a higher induction of inflammatory IL-1β and anti-inflammatory IL-10. Gingipains can also downregulate TREM-2 expression in microglia, impairing their ability to clear Aβ [40].

Additionally, leptomeningeal cells can transduce peripheral inflammatory signals to microglia, further amplifying the neuroinflammatory response [41, 42]. This interaction between genetic susceptibility, chronic infection, and microglial dysfunction plays a significant role in the pathogenesis linking periodontal disease to AD.

2.5. Three-way Relationships among P. gingivalis infection, AD and Age

Although often overlooked, oral health can influence the progression of various diseases, including AD. The prevalence of Alzheimer's disease (AD) increases with age, from 3% in people aged 65–74 to nearly 50% over 85 and poor dental care among the elderly further heightens this risk [43]. Research suggests that aging-related oxidative stress reduces the adaptability of mitochondria to the dynamic needs of neurons. This diminished flexibility may worsen mitochondrial dysfunction in neurons, especially when exposed to chronic conditions like periodontitis [44].

P. gingivalis may reach the brain via the bloodstream, linking it to AD. Studies suggest that antibodies against oral bacteria can predict cognitive decline a decade later. This delay may result from age-related weakening of the blood-brain barrier (BBB), allowing bacteria easier access to the brain. In younger individuals, a stronger immune system provides better protection. Also, it was reported that P. gingivalis suppressed adaptive immunity in AD patients [31]. Maintaining BBB integrity is essential for preserving central nervous system function throughout life [43].

3. Clinical significance and therapeutic implications

Given the aforementioned considerations regarding the relationship between periodontal disease and Alzheimer's disease (AD), periodontal prevention is of utmost importance. Greater attention should be paid in clinical practice to the early diagnosis of periodontal

disease, which would enable the timely implementation of measures aimed at halting its progression. Moreover, such interventions could also contribute to slowing the development of AD and other dementia-related disorders.

Patients diagnosed with AD also require specialized dental care, as they often experience impaired motor coordination and reduced manual skills. As a result, their oral hygiene tends to be inadequate, leading to an increased bacterial load. This suggests a possible reverse relationship, where Alzheimer’s disease may predispose individuals to the development of periodontal disease [43].

There is still no effective cure for Alzheimer's disease. Currently, research is underway on new treatment methods, including therapies aimed at controlling inflammation, eliminating periodontal pathogens, and counteracting neuroinflammation. Experiments on animal models have shown that a drug blocking gingipain may slow down neurodegeneration, giving scientists hope for an effective therapy in the future [45]. Additionally, there is a need for further studies on the impact of periodontal prevention on reducing the risk of neurodegenerative diseases, including AD. The growing body of evidence linking periodontal disease with Alzheimer's disease represents an important step toward better understanding the pathogenesis of AD and searching for more effective methods of prevention and treatment.

4. Conclusion

The growing body of evidence suggests a significant link between periodontal disease and Alzheimer's disease (AD), highlighting the complex interplay between chronic inflammation, microbial infection, and genetic susceptibility in the development of neurodegenerative disorders. The migration of *P. gingivalis* and other periodontal pathogens to the brain, along with the resulting activation of microglia and increased production of pro-inflammatory cytokines, appear to play a central role in driving neuroinflammation and neuronal damage in

AD. Moreover, genetic predispositions, such as mutations in microglia-related genes (e.g., TREM-2, CD33, CLU), further contribute to impaired Aβ clearance and the progression of AD.

Importantly, maintaining good oral health and preventing periodontal disease could be a valuable strategy in reducing the risk of developing AD and slowing its progression. Early diagnosis and targeted interventions for periodontitis may not only improve oral health outcomes but also have a protective effect on cognitive function and brain health. Future research should focus on better understanding the molecular mechanisms underlying the relationship between periodontal and neurodegenerative diseases, as well as exploring potential therapeutic approaches targeting both inflammation and microbial infection. While much remains to be discovered, addressing oral health as a modifiable risk factor for AD offers a promising avenue for improving overall brain health and developing more effective strategies for AD prevention and treatment.

Declaration of Generative AI and AI-assisted technologies in the writing process

On behalf of all authors, the corresponding author states that AI was used in the writing process to improve the readability and language of the manuscript.

Author's contribution

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