Journal of Complementary Medicine Research, ISSN: 2577-5669 Vol. 15, No.4,2024(pp.73-78)

RESEARCH ARTICLE WWW.JOCMR.COM

Association between Periodontal Disease and the Progression of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD), the leading cause of dementia, is characterised by progressive cognitive decline driven by amyloid-β accumulation, tau pathology, and chronic neuroinflammation. Periodontal disease (PD) is a highly prevalent chronic inflammatory condition initiated by dysbiotic oral biofilms. Growing evidence indicates a significant association between PD and the progression of AD through inflammatory and microbial mechanisms. Chronic periodontitis induces a persistent systemic inflammatory state, it may also compromise blood–brain barrier integrity and prime microglial activation. Periodontal pathogens, particularly *Porphyromonas gingivalis*, and their virulence factors have been identified in the brains of AD patients, where they promote amyloid-β production and neurodegeneration. Clinical and epidemiological studies report association between periodontal inflammation, tooth loss, and accelerated cognitive decline. A bidirectional relationship does exist which highlights the importance of integrated oral and neurological care and supports the need for further longitudinal and interventional studies.

Keywords: Alzheimer's disease; Periodontal disease; Neuroinflammation; *Porphyromonas gingivalis*

Introduction

Humans encounter various chronic conditions that can lead to significant disability. Among these, neurodegenerative diseases are the most limiting neurological conditions worldwide [1]. Alzheimer's disease (AD) is the primary cause of dementia, accounting for 60-80% of all cases,

and currently affects approximately 55 million individuals [1,2]. Characterised by a progressive deterioration of language and memory, the molecular hallmarks of AD include the extracellular accumulation of β-amyloid peptides and intraneuronal neurofibrillary tangles (NFTs) composed of Tau protein [1,3].

Another chronic disease affecting humans is periodontal disease (PD). It remains a global public health crisis, affecting approximately 50% of the world's population [1,4]. In dentate adults, the prevalence of periodontitis is nearly 62%, with severe cases affecting 23.6% of individuals [4]. Periodontitis is an irreversible inflammatory disorder of the tooth-supporting tissues, initiated by a dysbiotic biofilm and sustained by a maladaptive host immune response [1,5]. Historically viewed as a local oral infection, periodontitis is now recognised as a systemic condition linked to more than 50 systemic diseases, including cardiovascular disease, type 2 diabetes, and respiratory disorders [4,6].

Literature suggests a bidirectional relationship between AD and PD. Cognitive impairment in AD patients often leads to a decline in self-care and oral hygiene, exacerbating periodontal inflammation. Chronic periodontal infection, on the other hand, may serve as a risk factor that accelerates cognitive decline through systemic inflammatory burden and the migration of oral pathogens to the brain [1,7].

Pathogenesis of Alzheimer's Disease and the Role of Inflammation

The Amyloid cascade hypothesis suggests that the imbalance between β-amyloid production and clearance initiates a cascade of neuroinflammation, synaptic loss, and neuronal death. These brain changes often begin 20 years or more before clinical symptoms manifest [2,3].

Neuroinflammation was once thought to be a secondary response to neuronal death. However, it is now considered a core feature of AD. The process involves the persistent activation of microglia and astrocytes, the brain's resident immune cells. Pathological β-amyloid aggregates are detected as danger-associated molecular patterns by pattern recognition receptors on these cells. This activation triggers the release of pro-inflammatory cytokines, including Interleukin1β, Interleukin-6 and Tumour Necrosis Factor-alpha [3].

When these glial cells fail to clear amyloid deposits, a chronic inflammatory state persists. Specifically, the NLRP3 (Nucleotide-binding domain, Leucine-rich Repeat family, Pyrin domain-containing protein-3) inflammasome is activated, leading to the formation of ASC (apoptosis-associated speck-like protein) specks. These specks are released into the extracellular space, where they can "seed" and accelerate the aggregation of β-amyloid, creating a self-perpetuating inflammatory loop. This environment also activates kinases that lead to the hyperphosphorylation of Tau, resulting in the formation of neurotoxic tangles [1,3].

Pathogenesis of Periodontal Disease: Symbiosis to Dysbiosis

Periodontal health is maintained by a dynamic equilibrium between the oral microbiota and the host immune system, known as symbiosis. The transition to periodontitis involves a shift

toward dysbiosis, where Gram-negative anaerobic bacteria dominate the biofilm. The Keystone Pathogen Hypothesis proposes that certain low-abundance organisms, most notably *Porphyromonas gingivalis (P. gingivalis)*, can orchestrate this shift by subverting the host immune response [5,6].

P. gingivalis utilises a range of virulence factors to survive, including gingipains (proteolytic enzymes) and lipopolysaccharides (LPS). These factors allow the bacteria to evade neutrophils, degrade complement proteins like C3, and invade gingival epithelial cells. The resulting chronic inflammation leads to the formation of periodontal pockets and alveolar bone loss, providing a direct portal for bacteria and their toxins to enter the systemic circulation [1,2,5,7,8].

Link between Periodontitis and Alzheimer's progression

The Systemic Inflammatory Pathway: Periodontitis induces a low-grade systemic proinflammatory state, evidenced by elevated serum levels of C-reactive protein (CRP), fibrinogen, and pro-inflammatory cytokines. CRP levels correlate significantly with the severity of periodontitis and have been identified as a predictor for the development of AD up to 25 years later [1,4,9].

These peripheral cytokines can reach the brain through several routes:

- Via areas lacking a blood-brain barrier (BBB), such as the circumventricular organs [9].
- By crossing the BBB through cytokine-specific transporters [9].
- By increasing BBB permeability through the upregulation of matrix metalloproteinases like MMP-9, which degrades tight junction proteins [1,3,8].

Once in the central nervous system (CNS), these signals prime the microglial cells, making them respond with exaggerated intensity to the presence of amyloid plaques [3,9].

Direct Microbial Invasion and the Role of Gingipain: Pathogens like *P. gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* have been isolated from the brain tissue and cerebrospinal fluid (CSF) of AD patients. *P. gingivalis* may enter the CNS via the bloodstream or through neural pathways, such as the olfactory or trigeminal nerves [1,6,9].

Once *P. gingivalis* colonises the brain, it secretes gingipains, which are neurotoxic. Studies indicate that gingipains can cleave Tau protein and β-amyloid precursors, promoting the formation of the hallmark plaques and tangles. In animal models, oral infection with *P. gingivalis* leads to significant brain colonisation and increased β-amyloid production. Notably, the administration of gingipain inhibitors has been shown to reduce amyloid accumulation and prevent neurodegeneration in these models [1,8].

The IFITM3-Aβ Axis: IFITM3 stands for Interferon-Induced Transmembrane Protein 3. Recent research has elucidated a novel molecular link: the IFITM3-Aβ axis**.** Periodontal infection by *P. gingivalis* triggers an increase in Type I interferons (IFN-β) in the brain. This induces the expression of Interferon-induced transmembrane protein 3 (IFITM3), an innate immunity protein, predominantly within astrocytes. IFITM3 binds to the $\boldsymbol{\gamma}$-secretase complex, enhancing its activity and thereby increasing the production of β-amyloid. These findings suggest that periodontal-induced neuroinflammation directly drives the core pathology of AD through the innate immune system [8].

Clinical and Epidemiological Evidence

Longitudinal and Cross-Sectional Studies: The clinical association between these two diseases is supported by multiple systematic reviews. A meta-analysis of cross-sectional studies found that patients with AD exhibit higher levels of periodontal inflammation and deeper pocket depths compared to healthy controls. In a significant longitudinal study, participants with periodontitis at baseline experienced a six-fold increase in the rate of cognitive decline over a six-month follow-up period [1,6].

Furthermore, an umbrella review indicated that 14 out of 16 systematic reviews confirmed a positive correlation between PD and AD, with odds ratios (OR) for cognitive impairment reaching as high as 2.26 in patients with periodontitis. The strength of this association appears to increase with the severity of the periodontal condition. Severe periodontitis is linked to a 15 times greater risk of developing AD in some populations [1,6,7].

The Significance of Tooth Loss: Tooth loss, a terminal result of chronic PD, has also been implicated in cognitive deterioration. Research suggests that for every tooth lost, the risk of cognitive impairment increases by 1.4% and the risk of dementia by 1.1%. AD patients are characterised by a significantly greater number of missing teeth and higher rates of edentulism compared to non-dementia individuals. In monozygotic twins, the loss of teeth early in life was associated with a 5.5-fold increased risk for AD [1,7].

Shared Risk Factors and Systemic Comorbidities

The association between PD and AD is confounded by shared modifiable and non-modifiable risk factors. Both conditions show a higher prevalence in women. And their incidence increases dramatically with age. Shared acquired factors include smoking, physical inactivity, obesity, and poor dietary habits [1,2,6,7,9].

Diabetes mellitus represents a particularly strong link, as it has a well-established bidirectional relationship with periodontitis. Diabetes increases the risk of PD, while PD-induced systemic inflammation impairs glycemic control. Both diabetes and chronic periodontitis contribute to vascular pathology, which is a major risk factor for both vascular dementia and Alzheimer's disease. Cardiovascular disease also shares inflammatory pathways with PD, further complicating the clinical picture [1,4,7,9].

The Bidirectional Role

The relationship between PD and AD is not strictly unidirectional. As AD progresses, the resulting cognitive and functional decline significantly impairs a patient's ability to perform daily oral hygiene routines. This creates a vicious cycle where declining neurological health facilitates the progression of severe periodontitis, which then generates more systemic inflammation to further damage the brain [1,7].

Clinical Implications and Future Directions

Integrated Healthcare: Given the strong evidence linking oral health to neurological stability, it is imperative to expand dental consultations beyond the oral cavity. Dentists should be proactively involved in the multidisciplinary teams managing AD patients, and neurologists should screen for periodontal health as part of geriatric risk assessments [1,4,7].

Research Needs: While current literature converges on a link between PD and AD, many studies are cross-sectional and cannot confirm causality. There is a critical need for:

- Longitudinal studies with standardised measurements to track the progression of both diseases simultaneously [1,7].
- Randomised clinical trials (RCTs) to determine if periodontal therapy (e.g., professional scaling, use of antimicrobial agents) can definitively slow the rate of cognitive decline [1,6].
- Investigations into the gut-brain-oral axis to understand how the entire human microbiome influences neurodegeneration [1,6,7].

Conclusion

Growing evidence indicates a significant association between periodontal disease and the progression of Alzheimer's disease, driven by chronic systemic inflammation, microbial translocation, and dysregulated innate immune responses. Periodontitis may exacerbate neuroinflammation by compromising blood–brain barrier integrity, priming microglial activation, and promoting amyloid-β accumulation and tau pathology. The presence of periodontal pathogens, particularly *Porphyromonas gingivalis*, within the CNS strengthens the biological plausibility of this link. Clinically, greater periodontal severity and tooth loss correlate with accelerated cognitive decline. The relationship appears bidirectional, as cognitive impairment worsens oral hygiene and periodontal health. Integrating periodontal care into geriatric and neurological management may offer a modifiable strategy to mitigate cognitive deterioration.

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