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Review Article

The Importance of Dental Neuroscience Highlighting the Connection Between Periodontal Disease and Alzheimer's Disease

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Abstract

Periodontal disease has been associated with neurodegenerative processes, particularly Alzheimer's disease, highlighting the need for an integrated approach through Dental Neuroscience. Evidence indicates that periodontal pathogens, such as *Porphyromonas gingivalis*, can reach the Central Nervous System via axonal or haematogenous routes, triggering neuroinflammation and promoting the deposition of beta-amyloid and hyperphosphorylated tau protein. Experimental models and *post-mortem* analyses confirm its presence in the brains of patients with Alzheimer's disease, correlating with biomarkers of neurodegeneration. Oral dysbiosis and the gut-brain axis also modulate systemic inflammatory responses, affecting neuronal plasticity and cognitive functions. Epidemiological studies suggest that moderate or severe forms of periodontal disease significantly increase the risk of Alzheimer's disease, reinforcing the importance of early screening and prevention. Emerging strategies include gingipain inhibitors, oral probiotics, and anti-inflammatory nutritional interventions, which may reduce brain bacterial load and neuroinflammation. In this context, multidisciplinary approaches become essential for prevention and management. The consolidation of Dental Neuroscience as a scientific field broadens the understanding of the interface between oral health, the brain and public health, contributing to the training of professionals capable of acting in the prevention of neurodegenerative diseases through oral health. Given this context, the objective of this review of literature is to synthesise and discuss the pathophysiological, epidemiological and clinical evidence linking periodontal disease to Alzheimer's disease, as well as to explore the implications of this connection for integrated clinical practice from the perspective of Dental Neuroscience.

Keywords: *Periodontal Disease; Alzheimer's Disease; Neurosciences; Dentistry; Neurodegenerative Diseases.*

Introduction

This article aims to investigate the pathophysiological mechanisms linking periodontal disease to Alzheimer's disease. Dental Neuroscience presents the relationship between neurodegenerative diseases and oral health, with an emphasis on the gum-brain inflammatory axis.

Robust and recent evidence shows that chronic inflammation induced by periodontal pathogens, especially the microorganism *Porphyromonas gingivalis*, triggers neuroinflammation, compromises the blood-brain barrier, and stimulates the accumulation of beta-amyloid and hyperphosphorylated tau protein[1]. The transition of these microorganisms to the Central Nervous System via cranial nerves (trigeminal) or systemic circulation[2] and oral dysbiosis as a modulator of the gut-brain axis[3] are critical pathways in this association.

Based on the perspective of an integrative approach[4,5], this review proposes that periodontal disease and Alzheimer's disease share an interdependent multifactorial aetiology, where physical (chronic inflammation, dysbiosis), psychological (oxidative stress, cognitive decline) and emotional (loss of purpose, social isolation) imbalances feed back pathologically. In this model, gingival inflammation is not merely a local risk factor, but also an active component of systemic disharmony that accelerates neurodegeneration.

Epidemiological data demonstrate this synergy: moderate or severe periodontal disease increases the risk of Alzheimer's disease by 53%, highlighting the urgency of multidisciplinary approaches[6]. Alzheimer's disease affects approximately 55 million people globally, with projections indicating a threefold increase by 2050[7]. At the same time, periodontal disease has a high prevalence, affecting 45 to 50% of adults[8], and is an often underestimated factor in the genesis of neurodegenerative comorbidities, whose relevance is becoming increasingly evident as new scientific data emerges. The common denominator is persistent inflammation: pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and periodontal pathogens induce systemic immune responses that exacerbate neuronal loss[9]. The Gram-negative anaerobic bacterium *Porphyromonas gingivalis*, associated with periodontitis, deserves mention for its ability to colonise brain tissue, where its gingipains (proteases specific to *Porphyromonas gingivalis*) catalyse the aggregation of beta-amyloid (Aβ) and Tau protein, in addition to activating the NOD-like receptor family pyrin domain containing 3 (NLRP3-inflammasome) pathway, amplifying neuroinflammation[1,10].

In addition to infectious and inflammatory mechanisms, a psychoneuroimmunological approach allows us to understand these factors. Chronic stress, anxiety, and depression can negatively modulate the immune response, aggravating both periodontal dysbiosis and neuroinflammation. This perspective is supported by evidence showing that emotional imbalances are associated with elevated levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, and increased susceptibility to oral infections, thus creating a vicious cycle that can accelerate neurodegeneration[9].

Biological Mechanisms of the Connection between Periodontal Disease and Alzheimer's Disease

Translocation mechanisms and neuroinflammation triggered by periodontal pathogens

Periodontal pathogens can reach the Central Nervous System via the trigeminal and olfactory nerves, or via the systemic circulation[2]. *Porphyromonas gingivalis* is often detected in the brains of patients with Alzheimer's disease, where its gingipains degrade neuronal proteins, induce hyperphosphorylation of tau protein, and promote beta-amyloid aggregation[1].

A *post-mortem* study revealed a significant correlation between the levels of these proteases and tau protein biomarkers, suggesting a direct role in the pathogenesis of Alzheimer's disease. Other periodontal bacteria, such as *Fusobacterium nucleatum* and *Treponema denticola*, have also been associated with microglia activation via Toll-like receptor 2 (TLR-2) and Toll-like receptor 4 (TLR-4), amplifying neuroinflammation[11].

Furthermore, interactions between different oral pathogens can synergistically modulate microglia activation and cytokine production, suggesting that the composition of the oral microbiome influences the magnitude of neuroinflammation[12].

Experimental models in mice demonstrate that infection with *Porphyromonas gingivalis* increases beta-amyloid peptide deposits in the hippocampus by up to 300%, in addition to reducing spatial memory by approximately 40%[13].

Chronic inflammation of the periodontium plays a central role in disrupting the blood-brain barrier and activating neuroinflammatory cascades. Pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) produced in the periodontium increase the permeability of the blood-brain barrier, facilitating the entry of lipopolysaccharide and other inflammatory mediators into the Central Nervous System[10].

Chronic exposure to *Porphyromonas gingivalis* lipopolysaccharide induced activation of the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome and the production of beta-amyloid peptide 42 in murine models[11,14]. Recent studies demonstrate that *Porphyromonas gingivalis* directly activated the NOD-like receptor family, pyrin domain containing 3 inflammasome in microglia cells, promoting the sustained release of pro-inflammatory interleukins, such as IL-1β and IL-18, contributing significantly to neurodegeneration[14].

In addition to this pathway, the pathogen employs sophisticated immune evasion mechanisms. Evidence indicates that *Porphyromonas gingivalis* can selectively interfere with the endocytic pathway of NOD-like receptor family, pyrin domain containing 3 inflammasome activation, suppressing activation induced by other periodontal pathogens such as *Fusobacterium nucleatum* and even *Escherichia coli*, without affecting classic extracellular stimuli[13]. This modulation occurs through the reduction of particle uptake via endocytosis, a new mechanism of microbial interference in inflammatory signalling[1].

Thus, periodontal inflammation is not limited to gum tissue, but acts as a systemic trigger, modulating central immune responses that accelerate protein aggregation and neuronal degeneration observed in Alzheimer's disease[10,14].

Oral Dysbiosis and the Gut-Brain Axis

Oral dysbiosis alters the gut microbiome, elevating serum IL-17 and compromising the epithelial barrier, increasing the release of inflammatory mediators such as lipopolysaccharide and IL-1β, which reach the Central Nervous System via the vagus nerve[3]. In murine models, metabolites such as butyric acid modulate hippocampal neurogenesis, while lipopolysaccharide reduces Brain-Derived Neurotrophic Factor by 50%, affecting synaptic plasticity. The reduction of commensal bacteria (e.g., *Rothia*) aggravates cerebral vasodilation, contributing to ischaemia, necrosis, and cognitive decline[12].

Preclinical and Clinical Evidence

Studies in Animal Models and Neuropathology

Experimental models in mice demonstrate that infection with *Porphyromonas gingivalis* significantly increases beta-amyloid 42 peptide deposits in the hippocampus and cortex, in addition to compromising spatial memory[11,13]. These findings are corroborated by *post-mortem* analyses of human brains, where gingipains were detected in 96% of samples from patients with Alzheimer's disease, even in preclinical stages[1]. Persistent microglial activation and elevated TNF-α observed in these models reinforce the role of neuroinflammation in pathogenesis[11].

Oral Microbiome and Biomarkers

Metagenomic studies have identified a dysbiotic profile in the saliva of patients with Alzheimer's disease, characterised by an enrichment of *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Prevotella intermedia*, and a reduction in commensals such as *Rothia mucilaginosa* [12,19]. These changes correlate with serum biomarkers of the disease, including tau protein phosphorylated at threonine 181 and beta-amyloid peptide 42[9].

Epidemiological Studies

A meta-analysis involving more than 120,000 participants demonstrated that moderate or severe periodontal disease increases the risk of developing Alzheimer's disease by approximately 53%, regardless of factors such as diabetes and smoking[6]. Another longitudinal study showed that individuals with a long history of periodontitis (>10 years) experience a cognitive decline that is approximately 30% faster[18]. In addition, recent systematic reviews corroborate the elucidation of this association, emphasising that periodontal health should be considered a relevant component in the prevention of dementia[16,17].

Therapeutic Perspectives

Among the emerging strategies, the development of specific inhibitors for gingipains, such as the compound COR388, stands out. In animal models, this approach has proven superior to the use of broad-spectrum antibiotics (e.g., moxifloxacin), reducing the bacterial load in the brain and the formation of amyloid plaques without inducing bacterial resistance[1].

In addition to biological and pharmacological mechanisms, a broader understanding of this connection requires a multifactorial view of the patient. In this sense, Keppe[4] (2003) proposes a psychosomatic approach to this association. Although not part of conventional biomedical literature, this perspective offers a complementary view of the psychosocial factors involved[20]. In addition to the pathophysiological mechanisms described, it is essential to consider the psychological dimension in understanding periodontal disease and its interface with Alzheimer's disease. Evidence suggests that emotional and psychosocial factors, such as chronic stress, depression, and anxiety, influence directly the progression of periodontal disease by compromising the immune response, elevating cortisol levels, and impacting negatively treatment adherence[4,20].

Given this, the interaction between periodontal disease and Alzheimer's disease can be understood in three interdependent dimensions:

- Physical: chronic gingival inflammation induced by *Porphyromonas gingivalis*, oxidative stress, and exacerbated immune response[1,10];
- Psychological: anxiety, depression, and cognitive decline, which reduce therapeutic adherence and dysregulate the neuroimmune axis[9];
- Psychosocial: social isolation, loss of self-esteem, and negative impact on quality of life resulting from tooth loss and orofacial pain[6].

In this view, interventions should simultaneously address the three imbalances: physical (periodontal therapy), psychological (cognitive and therapeutic support) and emotional (social support networks).

Clinical and Therapeutic Implications

Prevention and Early Diagnosis:

- Screening: patients with periodontal disease should undergo annual cognitive assessment[18];
- Biomarkers: saliva and gingival fluid can be used for early detection of *Porphyromonas gingivalis* and pro-inflammatory cytokines[19];
- Psychological approach: recognition of the influence of psychological factors, such as stress, anxiety, and depression, on the progression of periodontal disease is fundamental to its prevention and integrated clinical management[4,20].

Emerging Therapies

Gingipain Inhibitors

In animal model studies, COR388 - a selective inhibitor of gingipains - has been shown to reduce the brain load of this pathogen *Porphyromonas gingivalis* by up to 90% and decrease beta-amyloid peptide formation by 50%. The results suggest that specific blockade of gingipains may interrupt the direct neurotoxicity and protein aggregation characteristic of Alzheimer's disease[1].

Oral Probiotics

Lactobacillus reuteri and *Bifidobacterium* spp. have been studied for their ability to modulate oral and intestinal microbiota, reducing gingival inflammation and systemic IL-6 levels. These probiotics can restore microbial balance, inhibit colonisation by periodontal pathogens, and attenuate the inflammatory immune response, with potential neuroprotective impact via the gut-brain axis[21].

Anti-inflammatory Nutrition

Rich diets in omega-3 fatty acids and polyphenols (such as curcumin) modulate oral and intestinal microbiota positively, reduce systemic inflammation, and have been shown to decrease beta-amyloid peptide load in experimental models. These compounds act by inhibiting pro-inflammatory pathways (such as NF-κB and NLRP3), strengthening the epithelial barrier and reducing bacterial translocation, which may contribute to neuroprotection and slow the progression of neurodegenerative diseases[3].

Multidisciplinary Approach

Given the evidence, it is imperative to adopt integrated clinical protocols that simultaneously address oral infection, systemic comorbidities, and psychosocial aspects. This multidisciplinary approach should include:

1. Control of periodontal infection through non-surgical therapy (scaling and root planing)[19];

2. Psychological support to improve treatment adherence and modulate stress factors that aggravate inflammation[4,20];

3. Rigorous management of comorbidities, such as diabetes, which are a common risk factor and exacerbator for both conditions[21].

This three-pronged strategy aims not only to interrupt the oral route of neuroinflammation, but also to promote a positive impact on patients' quality of life and rate of cognitive decline[21].

Final Considerations

In summary, this review consolidates robust evidence that positions periodontal disease as a modifiable and clinically relevant risk factor for Alzheimer's disease, mediated by a multifaceted gum-brain axis. The elucidated pathophysiological mechanisms, including the translocation of *Porphyromonas gingivalis* to the Central Nervous System, the activation of neuroinflammatory cascades via the NOD family receptor (NLRP3-inflammasome), and the modulation of the gut-brain axis by oral dysbiosis, establish a plausible causal relationship between chronic oral infection and neurodegeneration[1-3,10]. Far-reaching epidemiological data corroborate this association, revealing that moderate or severe periodontal disease significantly increases the risk of Alzheimer's disease[6], while *post-mortem* analyses detect gingipains in 96% of the brains of patients with the disease[1].

In addition to biological mechanisms, a psychoneuroimmunological perspective broadens this understanding, demonstrating how physical, psychological, and psychosocial imbalances interact synergistically to accelerate cognitive decline. In this integrative model, cerebral colonisation by *Porphyromonas gingivalis* is not an isolated event, but part of a systemic crisis in which immune dysfunction, oxidative stress and psychosocial fragility converge to compromise neural homeostasis[4,6,9,20].

The consolidation of Dental Neuroscience as an integrative field offers an innovative model for tackling neurodegenerative diseases, reinforcing oral health as an indispensable pillar of overall health. Future studies, particularly randomised and longitudinal clinical trials, are needed to validate the efficacy of combined interventions and translate this evidence into tangible clinical protocols.

Conflict of Interest

The authors declare that there is no conflict of interest.

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