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Original Article

Relationship Between Periodontitis and Neuroinflammation: A Narrative Review

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ABSTRACT

Periodontitis, a chronic inflammatory condition affecting the tissues supporting the teeth, is primarily caused by bacterial infection. Recent research has increasingly focused on its potential systemic implications particularly its link to neuroinflammation. Neuroinflammation , characterized by inflammation of the nervous tissue is a hallmark of several neurodegenerative diseases , including Alzheimer's disease (AD) and Parkinson's disease (PD). This review synthesizes current connection between periodontitis and neuroinflammation highlighting the biological mechanisms and potential implications for understanding and managing neurodegenerative diseases.

Keywords: Relationship, Periodontitis, Neuroinflammation, Alzheimer's disease (AD), Parkinson's disease (PD)

INTRODUCTION

Periodontitis, a chronic, inflammatory disease, induces systemic inflammation and contributes to the development of neurodegenerative diseases.[1] Periodontal disease (PD), or periodontitis, is an oral inflammatory disease caused by the host's immunological response to periodontal pathogens.[2] PD is initiated by dysbiosis of the microbiome of the oral cavity and results in local inflammation, eventually contributing to chronic systemic inflammation[2, 3]. Recent research has increasingly focused on its potential systemic implications particularly its link to neuroinflammation. Recent research has increasingly focused on its potential systemic implications particularly its link to neuroinflammation Periodontitis is associated with neurodegenerative diseases and neuroinflammatory processes through circulating mediators or direct access of the oral microbes to the CNS via systemic circulation [4,5,6]. The precise ethology of the most common neurodegenerative disorders, such as sporadic Alzheimer's, Parkinson's diseases and multiple sclerosis (AD, PD, and MS, respectively), remains to be revealed. Chronic neuroinflammation is a well-recognized component of these disorders, and evidence suggests that systemic inflammation is a possible stimulus for neuroinflammation development. [1] . Clinical evidence has suggested that patients with periodontitis are at a higher risk of developing PD and MS. This nexus among the brain, periodontal disease, and systemic inflammation heralds new ways in which microglial cells, the main innate immune cells, and astrocytes, the crucial regulators of innate and adaptive immune responses in the brain, contribute to brain pathology. Currently, the lack of understanding of the pathogenesis of neurodegeneration is hindering treatment development. However, we may prevent this pathogenesis by tackling one of its possible contributors (periodontitis) for systemic inflammation through simple preventive oral hygiene measures. Numerous studies have found a significant association between periodontitis and cognitive decline. For example, a large cohort study demonstrated that individuals with severe periodontitis had a higher risk of developing AD compared to those with healthy gums. Case control studies have further supported this link showing that patients with AD are more likely to have a history of periodontitis. Some interventional studies suggest that periodontal treatment may reduce systemic inflammation and potentially lower the risk of cognitive decline.

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Animal models have been instrumental in elucidating the mechanisms by which periodontitis may influence neuroinflammation. For instance mouse models have shown increased brain inflammation and cognitive impairment following oral infection with Gingivalis. These studies provide direct evidence of the impact of periodontal pathogens on the CNS and support the hypothesis that periodontitis can exacerbate neuroinflammatory processes.

Biological Mechanisms Linking Periodontitis and Neuroinflammation

1. Bacterial Invasion and Dissemination

It has been proposed that periodontal disease can initiate or contribute to the AD pathogenesis through multiple pathways, including key periodontal pathogens. Dysbiotic oral bacteria can release bacterial products into the bloodstream and eventually cross the brain-blood barrier; these bacteria can also cause alterations to gut microbiota that enhance inflammation and potentially affect brain function via the gut–brain axis. This translocation of bacteria and bacterial products can trigger an immune response within the brain leading to immune response. The trigeminal nerve has been suggested as another route for connecting oral bacterial products to the brain. Different species of *Treponema* associated with periodontitis were detected in the brains of AD cases.[7] Lipopolysaccharide (LPS) and gingipains of *Porphyromonas gingivalis*, a prominent PD-associated bacterial species in humans, were also detected in the brains of AD patients .[8,9] In mice, neuroinflammation and amyloid plaque formation developed after repeated oral application of *P. gingivalis*[10], suggesting that both infectious and inflammatory mechanisms are plausible in the link between PD and neurodegenerative processes.

2. Systemic inflammation

Periodontitis is linked with several systemic diseases and conditions like cardiovascular diseases (atherosclerosis), obesity, respiratory infections, adverse pregnancy outcome, rheumatoid arthritis, and diabetes mellitus[11.12] as well as gut microbiota dysbiosis. Moreover, hyperactivated systemic inflammatory response, during periodontal disease, may in turn contribute with neuroinflammation and AD.[13] Thus, periodontitis is considered as a real additional source of oral bacterial pathogens and bacterial molecules like LPS, flagellin, peptidoglycan or DNA, and pro-inflammatory molecules, and readily modifiable risk factor for AD.[14,15] Periodontal inflammation can expand causing changes in the intestinal microflora and subsequently exacerbate host's systemic inflammatory response. Dysbiotic intestinal microbiome, often accompanied by fungi and parasitic worms, jointly produces and releases onto the surface of the intestinal mucosa a multi-component mixture of secretion substances and microbial metabolic products containing a large group of compounds significantly increasing the innate immune function, elevating production of cytokines and inflammatory mediators. These compounds further increase the permeability of the intestinal mucosa and the permeability of the blood-brain barrier, significantly intensify inflammatory reactions, and induce amyloid aggregation and neuroinflammation.

3. Molecular Mimicry

In general, periodontal bacteria can actively modulate the innate immune response and their products can provoke the inflammatory response, whether this is at oral or extra-oral sites. Aberrant immunity represents a general explanation for the adverse effects of periodontitis on systemic diseases, but perhaps the most robust evidence for a direct role of periodontal bacteria is the ability of *P. gingivalis* to promote neuroinflammation via molecular mimicry. Notably, citrullinated proteins are present in PD gingival tissue (GT), and increased PAD activity has been detected in PD gingival crevicular fluid.[16,17] Moreover, *Porphyromonas gingivalis* (*Pg*), a key pathogen driving PD,[18] is the only pathogen known to express a PAD enzyme (*P*.PAD),[19] capable of citrullinating bacterial as well as host proteins, including the RA candidate autoantigens fibrinogen, α-enolase, vimentin and histones [21,23]. A number of reports also suggest *P*.PAD can auto citrullinate [20, 21,22,23]. With citrullinated proteins exposed in the bacteria-rich inflamed gingiva, we hypothesize that this milieu may facilitate break of tolerance and production of ACPA,[24] possibly by mechanisms of molecular mimicry. Increased protein citrullination (PC) and dysregulated protein arginine deiminase (PAD) activity have been observed in several

neurodegenerative diseases. *gingivalis*-mediated inflammasome activity and neuroinflammation have been shown to be activated in AD brains.[25] Recent research has revealed the important correlation between mitochondrial dysfunction in the pathophysiology of neurodegenerative diseases.[26,27] The role of mitochondria during neuroinflammation and neurodegeneration has unravelled mitochondria-related immunometabolism processes that may serve as promising therapeutic targets for AD and ADRD.[28,29] *P. gingivalis*-LPS can induce neuroinflammation and lead to the progression of neuropathological changes. However, the definite mechanisms of *P. gingivalis*-LPS-mediated mitochondrial dysfunction remain under-explored.

4. Amyloidogenesis

Until very recently, the amyloid-beta hypothesis as the principal driver for Alzheimer's disease has dominated this research field, while other hypotheses were relegated to secondary areas of research.). And in the past several years, several published expert opinion articles have stressed interactions between all three of these schools of thought. As an extension of correlation studies between periodontal disease and Alzheimer's disease, using special imaging techniques to visualize amyloid-beta deposits in the brain, higher levels were observed in patients with clinical attachment loss from periodontal disease, particularly in those patients who also carried the APOE 4 genotype, the most common genetic marker for Alzheimer's disease risk.[30] In addition, in patients with early stages of Alzheimer's disease, changes in serum amyloid-beta levels have been reported to be positively associated with clinical periodontal disease.[31]

IMPLICATIONS AND FUTURE DIRECTIONS

Understanding the link between periodontitis and neuroinflammation has significant implications for the management of neurodegenerative diseases. If periodontitis is confirmed as a modifiable risk factor, it could lead to new preventive and therapeutic strategies including:

1. Preventive oral health Care: Promoting oral hygiene and regular dental checkups could potentially reduce the risk of neuroinflammatory diseases.

2. Integrated Healthcare approaches: collaborative care models involving both dental and medical professionals could enhance early detection and management of periodontitis in patients at a risk for neurodegenerative diseases.

3. Targeted therapies: Research into the specific mechanisms linking periodontitis and neuroinflammation may identify novel therapeutic targets such as anti-inflammatory treatments, vaccine against periodontal pathogens and s systemic administration of gingipain inhibitors may be one of several approaches to address the upstream events and risks of Alzheimer's disease before the clinical appearance of declines in cognitive and motor function. Such targeted long-term approaches to *P. gingivalis* and periodontal treatment, in general, can be considered part of a personalized medicine/personalized dentistry approach that would combine targeted approaches to bacteria with drugs to reduce amyloid, reduce the inflammatory response in the mouth and the brain, lifestyle modifications, and assessment and modification of other risk.

CONCLUSIONS

The growing body of literature suggests a significant association between periodontal disease and neuroinflammation, with potential implications for the understanding and management of neurodegenerative diseases. While the evidence is compelling further research is needed to establish causality and to explore the underlying mechanisms in greater detail. New therapeutic strategies could focus on examining the potential neuroprotective activity of disease- preventing and modifying actions of periodontal disease treatments in the prevention and progression of neurodegenerative diseases before development of overt dementia. By advancing our knowledge in this area, we may uncover new opportunities for preventing and treating debilitating conditions like Alzheimer's and Parkinson's disease through improved oral care.

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