Literature Review

MedInform

DOI: 10.18044/MEDINFORM.2024112.1933

ISSUE 2, 2024

Influence of the Red Complex Periodontal Pathogens on the Pathogenetic Mechanisms of Alzheimer's disease: a literature review

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Abstract

In recent years, there has been growing interest in the systemic implications of periodontal disease and its association with various systemic disorders. Among these is the potential influence of periodontitis on Alzheimer's disease, the leading cause of dementia in the elderly population worldwide.

Periodontal pathogens, grouped into the Socransky complexes, have been the focus of extensive studies over recent decades. The bacteria of the red complex (P. gingivalis, T. denticola, and T. forsythia) exhibit cooperative behavior within the dental biofilm and are directly associated with the progression of periodontal destruction. Concurrently, three key pathogenetic mechanisms of Alzheimer's disease are under active investigation: beta-amyloid accumulation in the brain, tau hyperphosphorylation and microglial activation.

Recent studies indicate the potential for bacteria within the red complex to impact all of these mechanisms. Although the existence of a direct causal link between periodontal disease and Alzheimer's disease remains a topic of debate, growing evidence suggests a correlation between these diseases.

The objective of this review is to present the existing scientific literature on the impact of each of the red complex pathogens on the pathogenetic mechanisms of Alzheimer's disease.

Keywords: Alzheimer's disease, periodontal pathogens, periodontitis

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that results in cognitive dysfunction, memory loss, depression, anxiety, and ultimately leading to severely decreased quality of life (1). The disease was first described in the early 20th century by Alois Alzheimer and has since become a leading cause of dementia in the elderly population. In the coming decades, the number of AD sufferers is expected to increase significantly, with projections suggesting the number in USA may reach 16 million by mid-century (2). While

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the pathogenesis of AD remains controversial in some aspects, three main pathological features of the disease have been identified: the accumulation of beta-amyloid plaques in the hippocampus and cortex; hyperphosphorylation of tau protein and formation of neurofibrillary tangles (NFTs); microglial activation and neuroinflammation. These mechanisms do not act in isolation, but rather develop simultaneously, with complex interrelationships (3).
Periodontitis is a chronic inflammatory immunomodulated disease, associated with a specific bacterial flora. It is postulated that microbial biofilm accumulation, involving multiple species, triggers a cascade of immune processes, which ultimately lead to an aberrant immune response and destruction of the tooth-supporting tissues. The key periodontal pathogens that emerge in the later stages of biofilm formation belong to the Socransky red complex, which includes the gram-negative anaerobes Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia (4). The presence of bacterial invasion and an altered host immune response have been associated with several systemic disorders, including cardiovascular, respiratory, endocrine and neurodegenerative diseases, such as Alzheimer's disease (5).

The existence of a bidirectional relationship between Alzheimer's disease and periodontitis has been repeatedly discussed in the literature (6). However, the question of whether there is a direct causal link between them remains a topic of controversy. The aim of this review is to present recent information on several key mechanisms that are likely to link AD to PD.

Review Results

1. Pathogenetic mechanisms of AD

1.1. Amyloid-β plaque depositions

Beta-amyloid (Aβ) is a relatively well-known misfolded peptide whose accumulations in the hippocampus and cerebral cortex, known as "senile plaques", are a prominent feature of Alzheimer's disease. Despite its notorious reputation, Aβ plays a role in several physiological processes within the brain, such as antimicrobial activity, regulation of synaptic transmission in the hippocampus, and maintenance of the blood-brain barrier (7). When secreted into the extracellular space of the brain, it can be cleared by circulation and cerebrospinal fluid (CSF). Aβ is typically produced by astrocytes and neurons, resulting in the formation of spherical protein structures comprising 38-42 amino acids. In cognitively healthy individuals, the most prevalent isoform is Aβ1-40, with Aβ1-42 being the second most common. Aβ1-40 originates from the vascular endothelium, whereas Aβ1-42 constitutes the senile plaques (8). Some mechanisms lead to a notable increase in Aβ1-42 production, resulting in a shift in the Aβ1-40/Aβ1-42 ratio, which plays a role in the pathogenesis of late-onset Alzheimer's disease.
Studies suggest a correlation between serum Aβ levels and the presence of periodontitis in elderly patients. Those with severe periodontitis demonstrate elevated levels of Aβ1-42 and a higher Aβ1-42:Aβ1-40 ratio. Moreover, a direct correlation was identified between Aβ accumulations and cognitive impairment in patients with severe periodontitis (8).

1.2. Hyperphosphorylation of tau-protein

Tau belongs to the group of proteins associated with the microtubules of the neuronal cytoskeleton. Its main biological role is to stabilize microtubules, but it is also involved in the neurogenesis and other cellular processes. Diseases associated with tau dysfunction are known as tauopathies (9,10). The most commonly described post-translational modification of tau is phosphorylation. An abnormal course of this process leads to the formation of hyperphosphorylated tau, a change in its neuronal localization and, as a result,

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destabilization of microtubules and intracellular aggregation of the protein. The aggregates thus formed are known as neurofibrillary tangles (NFTs), which are a defining feature of AD (11).

1.3. Microglial activation

The role of resident cells of the innate immune system in the brain is played by microglial cells. Their physiological role is related to brain development and clearance of infectious agents, toxins and debris. Some authors divide microglia into M1-type (pro-inflammatory) and M2-type (neuroprotective). However, more recent studies have identified different subtypes such as so-called disease-associated microglia (DAM) (3). Peripheral immune cells also appear to be involved in the neuroinflammatory process in AD, as dysfunction of the blood-brain barrier and the choroid plexus, leading to migration of immune cells into the central nervous system (CNS) (3).

The process of microglial activation probably precedes the manifestation of the disease. The role of the so-called DAM appears to be twofold: in the early stages it has a neuroprotective effect by clearing Aß plaques, but as the disease progresses it maintains the inflammation that leads to neurodegeneration (3). Activated microglial cells release pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and CRP. This leads to a significant increase in the neurotoxic action of Aβ (1).

2. Periodontal pathogens and their influence

Many studies hypothesize that periodontitis-associated bacteria appear to play a pivotal role in the induction of neuroinflammation. Furthermore, the prevailing neuropathological characteristics of AD are likely to be linked with chronic inflammation and microglial activation (3,12). Several studies have demonstrated that periodontal pathogens may access the CNS via the systemic circulation and the neuronal transport pathway to the trigeminal ganglion and the brain (12).

2.1. Porphyromonas gingivalis

P. gingivalis (P.g.) is a well studied periodontal pathogen. It is a Gram-negative, asaccharolytic, anaerobic species that has several virulence factors: lipopolysaccharides (LPS); cysteine proteases, known as gingipains; other enzymes; metabolites; outer membrane vesicles (OMVs), containing LPS, gingipains or other enzymes (12,13).

Experiments conducted on animal models of P. gingivalis-LPS induced periodontitis demonstrated an acute elevation in Aβ1-40 levels during the initial two-week period, followed by a gradual decline and a subsequent significant increase in Aβ1-42 levels. A strong positive correlation was observed between alveolar bone loss and serum Aβ levels (14).

A further study has demonstrated that LPSs delivered to the gingival sulcus induce neuroinflammation, potentially via the toll-like receptor 4 (TLR4)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway, which may result in cognitive impairment. LPSs stimulated microglia in the cortex and hippocampus of the examined mice (15). In the brains of mice orally infected with P. gingivalis, a significant increase in Aβ1-42 levels was observed, which is likely associated with the antibacterial action of the latter (12).

Other research teams have hypothesised that gingipains play a crucial role in the pathogenesis of AD. The presence of P. gingivalis DNA and gingipain antibodies has been identified in the brains and the CSF of patients diagnosed with AD. Additionally, antibodies have been detected in individuals exhibiting pathological processes characteristic of AD, yet without the presence of dementia. Additionally, gingipains have been demonstrated to possess the capacity to fragment tau protein by activating caspase-3, which can both phosphorylate and cleave tau. Administration of gingipain inhibitors has been reported to positively affect the course of the disease (12).

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2.2. Treponema denticola

T. denticola (T.d.) is a gram-negative, anaerobic spirochete (4). Spirochetes are slow-growing bacteria with marked neurotropism, which suggests the possibility of oral treponemes and T. denticola in particular to enter the CNS (16).

There are suggestions that T.d. may access the brain due to the existence of a direct connection between it and periodontal free nerve endings and proprioceptors. T.d. may reach the brain via the trigeminal nerve, where it could remain latent in the trigeminal ganglion (16).

Alternatively, it may reach the nucleus mesencephalicus n. trigemini and subsequently the associated locus coeruleus, the noradrenaline-producing nucleus in the pons that is involved in certain neurodegenerative diseases such as Alzheimer's disease (16). The presence of oral treponemes in the brains of AD patients is significantly more prevalent than in healthy controls (17).

Furthermore, a greater diversity of oral Treponema species is observed in AD patients compared to healthy controls with the presence of Treponema (17).

Other recent studies have demonstrated that a laboratory oral infection of mice with T. denticola results in tau protein hyperphosphorylation through the activation of neuroinflammation in the hippocampus (10) and activation of β-secretase and γ-secretase. This has been shown to lead to an increase in the production and hippocampal deposition of Aβ1-40 and Aβ1-42 from the amyloid precursor protein (APP) (18).

2.3. Tannerella forsythia

Tannerella forsythia (T.F., formerly Bacteroides forsythus) is an anaerobic, Gram-negative microorganism (4). In comparison to the other microorganisms of the red complex that have already been described, the potential role of T.f. in the development of AD is less understood.

Some studies have indicated that T.f. affects T-cell immune response and alters kynurenine metabolism (19).

Conclusion

The potential link between periodontitis and Alzheimer's disease, particularly through the involvement of red complex pathogens, offers a new perspective on the broader systemic impact of periodontal infections. Future research should aim to clarify the causal mechanisms between periodontitis and Alzheimer's and explore the therapeutic potential of periodontal treatment as a preventative strategy for Alzheimer's disease or provide diagnostic markers for its early detection.

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DOI: 10.18044/MEDINFORM.2024112.1933 ISSUE 2, 2024

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Georgiev P, Dimitrov D, Influence of the Red Complex Periodontal Pathogens on the Pathogenetic Mechanisms of Alzheimer's disease: a literature review, Medinform 2024; 11(2):1933-1938.