Review Article

Porphyromonas gingivalis and Alzheimer's Disease: A Contemporary Review

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Abstract Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline and neuropathological hallmarks such as amyloid beta plaques and neurofibrillary tangles. In recent years, chronic infections have been proposed as potential contributors to Alzheimer's disease pathogenesis. Periodontitis, a common chronic inflammatory condition, is predominantly associated with Porphyromonas gingivalis, a gram-negative anaerobic bacterium. Emerging evidence suggests that P. gingivalis may influence Alzheimer's disease development through systemic inflammation, blood brain barrier disruption, and direct neurotoxic effects of its virulence factors. This review summarizes current evidence from experimental and clinical studies linking P. gingivalis with Alzheimer's disease and discusses possible mechanisms and implications for future research.

Keywords: Alzheimer's disease; Cytokines; Gingipains; Neurodegeneration; Porphyromonas gingivalis

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INTRODUCTION

Alzheimer's disease is the most prevalent cause of dementia worldwide and represents a major public health concern. Currently around 55million people worldwide have dementia which is expected to rise to 78 million by 2030.[1] It is characterized by progressive memory loss, impaired cognition, and behavioral changes, with pathological hallmarks including extracellular amyloid beta deposition and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. While genetic and metabolic factors play a central role in disease development, increasing attention has been directed toward chronic inflammation and infectious agents as contributors to neurodegeneration.[2] Periodontitis is a chronic inflammatory disease of the supporting tissues of the teeth and is highly prevalent in adults and the elderly. Porphyromonas gingivalis is considered a keystone pathogen in periodontitis due to its ability to dysregulate host immune responses and promote microbial dysbiosis.[3] The systemic dissemination of periodontal pathogens and their products have been implicated in several systemic diseases, prompting investigation into their potential role in neurodegenerative disorders such as Alzheimer's disease.

Biological Characteristics of Porphyromonas gingivalis

Porphyromonas gingivalis possesses a range of virulence factors that facilitate persistence and tissue destruction. These include lipopolysaccharide, fimbriae, gingipains, and outer membrane vesicles. Gingipains are cysteine proteases that degrade host proteins, interfere with immune signaling, and promote chronic inflammation. Outer membrane vesicles act as carriers for these virulence factors, enabling their dissemination beyond the oral cavity.[4]

Disruption of blood brain barrier

The blood brain barrier is essential for maintaining central nervous system homeostasis. Experimental studies have demonstrated that bacteremia induced by P. gingivalis can compromise blood brain barrier integrity by altering endothelial tight junction proteins and increasing transcellular permeability. Gingipains and bacterial lipopolysaccharide have been shown to disrupt endothelial function, potentially allowing bacterial components and inflammatory mediators to access brain tissue.[5]

Systemic and Neuroinflammation

Chronic periodontal infection results in sustained systemic inflammation, characterized by elevated circulating levels of proinflammatory cytokines such as interleukin 1 beta, interleukin 6, and tumor necrosis factor alpha. These mediators may cross the blood brain barrier or activate endothelial and microglial cells, leading to neuroinflammation. Activated microglia contribute to neuronal damage, synaptic loss, and progression of Alzheimer's pathology.[3]

Amyloid Beta Deposition and Tau Pathology

Accumulating evidence suggests that P. gingivalis may influence key molecular events involved in Alzheimer's disease. Gingipains have been detected in post mortem brain tissue of individuals with Alzheimer's disease, and their levels correlate with tau and ubiquitin pathology.[6] Experimental animal models demonstrate that oral infection with P. gingivalis results in increased amyloid beta 1–42 production and deposition within the brain. In addition, P. gingivalis components have been shown to activate beta secretase and kinases involved in tau phosphorylation, thereby promoting the formation of neurofibrillary tangles.[7] These findings suggest a mechanistic link between periodontal infection and classical Alzheimer's disease pathology.[8]

Role of Outer Membrane Vesicles

Outer membrane vesicles released by P. gingivalis are capable of transporting gingipains and lipopolysaccharide systemically. Experimental evidence indicates that these vesicles may cross the blood brain barrier and induce localized inflammation within neural tissue. Their ability to act independently of live bacteria highlights an indirect yet biologically plausible pathway by which periodontal infection may influence neurodegeneration.[9] When the observed teeth express the trait, it was marked and graded among 1 to 7 scores based on degree of expression. When observed teeth do not express the trait it was scored as Type. The teeth were examined by two observers independently to eliminate intra-observer variation in interpretation.

Clinical and Epidemiological Evidence

Several clinical studies have identified P. gingivalis DNA, lipopolysaccharide, and gingipains in the brains and cerebrospinal fluid of patients diagnosed with Alzheimer's disease. These findings provide direct evidence of exposure of brain tissue to periodontal pathogens or their products.[10] Systematic reviews and observational studies have reported associations between periodontitis severity and cognitive decline. There is a measurable progression towards development of Alzheimer's within 1-5yrs. The toxin gingipains produced by P gingivalis can be found in the brain and cerebrospinal fluid of AD. A hallmark of Alzheimer's is elevated cytokines seen in periodontitis associated with neuro inflammation. History of severe periodontal disease increases the risk of Alzheimer's by 5 folds.[11] However, these findings remain associative, and causality has not been definitively established due to potential confounding factors such as age, genetics, and lifestyle.[12,13]

Limitations and Research Gaps

Despite strong biological plausibility, current evidence does not conclusively establish a causal relationship between P. gingivalis infection and Alzheimer's disease. Many studies are cross sectional or experimental in nature, limiting their applicability to human disease progression. Detection of bacterial DNA or proteins does not necessarily indicate active infection within the brain. Longitudinal studies and interventional trials evaluating the effect of periodontal therapy on cognitive outcomes are required.

CONCLUSION

Current evidence suggests a biologically plausible association between chronic Porphyromonas gingivalis infection and Alzheimer's disease.

Mechanisms involving blood brain barrier disruption, systemic and neuroinflammation, and direct modulation of amyloid and tau pathology have been demonstrated in experimental models and supported by clinical observations.

Although causality remains unproven, these findings highlight the importance of periodontal health in systemic disease prevention and warrant further investigation into the role of oral pathogens in neurodegeneration.

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