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Porphyromonas gingivalis and Alzheimer's disease: A narrative review

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Abstract

Objective: The purpose of this review is to address the purported association of periodontitis and the microbial pathogen, *Porphyromonas gingivalis* (*P. gingivalis*), with Alzheimer's disease (AD).

Methods: A scoping search was conducted using terms related to biological plausibility, comorbid associations of periodontitis, *P. gingivalis* and AD. Ovid Medline and PubMed were used to obtain abstracts which, in turn, were used to select papers for further evaluation. Special attention was given to articles addressing confounders, risk factors, and causality. A total of 113 papers from the basic science and medical literature and 48 papers from the dental literature, covering the years 2010 through May 2025 were reviewed.

Results: Evidence exists showing that inflammation associated with periodontitis and *P. gingivalis* infection has implications for brain health. There is evidence to establish biologic plausibility for a microbial role in promoting neuroinflammation and neurodegeneration as seen in AD.

Conclusion: There is evidence that both *P. gingivalis* and periodontitis satisfy the requirements of biological plausibility, have comorbid relationships, and may be risk factors for AD. However, there is insufficient evidence to establish *P. gingivalis* or periodontitis as independent causes of AD.

Keywords: *Porphyromonas gingivalis. Alzheimer's Disease. Chronic periodontitis. Risk factors. Virulence factors.*

Introduction

Severe periodontitis has a high prevalence, affecting 11.2% of the world's population making it the sixth most common human disease[1]. Even in developed countries, such as the United States (U.S.), the prevalence of severe periodontitis can be significant, i.e., 7.8% for adults, age 30 to 79 years[2]. Based on the latest U.S. census data, this prevalence of disease extrapolates to roughly 6.5 million people[3].

A significant body of literature is supportive of independent associations between severe periodontitis and a variety of systemic diseases, such as atherosclerosis[4,5], cardiovascular disease[1,6], stroke[7-10], and Alzheimer's disease[11-14]. Thus, the purpose of the present narrative review is to address the purported association of periodontitis and, more specifically, of *Porphyromonas gingivalis* (*P. gingivalis*), with Alzheimer's disease (AD).

Methods

A scoping search was conducted using terms related to biological plausibility, comorbid associations of both periodontitis and AD, and virulence factors associated with *P. gingivalis*. Ovid Medline, PubMed and the reference sections of published papers were used to obtain abstracts which, in turn, were used to select papers for further evaluation. Special attention was given to articles addressing confounders, risk factors, and causality. A total of 113 papers from the basic science and medical literature, and 48 papers from the dental literature, covering the years 2010 through May 2025, were reviewed.

Relevant terminology

Assessment of the literature pertaining to periodontitis and its association with various systemic diseases requires the reader to differentiate between biologic plausibility, causality, conflation, risk factors, comorbidity, and confounders.

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Biological plausibility involves rational thought in the evaluation of a possible cause-and-effect relationship between a biological factor and a particular disease. Evidence-based criteria for treatment of a disease are ultimately based on biological plausibility, as the concept helps in assessing the strength of evidence and associations observed in epidemiological studies[15,16].

Causality, in simple terms, is the relationship between cause and effect. A more sophisticated definition is that causation refers to a process in which an initial event induces the occurrence of a subsequent event[17]. In the pathobiology realm, causality is difficult to prove[18]. Studies proving causality require significant assumptions, in-depth subject-matter knowledge, precise statistical analysis, and consideration of alternative explanations[19]. Interestingly, in 2017, the World Health Organization proclaimed the term causal association *"is only used if there is no other factor intervening in the processes"*[20]. Any discussion of causality is incomplete without noting the contributions of the Bradford-Hill criteria[21]. The Bradford Hill criteria provide a framework for moving from an observed association to a conclusion of causation. The nine criteria are: strength of association between a risk factor and outcome; consistency of findings; specificity of association, i.e., a one-to-one relationship between risk factor and outcome; temporality sequence or exposure must precede outcome; a dose-response gradient; biologic plausibility or a feasible biologic mechanism; coherence between epidemiological and laboratory findings; experimental evidence; and similarities between the observed association and any other associations or an analogous event[21].

Conflation can be defined as the erroneous fusion or blending of two similar but disparate concepts into one, which in medical research is often referred to as "being equal to"[22]. Conflation is more commonly noted in observational studies, and generally results in biased estimates or conclusions[22].

With respect to disease, risk factors are defined as a characteristics that are associated with an increased prevalence of a disease[23]. In the case of periodontal disease, most risk factors are modifiable and include poor oral hygiene, tobacco use, alcohol consumption, psychological stress, depression, osteoporosis, and metabolic syndrome[24,25]. Examples of non-modifiable risk factors are genetic susceptibility, and age[23-25].

Comorbidity simply refers to the simultaneous presence of two or more medical conditions[26,27]. As previously noted, there are associations between periodontitis and a variety of comorbid systemic diseases. For many of these associations, shared inflammatory pathways appear to be the common contributing factor[27].

In research designed to determine a potential cause-and-effect relationship, a confounding variable is an unmeasured third factor that may influence either the cause or the effect, or both. It's important to consider potential confounding variables and account for them in clinical trials, to ensure that treatment outcomes are valid. Unidentified or unaccounted for confounders can introduce bias and/or cause an invalid interpretation of results. In epidemiological studies of periodontal disease, it appears that age, gender and race are the most frequently included confounders[28,29].

Epidemiology of Alzheimer's disease

AD is the most common form of dementia and one of the leading sources of morbidity and mortality in the elderly. The incidence and prevalence of AD is reportedly increasing but likely underestimated, due to underdiagnosis and misdiagnosis[30,31]. The global prevalence of dementia was estimated to be 57.4 (95% uncertainty interval 50.4 – 65.1) million in 2019, and was predicted to be more than doubled over the next 30 years to 2050[31]. Li et al.[32] have noted that between the years 1990 and 2019, the incidence and prevalence of AD and other dementias increased by 147.95% and 160.84%, respectively. The authors also reported that smoking was a major risk factor in men, while obesity was the major risk factor for women[32].

Etiology of Alzheimer's disease

Despite improved understanding of the pathogenesis of AD, the etiology remains unclear. Current treatment protocols do not prevent the disease and only marginally impact progression[33-35]. AD may be considered a multifactorial disease with multiple risk factors, such as increasing age, genetics, vascular disease, head trauma, environmental factors, and infection[33,35,36].

There is ample evidence that pathogens within the oral microbiome can be a factor in cerebrovascular and neurodegenerative pathology[37-40]. Invasive pathogenic bacteria can exhibit a variety of immunomodulatory functions, including the activation of systemic pro-inflammatory cytokines[41]. Interestingly, amyloid-β has been shown to express antiviral and antimicrobial activity, a characteristic that may help explain its accumulation in brain parenchymal tissues that have experienced bacterial infection[36,42-44].

The neuropathologic changes in AD include disseminated neuritic plaques with discernible extracellular beta-amyloid deposition, dystrophic neurites, and neurofibrillary tangles that include intracellular accumulation of tau protein[45,46]. Additionally, these features are associated with activated astrocytes and the proliferation and activation of microglial cells. Microglia cells are the resident macrophages of the central nervous system and function in much the same manner as their more peripheral counterparts[47]. Both astrocytes and activated microglia cells contribute to neuroinflammation

and neurodegeneration phenomena[48-52]. Indeed, a recent study has reported that microglia cells in the brains of people with Alzheimer's disease were more likely to be in a pre-inflammatory state and more likely to produce inflammatory mediators that damage brain cells[53].

Periodontitis and Alzheimer's disease

Stage III and IV periodontitis[54] and AD are relatively common comorbid conditions in the elderly[2,14,26,55-58]. Several papers have noted that periodontitis is associated with increased severity of dementia and a more rapid cognitive decline in AD[55-60]. Interestingly, as noted previously, the number of U.S. adults between the ages of 30 and 75 years afflicted with severe periodontitis is reported at 7.8%, or approximately 6.5 million adults[2]. The Alzheimer's Association reports that 6.9 million U.S. adults, age ≥ 65 years, have AD, which extrapolates to roughly 7% of the population[61].

Porphyromonas gingivalis

Contemporary opinion holds that periodontitis is an inflammatory disease involving a community of bacteria in which various communal species are in a dysbiotic state[62-65]. The dysbiosis, when combined with the host immune response, favors establishment of chronic inflammation in the periodontal tissues[65,66]. If not treated, or if inadequately treated, the host inflammatory response persists and initiates a degradation of the tooth-supporting tissues and, in advanced stages, may lead to loss of teeth[67]. The biofilm associated with periodontitis exhibits a wonderfully complex microbial community (Fig. 1), which is predominately anaerobic, Gram-negative, and proteolytic. An often cited offender and initiator of dysbiosis in the biofilm associated with periodontitis is *P. gingivalis*[62,66,67].

P. gingivalis is a short rod-shaped, Gram negative, anaerobic, asaccharolytic bacterium that forms black-brown colonies on enriched blood agar. *P. gingivalis* has been detected in ≈ 86% of subgingival plaque samples from periodontitis patients[68]. The microbe is a critical component in the pathogenesis and progression of periodontitis. Indeed, it has been characterized as a 'keystone' pathogen whose association with other bacteria can dictate the conversion of a biofilm composed of commensal microorganisms into a complex dysbiotic biofilm that interacts in an adversarial manner with the host immune system, which, in turn, results in a tissue destructive inflammatory response, i.e., periodontitis[68-71].

P. gingivalis possesses a number of virulence factors that help define its' pathogeny[68,72,73]. For example, the virulence factors of *P. gingivalis* play important roles in microbial coaggregation, biofilm formation, oral biofilm dysbiosis, and the pathogenesis of periodontitis. The primary virulence factors of *P. gingivalis* include:

1) Lipopolysaccharide (LPS), a major component of the outer cell membrane, with a well-established ability to cause inflammation[74,75].

2) Fimbriae, which are filamentous surface appendages, extending from the outer cell membrane (Fig. 2), that function in bacterial motility, adhesion to host cells, and facilitate invasion into host cells and tissues[76,77].

3) The capsule, which, in the case of *P. gingivalis,* serves multiple functions. For example, the capsule protects against phagocytosis by host leukocytes, facilitates co-aggregation with other bacteria in the assembly of a biofilm mass, and can induce host immune responses, such as cytokine expression by dendritic cells and chemokine expression by macrophages[67,73,78,79].

4) Outer membrane vesicles (OMVs), produced via blebbing of prokaryotic (bacteria) membranes (Fig. 2), have frequently been identified as cell debris or artifacts induced

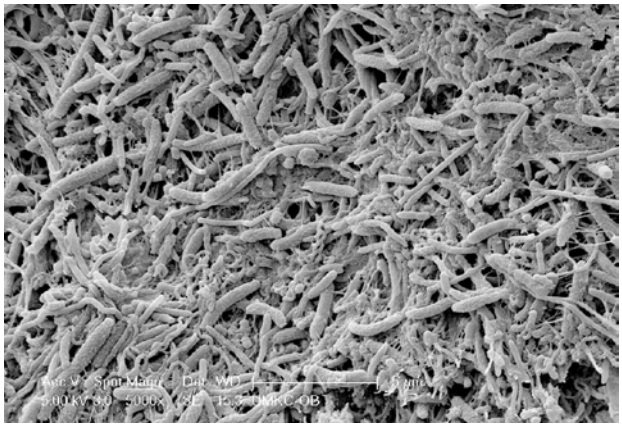

Figure 1. Scanning electron microscopy view of a complex, mature biofilm on the root of a tooth extracted due to advanced periodontitis (stage IV). Identifiable morphotypes of bacteria include long, short and curved rods of various diameters, fusiforms, spirochetes, and cocci. Original magnification of 5,000x. Bar = 5 µm.

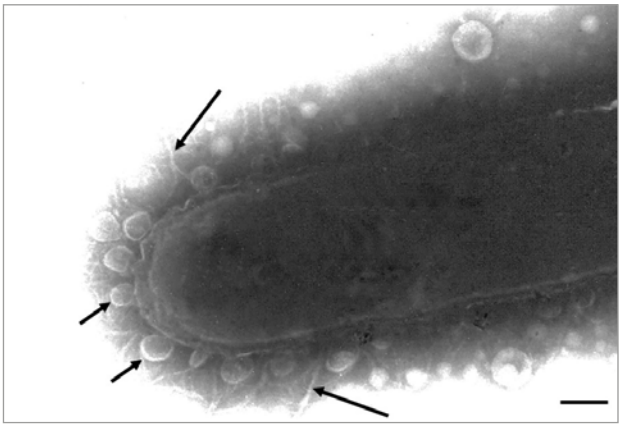

Figure 2. Transmission electron microscopy view of unsectioned, negative-stained P. gingivalis (ATCC 33277), demonstrating outer membrane vesicles (short arrow) and fimbria (long arrow). Stained with 2% potassium phosphotungstate. Original magnification of 5,000x. Bar = 0.05 µm.

by processing for electron microscopy. However, research on OMVs has shown them to be involved in the transport of molecular effectors, cell-cell interactions, nutrients, host cell immune modulation and dysregulation, bacterial aggregation, and biofilm formation[80]. OMVs of *P. gingivalis* are reported to contain a toxic complex of LPS, proteolytic enzymes, gingipain, and pathogen-derived DNA and RNA[81-83].

5) Gingipain is a family of cysteine proteinases that, depending on the strain of *P. gingivalis,* can either be anchored on the bacterial membrane or released via OMVs into the extracellular environment[84]. Gingipains are potent virulence factors and account for 85% of extracellular proteolytic activity of *P gingivalis*. Gingipains dysregulate the host immune response and promote inflammation, inactivation of immune inhibitors, and cleavage of immune cell receptors[85]. In addition, gingipains can degrade macrophage CD14 and thereby avoid phagocytosis by host leukocytes and induce loss of viability in host fibroblasts and endothelial cells[86,87]. Gingipains have also been implicated in the activation of *P. gingivalis* collagenase and degradation of type I collagen[88]. *In vitro* studies have shown *P. gingivalis* capable of increasing collagen degradation through a combination of increased activation of human gingival fibroblast matrix metalloproteinase (MMP) and decreasing levels of tissue inhibitor of metalloproteinase-1 (TIMP-1)[89,90]. *P. gingivalis* also up-regulates mRNA expression of multiple MMPs and TIMPs[89].

6) *Porphyromonas gingivalis* can invade epithelial cells and other periodontal tissue cells, and thus evade host antimicrobial defenses. In doing so, the microbe utilizes a variety of virulence factors that cause deregulation of the host innate immune and inflammatory responses. For example, *P. gingivalis* has been shown to subvert the response of neutrophils, the most efficient phagocyte in the inflammatory process, by utilizing gingipains, serine proteases, lipid phosphatases, lipopolysaccharide, and fimbriae[85,91]. Disruption of the host immune response allows for opportunistic tissue invasion and promotes inflammation and tissue damage[73].

Porphyromonas gingivalis and Alzheimer's disease

Even a cursory review of current literature reveals that inflammation is a major component in the pathogenesis of neurodegeneration seen in AD and possibly other forms of dementia. The role of neuroinflammation in AD raises the question of whether chronic inflammatory conditions or inflammation promoting factors peripheral to the central nervous system (CNS) contribute to the CNS inflammatory burden.

The role attributed to *P. gingivalis* in periodontitis almost makes it a surrogate microbe for the disease. Clearly *P. gingivalis* is not a singular microbial pathogen in the cause and progression of periodontitis. Certainly, other pathogens and their panel of virulence factors play critical roles in periodontitis and, indirectly, in the promotion of systemic inflammation, and potentially in AD[92-95]. Multiple studies have established that elevated antibodies to periodontal bacteria are associated with an increased systemic pro-inflammatory state; and that increased levels of pro-inflammatory cytokines have been associated with an increased rate of cognitive decline in Alzheimer's disease[55,57,96-98].

As previously noted, *P. gingivalis* is just one of several bacterial pathogens that have been associated with AD in the research literature. However, in terms of pathogenicity, prominent role in severe periodontitis, generation of peripheral inflammation, and ability to invade the CNS, *P. gingivalis* has become the target microbe for studies designed to determine the biological plausibility and potential role as risk factors of microbes in AD. Consider, for example, depending on serotype, that *P. gingivalis* can be capsulated or non-capsulated, and both are highly pathogenic. The non-capsulated *P. gingivalis* can generate neurodegenerative AD-like changes *in vitro*; and a capsulated *P. gingivalis* has been shown to produce the cardinal hallmark lesions of AD in an animal model and *in vitro*[99,100]. All *P. gingivalis* serotypes express proteases that enable cleavage of the precursor of amyloid- and tau protein, resulting in the formation of amyloid- and neurofibrillary tangles. Tau is a substrate for gingipains that cleave tau into various peptides. *P. gingivalis* related inflammation has metabolic implications for brain health, as the microbe has been isolated from both atherosclerotic plaque[101] and the brains of AD patients[102-106]. The finding of microbes in brain tissue verifies the invasiveness of the organisms and supports the hypothesis for a microbial role in promoting neuroinflammation and neurodegeneration as seen in AD[107-111].

The pathways for microbial access to the brain include, among several, a damaged blood-brain barrier or through a nerve trunk[19,107]. *P. gingivalis* can trigger both peripheral and cerebral immune responses[108] and, when combined with defective susceptibility genes (such as apolipoprotein E4 and complement receptor 1), can prime microglial cells into the pro-inflammatory phenotype[112] often associated with AD.

When the aggregate of published evidence is evaluated, there is a compelling argument supporting the biological plausibility for *P. gingivalis* as a comorbidity or conceivably a risk factor in AD pathophysiology (Fig. 3). However, there is insufficient evidence indicating a causal role for severe periodontitis or *P. gingivalis* infection. Clearly, there is no universally accepted answer to the question: Does improvement in periodontal health lower the risk of developing Alzheimer's disease?

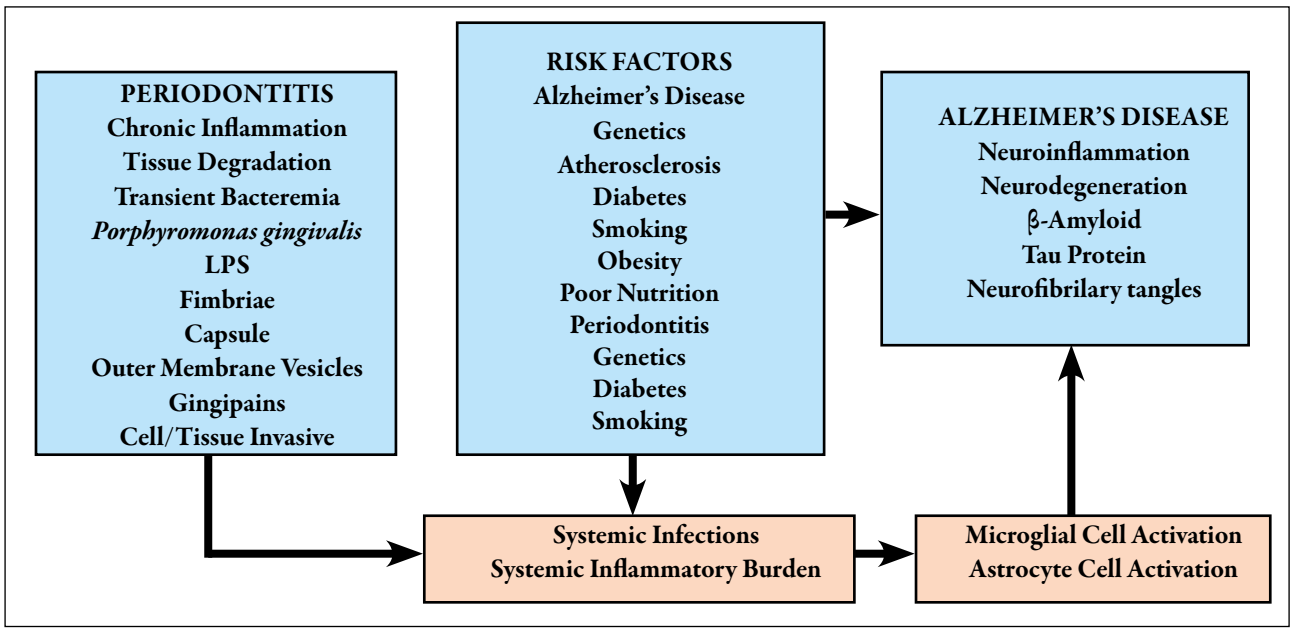

Figure 3. Biological plausibility of the relationship between periodontitis and Alzheimer's disease.

Caveat

To paraphrase Abt et al.[113], when confronted with numerous clinical studies, all reaching the conclusion that periodontitis is 'associated' with AD, how does one judge the importance of such studies? The studies generally use similar designs, share similar limitations and reach similar conclusions. The clinician must be aware of comorbid conditions, confounding factors, and conflation in such studies. And most importantly, the concept that association with a specific disease or a correlational finding does not mean causality[114].

Conclusions

Although there is no evidence establishing periodontitis or *P. gingivalis* as causative of AD, inflammation is an important host response in the comorbid conditions of periodontitis and Alzheimer's disease (AD). Further, there is evidence that both *P. gingivalis* and periodontitis may be risk factors for AD. Given the role of *P. gingivalis* in stages III and IV periodontitis and the role of periodontitis as a comorbid condition with AD, it seems reasonable that physicians should include a visual examination of the teeth and gingivae as part of every patient's physical assessment, and that dentists and dental hygienists should conduct a complete periodontal examination when providing routine patient care[115,116]. To do less is a disservice to the patient.

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Conception or design of the study: CMC.

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Writing the article: CMC, DES.

Critical revision of the article: CMC, DES, P-CL, KMS, SRM.

Final approval of the article: CMC, DES, P-CL, KMS, SRM.

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