Alzheimer’s disease and periodontitis – an elusive link

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Summary

Alzheimer’s disease is the preeminent cause and commonest form of dementia. It is clinically characterized by a progressive descent in the cognitive function, which commences with deterioration in memory. The exact etiology and pathophysiologic mechanism of Alzheimer’s disease is still not fully understood. However, it is hypothesized that neuroinflammation plays a critical role in the pathogenesis of Alzheimer’s disease. Alzheimer’s disease is marked by salient inflammatory features, characterized by microglial activation and escalation in the levels of pro-inflammatory cytokines in the affected regions. Studies have suggested a probable role of systemic infection conducing to inflammatory status of the central nervous system. Periodontitis is common oral infection affiliated with gram negative, anaerobic bacteria, capable of orchestrating localized and systemic infections in the subject. Periodontitis is known to elicit a “low grade systemic inflammation” by release of pro-inflammatory cytokines into systemic circulation. This review elucidates the possible role of periodontitis in exacerbating Alzheimer’s disease. Periodontitis may bear the potential to affect the onset and progression of Alzheimer’s disease. Periodontitis shares the two important features of Alzheimer’s disease namely oxidative damage and inflammation, which are exhibited in the brain pathology of Alzheimer’s disease. Periodontitis can be treated and hence it is a modifiable risk factor for Alzheimer’s disease.

Key words: Alzheimer’s disease, periodontitis, cytokines, systemic inflammation, periodontal pathogen.

INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly age group and a major health problem in the geriatric subjects worldwide. The incidence of AD rises significantly with age, reaching almost 50% in subjects aged 85 years. AD is seen as an interaction between genetic and environmental factors. The hallmark of AD is progressive cognitive impairment with impaired judgment and decision making, followed by psycho-behavioral disturbances and language disability. Periodontitis is the most common oral infection afflicting the human race. Prevalent worldwide, periodontitis is the major cause for tooth loss in adults worldwide. The present review elucidates the enigmatic link between AD and periodontitis, showcasing the pathophysiology and possible implications of the association. This review is prepared by screening the PubMed database, utilizing keywords like “Alzheimer’s disease”, “periodontitis”, “cytokines”, “systemic inflammation” and “periodontal pathogen.” Systematic reviews, meta-analysis and original articles pertaining to the subject from 1994 to 2012, were referred. Human and animal studies published in English were considered.

PATHOGENESIS OF ALZHEIMER’S DISEASE

AD is an age associated complex neurodegenerative disorder with multiple etiologies for initiation and progression. However, till date there is no confirmed or accepted model which can provide optimal explanation for the complex pathophysiology of this desolating disorder. The most significant hallmark of this disorder is the formation of extracellular amyloid β-peptide (AβP) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyper-
phosphorylated tau protein, followed by consequent loss of neuronal synapses and neuronal degeneration. This leads to diminution of essential neurotransmitters.3 Enhanced expression of the amyloid precursor protein (APP) gene caused as a result of genetic aberration may be a risk factor for late-onset AD. Apolipoprotein epsilon4 (APOEε4) allele is genetically linked to majority of the AD cases.4 AbβP, the main component of amyloid plaques is derived from APP by proteolytic cleavage. Studies corroborate the hypothesis that APP and AbβP are instrumental in the pathogenesis of AD.2 The NFTs are constituted of hyperphosphorylated forms of the microtubule-associated protein tau. The microtubule-associated tau protein is responsible for the stability of microtubules in neurons. Hyperphosphorylated tau is insoluble with low affinity for microtubules, jeopardizing the microtubule stabilization, thus conducing to synaptic dysfunction and neurodegeneration. Hyperphosphorylation of tau takes place as a result of inflammation, oxidative stress, up-regulation of tau kinases and down-regulation of phosphatases.5 However studies have revealed the interplay of other factors apart from the characteristic AbβP plaques and intraneuronal NFTs for the complete evolution of AD.6 AbβP exerts detrimental effects on the neurovascular endothelial cells, either by direct action or causing local inflammation. Inflammation leads to AbβP formation in the cerebral microvasculature and AbβP, in turn, stimulates the release of pro-inflammatory mediators.7 Initially, AD was conceived as a disorder related to the augmentation in the synthesis and decline in the degradation of AbβP. Now, impaired clearance is also stated as a co-factor. This hypothesis has been proposed as the “amyloid cascade hypothesis” of AD, with APP playing a pivotal role.8 In AD, the neuroinflammation is significantly exaggerated. It is hypothesized that neuroinflammation may be a result of pro-inflammatory cytokines, reactive oxygen and nitrogen species, instrumental in activation of microglia and abetting the formation of NFTs.9,10 AbβP plaques in AD affected brains are closely affiliated with reactive astrocytes and activated microglial cells, which exhibit exuberant expression of cytokines and acute-phase proteins.11 Microglia cells are mononuclear phagocytes present in the brain, committed to thwart any noxious injury within the central nervous system and achieve brain homeostasis. In health, microglial cells maintain a neuroprotective function by clearing the AbβP plaques.12

They also express several neurotrophic factors, such as insulin-like growth factor (IGF)-1, brain-derived neurotrophic factor, transforming growth factor-β and nerve growth factor. In states of peripheral or systemic inflammation, the molecular and cellular components extend the inflammatory signals to the brain via different pathways. Under normal conditions, the inflammatory response is suitably regulated to avoid uncontrolled inflammatory damage.13 However, the normal regulatory mechanisms may become deficient with aging and genetic predisposition.14,15 Thus, a sustained inflammatory response persists. During these states, the microglial cells in the brain are programmed to switch their phenotypes to produce neurotoxic substances in event of exposure to the systemic inflammatory signals. Thus, instead of confronting with a protective response to these systemic inflammatory signals an exaggerated response is elicited by the diseased microglia, contributing to the pathogenesis of AD. The “fired up” microglia changes its morphology and releases a number of cell antigens. These are referred to as ‘activated microglia’. Activation of microglia results in expression of various pro-inflammatory factors. The uncontrolled release of these factors can induce neural damage. The microglial function may be likened to a “double-edged sword” being either damaging or protective depending on the context.13,16 Chronic inflammation and cytokine up-regulation conduces to tau hyperphosphorylation in experimental mice model of AD.17 It has been observed that, chronic lipopolysaccharide (LPS)-induced neuroinflammation ensues in the elevated levels of intraneuronal AbβP in transgenic mice. This may contribute to the deterioration of AD affected brain.18,19

**Periodontitis – a Low Grade Systemic Disease**

Periodontitis is a polymicrobial inflammatory disorder of the tooth investing tissues, resulting from microorganisms residing within the dental plaque. Periodontitis is characterized by bleeding and purulent discharge from the gums, progressive deepening of gingival sulcus (referred as pocket formation), oral halitosis, spacing between the teeth and mobility of teeth in advanced stages.20 Dental plaque, the principal cause of periodontitis, exists in the form of biofilm. The gram negative and anaerobic species colonize in the periodontal pocket milieu. The predominant periodontal pathogens involved in periodontitis are Aggregatibacter actinomycetemcomitans (Aa), Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Fusobacterium nucleatum (Fn), Tannerella forsythensis (Tf), Eikenella corrodens (Ec) and Treponema denticola (Td).21,22 The present model to explain the pathogenesis of periodontitis was proposed by Page and Kornman (figure 1).23 The periodontal pathogenic flora releases an array of pro-

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teolytic enzymes, which are implemental in destruction of soft and hard tissues supporting the teeth. The gram negative bacterial LPS also adds to the tissue destruction by amplifying the host response, resulting in the expression of pro-inflammatory factors like interleukin (IL)-1α and -1β, IL-6, tumor necrosis factor (TNF) – α, prostanooids, matrix metalloproteinases (MMP), by the host tissue cells. Host defense cells like neutrophils, monocytes secrete cytokines such as IL-1α and 1β, TNF - α in the diseased periodontal site. These cytokines act as crucial factors in host mediated bone resorption and periodontal tissue destruction. Host response in periodontal disease may act as the diabolical “double-edged sword” leading to self destruction, due to the exaggerated expression of tissue proteolytic enzymes. The ulcerated periodontal pocket lining furnishes a portal access for the bacteria and their noxious products, into the systemic circulation. It is reported that the total surface area of the ulcerated periodontal pocket lining in patient with severe periodontitis is approximately 15-20 cm². In periodontitis, the locally produced cytokines and pro-inflammatory products are actually streamed through the ulcerated periodontal pocket lining, into systemic circulation. This alters the character of periodontitis from a local disease to that of a systemic disorder, capable of sustaining “low grade systemic inflammation.” This low grade inflammation is conceived to perturb the general systemic health and exasperate other systemic disorders. Thus periodontitis can be marked as a “low grade systemic disease”. Studies have isolated a number of systemic inflammatory biomarkers, reiterating a positive association of periodontitis with systemic inflammation. Surrogate markers of host response against periodontal infection like cytokines, chemokines, inflammation markers, anti-phospholipid antibodies, antibodies to periodontal pathogens can be demonstrated in serum.

The concept of “periodontal medicine” associates periodontitis as a risk factor with a large number of systemic disorders. Periodontal inflammation and atherosclerotic cardiovascular diseases (ACD) display a concomitant increase in the levels of inflammatory systemic markers like acute phase reactants, interleukins and TNF-α. Meta-analyses have concluded that subjects with periodontitis are at a serious risk of ACD.

**AD and Periodontitis – A Plausible Link**

The exact mechanism involved in the pathogenesis of AD is still unknown. Inflammation is known to play a pivotal role in this process. It is proposed that periodontitis can lead to progression of AD by two probable mechanisms (figure 2):

- Periodontitis preceding systemic inflammation/infecion
- Bacterial and viral influence

According to the first mechanism, periodontal pathogens and the host response elevate the levels of pro-inflammatory cytokines. An array of cytokines and pro-inflamm-
Transforming Growth Factor-β, chemokines (Monocyte Chemotactic Protein, IL-8, Macrophage Migration Inhibitory Factor, Monokine Induced by γ-Interferon, Fractal-kine) have been implicated as serum and plasma biomarkers for pathogenesis of AD. TNF-α expression is up-regulated in AD and it is considered to be the crucial inflammatory cytokine, regulating cellular cascade of events in neuroinflammatory response. TNF-α exacerbates gliosis, demyelination, inflammation, blood-brain-barrier deterioration and cell death. Thus, TNF-α plays a pivotal role in the neurodegenerative disease process. Studies on mice models have revealed salutary effects of anti-inflammatory agents in the amelioration of neuroinflammation and amyloid plaque deposition. A significant decrease in the levels of IL-1β and glial fibrillary acidic protein levels as well as diminished plaque load was observed in mice treated with non steroidal anti-inflammatory agent.

FIGURE 2 Possible pathways for the pathogenesis of Alzheimer’s disease.
The Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT), corroborates the hypothesis that the beneficial role of anti-inflammatory drugs is evident only in the early, asymptomatic, phases of the disease.40 Inflammation could serve as a connecting link between periodontitis and AD. However, there are no animal studies, specifically addressing the causal relationship of periodontal inflammation to AD, in the literature. Dementia may be designated as a complex disorder associated with an interaction between genetics and diseases related to systemic inflammation, including diabetes mellitus and environmental factors like smoking. Cross-sectional and longitudinal studies have revealed dementia in subjects with poor oral health.41-43

Rai et al. observed statistically significant difference between patients and controls, concerned to the clinical periodontal parameters like gingival inflammation, dental plaque, bleeding on probing and probing pocket depth. Total counts of WBCs, neutrophils, thrombocytes and levels of pro-inflammatory markers like CRP, MMP-8, MMP-9 and TNF-α were significantly elevated in subjects with dementia and periodontitis in contrast to healthy individuals serving as controls. RBC counts, total IGF-1 and Hb levels were diminished in subjects with dementia and periodontitis, in comparison to healthy control subjects. However, these parameters scored significantly higher in dementia as compared to periodontitis patients. An inverse relation was noted in the levels of TNF-α, MMP-8, MMP-9 and CRP levels compared to free IGF-1 concentrations.44 There is a lack of direct clinical evidence for a causal relationship between periodontitis and AD. However, studies have observed that increased systemic/peripheral inflammation can be a contributory risk factor for AD.45-48

ROLE OF PERIODONTAL PATHOGENS IN AD
Periodontal pathogens in periodontitis like Aa, Pg, Pi, Tf, Fn are tissue invasive.45,50 This property enables the pathogens to escape from the extracellular host defense system and replicate in the host tissues. The spirochetal species in the periodontal plaque possess a wide range of virulence factors aiding in confronting the host defense mechanisms and enhancing its ability to invade the periodontal host tissues.51 Spirochete plaques or masses in the brain resemble senile plaques of AD.52

Riviere et al. isolated spirochetal species like Td, Treponema pectinovorum, Treponema vincentii, Treponema amylovorum, Treponema maltophilum, Treponema medium and Treponema socrantskii from the brains of AD subjects, utilizing specific PCR. Td was isolated in 14 of 16 AD subjects and 4 of 18 non AD subjects. Molecular and immunological techniques endorsed the existence of Palladium species in trigeminal ganglion specimen and cortex of AD-affected subjects. AD brain specimens depicted more Treponema species in comparison to control groups. It is speculated that Treponema from oral cavity must have gained access to the brain cortex via the trigeminal nerve.53 A significant association has been displayed between spirochetes and AD. Spirochetes were detected in the brain in 93.7% of AD cases and in 33.3% of controls. Borrelia burgdorferi was isolated 13 times more frequently in AD cases than in controls. Considering all the studies, involving spirochetal species detected in the brain, it can be reasoned that the frequency of spirochetes exceeds more than eight times higher in AD cases (90/131; 68.7%) than in control groups (6/71; 8.41%). The spirochetes may nurture a perpetual infective and inflammatory process evoking neuronal damage and dysfunction.52,54 Study subjects with elevated levels of Pg antibodies in the serum had significantly greater odds of cognitive impairment. This finding was constant even after adjusting for the potential socio-demographic and vascular confounders. Nevertheless, the association of cognitive impairment with antibodies to Aa was weak.55 In a longitudinal study, subjects with AD and moderate cognitive impairment (MCI) showed a significant increase in the levels of serum antibodies to Pi and Fn at the baseline, earlier to the diagnosis of the neurological deficit. The subjects with AD demonstrated significantly higher level of antibody to Td and Pg observed at the baseline. The sera analysis of these subjects was carried out before the diagnosis of AD or MCI.56

Herpes simplex virus type 1 (HSV-1) is a common neurotropic virus that infects elderly subjects. HSV-1 is shown to be present in the brain of AD subjects. A causal role was attributed to this virus for triggering AD. Studies have noticed HSV-1 DNA in the brain of AD subjects.57,58 Polymerase chain reaction (PCR) technique has demonstrated HSV-1 DNA in the brains of large number of elderly individuals, with or without AD. This was less conspicuous in younger subjects, serving as controls.59 Wozniak et al. utilized Enzyme-linked Immunosorbet Assay (ELISA) to isolate antibodies to HSV-1 in the CSF of AD patients. Although the occurrence of anti-HSV-1 antibodies was significantly higher in AD patients than in younger controls, there was a lack of significant difference between the AD and age-matched control groups.60 Letenneur et al. observed an additional presence of IgM along with IgG in the sera of 512 elderly patients, initially free of dementia. In this prospective study, during 14 years of follow up, 77 cases of AD were diagnosed. Sub-
jects nurturing IgM displayed a significantly higher risk of developing AD. The presence of IgM is indicative of active primary infection or reactivation of the viral infection. Thus, the authors concluded a correlation between reactivation of HSV-1 seropositivity and AD. Viruses could be directly implicated in the pathogenesis of AD. HSV possesses glycoprotein structure that mimics the amino acid sequence of AβP and tau protein and may accumulate in the brain like AβP. It was noted that HSV-1 is capable of interfering with APP metabolism and may impart to AD development. HSV-1 infection is also a predisposing factor for AD in subjects with the APOE4 allele.

**Discussion**

Cognitive disorders like AD have escalated steeply in the population of developed countries. This trend is observed at an alarming proportion in developing nations.

The commonly accepted hypothesis for this disorder is the excessive accretion of AβP, including accumulation of abnormally phosphorylated tau proteins in the brain of the affected individuals. Neuroinflammation is a principal factor for the pathogenesis of AD. Systemic inflammation is instrumental in exacerbation of the neuronal degeneration, orchestrated by the activation of primed microglia. Chronic periodontal inflammation, in periodontitis serves as a perennial source for the up-regulated levels of systemic pro-inflammatory factors. Periodontitis is a polymicrobial infection, characterized by the presence of various bacteria and viruses in the periodontal pocket milieu. These agents, along with their products are capable of compromising the BBB and entering the brain. In the brain, these agents can exert the adverse effects either directly or indirectly by affecting the vascular integrity (figure 2). The brain invading spirochetal species can perpetuate a constant chronic inflammatory process operated by activation of the innate immune responses, involving the various signaling pathways, resulting in neuronal degeneration. Viruses, particularly HSV, can access the brain via blood stream or nerve fibers. Latent viruses may be reactivated by stress and inflammation. Pg is known to express factors responsible for platelet aggregation and induce atheromatous changes. This may contribute to the pathogenesis of atherosclerotic vascular diseases, conducting for cognitive impairment and AD. Recent literature has referred to the link between genetic polymorphisms, and progression of periodontal disease. Periodontitis susceptible subjects harbor a hyper-inflammatory phenotype. In response to antigenic stimulus, these subjects exhibit a multifold expression of pro-inflammatory mediators. Gene polymorphism involved in periodontal inflammation could be a conceivable nexus between periodontitis and AD. It is proposed that inflammation may act as an elusive link between periodontitis and pathogenesis of AD. Till date there is no evidence of a causal relationship between periodontitis and AD. Periodontitis can intensify the systemic bio-burden and contribute to a “low grade systemic inflammation”. It may be accounted as one of the possible risk factors for perpetuating the neurodegenerative process in AD.

**Conclusion**

AD involves a complex pathophysiology; the exact etiopathology of which is unknown. It is proposed that inflammation could be operating as the central mechanism. Both, AD and periodontitis share the same characteristic features of chronicity with inflammation as the common link between them. Presently, studies addressing the role of periodontitis in cognitive function are limited. Systematic, multicentric longitudinal studies, with large sample sizes, should be carried out to scrutinize the association between AD and periodontitis. Periodontitis may lead to exacerbation and share risk factors with cognitive impairment related disorders. Interventional studies should be carried out to evaluate a potential benefit in periodontitis subjects with mild cognitive disorders. Levels of pro-inflammatory mediators can be de-escalated with periodontal treatment, abbreviating systemic inflammation. Presently, it may be stated that periodontitis may pose as a potential risk factor for the development of AD. An insufficient body of evidence based literature fails to endorse a causal relationship. Subjects, particularly in the geriatric category should be strongly motivated and frequent visits for periodontal maintenance should be duly emphasized. The dental professional and neurologist need to coordinate consistently regarding the methodical management of geriatric patients.

**Resumo**

A doença de Alzheimer e periodontite - um esquivo link

A doença de Alzheimer é uma proeminente causa e a forma mais comum de demência. Caracteriza-se clinicamente por uma progressiva diminuição da função cognitiva, que tem início com a deterioração da memória. A exata etiologia e o mecanismo fisiopatológico da doença de Alzheimer ainda não são totalmente compreendidos. No entanto, postula-se que a neuroinflamação desempenhe
um papel crucial na patogênese da doença de Alzheimer. A doença de Alzheimer é caracterizada por importantes características inflamatórias, assinalada pela açãoção microgrial e escalada dos níveis de citocinas pró-inflamatórias nas regiões afetadas. Estudos têm sugerido um provável papel de infecção sistêmica imbuída de estado inflamatório do sistema nervoso central. Periodontite é uma infecção oral comum associada a germes Gram-negativos, anaeróbios, capaz de orquestrar infecções localizadas e sistêmicas no paciente. É conhecida por suscitar características inflamatórias, assinalada pela ativação mieloproliferative e escalada dos níveis de citocinas pró-inflamatórias na circulação sistêmica. Esta revisão elucida o possível papel da periodontite no agravamento da doença de Alzheimer e pode ter o potencial de afetar o início e a progressão da doença de Alzheimer. Periodontite partilha as duas importantes características da doença de Alzheimer: dano oxidativo e inflamação, que estão presentes na patologia do cérebro com doença de Alzheimer. Periodontite pode ser tratada e, portanto, é um fator de risco modificável para a doença de Alzheimer.

**Unitermos:** doença de Alzheimer, periodontite, citocinas, inflamação sistêmica, patógeno periodontal.

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