

## Alzheimer's Disease And Periodontitis A Exclusive Link

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**Abstract:** Alzheimer's disease (AD), the paramount cause and the most common form of dementia, is clinically characterized by a progressive descent in the cognitive function, which commences with deterioration in memory. Further investigations are required to gain full understanding of the exact etiology and pathophysiological mechanism of this disease. The disease is noticeable by the classical inflammatory features and typified by microglial activation. Also, the affected regions demonstrate a significant rise in the levels of pro-inflammatory cytokines. The largely accepted hypothesis states that neuroinflammation plays a critical role in the pathogenesis of AD. Periodontitis results in low grade systemic inflammation through the release of pro-inflammatory cytokines into systemic circulation. Periodontitis often results in oxidative damage and inflammation, which are also displayed in the brain pathology of Alzheimer's disease. As Periodontitis is a treatable disease, it is considered as a modifiable risk factor for Alzheimer's disease. This research paper explores the enigmatic link between AD and Periodontitis. A review is presented on the investigations on the role of Periodontitis in aggravating Alzheimer's disease. The further investigations are targeted towards the adverse effects that Periodontitis may bear towards the onset and progression of AD.

**Keywords:** Alzheimer's disease, periodontitis, systemic inflammation, infection, periodontal pathogen.

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### I. Introduction

AD is one of the most common causes of dementia in the population aged 60 years and above.<sup>1</sup> Moreover, AD has emerged as a major health problem in the geriatric subjects worldwide.<sup>2</sup> The onset of AD could be either at a early age or in the later part of the life.<sup>3</sup> Whereas the early onset AD is usually due to the genetic structure, the late onset of AD, which is most frequently encountered, is considered to be a result of interaction between genetic and environmental factors.<sup>3</sup> Besides age being the major risk factor for AD, the other risk factors for late onset AD may comprise of family history, education, high fat diet, hypertension, diabetes, history of head trauma, and susceptibility of genes such as apolipoprotein E (APOE). Out of these risk factors, age, family history, and APOE are considered to be the widely accepted risk factors. Periodontitis is also considered to be one of the probable risk factors for AD.<sup>3</sup>

Patients of AD are more often than not found to be older people, with more than 50% falling under the age group of above 85 years. Thus, there is relationship between AD and the age of the patient. AD is seen as an interaction between genetic and environmental factors. The characteristics of AD are: (a) progressive cognitive impairment with impaired judgment and decision making, (b) psycho-behavioural disturbances, and (c) language disability.<sup>2</sup> There still exists gaps in the understanding of the molecular mechanisms involved in the etiopathogenesis of AD. However, a commonly observed pathological characteristic of AD is the accumulation of A  $\beta$ -amyloid (A $\beta$ ) and the hyperphosphorylation of tau in the brain.<sup>1</sup> Another major factor associated with the acceleration in onset and progression of AD is neuroinflammation through Interleukin-1  $\beta$  (IL-1 $\beta$ ). The release of multiple inflammatory mediators by activated microglia is driven by IL-1 $\beta$ . Consequently this results in self-propagating neuroinflammation. The secretion of proinflammatory molecules by microglia support the progression of AD.<sup>4</sup> Clinical studies have reported with evidence the extent of microglial activation during the early progression of AD and mild cognitive impairment (MCI).<sup>5</sup> IL-1 $\beta$  expression has been detected in the plaque-surrounding microglia in the AD brain, suggesting that the IL-1 $\beta$  released from the plaque surrounding microglia may contribute to neuronal dysfunction by promoting the formation of dystrophic neurites and via direct neurotoxicity.<sup>1</sup>

Periodontitis is a common chronic multi-bacterial infection which mainly affects the supporting structures of the teeth. This results in a significant bacterial and inflammatory load in the body. Periodontitis is a form of chronic systemic inflammation, which initiates and/or speeds up the progression of AD.<sup>1</sup> additionally, it is also responsible for other systemic inflammatory diseases, such as atherosclerosis and diabetes.<sup>1</sup> The impact of periodontitis on AD has been reported in a number of clinical studies. The recent experimental studies have specified the route of transduction of inflammatory signals from periodontitis to the brain. The current

understanding of the link between periodontitis and AD will be reviewed and presented in the succeeding sections.

## **II. Alzheimer's Disease And Periodontitis – The Probable Link**

In the present era, there still exists a gap in information which does not allow us from acquiring the knowledge about the exact mechanism involved in the pathogenesis of AD. Although, it is accepted that the inflammation plays a vital role in this process, it is proposed that periodontitis can lead to progression of AD by following probable mechanisms<sup>2</sup>

- First Mechanism: Periodontitis preceding systemic inflammation/infection
- Second Mechanism: Bacterial and viral influence

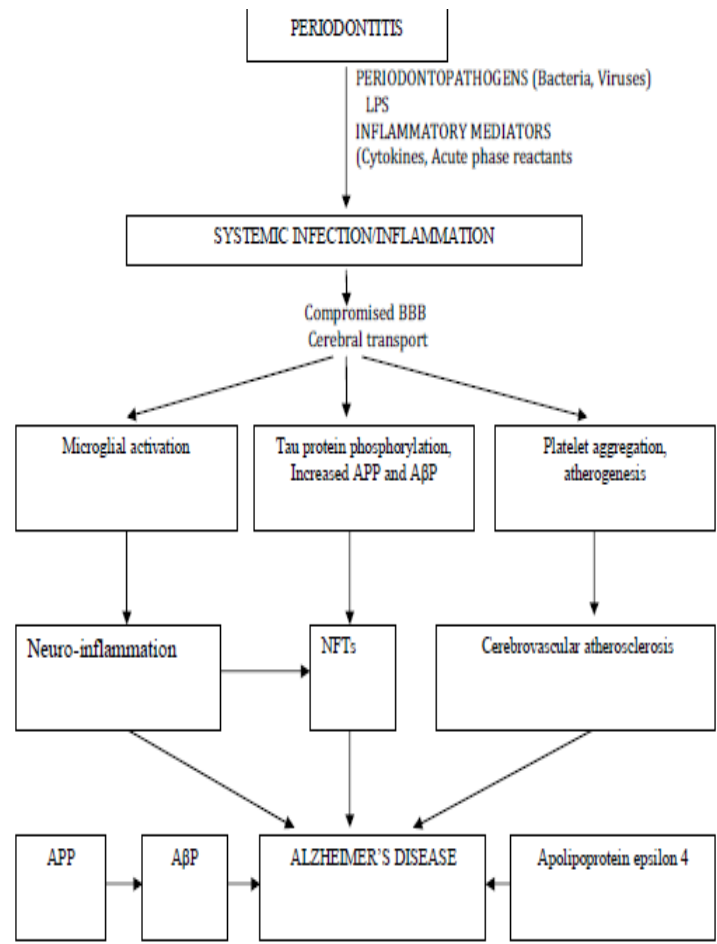
As per the first mechanism, periodontal pathogens and the host response elevate the levels of pro-inflammatory cytokines. The systemic inflammation is further burdened by the release of cytokines and pro-inflammatory agents in the systemic circulation. As a consequence of this, the periodontitis results in a state of systemic/peripheral inflammation. The pro-inflammatory molecules can compromise the blood brain barrier (BBB) and gain access to the cerebral regions.<sup>23</sup>This may result in activation of microglial cells and the adverse events leading to neuronal damage.

The second mechanism may involve invasion of the brain by bacteria and viruses residing in the dental plaque biofilm. This can occur directly through cerebral transport via blood stream or via peripheral nerves. There is appreciable evidence blaming the inflammatory mechanisms within the central nervous system for the cognitive impairment, as that presented in AD. This involves cytokine initiated interactions between neurons and glial cells. Various cytokines consisting of interleukin family, TNF- $\alpha$ , transforming Growth Factor- $\beta$ , have been implicated as serum and plasma biomarkers for pathogenesis of AD.<sup>24</sup> TNF- $\alpha$  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- $\alpha$  exacerbates gliosis, demyelination, inflammation, blood-brain-barrier deterioration and cell death. Thus, TNF- $\alpha$  plays a pivotal role in the neurodegenerative disease process.<sup>25,26.</sup>

The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), validates the hypothesis that the beneficial role of anti-inflammatory drugs is evident only in the early, asymptomatic, phases of the disease.<sup>27</sup> Inflammation could serve as a connecting link between periodontitis and AD. Thus, the 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. Through the cross sectional and longitudinal studies, Ship et al., Weyant et al, and Arrive et al. have arrived at a conclusion about the dementia in subjects with poor oral health.<sup>28,29,30.</sup>

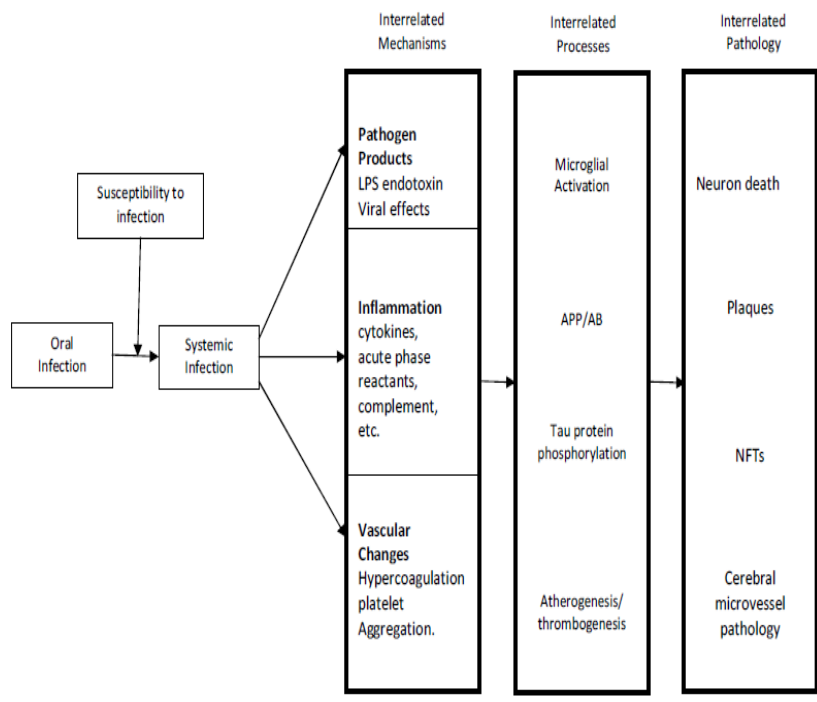
Rai et al. observed that total counts of WBCs, neutrophils, thrombocytes and levels of pro-inflammatory markers like CRP, MMP-8, MMP-9 and TNF- $\alpha$  were found to be notably elevated in subjects with dementia and periodontitis as compared to the healthy individuals serving as controls.<sup>31</sup>There 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.<sup>32</sup>

Riviere et al. isolated spirochetal species like *T. denticola* from the brain of AD subjects, utilizing specific PCR. 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.<sup>33</sup> A significant association has been displayed between spirochetes and AD.<sup>3</sup> In a longitudinal study by Stein et al, subjects with AD and moderate cognitive impairment (MCI) were found with a significantly increased level of serum antibodies to *P.intermedia*, *F.nucleatum*, *T.denticola*, *P.gingivalis* at the baseline.<sup>34</sup> Even though specific infectious agents are key in the development of periodontitis, it is unlikely that a single agent or even a small group of pathogens are the only cause or modulator of this complex disease.<sup>35</sup>



**Abbreviations:** LPSLPS-lipopolysaccharide; BBB-blood brain barrier; APP-amyloid precursor protein;AβP-amyloid beta protein; NFTs-neurofibrillary tangles.

**Figure 1-** Possible pathways for the pathogenesis of Alzheimer's disease.<sup>2</sup>



**Abbreviations:** LPS, lipopolysaccharide; APP, amyloid precursor protein; AB, amyloid beta; NFTs, neurofibrillary tangles.

**Figure 2** Proposed pathways between periodontal infection and Alzheimer's disease pathology.<sup>6</sup>

### III. Conclusion

AD involves a complex pathophysiology; the exact etiopathology of which is yet unknown. Inflammation plays the central role and is a common link between AD and Periodontitis. Currently, studies associating the role of periodontitis in AD are limited. Systematic, multicentric longitudinal studies, with large sample sizes, are to be carried out to examine 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. There can be a reduction in levels of inflammatory mediators following periodontal treatment thus downgrading systemic inflammatory load. Presently, it may be acknowledged that periodontitis may act 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 periodontist and neurologist need to co-ordinate consistently regarding the methodical management of geriatric patients.

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