Review Article

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RELATIONSHIP BETWEEN ALZHEIMER'S DISEASE AND PERIODONTAL DISEASE-A BRIEF REVIEW

Rino Roopak Soman[1],Shibu Thomas Sebastian[2]

1.Reader, Department of Periodontics,Pushpagiri College of Dental Sciences,Thiruvalla.
2.Senior lecturer,Department of Public Health Dentistry, Pushpagiri College of Dental Sciences,Thiruvalla.

ABSTRACT:

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. It is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. 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. Periodontal infections may result in harmful pathogenic products leading to systemic inflammatory responses. Elevated systemic inflammatory response may contribute to the exacerbation of existing brain pathologies. Infections may also contribute to vascular pathology with the potential to impact brain function. This review elucidates the possible role of periodontitis in exacerbating 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.

Keywords: Alzheimer's disease,Periodontitis,Inflammatory mediators.

INTRODUCTION:

Alzheimer's disease (AD) is an irreversible, progressive loss of brain tissue that slowly destroys memory and thinking skills, and eventually lead a severely compromised quality of life.Periodontal disease and Alzheimer's disease are chronic conditions that commonly affect the elderly. Numerous cross sectional studies address the oral health status of individuals with AD and dementia.[1] Overall, evidence indicates that Alzheimer's patients exhibit poor oral health, including increased plaque, bleeding, and calculus than age- and gender-matched controls.[2] While it is true that Alzheimer's patients may be unable to adequately perform oral hygiene measures, thereby facilitating the development of periodontal disease[3], a potential exists for a bi-directional relationship.

AD progressively shows increased severity, resulting in impairment of cognitive skills. In the mild to moderate stages of AD, the cognitive decline includes memory loss, language problems, gradual disorientation in time and space, difficulties in performing normal daily activities, and inabilities to learn new things.[4] People with AD who have difficulties in motor skills and in the ability to perform oral and

*Corresponding Author Address: Dr. Rino Roopak Soman Email: drrinoroopak@gmail.com

personal care have an increased risk for developing medical complications and stomatological disorders. In the severe stage, cognitive abilities are severely impaired, progressing to complete loss of recent and remote memory. As a result, people with severe AD become dependents and require caregivers.[5]

PATHOPHYSIOLOGY OF AD

The major pathological hallmarks of AD, first described by Alios Alziemer in 1907, the classic pathologic hallmarks of AD are two types of aggregate. The β-amyloid plaque the main constituent of which is the 40-43 aminoacid, Long amyloid beta(A^2) peptide, The neurofibrillary tangle,the main constituent of which is a structural protein. In addition amore recently accepted hallmark of AD is brain inflammation, specifically an innate inflammatory response by the nervous system that is likely to reflect an attempt to clear (A^2) deposits and other forms of AD pathology.[6]

There is substantial evidence that brain (A^2) deposits become a nidus for innate inflammatory responses particularly in the context of microglial reactions to(A^2).microglia are small glial cells of mesodermal origin that are distributed throughout the gray and white matter of the nervous system.[7]At rest, they are believed to play supportive roles for neurons. However fundamentally they are specialized immune cells, related to macrophages, which can take on attack and pathogenic roles when activated. Like activated microglia secrete a wide range of inflammatory mediators, are capable of migrating to sites of inflammatory activity and exhibit scavenger responses to damaged tissue and accumulations of abnormal proteins. By contrast there seems to be little to no involvement of leukocytes or monocytes. For these reasons activated microglia are widely considered to play a pivotal role in AD inflammation.

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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

- Periodontitis preceding systemic inflammation/infection
- 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-inflammatory agents are spurted out in systemic circulation adding to the systemic inflammatory burden. Thus, periodontitis may produce a state of systemic/peripheral inflammation. These pro-inflammatory molecules can compromise the blood brain barrier (BBB) and gain access to the cerebral regions..This may result in priming/activation of microglial cells and the adverse repercussions leading to neuronal damage.[8]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.

Periodontitis contributes to cognitive impairment and people with poor oral hygiene and periodontitis may be at a greater risk of developing Alzheimer's disease (AD).[9]The flora of periodontal disease consists largely of gram negative bacteria which has specific receptors in the brain. Brain infections by gram negative bacteria have been linked to alzheimer's etiology, specifically late-onset sporadic AD. A recent histologic study demonstrated the presence of gram negative bacteria Chlamydia pneumonia in cells of affected brain regions in 17 of 19 post mortem Alzheimer's brains, while brains of controls were not infected in individuals with oral hygiene the number of oral pathologic bacteria reaching circulation is low.[10]

As early as 1891, it was suggested that oral bacteria could "lodge in some weak point in the brain" and result in brain infection and abscess. Indeed, there are numerous reports of brain infection testing positive for oral bacteria, with most cases specifically linked to periodontal pathogens.[11] Brain infection by one such bacteria, Actinobacillus actinomycetemcomitans, is associated with coagulative necrosis of cortical cells and white matter.

It is also possible that pathogenic bacteria do not infect the brain but rather induce a systemic inflammatory response leading to injury of brain tissue. Since host responses to periodontal disease, such as up regulation of proinflammatory mediators, show significant positive correlation with coronary artery disease and premature birth, neuropathological responses may also be induced ever, this number increases twofold to tenfold in persons with periodontal disease.[12]

Inflammation is a recurrent theme among investigations of oral and systemic diseases. The cascade of inflammatory events associated with periodontal disease begins with endotoxin, a high molecular weight lipopolysaccharide found in the cell wall of gram-negative periodontal bacteria. Endotoxin initiates inflammation locally in the periodontal pocket by stimulating inflammatory cells such as monocytes, macrophages, fibroblasts and T cells to produce cytokines and prostaglandins (PGE_2). Cytokines transmit information from cell to cell at very low levels, in the nanomolar to picomolar range. Some of the most important inflammatory cytokines associated with periodontal disease are interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tissue necrotizing factor-alpha (TNF-α). IL-1 and TNF-α signal hepatic cells to produce several Type 1 acute phase proteins, among them CRP.[11]

Brain mononuclear phagocytes, especially microglia (brain resident macrophages), function to protect the nervous system by scavenging for debris, killing microbial pathogens and regulating immune responses.[13] Microglia are activated by a variety of environmental stimuli, including pro-inflammatory cytokines and bacterial lipopolysaccharides, which initiate a cascade of events that can best be characterized as a neuroinflammatory

process. Recent evidence suggests that systemic inflammation is associated with signals that pass from the blood to the brain via perivascular macrophages and microglia.The resultant neuroinflammatory responses include secretion of neurotoxic factors causing cell injury and death throughout the central nervous system.[14]

INFLAMMATORY MEDIATORS OF PERIODONTAL DISEASE

Investigators have found markers of systemic inflammation when analyzing the serum of individuals with periodontal infections. A study by Ebersole and colleagues showed that levels of endotoxin detectable in the blood increase with the level of oral disease. Periodontal pathogens have been shown to elicit a circulating antibody response. Abnormally elevated serum levels of PGE_2 and CRP have been found in people with periodontitis.Bretz and colleagues found significantly higher levels of IL-6 in the blood of those with extensive periodontal disease compared with controls. This findings is noteworthy because IL-6 is associated with local production of amyloidprotiens, and in alziemers brain it may regulate production of amyloid protiens found in neutritic plaques, cytokines have been implicated in pathophysiology of several psychiatric disorders, including AD because of their ability to stimulate neurochemical, neuroendocrine and neuroimmune changes in the brain.[12]

The third national health and nutrition examination survey (NHANESIII) showed that gingival bleeding, loss of periodontal attachment and serum P.gingivalis IgG were significantly associated with cognitive function even after extensive adjustments for confounders[15].

ROLE OF PERIODONTAL PATHOGENS IN AD

Periodontal pathogens in periodontitis like *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis,Tannerella forsythia,Treponemadenticola,Fusobacteriumnucleatum,Prevotellaintermedia* are tissue invasive.[16] 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 with the host defense mechanisms and enhancing its ability to invade the periodontal host tissues.Spirochetes attach to host cells through their surface components including collagen binding proteins, bacterial amyloids and pore forming proteins through activation of plasminogen and factor XII,bacterial amyloids contribute to inflammation and modulate blood coagulation .The innate immune system enables host cells to recognize spirochetes, execute proinflammatory defenses, and start adaptive immune responses.[17]

CONCLUSION:

AD is a significant health problem that will likely become even greater as the population ages. It is established that AD contributes to deterioration in oral health.Some studies suggest that oral disease contributes to AD or cognitive impairment. However, data supporting a bi-directional association is limited, and it is

currently unclear which occurs first, oral disease or AD. Both, AD and periodontitis share the same characteristic features of chronicity with inflammation the common link between them

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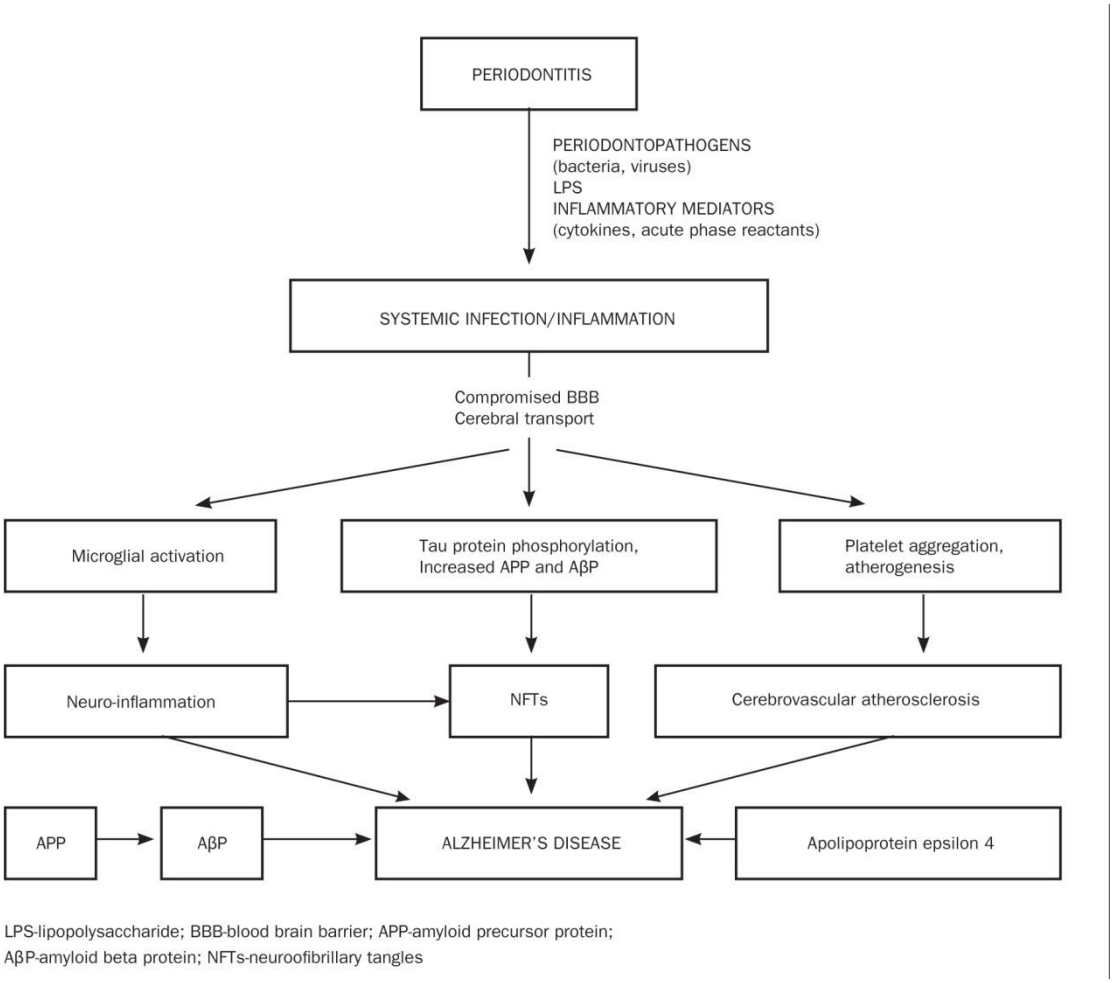
FIGURE:

Fig: 1 Possible pathways for the pathogenesis of Alzheimer's disease

Image courtesy: Page RC, Kornman KS. The pathogenesis of human periodontitis: An introduction. Periodontol 2000. 1997;14:9-11.



LPS-lipopolysaccharide; BBB-blood brain barrier; APP-amyloid precursor protein; AβP-amyloid beta protein; NFTs-neuroofibrillary tangles