RELATIONSHIP BETWEEN ALZHEIMER'S DISEASE & PERIODONTITIS -A LITERATURE REVIEW

Nivetha K¹, Ayswarya V Vummidi², Paavai Ilango^{3*}, Abirami T⁴, Arulpari Mahalingam⁵, Vineela Katam Reddy⁶, Angel Infant R⁷, Meenambal A⁸

¹Intern, Department of Periodontology, Priyadarshini Dental College and Hospital, Thiruvallur, Tamil Nadu, India

²MDS, Senior lecturer, Department of Periodontology, Priyadarshini Dental College and Hospital, Thiruvallur, Tamil Nadu, India

^{3*}MDS, Professor and Head, Department of Periodontology, Priyadarshini Dental College and Hospital, Thiruvallur, Tamil Nadu, India

⁴MDS, Senior lecturer, Department of Periodontology, Priyadarshini Dental College and Hospital, Thiruvallur, Tamil Nadu, India

⁵MDS, Professor, Department of Pedodontics, Thai Moogambigai Dental College and Hospital, Chennai, Tamil Nadu, India

⁶MDS, Professor, Department of Periodontology, Indira Gandhi Institute of Dental Sciences, Pondicherry, Tamil Nadu, India

⁷BDS, Tutor, Department of Periodontology, Priyadarshini Dental College and Hospital, Thiruvallur, Tamil Nadu, India

⁸BDS, Tutor, Department of periodontology, Priyadarshini Dental College and Hospital, Thiruvallur, Tamil Nadu, India

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Corresponding author: Dr. Paavai Ilango

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Abstract

Periodontitis is the microbial infection often causing inflammation of the gingiva, bone loss and tooth mobility. Apart from periodontitis, periodontal bacteria like Porphyromonas gingivalis, Spirochetes, Treponema denticola are known to cause systemic diseases such as cardiovascular diseases, preterm low birth weight infants, Alzheimer's diseases etc. Alzheimer's disease is a progressive mental deterioration of the brain that can occur in middle or old aged individual due to generalized degeneration of neurons in the brain. Literature has shown that inflammation plays a vital role in the progression of Alzheimer's disease where periodontitis is a risk factor proving the focal infection theory. This article reviews the relationship of periodontitis in Alzheimer's disease and its role in modifying the disease.

Keywords: Alzheimer's Disease, Chronic Periodontitis, Periomedicine, Inflammation

Introduction

Inflammation is known to be a protective response that focuses on the removal of stimuli responsible for damage to the tissues, thereby leading to restoration of health. Periodontitis is an inflammatory condition representing the response of periodontal tissues to bacteria like Porphyromonas gingivalis, Treponema denticola and Spirochetes. Periodontitis leads to inflammation of gingival and destruction of periodontal tissues. The characteristics of periodontitis include microbial biofilm formation, gingival inflammation, alveolar bone loss and attachment loss.¹

Periodontal medicine establishes a strong relation between periodontal health or disease and systemic condition. Periodontitis as a source of inflammation contribute to exacerbate many systemic diseases like diabetes, cardiovascular diseases, respiratory diseases, pregnancy (PROM- Premature rupture of membrane), neurological diseases etc. Hence, periodontitis is not limited to destruction of periodontal tissues; but also modify systemic diseases and vice versa.² Thus, a proven

two-way relationship exists between periodontal disease and systemic health or disease.

Untreated periodontitis can alter various systemic diseases progression and one such is Alzheimer's disease. Alzheimer's disease is a progressive disease that degenerates brain cell connection and the cells die eventually destroying memory and other mental functions.

Though periodontopathic bacteria are responsible for the occurrence of periodontal disease, the progression of disease mainly depends on host inflammatory response.³ In a healthy periodontium, a balance between bacteria and host response is well maintained, whereas in periodontitis, that balance is disrupted; as the periodontal bacteria and their products enter the blood stream from periodontal pockets, resulting in bacteremia and dissemination of its products in systemic circulation, following which innate and adaptive immune response results in changes of local vasculature, generation of an inflammatory response and the secretion of pro-inflammatory cytokines like Tumor necrosis factor- α (TNF- α), Interleukin-1(IL-1) and Interleukin-6(IL-6). This

leads to the activation of osteoclasts, Matrix metallo proteins(MMP) and decreased collagen activity.⁴ Thus, the disease is exhibited with clinical signs of tissue and bone destruction. This immuno-inflammatory condition is said to play a vital role in the onset and progression of alzheimer's disease, though its pathogenesis is not completely understood.

Alzheimer's disease is characterised by lack of memory, feeling difficulty in thinking & understanding, confusion, problems with language, disorientation, mood swings, wandering or getting lost, not managing self-care, aggression, depression, repetition of meaningless own words, inability to coordinate muscle movements, gradually leading to loss of body functions and death.⁵

Plaque and neuro-fibrillary tangles in the brain are considered as the reason for progression of the disease. Barry et al in 1980 classified the progression of Alzheimer's disease into 7 stages. Normal, Normal aged forgetfulness, mild cognitive impairment, mild Alzheimer's disease, moderate Alzheimer's, moderately severe Alzheimer's disease, severe Alzheimer's disease and death.⁶ Though Alzheimer's disease cannot be completely treated symptoms can be improved temporarily by medications and relieving the risk factors. The etiology of alzheimer's disease is yet to be fully understood. Many studies reveal that 70% of the etiology is hereditary and other causes involved includes head injuries and depression.⁷

The clinical sequence of alzheimer's disease is initiated by dysfunction of autophagy.⁸ Autophagy is a lysosome dependent, homeostatic process, in which organelles and proteins are degraded and recycled into energy. It is specifically important in non-proliferative cells, like neurons where its failure leads to neurodegenerative diseases. Physiologically as cells are aging, the unnecessary proteins or those produced in excess that alter cellular balance are eliminated rapidly. The complete disintegration of unnecessary proteins like Amyloid β protein(A β) which is necessary for cell viability are done by proteasomal digestion and autophagy. Thus, Alzheimer's disease is initiated from inflammation by A β -amyloid proteins, hyper-phosphorylated tau protein or components of degenerated neurons. Evidently, microglial cells at low levels are neuro-protective in nature.⁹ When exposed to systemic inflammatory signals or by aging, the microglial cells are activated which alter the normal cell morphology by secreting antigen. This induces neuro-degeneration leading to the progression of Alzheimer's disease.^{10,11,12}

Discussion

Link between Alzheimer's and periodontitis:

Inflammation seems to play a vital role in association between Alzheimer's disease and Periodontitis. Periodontal disease through the production of cytokines and angiogenic factors cause cognitive disorders.¹³ There are various mechanism which brings a phenomenal association between Alzheimer's disease and periodontitis. These mechanisms involve bacteria and their products, inflammatory mediators and vascular changes ultimately progressing to Alzheimer's disease.¹⁴

A. Based on microbial association:

Several researches have been conducted to establish the association of periodontitis causing Alzheimer's disease. Periodontal bacteria from periodontitis affect the function of brain by inflammatory molecules.^{15,16}

- Dominy et al on analyzing the brain tissue, spinal fluid and saliva from Alzheimer's disease patients found that Porphyromonas gingivalis, an important pathogen in the development of chronic periodontitis plays a significant role in developing Amyloid β plaques, dementia and Alzheimer's disease.^{17,18,19,20,21} Toxic proteases from the bacterium called gingipains secreted by Porphyromonas gingivalis are found in the brain samples of Alzheimer's disease patients which mediates the toxicity of pathogen in fibroblast, endothelial and epithelial cells.^{22,23,24} Dominy et al found COR388 as the effective gingipain inhibitor in a mouse model as it was able to reduce neuro inflammation in the brain by reducing the Porphyromonas gingivalis bacteria.²⁵
- Poole et al have reported that Porphyromonas gingivalis lipopolysaccharide have been found in the brains of Alzheimer's disease patients, supporting the hypothesis that Porphyromonas gingivalis play an important role in the pathogenesis of Alzheimer's disease.²⁶ Porphyromonas gingivalis can also enter the brain by infecting monocytes followed by brain recruitment.²⁷ Porphyromonas gingivalis cross the blood brain barrier and affect the brain activity by releasing cytokines resulting in Alzheimer's disease.²⁸
- Balin et al has reported that Chlamydia pneumoniae was present in 19 post-mortem brain sample of Alzheimer's disease patients influencing the role of this particular bacteria in the pathogenesis of Alzheimer's disease.²⁹
- Borrelia burgdorferi spirochetes along with beta amyloid deposits were also found were found in the blood and Cerebrospinal fluid of Alzheimer's disease patients. Miklossy et al observed that beta amyloid precursor proteins and p-taus was produced by neuronal

cells when exposed to *Borrelia burgdorferi* contributing to the pathogenesis of Alzheimer's disease.³⁰

- Riviere et al showed *Treponema denticola*, a prominent periopathogen found in 16 postmortem brain samples of Alzheimer's disease patients.³¹
- Bacterial products also can indirectly increase the brain pro-inflammatory cytokine pool in addition to peripheral pro-inflammatory molecules.

B. Based on microbial products association:

- Wu Z and Naganishi et al reported that in chronic Periodontitis, Lipopolysaccharide B, flagellin and cytokines like Interleukin-1 and Tumor necrosis factor- α secreted by macrophages, activates the old microglial cells which releases inflammatory cytokines, causing the expression and activity of beta-site amyloid precursor protein cleaving enzyme1 (BACE1) gene, resulting in Amyloid beta production in the brain causing Alzheimer's disease.³²
- Cortexyme et al conducted a test in mice and found that *Porphyromonas gingivalis* led to production of beta-amyloid proteins in rat brain and gingipains were found to be the toxic substance. Broad spectrum antibiotics were not used in treating Alzheimer's disease because *Porphyromonas gingivalis* due to the presence of gingipain were resistant to broad spectrum antibiotics, hence narrow spectrum antibiotics blocking gingipain proteolytic activity came into emergence.^{33,34,35,36}

C. Based on pro-inflammatory cytokines:

a) According to the first mechanism, the host response release pro-inflammatory cytokines periodontopathic bacteria. When these cytokines are more, they reach the systemic circulation leading to systemic burden and inflammation eventually. Brain is a vital organ protected by blood brain barrier. These pro-inflammatory molecules can enter the brain when it lacks its barrier. When the pro-inflammatory molecules enter brain in the absence of barrier, they activate the microglial cells causing neuronal degeneration. They also can enter the brain with blood brain barrier by crossing fenestrated capillaries, using cytokine-specific transporters, increasing the permeability of brain's barrier or by producing cytokine by brain endothelial cells.⁴ When it reaches the brain in the presence of barrier, the pro-inflammatory molecules increase the cytokine pool or stimulate the glial cells to synthesize additional pro inflammatory cytokines.³

b) The second mechanism is thought to be by neuronal, where brain cytokines are raised by stimulation of sensory fibers of peripheral nerves like olfactory³⁷ or trigeminal by peripheral cytokines.³⁸

c) Another mechanism by which inflammatory changes in the brain are induced is by activating peripheral inflammatory cells such as T cells and macrophages which are capable of gaining access to the brain contributing inflammatory process.

D. Based on genetic & environmental factors:

- Genetic factors like Interleukin-1 gene polymorphism, Tumor necrosis factor- α gene polymorphism and environmental factors like smoking also play a role in relation between Alzheimer's disease and periodontitis.³⁹

Overall, this literature review suggests that periodontitis causing systemic inflammation has a significant relationship with the Alzheimer's disease. Though anti-inflammatory drugs cannot prevent the Alzheimer's disease, they can always slow down its progression by its influence on the pro-inflammatory molecules which is the main reason for link between Alzheimer's disease and periodontitis.⁴⁰

Conclusion

Based on the literature, it is evident that there is a profound association between periodontitis, which is a modifiable risk factor and Alzheimer's disease. Though Alzheimer's disease is untreatable, correcting the risk factor would lead to palliative improvement in the condition. Thus focusing on periodontal therapy, would serve as an adjunct therapeutic measure in the management of Alzheimer's disease.

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