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RESEARCH ARTICLE

ALZHEIMERS DISEASE AND PERIODONTITIS – A CORRELATION

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ABSTRACT

Background: In spite of the relatively minimal knowledge on the etiology and pathogenesis of Alzheimer's disease inflammatory activity in the brain has been proposed to be the most plausible cause. Researches have indicated that, peripheral infection /inflammation can have an impact on infection in central nervous system. Chronic periodontitis is a common peripheral infection with predominant bacterial etiology and a marked increase in the serum C Reactive Protein count. Periodontitis, lately has been known to be involved in various systemic diseases including Alzheimer's disease. **Methods:** A literature review was performed by referring to the scientific papers on the internet from the PubMed and Google Scholar and databases from 1985 to 2019 The present article reviews the pathogenesis of periodontitis associated with Alzheimer's disease along with few probable mechanism by which periodontitis can contribute to Alzheimer's disease. **Result:** Periodontal disease can influence Alzheimer's disease through different mechanism. **Conclusion** Because Periodontitis is a treatable disease it could be a modifiable risk factor for Alzheimer's disease.

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INTRODUCTION

The increased life expectancy, thanks to the improved health care facilities and general awareness on personal health care, has led to an astounding increase in the proportion of the elderly, making them the rapidly amassing fragment of the entire world population. This scenario, however, has added an astonishing number of dementia cases to the existing ones, as it is largely an age related disorder. Dementia is an acquired and persistent compromise in multiple cognitive domains that is severe enough to interfere with everyday functioning (Dekosky, 2008). Alzheimer's disease is the most frequently observed reason for primary degenerative dementia. Developing homogenously from the initial signs of compromised memory to enhanced cognitive loss, the disease follows a forward course that ultimately ends in total disability and death (Small, 2000). The incidence of the disease is found to be almost 50% in the elderly above 85 years, suggesting a directly proportional relationship with age (Ferri, 2005). This is bound to rise the prevalence of AD in the coming 50 years affecting around 14 million people (Kamer, 2008).

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The disease is characterized by a gradual decline in cognitive skills along with inability in decision making succeeded by Psycho behavioural impairments and language disability all of which has led to poor oral hygiene conditions in AD patients (Galimberti, 2012; Vahabi, 2018). Neuroinflammation, a critical characteristic of AD, might have an important part in the associated cognitive dysfunctions (McGeer, 2010). Interleukin – 1b triggers the activated microglia to dispense a variety of inflammatory mediators which themselves impart neuro inflammation, making it the fundamental molecule causing the same in AD (Schwab, 2008). Clinical studies have given validation of the magnitude of microglial stimulation in early AD and mild cognitive impairment (MCI) (Venneti, 2008). Plaque present around the microglia of patients with AD showed evidence of IL 1b activity (Shaftel, 2008) which point towards the role of IL – 1b in neuronal dysfunction by stimulating the synthesis of dystrophic neuritis and via direct neurotoxicity. The fact that sysytemic infection/inflammation can vary the neuroinflammatory activity in the brain has been well documented (Perry, 2003). Periodontitis is a chronic inflammatory disease of multi factorial etiology, which is predominantly bacterial, that adversely affects the health of the attachment apparatus, leading to substantial increase in microbial and inflammatory levels in the body. Apart from causing systemic inflammatory diseases like atherosclerosis

and diabetes, periodontitis can commence or accelerate the rate of advancement of AD directly (Pischon, 2007). Multiple authors have successfully validated the effect of periodontitis on AD, and the channelling of inflammatory signals from periodontitis to brain has been proved by recent experimental studies. According to the "inflammatory model" proposed by Kamer *et al*, periodontal diseases trigger the formation of several systemic inflammatory products that triggers the formation of Amyloidβ (Aβ) and tau proteins in the cerebral tissue followed by the neuropathology that is Alzheimer's disease (Kamer, 2008)

Pathogenesis of Ad: "Inflammatory hypothesis' being one among the most accepted in the pathogenesis of AD, talks about a self-perpetuating and progressive cerebral inflammation that concludes as neurodegeneration (McGeer 2001). There are no definitive inflammatory factors acknowledged till date (Kamera, 2008). The inflammatory activity could be provoked by various pathologic characteristics of the disease comprising mainly of A-amyloid 1-42 peptide (A-42) identified in senile plaques, hyperphosphorylated tau protein (P-Tau) encompassing the neurofibrillary tangles, or constituents of degenerated neurons (Akiyama, 2000). As a consequence of the same, the microglial cells are activated. These cells at minor concentrations are known to have protective activity. They function as mononuclear phagocytes against the harmful injuries to the central nervous system and thus play an important role in managing the brain homeostasis. They serve the neuroprotective function by eliminating the AβP plaques (Fetler, 2005). Progression in age along with genetic susceptibility tend to adversely affect the neuroprotective capacity of the microglial cells leading to chronic inflammatory reaction s in the CNS (Schram, 2007; Arosio, 2004). As a consequence, the microglial cells, when in contact with the systemic inflammatory signs, induce their phenotypes to create neurotoxic products. This in turn induces the pathogenesis of AD. These "activated microglial cells" undergoes a change in their morphology, and starts the production of cell antigens leading to uninhibited activity of pro inflammatory components. This in turn leads to neurodegeneration (von Bernhardi, 2004).

Microglial Cells In Ad: The protective or destructive activity of te microglial cells is mainly governed by the circumstances (Weitz, 2012; Perry, 2001; Kitazawa, 2005). These cells upon stimulation tend to produce various pro inflammatory cytokines including tumournecrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and C-reactive protein (CRP). These molecules, when present in an elevated concentration, functions via the via paracrine and/or autocrine pathways and induces the glial cells into increased production of Aβ42, P-Tau, and proinflammatory molecules. This in turn results in the activation of a pathway wherein the inflammatory mediators stimulate glial cells and activates the molecular pathway that commences in neurodegeneration (McGeer, 2001). Antibodies against TNF-α, IL-1β, IL-6, CRP, and complement proteins are acted upon by the reactive astrocytes and activated microglial cells linked with the senile plaque (Akiyama, 2000). A bi-directional mechanism is activated wherein TNF-α, IL-1β, and IL-6 induces the production of Aβ42 and the phosphorylation of tau protein and vice-versa (McGeer, 2001; Konsman, 2007; Gosselin, 2007). Various studies conducted to establish the possible association between CRP levels and other systemic inflammatory markers in the commencement of AD, has found out a proportional escalation in the risk of developing AD when the CRP levels are high (Engelhart *et al*., 2004; Yaffe *et al*., 2004).

Mechanisms involved in spread of inflammation to brain

Two mechanisms have been proposed:

- Systemic circulation
- Neural pathways

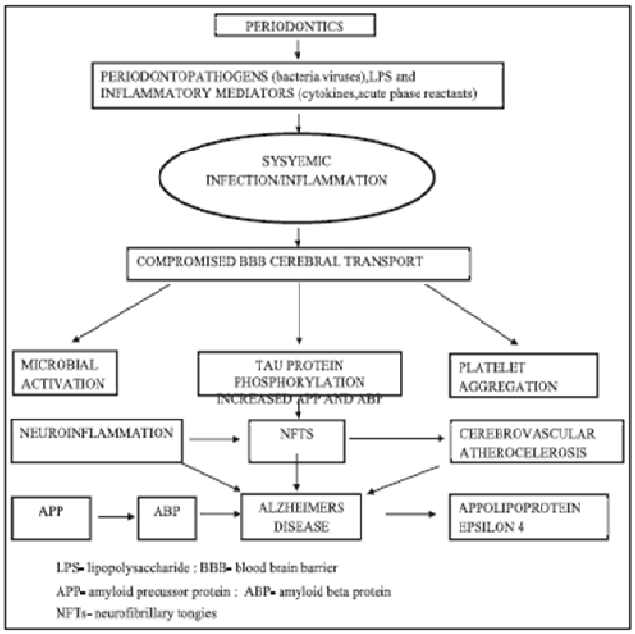
In the systemic circulation:

- Areas which lack blood brain barrier (BBB).
- areas in brain with blood brain barrier through:

(a) Fenestrated capillaries of the BBB,
(b) Using cytokine-specific transporters,
(c) Increasing the permeability of BBB, or
(d) Endothelial cells of the brain are activated to produce cytokine-inducing signalling molecules such as nitric oxide or prostanoids (Nagraj, 2015).

In neuronal pathway (Dantzer *et al*., 2000): Afferent nerve fibres of the peripheral nerves get stimulated by the peripheral cytokine leading to an elevated brain cytokine level. The channels or compartments linked with the peripheral nerves are also used to gain access to the brain (Nagraj, 2015). Other mechanism include the presence of receptors for CD14 present in the brain which can get activated by LPS derived from invasive bacteria or AD AβP, which in turn will activate CD14 cells. This further increases brain cytokines and hypothetically contributes to the inflammatory burden of AD. The lipopolysaccharide (LPS) of gram-negative bacteria is a readily recognized, pathogen-associated molecular pattern that triggers the innateimmune response and increases peripheral proinflammatory cytokines by activating the CD14 receptor. Studies have shown that CD14 receptors are present on areas of the brain that are exposed to the systemic circulation such as the circumventricular areas, leptomeninges, and choroid plexus. On intravenous injection with LPS, CD14 receptors are up-regulated not only in areas exposed to the LPS but also throughout the brain, demonstrating that LPS is capable of influencing the CD14 profile in the brain even in the absence of direct contact between LPS and CD14. Thus,CD14 can be activated by LPS derived from invasive bacteria or AD amyloid β protein, thus increasing further brain cytokines and hypothetically contributing to the inflammatory burden of AD (Inflammation and Alzheimer's disease, 2008).

Role of bacteria in the pathogenesis of alz dis: Several bacterial pathogens have been proposed to directly act as triggers or cofactors in the aetiology/pathogenesis of AD (Itzhaki, 2004). Few studies on the role of specific bacteria in the pathogenesis of AD have been conducted, and most have focused on *Chlamydia pneumoniae* and spirochetes. However, reports for both pathogens have been contradictory. *Borrelia burgdorferi* spirochetes were detected inblood and cerebrospinal fluid of AD patients, with *B burgdorferi* antigens co-localized with beta-amyloid deposits, and it was observed that glial and neuronal cells exposed to *B burgdorferi* synthesized amyloid precursor protein and P-taus (Miklossy, 2006). *Treponema denticola* is a prominent periodontal pathogen associated with moderate to severe periodontitis (Ellen, 2005). *Treponema* species including *T denticola* were detected in 14 of 16 post-mortem AD specimens but only detected in 4 of 18 age-matched non-A D specimens.



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Furthermore, specimens from AD subjects had a greater number of *Treponema* species than controls (Riviere, 2002). These results suggest that bacteria, including periodontopathic bacteria, can invade the brain, circulation, and the other mechanism by way of peripheral nerve pathways. Periodontopathic bacteria could potentially use both pathways.

Periodontal Diseases as a Source of Systemic Inflammation: Periodontal diseases are of inflammatory origin affecting the supporting structures of the teeth. The most prevalent periodontal diseases are caused by the interaction of specific bacteria with components of the host immune response in disease-susceptible individuals. Clinically, destruction of the periodontal ligament and surrounding alveolar bone in periodontitis creates deep, ulcerated pockets around affected teeth. The total surface area of the inflamed periodontal pockets within a single subject with moderate to severe periodontitis has been estimated to range from 8 to 20 cm^2, depending on the number of teeth affected. Thus, the inflamed ulcerated periodontal pocket can be a very significant source of inflammatory and pathogen-derived mediators. In view of the profile of bacterial species associated with periodontitis and the unique availability of the periodontal pocket to the circulation and to nervous tissue, it is not surprising that periodontitis can have significant systemic effects (Kamer, 2008). Periodontal bacteria can elicit systemic effects through different mechanisms. First, periodontal bacteria can directly induce pathology by invasion into contiguous body spaces, and Ludwig's angina is an extreme example of this type of pathology. Second, bacteria and its products can be aspirated and induce pulmonary pathology (Scannapieco, 2003). Third, periodontal bacteria might gain access to the systemic circulation and subsequently colonize a distant anatomic site. For example, periodontal bacteria have been implicated in several systemic diseases including endocarditis and brain and lung abscesses (Zijlstra, 1992). In these examples, periodontal bacteria can be isolated and cultured from the affected sites. Bacterial end otoxin or other bacterial products (virulence factors) might also gain access to the systemic circulation and affect various pathologic processes at distant sites. Still another mechanism involves the host response.

Challenged by bacteria, the host produces a multitude of mediators including cytokines that gain access to the circulation. Collectively, these mechanisms account for many systemic disorders with an inflammatory basis.

Periodontal infection can induce systemic pathology: A single periodontal pocket can harbor as many as 300 million organisms (Socransky, 2002). Largely consisting of gram negative bacterial species, periodontal bacteria can incite systemic effects through bacteremia, endotoxemia, and virulence factor release into the circulation. Bacteremia might result from major and minor surgical procedures and routine daily procedures including flossing, brushing, and mastication in subjects with periodontitis comparable to those induced by dental procedures (Lucas, 2000). Most periodontal pathogenic species are gram-negative, colonize sub gingival dental biofilm adjacent to the ulcerated periodontal pocket, and are capable of proteolytic enzyme synthesis that can degrade the host basement membrane and gain access to the systemic circulation. Several periodontal bacterial species have been associated with inflammatory systemic diseases. Periodontitis might exert systemic effects through elevation of proinflammatory cytokines and other inflammatory mediators.

Periodontitis as a risk factor for alzheimer's disease: On the basis of the contribution of moderate to severe periodontitis to systemic inflammation and the potential role of inflammation in the etiology and progression of AD, it was proposed that chronic periodontitis might be a risk factor in the incidence and progression of AD. Periodontitis is a chronic inflammatory disease resulting in years of locally increased proinflammatory molecules that surround the trigeminal cranial nerve endings. Periodontitis also results inyears of systemic host exposure to proinflammatory cytokines and other systemic markers of inflammation such as CRP. Therefore, hypothetically, periodontal-derived cytokines could reach the brain by both systemic and neural pathways and amplify brain cytokine pools. Periodontal pathogens associated with moderate to severe periodontitis are gram-negative anaerobic species, rich in end otoxin/LPS that can stimulate proinflammatory cytokines and CD14activity. In addition, several bacteria associated with severe or progressive periodontitis are capable of invading tissues including *A actinomycetemcomitans, P gingivalis*, and *Tdenticola*. *T denticola* is from the same class as *T palidum,* known to invade brain tissue and to induce chronic inflammation, cortical atrophy, and amyloid deposition in subjects with syphilis. According to the model proposed by Kamer *et al*, cytokines are produced locally during periodontal inflammation and systemically due to periodontal endotoxemia. These cytokines will act on the already primed glial cells, resulting in an amplified reaction and progression of AD. Another way to increase brain inflammatory molecule pool is by the direct action of bacteria or bacterial products as demonstrated by *T palidum*. The progression of AD might manifest clinically as earlier onset or as more severe disease. Inflammation is a prominent component of both AD and chronic periodontitis (Dantzer, 2000).

Role of genetics: Because hyperinflammatory phenotype is considered to play a role in Alzheimer's disease and incertain forms of periodontal disease, polymorphisms of genes involved in inflammatory processes,like IL-1 and TNF-alpha polymorphisms, could be a common risk factor for both the diseases (Galbraith 1999; Nicoll 2000; McCusker 2001). APOE e4 allele is considered to be a strong risk factor for

Alzheimer's disease. Investigations focused on these genetic markers are warranted as these markers could prove to be valuable tools in the early detection of individuals at risk for the development of either of the diseases. In summary systemic inflammation produced by periodontal bacteria and the entry of pathogen products into the brain may increase brain inflammation and contribute to the development of Alzheimer's pathology or hasten the course of the disease in susceptible individuals.

Conclusion

Periodontitis being identified as a disease that is both treatable and cure able holds significant importance in its possible association with Alzheimer's disease. The elimination of periodontitis as a risk factor by the effective treatment modalities could favor the decrease in chances of getting AD. Hence the identification of AD biomarkers at the early stages of Periodontitis will help in arresting the progression of the same.

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