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The Role of Periodontitis as Modifiable Risk Factor for Alzheimer's Disease- A Recent Update

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Abstract

Alzheimer's disease (AD) is among the most common form of dementia affecting geriatric population. Various studies have been carried out to understand the etiopathogenesis of the disease. However, no definite cause has been established and thereby, there is no definite treatment/cure available for eradication of same. The solution for managing the disease is to control the risk factors or triggering factors related to progression or worsening of the condition. Among various risk factors of AD, invasion of the oral pathogens in the brain tissue due to periodontitis (PD) has been associated as risk factor. Various studies had been carried out to state an association between PD and AD. Thereby, this article will discuss most recent evidences available to claim the role of PD as modifiable risk factor in mechanism of AD.

Keywords: *Alzheimer's disease, periodontitis, cytokines, systemic inflammation, periodontal pathogens.*

1. Introduction

There are currently over 55 million cases of dementia present globally. Alzheimer's disease (AD) represents 60-70% of these cases[1]. According to the World Alzheimer's Disease report, 2019, the number of people living with dementia is expected to reach 55 million, with a projected increase to 139 million by 2050 at present rate[2]. The present article updates about the possible link between AD and periodontitis.

Pathogenesis and correlation of Alzheimer's disease with Periodontitis

AD is a complex neurodegenerative disorder related to age with various aetiologies for its origin and progression. It's a chronic neuroinflammatory illness that causes atrophy of brain tissues, resulting in cognitive deficits and, in severe cases, death **Error! Bookmark not defined.** . Systemic inflammation has been shown in studies to exacerbate neurodegeneration by activating primed microglial cells.[3] Both acute and chronic inflammation, that increases many proinflammatory agents, also leads to an increase in cognitive impairment in Alzheimer's disease[4].

Dr. Alois Alzheimer originally described the development of a collection of thick deposits or plaques outside the neurons and bands of fibers or tangles within the brain cells in the autopsied brain of a lady who had memory problems for years[5]. The two main pathogenic features of AD, neurofibrillary tangles (NFT) and amyloid beta (Aβ), are present in these plaques. Increased expression of the amyloid precursor protein (APP) gene owing to a genetic mutation is one probable risk factor for late-onset AD. Apolipoprotein epsilon4 (APOEε4) allele is genetically associated to majority of the AD cases[5]. Other factors that contribute to this includes increased inflammation, oxidative stress, and nerve cell death[6]. Modifiable risk factors have the potential to negatively impact cognitive function and accelerate the development of underlying brain disorders. Therefore, these variables may have an earlier clinical start of dementia.

Bacteria-induced inflammation known as periodontitis causes loss of the tooth supporting tissues. The release of pro-inflammatory cytokines into the systemic circulation in periodontitis is well known to promote "low grade systemic inflammation.". **Error! Bookmark not defined.**

There are two likely mechanisms to explain that periodontitis might accelerate the development of AD as shown in [Fig I][6,7]:

• Periodontitis leading to systemic inflammation/infection [First mechanism]

• Influence of bacteria and viruses [Second mechanism]

According to the **first mechanism**, pro-inflammatory cytokines are increased as a result of periodontal bacteria and the host response. Pro-inflammatory agents and a variety of cytokines enter the bloodstream, increasing the burden of systemic inflammation. Consequently, inducing systemic/peripheral inflammation by periodontitis. These pro-inflammatory molecules can penetrate the blood-brain barrier (BBB) and enter the cerebral regions. This might cause neuronal injury by activating microglial cells. There is evidence that, although the blood–brain barrier (BBB) normally blocks substances from entering the brain, there are specific situations in which inflammatory cytokines may enter or affect the brain[9]. Certain transport mechanisms may allow pro-inflammatory cytokines to cross intact BBB[10]. Cytokines can also access the circumventricular organs at the brain's base through fenestrated capillaries, which are outside the BBB and more readily pierced[11].

Interleukin 1 (IL 1), Interleukin 6 (IL 6), C Reactive Protein (CRP), and Tumor Necrosis Factor (TNF-) are inflammatory mediators associated with periodontal disease that may aggravate cognitive loss in Alzheimer's disease[12,13]. TNF- plays an important role in the progression of neurodegenerative illnesses by promoting gliosis, demyelination, inflammation, degradation of the blood-brain barrier, and cell death[14,15]. According to research including 300 participants, high baseline levels of TNF- were linked to a fourfold increase in the rate of cognitive deterioration**Error! Bookmark not defined.**. Alzheimer's patients have higher blood concentrations of TNF-α, according to several additional studies[16,17 ,18 ,19]. IL-1 promotes the production and translation of AβPP mRNA, which is processed to create Aβ2, and is linked to Aβ in amyloid plaques Alzheimer's patients experienced a faster rate of cognitive impairment when their blood levels of IL-1 β and systemic infection incidence were high **Error! Bookmark not defined.**. In pathological circumstances, IL-6 levels rise, promoting immunological and inflammatory responses that change CNS cell growth and differentiation. A number of studies have found higher levels of IL-6 in the serum or plasma of Alzheimer's patients compared to controls[20,21 ,22 ,23]. Patients with AD have greater levels of C-reactive protein, a nonspecific inflammatory marker, in their blood and brain[24]. When compared to controls, the temporal cortex of AD patients contains greater amounts of the acute phase proteins IL-1, IL-6, and CRP[25,26,27]. A drop in CRP has also been observed in a few recent trials including Alzheimer's patients[28,29]. According to a 2020 systematic review, PD can cause a peripheral inflammatory environment by introducing pathogenic bacteria that are either directly or indirectly related to periodontal abnormalities, as well as proinflammatory cytokines that are locally generated at the periodontal level as a result of bacterial colonization[30].

According to the **second mechanism**, the entry of germs and viruses from the tooth plaque biofilm into the brain might be a risk factor for AD. The entry of germs and viruses can happen directly through peripheral nerves or cerebral transfer via the blood stream. This describes how glial cells connect with the immune system via the blood vascular system, namely the choroid plexus and circumventricular organs, which do not form part of BBB[31]. This region of the brain includes cells that can detect lipopolysaccharides (LPS) in the peripheral blood circulation[32,33]. As a result, components of systemic infections, such those brought on by oral pathogens, affect every organ, including the central nervous system (CNS)[33,34 ,35 ,36 ,37.]

Periodontal infections that cause periodontitis and are tissue invasive include Aggregatibacter Actinomycetemcomitans (Aa), Porphyromonas gingivalis (Pg), Prevotella intermedia (Pi), Tanerella forsythia (Tf), and Fusobacterium nucleatum (Fn)[38,39]. Because of this characteristic, the infections are able to evade the host defense mechanism and spread throughout the host tissues**Error! Bookmark not defined.**. The Hajishengallis et al. keystone theory aids in the explanation of the possibility that Pg contributes to the early onset of a neurodegenerative disease like AD[40]. Treponema denticoli, Treponema pectinovorum, Treponema vincentii, Treponema amylovorum, Treponema maltophilum, Treponema medium, and Treponema socranskii were among the spirochetal species that Riviere et al. recovered from brains of AD patients[41]. In a University of Kentucky, serum antibody levels to periodontal disease-causing bacteria were compared to those of control people in individuals who subsequently converted to AD. Participant's IgG antibody levels to seven oral bacteria associated to periodontitis were measured: Aa, Pg, Campylobacter rectus, Treponema denticola, Fn, Tannerella forsythia, and Pi. Study participants exhibited a considerably higher risk of cognitive impairment if their blood levels of Pg antibodies were raised. Compared to the control groups, AD brain specimens showed a higher number of Treponema species. It is hypothesized that the trigeminal nerve provided

Treponema from the mouth cavity with access to the cerebral cortex. This study offered proof that a long-term periodontal infection in the mouth may raise the chance of AD expression[42,43]. A scoping review conducted in 2023 by Lamphere et al. found that Pg could have a role in the pathophysiology of AD by inducing neuroinflammation and neurodegradation through the activation of the host inflammatory immune response (HIIR). The results of inflammation indicated that there was an overlap in the mechanisms behind PD and AD, as seen by elevated levels of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in the presence of both disorders[44].

It has been demonstrated that oral bacteria, including as Streptococcus sanguis and Pg, cause the production of platelet aggregation proteins, which may contribute to the development of thrombi and atheromas and cause vascular disease[45]. According to a recent comprehensive analysis published in 2021, people with AD have been discovered to include periodontopathogenic bacteria (PD) that include Pg, Fn, An, and Aa. These bacteria are either associated with a greater risk of AD incidence or mortality[46]. It has been discovered that, in the absence of other variables, a high degree of atherosclerosis increases the likelihood of cognitive deterioration. The well-known risk factor for sporadic late-onset AD is inheritance of the apolipoprotein (APOEo4) gene allele, which is also dependent on environmental variables for its advancement. Sporadic late-onset AD is characterized by genetic susceptibility features[47].

4. Conclusion

Thus from the above studies we can draw the conclusion that periodontitis can be a modifiable risk factor for Alzheimer's disease. To identify trends more precisely and comprehend the processes between periodontitis and Alzheimer's disease, more thorough study is needed in different settings and over longer time spans in the future. Improving dental hygiene habits and treating periodontitis in a timely manner can help lower the risk of cognitive deterioration in elderly people.

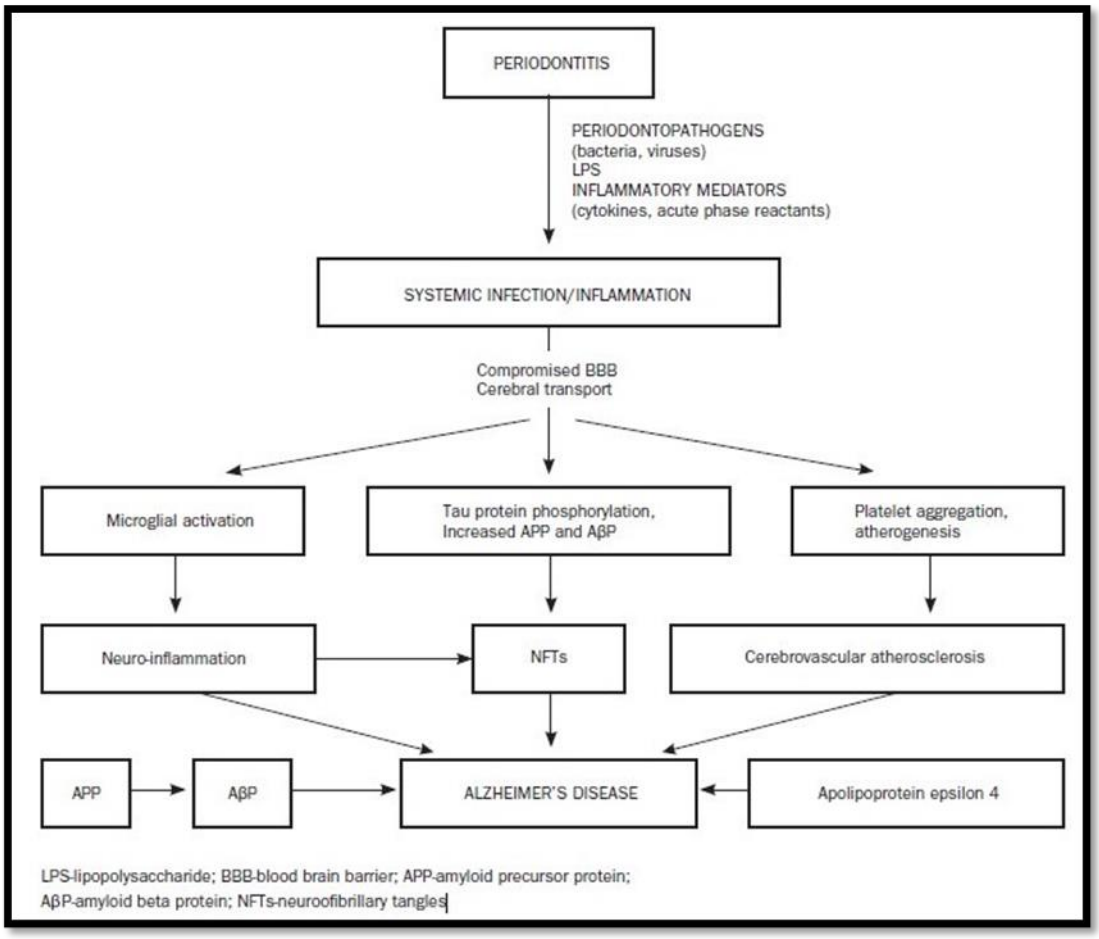

Fig I: Possible pathways for the pathogenesis of Alzheimer's disease.**Error! Bookmark not defined.**

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