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"PERIODONTITIS AND ALZHEIMER'S DISEASE – EXPLORING THE INTERCONNECTION"

Dental Sciences

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ABSTRACT

Alzheimer's disease(AD), a neurodegenerative disorder, unfolds gradually, impacting the memory, thinking and behaviour of the individuals.It involves accumulation of senile plaques in cortical and limbic areas of brain resulting in atrophy of brain and neuronal death. Periodontitis has been linked to the progression of Alzheimer's disease. It's considered a low grade systemic condition that triggers the release pro-inflammatory cytokines, leading to an escalation in C-reactive protein. Oxidative damage and inflammation, seen in both disease and periodontitis, manifest in the brain pathology of Alzheimer's disease.This review article aims to elucidate the connection between the causation of periodontitis and Alzheimer's disease, shedding light on their bidirectional relationship.

KEYWORDS

Alzheimer's Disease, Inflammation, Periodontitis, Pro-inflammatory cytokines, C-reactive protein.

INTRODUCTION

Alois Alzheimer, German neuropathologist discovered Alzheimer's Disease in 1906, determined it as progressive neurodegenerative disorder characterised by cognitive & behavioural impairment. These include memory deterioration, incapacity to encode new memories, challenges in logical reasoning, and language impairment[1]. The prevalence of Alzheimer's disease rises substantially with age, approaching nearly 50% among individuals who are 85 years old[2]. The global importance of Alzheimer's disease has garnered considerable attention, given that AD and various types of dementia were the 7th leading cause of death worldwide in 2019[3]. Despite extensive research spanning decades, the precise mechanisms underlying the development of degenerative neurodisorders like AD remain elusive.The primary targets for therapeutic intervention in AD is the accumulation of aggregates, often referred to as plaques, and the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein[4].

The inflammatory disease of periodontium is the seventh, most prevalent disease worldwide (Institute for Health Metrics And Evaluation,IHME,2020)[5]. Prior studies have shown that PD is linked to systemic conditions such as diabetes, cardiovascular diseases, and rheumatoid arthritis. Current findings indicate that oral dysbiosis can hasten the development of AD pathological features. This review explores the connection between Alzheimer's disease and periodontitis, shedding light on how periodontal disease impacts the advancement of AD.

Pathogenesis Of Alzheimer's Disease

Alzheimer's Disease (AD) is characterized by the loss of neurons and the presence of two distinct abnormal structures in the brain: senile plaques and neurofibrillary tangles(NFTs). Senile plaques consist of a protein called β-amyloid (Aβ), while neurofibrillary tangles are formed by an altered protein called tau, which has been excessively phosphorylated. These changes result in the progression of Alzheimer's, affecting cognitive function and overall brain health[6].

The Aβ is a polypeptide fragment that is formed by the amino acids released by the cleavage of amyloid precursor protein (APP, a 695-amino acid membrane-localized protein)[7]. In healthy physiological conditions, Aβ peptides are typically engulfed and broken down by enzymes within immune cells such as monocytes, macrophages, and neutrophils. These cells then eliminate the degraded Aβ through excretion in bile and urine. However, when the clearance process becomes inefficient or if there is an overproduction of Aβ, these protein aggregates accumulate outside the brain cells, inducing the formation of senile Aβ plaques[1].Fibrillary intracytoplasmic structures in neurons, known as neurofibrillary tangles, are formed by a protein called tau. The tau protein primarily functions to stabilize axonal microtubules. Microtubules, which traverse neuronal axons, are crucial for intracellular transport. The tau protein is responsible for preserving the cohesion of microtubule assembly[8]. *When tau becomes abnormally hyperphosphorylated, it destabilizes the assemblies of tubulin in neuronal axons thereby leading to the origination of NFTs (*Figure 1)[9].

Apart from the neuronal elements of Aβ plaques and tauopathies, the involved mechanisms of the immune system inside glial cells play a significant part in the progression and severity of AD. These immune responses involving glial cells contribute to the overall pathological process and worsening of the condition[1].

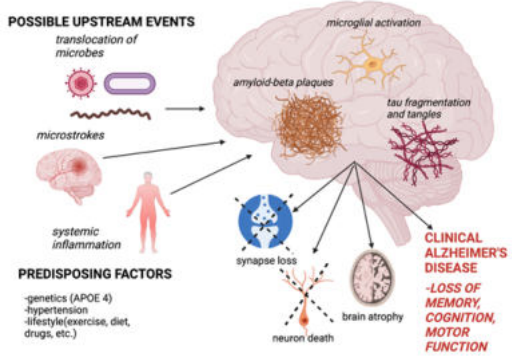

Figure 1. A visual illustration depicting the advancement of Alzheimer's Disease involves the interplay of various factors, including Aβ plaques and tauopathies, as well as glia-mediated immunological mechanisms, which contribute to the progression and severity of the condition.

Microglial Activation In Alzheimer's Disease

Microglia cells, which are mononuclear phagocytes within the brain, serve in maintaining the CNS homeostasis and protect neurons by clearing Aβ plaques. In a healthy state, microglia exhibit neuroprotective functions. However, when activated or stimulated, they produce pro-inflammatory cytokines which stimulate glial cells through paracrine and autocrine pathways, leading to increased production of Aβ42, P-Tau, and pro-inflammatory molecules. This process results in a self-perpetuating cycle where inflammatory mediators both activate glial cells and trigger molecular pathways contributing to neurodegeneration. Unrestrained release of these factors can cause neural damage. Microglial function can be perceived as a "double-edged sword," since it has the potential to either safeguard or jeopardize neurons depending on the context[10].

Periodontal Inflammation

Periodontitis is a multimicrobial inflammatory disorder of the oral

cavity caused by dental plaque microbes. It's characterized by bleeding, pus, deepening gum pockets, bad breath, tooth spacing, and mobility in severe cases. Bacterial invasion impacts the tissues surrounding the tooth, leading to the oral health concern[2].

Pathogens that are responsible for causing periodontal disease comprise of red and orange complex bacterias, these are *P. gingivalis, T. forsythia, P. intermedia. E. corrodens, F. nucleatum, A. actinomycetemcomitans* and *T. denticola*. Keystone pathogen, that induces dysbiosis of its companion species which results in periodontal inflammation is namely *P. gingivalis*[11].

These microorganisms destroy the gingival & periodontal tissues that support teeth by secreting many proteolytic enzymes. Further, when LPSs are secreted by the gram-negative bacteria there is an induction in the levels of various proinflammatory factors/cytokines such as IL(1α, 6, 1β,), TNF-α, prostanoids, and MMP which are produced by different immune cells like neutrophils as well as monocytes hence amplifying the destruction of periodontal tissues. Consequently, the host response assumes a complex "dual role," exacerbating tissue destruction through the amplified expression of proteolytic enzymes, thus contributing to self-inflicted damage[9].

Role Of Periodontal Pathogens in Alzheimer's Disease

The bacteria linked to Alzheimer's Disease (AD) predominantly include periodontal pathogens, present in dental plaque on tooth surfaces. These bacteria comprise Gram-negative species such as *P. gingivalis*, and other periodontal pathogens, as discussed earlier. It has been researched that keystone pathogens namely *T. denticola* and *P. gingivalis* could play positive role in the initiation and advancement of Alzheimer's disease, though further research is compulsory to comprehensively grasp the connection between oral health and brain health[7]. An expanding body of evidence indicates that P. gingivalis can elevate the synthesis of Aβ plaques, tau phosphorylation and neuroinflammation, potentially contributing to AD. P. gingivalis causes periodontitis, elevates pro-inflammatory cytokine levels, and causes inflammation. Cytokines are signaling proteins that help cellular passage in the brain, thus enabling *P. gingivalis,* OMVs (Outer Membrane Vesicles) , or its secretions to pass through[12]. Furthermore, in major ways LPS and gingipain contribute to *P. gingivalis* virulence and have been shown to cause direct tissue destruction, spread inflammation, and regulate the host's immune response from acute to chronic periodontitis. *The gingipain have the ability to directly invade the endothelial cells, that can cause severe injury to the cerebral microvasculature, which in turn makes the endothelial tight junctions to degenerate and increase the permeability of the BBB[13]. The other virulent factor, that emerges as a potential contributor to neurodegeneration is lipopolysaccharides (LPS) of P. gingivalis. Pathogen- associated molecular patterns (PAMPs) such as LPS recognize & bind with pattern recognition receptors (PRR) that are Toll-like receptors (TLR) selectively expressed by microglial cells. This mechanism activates the inflammatory response in glial cells*[1].

Inter-Relation between Periodontal Disease and Alzheimer's Disease

This situation is akin to the chicken & egg dilemma, which came first? As the causal relationship is not identified between these two disease entities. Patients suffering from Alzheimer disease have reported to have impaired cognitive skills, that leads to inadequate oral hygiene practices. However, poor oral hygiene remains a significant factor for periodontal disease as depicted in Figure 2 [1]. It is hypothesized that periodontitis could commit to the advancement of AD through two possible mechanisms:

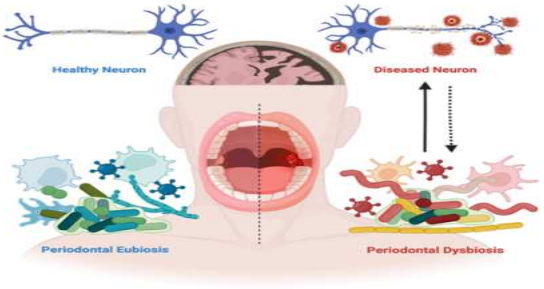

Figure 2. Illustration Demonstrating the Inter-relation Between Periodontitis and Alzheimer's Disease.

A. There is one hypothesis that suggests that periodontal pathogens enter the BBB, & cause direct damage to central nervous system with astrogliosis, demyelination and death of neuronal cells. Gliosis is a reactive response by astrocytes, which occurs as a result of any injury to brain tissue.It attempts to limit the neuronal damage. However, prolonged or excessive gliosis can result in scarring & inflammation of CNS[9]. The pathophysiological mechanism which potentially explains the association between periodontitis and Alzheimer's disease is depicted in Figure 3[14].

B. The other hypothesis is that, it can be through the increased levels of pro-inflammatory cytokines. This will lead to increase in the state of systemic peripheral inflammation. Ultimately affecting the health of microglial cells & result in neuronal damage, exacerbating the effects of neurodegeneration.

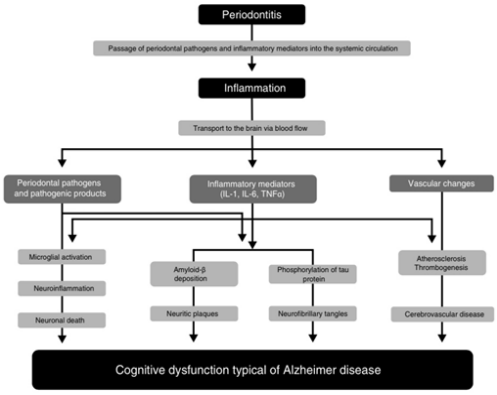

Figure 3. Pathophysiological mechanisms that potentially explain the association between periodontitis and Alzheimer's disease.

Implication Of Inflammation In Brain

Chronic or excessive neuroinflammation can have detrimental effects on brain health, including neurodegeneration, disruption of the blood-brain barrier, and cognitive decline, particularly in the elderly population. Comprehending these implications is vital for crafting precise treatments and strategies to alleviate the influence of neuroinflammation on brain function and general well being. Direct implications of bacterial infections in the elderly is said to affect memory via cytokine release in response to infection[15].

CONCLUSION

The interconnection among periodontitis and Alzheimer's disease represents burgeoning area of research with the potential to revolutionize our comprehension of these widespread conditions. According to the study conducted by Lamphere AK, Nieto VK, Kiser JR, Haddlesey, it was revealed that infection by P. gingivalis appears to be potentially associated to the pathogenesis of AD by activating the HIIR (Host Inflammatory Immune Response), causing neuroinflammation and neurodegeneration[16]. By exploring the shared pathophysiological mechanisms, we can develop novel therapeutic strategies and preventive measures that may improve the quality of life for millions of individuals affected by these diseases worldwide. Hence, it is recommended to take proactive measures to halt the advancement of periodontal disease thereby avoiding potential systemic consequences.

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