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The Microorganisms In Periodontal Disease Effects On Alzheimer's Disease

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Abstract

A neurological disease called Alzheimer's disease (AD) is significantly more likely to develop as people age. Several factors and aetiology contribute to dementia, such as increased levels of pro-inflammatory cytokines and microglial activation, inflammatory mediators that worsen brain inflammation in AD, and associations between tooth count and periodontal disease, cognitive ability, and Alzheimer's disease. Furthermore, this article discussed the relationships between Alzheimer's disease, periodontal disease, and bacteria associated with periodontal disease. The blood-brain barrier is weakened, and the risk of cerebrovascular illness is increased by periodontal disease-related factors (bacterial infection and chronic inflammation). The illnesses also cause inflammation in the brain. By worsening diabetes, periodontal disease may contribute indirectly to the aetiology of Alzheimer's disease. Even though the existing clinical evidence supports the comorbidity of periodontitis and AD, no research has been done to establish a causal connection between the two conditions. In conclusion, inflammation plays a crucial role in both periodontitis and AD. Since periodontitis is both preventable and treatable, people with periodontitis should be educated and treated to reduce the microbiological challenge and the hyperproduction of pro-inflammatory cytokines, thereby promoting a higher quality of life.

Keywords: Alzheimer's disease, periodontal disease, neuroinflammation, periodontitis-related diseases

Introduction

Age considerably raises the possibility of contracting Alzheimer's illness (AD), a neurodegenerative condition. It may start out early or late [1, 2]. Heightened pro-inflammatory cytokine quantities and microglial activation, those that all relate to the inflammatory state of the central nervous system, are notable hallmarks of AD (CNS) [3]. While gram-negative anaerobic bacteria are linked to periodontitis, a common mouth infection. Periodontitis is a "low-grade systemic disease" if inflammatory markers are released into the circulatory system and C-reactive protein levels rise (CRP). It has been well known as inflammation serves as a link between AD and periodontitis and plays a significant role in the progression of both illnesses [4]. Periodontal disease has an impact on the teeth's supporting structures, including the gums, alveolar bone, and other tissues (PD), which results in inflammation and tissue degeneration [5]. The gums, the alveolar bone, and other components that support the teeth are all affected by periodontal disease (PD), which results in inflammation and tissue degeneration [6]. The complicated etiology of PD involves pathogenic microorganisms found in tooth plaque that trigger host immune response [6]. The loss of jawbone and soft tissue necessary to support teeth occurs as a result of immunological responses and persistent systemic inflammation that are frequently caused by PD [6]. It is interesting to note that a sizable portion of the global population suffers from periodontal diseases, are these illnesses of the mouth that harm the tissues supporting the teeth [7]. If the inflammation is contained to the gingival tissues, they fall under the category of gum disease; however, if the inflammation spreads deeper into

the interconnected and skeletal tissue, it can take on a more damaging form, leading to the loss of bone and attachment, which may ultimately lead to tooth loss [8]. Through processes such as the spread of pro-inflammatory cytokines and/or germs from the mouth to extra-oral locations, this local inflammatory process may lead to a systemic inflammatory state [9, 10]. As a result, periodontitis may cause or worsen an inflammatory condition, particularly in senior individuals, which could impair memory and hasten the onset of neurodegenerative illnesses like AD. The Review's purpose is to discuss the relationship between AD and periodontitis that may exist. In addition, this review explores microorganism effects on AD and the systemic inflammation contributes to the worsening of neuroinflammation in the development of AD.

AD pathophysiology

A-amyloid 1-42 peptide (A-42) present in senile plaques, hyperphosphorylated tau protein (P-Tau) constituting NFTs, or elements of dying neurons all have a propensity to cause inflammation in AD [3, 11]. These pathologic alterations will likely excite microglial cells in turn. At low concentrations, these microglial cells have a protective character (concentration). By serving as mononuclear phagocytes to protect the central nervous system from any noxious harm, they assist for preserving homeostasis in the brain (CNS) [12]. Microglial cells help safeguard the nervous system in healthy people by removing A-P plaques [13]. The typical neuroprotective capacity of the microglial cells is reduced with advanced years and genetic susceptibility, leading to the maintenance of the inflammatory process inside the CNS [9]. As a result, when exposed to systemic inflammatory signals, brain microglial cells direct their morphologies to create neurotoxic chemicals [14, 15]. Instead of offering a defensive immunity to the signals of the inflammatory process, such a reaction of the microglial cells leads to the development of AD [16]. The so-called "activated microglial cells"—induced microglial cells that have undergone morphological changes and produce cell antigens—lead to the unchecked production of proinflammatory factors [17]. This unchecked expression of factor levels as in AD can result in neurodegeneration, implying that now the production of inflammatory molecules will aid there in the development of AD [18, 19].

As complementing components around senile plaques were found in post-mortem brain tissue from AD patients, a role for neuroinflammation in the pathophysiology of the disease has been suggested [20]. Numerous epidemiological studies that found that persistent use of nonsteroidal anti-inflammatory medicines lowers the chance of acquiring AD and that various inflammatory mediators are higher in the brain and cerebrospinal fluid of AD patients provided more evidence in favor of this theory [21, 22]. According to the conventional theory, A deposits or oligomers cause microglia to be recruited and activated, which causes them to produce inflammatory mediators that speed up this already occurring neurodegenerative process. Nevertheless, other writers contend that neuroinflammation plays a more significant part in the disease's development than was previously thought [23]. The idea that the central nervous system (CNS) is not an immune-isolated environment has also been revised, though there is growing evidence of a two-way communication between the brain and the peripheral immune system [23]. The peripheral systemic inflammation may play a crucial function in the advancement of AD's neurodegeneration as well as the genesis of the illness. The primary underlying process is the "priming" of microglia, which postulates that microglia acquire a "primed" phenotype, ready to exhibit a harmful pro-inflammatory response to subsequent assaults [23]. A variety of factors, including I aging, (ii) proteins linked to AD pathogenesis (such as A, tau), and (iii) systemic inflammation, may be the first triggers for microglia priming. Continued systemic inflammatory events would convert pre-activated microglia to an aggressive pro-inflammatory phenotype, accelerating neuroinflammation and neurodegeneration [2, 24]. Notably, at least five of the major avoidable risk factors for AD, including smoking, depression, hypertension, diabetes mellitus, and obesity, share a similar relationship with a systemic pro-inflammatory phenotype [25]. This provides additional evidence in favor of the idea that systemic inflammation may be fundamentally involved in the onset and progression of AD [26]. It is vital to remember that chronic complement system activation is linked to AD [18, 27]. Proteins linked to AD can system to be implemented, attract activated glia (astrocytes and microglia) to the amyloid plaque, and release cytokines that may contribute to neuronal degeneration in AD [9, 28, 29].

AD, Periodontal Disease-Related Bacteria, and Periodontal Disease

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There have been reports of links between tooth count and the presence or absence of periodontal disease, cognitive function, and Alzheimer's disease [30]. Individuals with edentulous jaws and few teeth have a higher frequency and incidence of dementia [31]. In addition, a meta-analysis indicated significant associations between dementia and many clinical indicators of periodontal diseases, such as periodontal probing depth (PPD), bleeding on probing (BOP), and gingival bleeding index (GBI), clinical attachment level (CAL), and plaque index (PI) [30]. After observing periodontal disease patients and healthy volunteers over 50 for ten years, it was shown that periodontal disease patients have a 1,7-fold higher risk of developing AD than healthy ones. In addition, people with periodontal disease exhibit a faster decline in cognitive function than healthy individuals [32]. In periodontitis patients, peripheral blood levels of inflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α are elevated; these inflammatory mediators may exacerbate brain inflammation in AD [26]. Chronic inflammation in peripheral organs can aggravate Alzheimer's disease's molecular aetiology [5, 33]. In addition to being a chronic inflammatory disease, the periodontal disease contributes to the development and progression of various conditions, including arteriosclerosis, diabetes, obesity, preterm delivery, and low birth weight in newborns [34].

It has been shown that changes in gut microbiota are associated with lifestyle-related conditions such as obesity, cardiovascular disease, and diabetes [24]. Recently, a link between the gut microbiome and dementia has been shown, and the microbiome-gut-brain axis may influence the gut microbiota's effect on the host's brain function [35]. Specifically, abnormalities in the gut flora cause cerebral inflammation, which can lead to amyloid deposition in the brain [36]. Therefore, enterobacteria may have a role in the development of Alzheimer's disease [30]. Significantly fewer enterotype I bacteria was seen in the gut flora of dementia patients compared to healthy individuals [36]. Intestinal Bacteroides species are more abundant in individuals with mild cognitive impairment (MCI) gut microbiome [35]. In addition, individuals with several Bacteroides species demonstrated hyperintensity of the white matter and parahippocampal atrophy [37]. These results suggest that an increase in specific gut bacteria may contribute to the genesis of dementia [24]. During the autopsy, it was reported that bacteria were discovered in the brains of AD patients [37]. It has been demonstrated that HSV1, *Chlamydia pneumonia*, spirochetes, and fungi cause brain inflammation, which results in synaptic dysfunction and neuronal cell death [37]. To defend the brain from invading germs, neurons produce amyloid (A), which has been discovered to fold, kill infections, and protect the brain [15]. Thus, A may function in the brain as an infection-causing innate immune molecule. On the other hand, it is hypothesised that A-containing bacteria are deposited in brain tissue, resulting in the formation of senile plaques that damage cranial nerves and worsen AD [38]. In addition to these bacteria, it is believed that periodontal pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Tannerella forsythensis*, and *Eikenella corrodens* contribute to the development of a variety of inflammatory diseases at distant organ sites, such as AD [10]. The relationship between *Porphyromonas gingivalis* and AD has generated much interest. *P. gingivalis*, a bacteria associated with periodontitis, was often identified in the brain tissue of AD patients who had had an autopsy [39]. However, the bacteria were not identified in normal human brain tissue [40]. Gingipain, a toxin produced by the same bacteria, has been frequently detected in the brains of AD patients, and a mouse model implies that the toxin may play a role in the onset of AD. *P. gingivalis* was administered directly into the oral cavities of AD model mice (APP-Tg mice) to generate experimental periodontitis, and the cognitive capacities of the *P. gingivalis* administration group and the non-administration group were assessed using a novel object recognition test [32, 41]. Cognitive function was significantly decreased in the *P. gingivalis* administration group compared to the control group [42]. In addition, A deposition, TNF-and IL-1 production, and LPS levels in the brain were more remarkable in the *P. gingivalis* treatment group than in the control group [43]. Additionally, it was shown that *P. gingivalis* LPS enhanced the manufacture of A in neurons and that the coexistence of LPS and A boosted the production of TNF-α and IL-1 in microglia cells [21, 44]. These data indicate that an infection with *P. gingivalis* and the subsequent inflammation impairs AD's performance [38, 45].

Relationship between neuroinflammation and periodontitis-related diseases

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The co-occurrence of periodontal disease and AD has been shown on two front lines [46]. The first line of evidence implies that Alzheimer's patients have lower oral health due to their deteriorating cognitive function, which impacts their oral hygiene habits [42]. The second idea is that untreated, periodontal disease may trigger or exacerbate AD-associated neuroinflammatory processes [44]. The absence of interventional trials indicating a direct link between periodontitis and AD must be emphasised [47]. Periodontitis is a chronic inflammatory disease brought on by gram-negative bacteria that stimulate an immuno-inflammatory response in the host, causing tooth apparatus destruction [14]. Bleeding following probing and clinical attachment loss are clinical symptoms of this condition [9, 13]. If the disease is left untreated or with poor treatment, the gums are often swollen and discoloured [30]. Dental calculus is frequently found on injured teeth, and tooth loss can result if inadequate treatment or the condition is left untreated [48]. Patients with periodontitis are frequently asymptomatic until the onset of crucial processes such as tooth abscesses and necrotising periodontal infections [49]. Consequently, periodontitis is commonly misdiagnosed by both patients and health professionals, despite its high prevalence among the adult populations of both industrialised and developing countries [50].

Periodontitis and AD: The Role of Inflammation

It is well acknowledged that inflammation plays a significant role in this process [9]. Two hypothesised mechanisms connect periodontitis to the progression of Alzheimer's disease [51]. Two hypotheses explain the relationship between periodontitis and AD [52]. According to the first mechanism, a surge in pro-inflammatory cytokines is induced by periodontopathic bacteria and the host's response [46]. These pro-inflammatory molecules are capable of penetrating the BBB and entering the brain [52]. This causes the activation/priming of microglial cells and neuronal damage [52]. This results in releasing numerous cytokines and pro-inflammatory substances into the systemic circulation, leading to a systemic inflammatory burden and peripheral inflammation [41]. The second mechanism is probably associated with the invasion of the brain by bacteria in dental plaque biofilm [32]. Plaque microorganisms can infiltrate the brain via the circulation or peripheral nerves [40]. These microorganisms and their metabolites trigger an inflammatory reaction in the central nervous system [40]. It is generally accepted and supported by crucial evidence that inflammation in the CNS produces cognitive deficits comparable to AD [40]. This inflammatory damage is caused by cytokine-mediated interactions between neurons and glial cells [53]. As for serum and plasma biomarkers for the aetiology of AD, the IL family, TNF-, transforming growth factor-, and chemokines (monocyte chemotactic protein, IL-8, macrophage migration inhibitory factor, and monokine produced by interferon) have been found [45, 54]. In neurodegenerative diseases, inflammation-induced cytokine production (especially TNF-α) is essential [25, 55]. The inflammatory response is exacerbated by TNF, which causes gliosis, demyelination, BBB disintegration, and cell death.

According to a study on mice, anti-inflammatory medications reduce neuroinflammation and amyloid plaque development in animal models [17]. Therefore, TNF- α plays an essential role in the neurodegenerative process [17]. The indicated anti-inflammatory drugs considerably reduce the anti-inflammatory effects of these cytokines and other pro-inflammatory molecules [17]. In addition, IL-1 and glial fibrillary acidic protein levels are considerably reduced in mice treated with a nonsteroidal anti-inflammatory agent [56].

The Alzheimer's disease The Anti-inflammatory Prevention Trial (ADAPT) examined the efficacy of anti-inflammatory pharmaceuticals and hypothesised that the favourable effect of anti-inflammatory treatments is only evident in the asymptomatic early stages of the disease [14]. In AD patients, elevated levels of IL-1 suggested cognitive decline [24, 57]. During a 2-month follow-up period, cognitive impairment was more prevalent among individuals with high baseline indicators than those without elevated baseline markers [58]. It is believed that dementia is a complex syndrome stemming from the interaction between genetics and systemic inflammatory conditions [59]. Blood levels of elevated inflammatory markers suggest the presence of dementia and cognitive impairment [59]. In both cross-sectional and longitudinal studies, poor oral health has been associated with dementia [59]. Thus, it is considered that periodontitis, which produces inflammatory chemicals in the systemic circulation, is an obvious risk factor for several systemic illnesses, including Alzheimer's disease [39, 59, 60].

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Conclusions

Inflammation has a crucial role in both periodontitis and AD, in conclusion. Since periodontitis is preventable and curable, people identified with periodontitis should be educated and treated to lessen the microbiological challenge and the hyper-production of pro-inflammatory cytokines, thus encouraging a greater quality of life, especially in the elderly. In addition, despite the availability of clinical data confirming the comorbidity of periodontitis and AD, as well as the discovery of blood antibodies to periodontal pathogens in AD, there is no study proving the causal link between periodontitis and AD. Based on previous research and our findings, we have outlined the connections between periodontal disease, periodontal disease-related microbes, and Alzheimer's disease. Circumstances associated with periodontal disease (bacterial infection and chronic inflammation) compromise the blood-brain barrier and raise the risk of cerebrovascular disease. Additionally, the disorders produce brain inflammation. Periodontal disease may indirectly increase the aetiology of Alzheimer's disease by aggravating diabetes.

Additionally, tooth loss diminishes cognitive function. Therefore, it is probable that both directly and indirectly, periodontal disease exacerbates the state of dementia. Consequently, periodontal care is deemed vital for dementia management. In contrast, periodontal disease patients frequently develop bacteremia owing to daily cleaning and chewing. In addition to treating periodontitis to avoid AD, invasive treatments like scaling and root planing must be used to prevent bacteremia. In addition, examining gut microbiota and oral microbiomes as possible risk factors for dementia may aid in the prevention of dementia by identifying potential risk factors. Changes in the bacterial flora are related to both quantitative and qualitative dietary changes. By figuring out what causes nutrition, bacterial flora, and dementia, it might be possible to come up with a new way to prevent dementia through better eating habits.

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