

Periodontal Disease and its Relevance in the Etiopathogenesis of Alzheimer Disease: A Literature Review

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Abstract

The aim of this review paper was to update the relationship between periodontal disease (PD) and Alzheimer's disease (AD) in order to determine if PD is associated with an increased risk of dementia severity and cognitive decline and to eventually conclude to possible therapeutic implications of this relationship.

Keywords: *Periodontitis; Periodontal Disease; Alzheimer Disease; Tooth Loss; Dementia*

Introduction

Alzheimer disease (AD) is a neurodegenerative disease characterized by generalized loss of numerous markers of social values leading to the onset of dementia. Its main symptoms include impairment of memory and judgment, attention span, sleep pattern disturbances, difficulty in performing familiar tasks and problem solving skills that are followed by severe apraxia and a global loss of cognitive abilities. As the disease progresses, the person experiences difficulty in performing neuromuscular actions such as swallowing, walking and even breathing [1].

In 2015, the World Health Organization has estimated that 46.8 million people worldwide are diagnosed as having dementia. This number is expected to increase to 74.7 million by 2030 and to 131.5 million by 2050. According to this report, there will be one new case of dementia in every 3 seconds [2]. Questions still arise today about how society can cope with such numbers and whether enough care can be provided.

The pathogenesis of AD has been a subject of great interest but is still not understood in its entirety. The role of the inflammation in this disease has been suggested to cause neuronal damages in the form of a positively reinforced cascade of events in the central nervous system. In consonance with this theory, periodontal pathogens and proinflammatory mediators may enter the nervous system from peripheral sources such as the oral cavity via the blood brain barrier and/or by the stimulation of peripheral nerves which amplifies the neurodegeneration. In this perspective, the periodontal disease may contribute to the evolution and the progression of AD.

Currently, there is no known cure for Alzheimer. Thus, investigating its association with periodontal disease might help understanding the disease mechanisms. Hence a review of the literature on the subject was undertaken. The purpose of this paper was to update the relationship between PD and AD in order to determine if the periodontitis is associated with both increased dementia severity and

cognitive decline risk and to conclude to how the alleged association between these conditions might infuse new hopes for therapeutic interventions that could prevent the progression of AD.

Overview of Alzheimer's disease

Described by Alois Alzheimer in 1907, AD is a degenerative brain disease and the most common cause leading to dementia [3]. In AD, the damage and destruction of neurons eventually affects parts of the brain, including those that enable a person to carry out basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require around-the-clock care. AD is ultimately fatal [4].

The disease symptoms vary among individuals. The most common initial symptom is a gradually worsening ability to remember new informations. This occurs because the first neurons to be damaged and destroyed are usually in brain regions involved in memory function. As neurons in the other parts of the brain are damaged and destroyed, individuals experience other difficulties such as decreased or poor judgment, Withdrawal from work or social activities as well as Changes in mood and personality, including apathy and depression.

In fact, two levels of cerebral lesions can be observed in an AD brain: extra and intra-cellular damage [4]. The extra cellular lesions are represented by bundles of non-vital cerebral cells within the amyloid substance, this substance being encoded by the chromosome 21. However, intra-cellular lesions concern the Tau protein which appears with an abnormally elevated degree of phosphorylation, leading to the disorganization of neuron structure. In certain families, corresponding mutations on chromosome 17 have been described [4]. The accumulation of the protein beta-amyloid also called β -amyloid plaques, outside neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons are two of several brain changes that contribute to the damage and destruction of neurons that result in memory loss and other symptoms of AD. As the brain changes advance, information transfer at synapses begins to fail, the number of synapses declines, and neurons eventually die. The accumulation of β -amyloid interferes with the neuron-to-neuron communication at synapses. Tau tangles block the transport of nutrients and other essential molecules inside neurons. This leads to cell death [4]. Therefore, the brain of an advanced AD individual shows inflammation, dramatic shrinkage from cell loss and widespread debris from dead and dying neurons.

These brain changes may begin 20 or more years before symptoms appear. When the initial changes occur, the brain compensates for them, enabling individuals to continue to function normally. As neuronal damage increases, the brain can no longer compensate for the changes and individuals show subtle cognitive decline. Later, neuronal damage is so significant that individuals show obvious cognitive decline, including symptoms such as memory loss or confusion as to time or place. Later still, basic bodily functions such as swallowing are impaired [3].

Place of inflammation in neurodegeneration

There is an increasing recognition that inflammation plays a critical role in neurodegenerative diseases of the central nerve system (CNS), including Alzheimer's disease. Differential immune responses involving the adaptive versus the innate immune system are observed at various stages of this neurodegenerative disease and may not only drive disease process but could serve as a therapeutic target. Ongoing investigations into the specific inflammatory mechanisms that play roles in disease causation and progression have revealed informations about the inflammation-driven neurodegeneration [5]. In consonance with this theory, inflammation causes neuronal damages in the form of a positively reinforced cascade of events in the CNS, beginning with stimulation of the glial cells in the brain to produce pro-inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1) and interleukin-6 (IL-6). These in turn stimulate the glial cells to produce pathologic protein molecules such as P-tau and Amyloid β 1-42 peptide that ultimately cause nerve cell damage [6]. Pro-inflammatory mediators may enter the nervous system from a peripheral sources such as the

oral cavity via the blood brain barrier (BBB) and/or by the stimulation of peripheral nerves, leading to the amplification of inflammatory molecules in the CNS [6].

Relevance of periodontal disease in the etiopathogenesis of Alzheimer's disease

Periodontal disease (PD) begins with gingivitis, the localized inflammation of the gingiva that is initiated by bacteria in the dental plaque. Chronic periodontitis occurs when untreated gingivitis progresses to the loss of the gingiva, alveolar bone and periodontal ligament, which creates the deep periodontal 'pockets' that are the hallmark of the disease and can eventually lead to tooth loss. Periodontal disease may contribute to the body's overall inflammatory burden, worsening systemic conditions such as diabetes mellitus and atherosclerosis [7].

The dental plaque biofilm is the most potent cause of direct and indirect periodontal tissue damage. Chronic gingivitis and chronic periodontitis are initiated and sustained by the microorganisms of the dental plaque. Indeed, the microbial biofilm has been extensively studied and can comprise around 150 species in a single person, and up to 800 different species have been identified in human dental plaque so far. Putative pathogens include Gram negative anaerobic bacteria such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia* etc. spirochetes such as *Treponema denticola* and even viruses (HSV, CMV...) [7].

The diversity and abundance of the specific bacteria in the biofilm are a function of a dynamic, multidirectional communication between bacteria, environment, host genetics, and its immune system [7]. The inflammatory response in PD includes the activation of leucocytes, neutrophils, T-lymphocytes and plasma cells. It also includes the release of antibodies, lipopolysaccharides (LPSs) and chemical inflammatory mediators, such as cytokines, chemokines and CRP. LPSs are present in the gram-negative bacterial cell walls and act as powerful stimulants for complex host responses. The initial surge of neutrophils at the site is followed by the release of cytokines by neutrophils and macrophages. The released chemical mediators include tumor necrosis factor-alpha (TNF- α), interleukin-1 (IL-1) and prostaglandins (PGs). The inflammatory process includes the stimulation of fibroblasts by IL-1 and the secretion of matrix metalloproteinases (MMPs) by polymorphonuclear neutrophils. While MMPs are responsible for increased collagen breakdown, TNF- α is primarily responsible for increased osteoclast activity that results in bone resorption. MMPs can also activate cytokines and chemokines, which can exacerbate the destructive process. The production of collagen is inhibited by reduced fibroblast activity in response to TNF- α .

Lymphocytes release antibodies as protective mechanisms. However, lymphocytes also activate the osteoclasts that result in bone loss. T-lymphocytes secrete the receptor activator nuclear factor kappa-B ligand (RANKL), which is involved in osteoclast activity and leads to bone resorption. The destructive inflammatory mediators are inhibited by the presence of osteoprotegerin and the secreted tissue inhibitors of metalloproteinases (TIMPs) [8].

Periodontal bacteria can enter the systemic circulation frequently during daily procedures such as flossing, brushing, and mastication particularly when periodontitis is present. In the blood and then tissues, keystone pathogens and other bacteria can further evade and subvert the immune system and metastasize at distant sites inducing focal inflammation [9].

It has been proposed that PD can initiate or contribute to the AD pathogenesis through multiple pathways. Infection-induced effects of AD have been reviewed critically in the literature. Miklossy proposed that oral bacteria including spirochetes could be possible candidates to invade the brain and contribute to AD pathology [10]. Moreover, *P. gingivalis*-derived LPS were also detected in the brains of AD patients [11]. Subjects with periodontitis have also a systemic inflammation characterized by elevated levels of IL-1, IL-6 and TNF- α and CRP which is thought to contribute to other inflammatory diseases such as cardiovascular diseases which are a risk factor for AD [9].

In fact the interaction between periodontal diseases and AD can be explained through direct and indirect links. First, periodontal pathogens and their virulence factors have the potential to disseminate across the systemic circulation to reach the brain. Poole S., *et*

al. [11] brought evidence that *Porphyromonas gingivalis* lipopolysaccharide (LPS) can access the AD brain during life and damage brain tissue. Miklossy J [10] was one of the first to demonstrate the role of *Spirochaetes* in brain matter. *Treponemas* (*T. pectinovorum*, *T. amylovorum*, *T. lecithinolyticum*, *T. maltophilum*, *T. medium*, *T. socranskii*) and *Borrelia burgdorferi* were detected in the brains of AD patients. Moreover, *T. denticola* have been found in the trigeminal ganglia of patients with AD, this finding reflected that one of the routes of transmission of oral infection to the brain may be via the branches of the trigeminal nerve.

Gargano LM., *et al.* [12] reported that HSV antibodies have been highly correlated with Alzheimer's diagnosis. These periodontopathogens are known to cause vascular endothelial dysfunction, blood brain barrier (BBB) injury and neuronal damages. In the other hand, the release of inflammatory mediators is a known consequence of periodontal disease. Cestari JA., *et al.* [13] showed that increased levels of TNF- α and IL-6 suggests their implication in the overlapping mechanisms between oral infections and AD. James M. Noble [14] reported that Serum IgG levels to common periodontal microbiota are associated with risk of developing incident AD. Gaur S., *et al.* [15] concluded that elevated levels of TNF- α , IL-1, IL-6 and CRP resulting from chronic periodontitis increase the risk of AD. This leads to the amplification of inflammatory molecules in the CNS and increases AD proteases as reported by AR Kamer., *et al.* [16] who brought evidence of an association between periodontal disease and brain A β load.

Thus, Inflammation is one of the key features of AD and it provides foundation that periodontal disease is a risk factor for cognitive impairment and dementia.

It is worth noticing that genes play an important role in this pathway.

According to Singhrao SK., *et al.* [17] the Apolipoprotein E allele ϵ 4 susceptibility gene has so far emerged as the most significant risk factor for both familiar and late-onset forms of AD. Stein PS., *et al.* [18] reported that individuals having this allele and fewer teeth had lower cognitive test scores at the first examination and declined more quickly compared with participants with neither of these risk factors or with either one risk factor alone. Interestingly, the susceptibility gene requires an environmental risk factor which can be an oral infection for the expression of the disease. Gaur S., *et al.* [4] defend that periodontal disease and AD share common genetic polymorphisms (IL-1, TNF- α and RAGE gene polymorphisms) which amplifies the risk of early development of chronic periodontitis and subsequent AD.

Dental deafferentations (DD)

According to Yi-Tai Jou [19], multiple recurrent Dental Deafferentations due to the loss of peripheral sensory receptors through time may weaken the integrated and coordinated local neurovascular circulation. The chronic accumulated effects from situations such as a sedentary lifestyle, lack of social stimulation, and complications of obesity may converge to aggravate this damaged functionality. As a result, reduction of synaptogenesis, neurogenesis and number of neurons themselves will be observed. It can also lead to significant cerebral hypoperfusion and initiate a vicious cycle of neurodegeneration by modification of neuronal metabolism and activity causing over-production of β -amyloid.

Modification of nutritional habits due to tooth loss

There is an agreement among researchers such as Takeuchi K., *et al.* [20], Nilsson H., *et al.* [21], Park H., *et al.* [22] and Minn YK., *et al.* [23] that tooth loss is associated with an increased risk of dementia and AD.

Kim JM., *et al.* [24] reported that having over 16 missing teeth was associated with severe cognitive impairment among Chinese older adults. Thus, having fewer teeth may be a marker of risk for dementia. This might be explained by specific nutritional deficits due to the absence of an efficient masticatory function.

Therapeutic implication of this association

This association between AD and PD can lead to therapeutic implications.

In this perspective, the treatment of periodontal disease would eventually prevent the onset and the progression of the cognitive decline in the future.

The findings of Takeuchi K., *et al.* [20] reveal the clinical importance of promoting and supporting opportunities for dental care and treatment, especially in terms of preservation of teeth from an early age in order to reduce the risk of dementia in later life. Yi-Tai Jou [19] recommended that saving more teeth and maintaining a high level of oral health in order to minimize avoidable Dental Deafferentations may potentially reduce and minimize the incidence of dementia and other neurodegenerative diseases. Thus, preservation of teeth is of crucial importance for the protection of the nervous system and cognition.

Conclusion

The current paper supports a significant link between PD and AD occurrence in later life through systemic inflammation. PD and tooth loss are risk factors for the development of AD and onset of dementia.

However, major findings are based on studies of medium scientific value. Today, there is a growing need to do more randomized clinical trials and longitudinal studies with uniform diagnostic criteria that would bring stronger scientific evidence to evaluate the effects of PD on cognition. If a clear causal relationship is established, periodontal treatment may decrease systemic inflammation and therefore reduce the risk for the development of AD which may have huge impact on the morbidity rate due to this severe condition especially in elderly patients.

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