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Neuroinflammation: The link between periodontal disease and Alzheimer's disease

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Abstract
Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a main causal factor of dementia.
Objective: The aim of this article is to illustrate the intra correlations among periodontal diseases, dementia and Alzheimer disease, tooth loss and the underlying inflammation which is the link among different phenomena. Methods: We provide a thorough review of the literature.
Results: Periodontitis plays a key role in the initiation of systemic peripheral inflammation which may lead to neuroinflammation in the brain. Neuroinflammation is a necessary prerequisite for the development of Alzheimer. The reported tooth loss due to periodontal disease further worsens the clinical situation and the quality of life of the patient both directly, through improper food intake, and indirectly through the dysfunction of the masticatory system.
Conclusion: Periodontitis may be prevented in advance, the periodontal peripheral inflammation may be avoided, thus avoiding the subsequent neuroinflammation. Despite the indications so far, a clear and well-established connection between periodontitis and AD has yet to be proved.

Keywords: Periodontitis, Alzheimer, tooth loss, inflammation, neuroinflammation

Introduction
Life expectancy has grown considerably in the past decades, thus leading in an increase of neurodegenerative and auto inflammatory diseases [1]. Patients with dementia are expected to triplicate in the time frame 2010-2050, with Alzheimer's disease being its main root cause [1-3]. Alzheimer's disease (AD) is a progressive neurodegenerative disorder. The World Alzheimer Report 2016 suggests that almost 47 million patients suffer from this disorder with an estimate of compounding increase. In particular, this number of afflicted people is expected to double every twenty years [4]. Regarding to the elderly, cardiovascular, cerebrovascular and malignancies remain the three major causes of death and disability followed by AD at the fourth place [4]. The increased average lifespan enhances its social and economic implications.
The progressive, gradual, and slow loss of functions of the nervous system defines AD. This loss of function persists, leading to major deterioration or even complete loss of cognitive functions. The aforementioned clinical signs define dementia [5]. Ideally, the detrimental consequences of AD should be restricted to improve the quality of life of the elderly [6].
An effective treatment for AD has yet to be found [1, 7]. As a result, research has focused on prevention, meaning regimens that could diminish the incidence of AD and dementia by modifying relevant risk factors [1, 3, 8] such as low socio economical level, environmental factors such as smoking, medical history including diabetes, cardiovascular disorders such as hypertension, obesity, and psychological disorders such as depression. The aforementioned factors are responsible for up to 50% of the cases of dementia and AD.
The innate immunological response of the brain is also of paramount important [9, 10]. Microglia are a type of neuroglia and account for 10–15% of all cells found within the brain. These resident macrophage cells, when activated, increase their cell density, express specific cell surface antigens, and display morphological changes [11]. Major peripheral inflammation may trigger such a cerebral pathophysiology not only as an additional factor but also as the main causing factor [11-13].

Periodontal diseases affect a major part of the adult population [14-16]. Gingivitis affects mainly the gingiva without affecting the underlying bone and connective tissue. Periodontitis affects the teeth supporting tissues, provoking the destruction of the underlying bone and connective tissue, leading to extensive tooth loss if left untreated [17, 18]. This oral, restricted in its extent, inflammation may trigger through positive feedback a generalized inflammation meaning that cytokines and bacteria migrate from the oral cavity to other areas [19]. In the case of AD, periodontitis enhances any preexisting inflammation in elderly patients, ultimately resulting in accelerated dementia.

AD and neuroinflammation

AD is characterized by senile plaques, neurofibrillary tangles and loss of synapses. β- and γ-secretases form, through a proteolytic process of the amyloid precursor protein (APP), a uniformly expressed transmembrane glycoprotein [39-43], amino acidic peptides, known as β-amyloid (Aβ) peptides [20]. The Aβ cascade hypothesis in AD claims that Aβ peptides accumulate and as a result synapses and neurons degenerate [21-23]. ‘‘Priming’’ of microglia, meaning that microglia resort to a ‘‘primed’’ phenotype, leads to the subsequent damaging pro-inflammatory response [24]. Priming occurs as a result of AD associated proteins such as the Aβ and tau, systematic inflammation and aging [24]. Neuroinflammation is noticed in postmortem brain tissue samples (various complement factors surround the senile plaques [25, 26]. Furthermore, the neuroinflammation theory is supported by the fact that chronic intake of non-steroidal anti-inflammatory drugs is negatively correlated to the possibility of manifesting dementia and AD [10, 26, 27], whereas pro inflammatory mediators are highly expressed in the brain and the cerebrospinal fluid in AD patients [28].

The initial hypothesis was that Aβ deposits and oligomers activate the microglia, which in turn release pro-inflammatory mediators, thus worsening the already in place neurodegeneration [24]. The alternative hypothesis is that neuroinflammation is not just the outcome of Aβ deposits [28-30]. Instead, it plays a key role in the pathogenesis of AD since the immune system of the central nervous system is not isolated and is constantly affected by the peripheral immune system [12, 29, 31]. The peripheral inflammation mediates the aforementioned priming of the microglia. Consequently, inflammation alters the phenotype of microglia, and this transition accelerates Neuroinflammation [12]. Smoking, hypertension, diabetes, obesity and depression, all risk factors subject to change and possibly preventable, enhance the systemic peripheral inflammation, thus instigating the priming of microglia and the subsequent neurodegeneration [12, 31].

Complement system’s regular activation is also associated to neuroinflammation and neurodegeneration [32, 33]. AD proteins may activate complement components and attract activated microglia and astrocytes which release cytokines near the extracellular senile plaques [32, 33].

Administered LPS (lipopolysaccharide) provokes peripheral inflammation, accordingly TNF-α (tumor necrosis factor-α), IL-1β (interleukin-1β) and IL-6 (interleukin-6) are expressed more ubiquitously, the transport of Aβ protein through the blood brain barrier is diminished and the cerebral levels of Aβ protein rise [34]. Elevated levels of TNF-a are associated positively to loss of cerebral functions [35].

Periphery and brain affect one another through multiple structures and phenomena such as: the vagal afferents which are an important neuronal component of the gut–brain axis allowing bottom-up information flow from the viscera to the CNS, the circumventricular organs which lack the blood brain barrier and finally the activated immune cells which enter the brain [29, 36]. The key parameter is aging since in young human beings, activated microglia trigger a reparative response while in elderly human beings, activated microglia accelerate the already ongoing neuroinflammation and neurodegeneration leading to loss of cerebral functions [13, 29].

Periodontitis and neuroinflammation

Comorbidity of periodontitis and AD may be attributed either to the poor oral hygiene since dementia aggravates the relevant habits [18, 37, 38] or to the periodontal inflammation which may enhance the AD associated Neuroinflammation [18, 37, 38].

In particular, periodontitis is a chronic disorder, attributed to gram negative bacteria [38, 40-42] and mainly characterized by BOP (bleeding on probing) and CAL (clinical attachment loss) [17]. Edema and discoloration of the soft tissue may be present, along with extensive deposits of dental calculus on the tooth surfaces. At the latest stage tooth loss is imminent due to extensive bone loss [40]. The lack of symptoms in the majority of cases, with the exception of periodontal abscesses and necrotizing ulcerative periodontal lesions, leads to hidden morbidity [15, 16]. The presence of periodontal pathogens, such as Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola triggers an immune response which is correlated to the extent of tissue damage [18, 40, 43]. CRP (C reactive protein) [44] and leptin [45] are highly expressed in chronic periodontitis and aggressive periodontitis respectively. The presence of periodontal pathogens may increase the possibility of manifesting autoimmune diseases, cardiovascular diseases, diabetes mellitus, AD, dementia in general, cancer and osteoporosis [18, 38, 41, 46-56]. Periodontitis may also enhance a preexisting atherosclerosis which in turn may lead to vascular dementia [57-59].

AD and periodontitis

Periodontitis and AD are positively correlated [43, 60]. Higher levels of cytokines and serum IgG antibodies are reported are associated with more severe periodontal disease and aggravated AD [43, 60]. In particular, the severity of periodontitis and the reported CAL are in accordance with the gradual cognitive deterioration of the AD patients.

Underlying mechanisms include the periodontitis induced bacteremia, the periodontitis induced cytokine release and the intrusion of bacteria through the trigeminal nerve in the brain [38, 55, 56, 61-67]. In particular, LPS-containing Gram-negative bacteria constitute the 4/5 of the subgingival biofilm and through their immunogens, they may trigger the peripheral inflammation and the subsequent Neuroinflammation [63, 68, 69]. The immune response involves the Toll-like receptor 2 and 4 pathways (similar to the immune response associated with AD) as well as cytokines (ILs, TGFβ, TNFα) and chemokines (MCP, MIF, MIG) by microglia and astrocytes. The aforementioned immune response in conjunction with the production of ROS/RNS and the activation of the complement system result in apoptosis and systematic inflammation [70-78].

LPS is associated with higher levels of Aβ peptides with concurrent increased permeability of the blood brain barrier [79]. Increased production of C reactive protein is associated with severe periodontitis and the presence of Porphyromonas gingivalis [44, 80-86]. Increased production of TNF-α is associated with the presence of the periodontal microorganisms Aggregatibacter actinomycetemcomitans,

Tannerella forsythia and Porphyromonas gingivalis and the respective antibodies [61, 65, 87]. Finally increased production of the Aβ precursor protein is also associated with chronic periodontitis, possibly because the periodontitis induced increased release of TNF-α and NF-κB regulate its production [88].

The extensive tooth loss, attributed to periodontal disease, results in poor nutrition, dysregulation of the masticatory system and possibly reduction in cerebral blood perfusion [89]. Most probably, tooth loss leads to inadequate intake of vitamins and/or nutrients [90-92] as well as to dysregulated mastication which in turn dysregulates the sending sensory information to the brain, which normally sustains the cognitive functions of the hippocampus [93]. This masticatory dysregulation may contribute to the deterioration of the learning and spatial memory dependent functions of the hippocampus as well as to pathological morphological alterations [94]. In addition, acetylcholine levels diminish, and the hippocampus pyramidal cells decrease in numbers, also associated with impairment of the masticatory system [95].

Take home message

Since periodontitis may be prevented and treated in advance, the periodontal peripheral inflammation may be avoided, thus disabling both its enhancing effect on any preexisting neuroinflammation and the possibility of initiating it [96]. In older patients, more frequent periodontal checkups are to be suggested, to diagnose periodontitis in its early stages. Despite the indications so far, a clear and well-established connection between periodontitis and AD has yet to be proved.

Furthermore, full mouth dental rehabilitation and proper routine of oral hygiene are difficult to maintain but of crucial importance. Periimplantitis is more frequent in patients manifesting dementia [97]. However, proper care provided by health professionals may restrict the peripheral inflammation due to periodontitis and periimplantitis and improve the function of the masticatory system through implant supported overdentures [95, 97].

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