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Review Article

Alzheimer's Neuropathology and its Possible Association with Periodontal Disease

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Abstract

Dementia is a severe public health issue that affects 47 million people in the world. The most common cause of dementia is Alzheimer's disease, a progressive and irreversible neurodegenerative disorder that affects 60% to 80% of all patients diagnosed with dementia. Alzheimer's disease is characterized by cortical and subcortical atrophy, neurofibrillary degeneration and accumulation of amyloid plaques in the brain, and it severely affects the quality of life of those who have it. The prevention of this disease involves identifying the risk factors that might activate or aggravate its neurodegenerative process. In this context, recent studies are evaluating a possible association between Alzheimer's disease and periodontitis, in the sense that the induction of a chronic inflammatory state by the periodontal disease seems to develop or aggravate neuroinflammatory states that are typical of Alzheimer's disease. The extensive study of bibliographic contents available at the PubMed platform, which resulted from a search with the terms "Alzheimer's disease", "dementia", "systemic diseases", "periodontitis", "periodontal disease", "amyloid plaques" and "prevention", as well as the study of the books Clinical Periodontology and Implant Dentistry and Enfermedad de Alzheimer y otras Demencias, allowed to gather the latest information on a likely association between periodontal disease and Alzheimer's disease. Considering the high prevalence of these conditions and the significance of Alzheimer's as a Public health problem, it becomes imperative to study the modifiable risk factors associated with this serious and incurable condition.

Keywords: Alzheimer's Disease; Dementia; Systemic Diseases; Periodontitis; Periodontal Disease; Amyloid Plaques; Prevention

Introduction

The term "dementia" designates a set of disorders related to neurologic injuries, commonly of a Degenerative origin. The dementia syndrome is defined by the presence of cognitive, psychic and behavioral disorders of such severity that affects the individual's autonomy and his capacity to carry out daily activities. Consequently, The diseased becomes dependent of others, which makes dementia one of the main causes of disability and dependency in older adults. The negative impact of dementia on a global scale is significant, and its high prevalence makes it necessary to prevent and reinforce strategies around this health problem. Alzheimer's disease represents 60% to 80% of all dementia cases, being the most frequent in the group of illnesses covered by the term "dementia" [1-4].

The prevalence rate is high, with dementia affecting 47 million people worldwide in 2015, a number that is estimated to increase to 75 million in 2030 and to 132 million in 2050. Recent assessments estimate that, globally, 9.9 million people develop dementia every year, which means a new case every three seconds. It affects mostly women and individuals aged over 60, and its prevalence increases with age [5].

The etiology of Alzheimer's disease isn't fully understood yet; however, it is known that it may result from genetic factors or from the association between genetic and environmental factors, such as depression, hypertension, diabetes mellitus, obesity, sedentarism, alcohol consumption, smoking, among others. The study of possible risk factors associated with the onset or worsening of sporadic and/or late familial forms of Alzheimer's disease is vast and some

authors have described periodontal disease as a possible risk factor [6-9].

Periodontitis is a prevalent and persistent infectious disease associated with anaerobic Gram-negative bacteria and viruses. According to the World Health Organization, approximately 5 to 20% of older adults (aged ≥ 65) suffer from severe forms of periodontal disease, which, if untreated, may result in tooth loss. This pathology of the oral cavity's support tissues has been associated with various systemic conditions, such as cardiovascular diseases, rheumatoid arthritis, diabetes mellitus and, more recently, Alzheimer's [10-19].

The objective of this review is to study the neuropathology of Alzheimer's disease , to understand how it can be related to periodontal disease and what is the importance of clarifying a possible association between periodontitis and Alzheimer's disease.

Material and Methods

The bibliographic content selected for the development of this review was acquired on the Pubmed platform. A search with the terms "Alzheimer's disease", "dementia", "systemic diseases", "periodontitis", "periodontal disease", "amyloid plaques" and "prevention" allowed to gather scientific papers about the topic under study. In a first stage, the papers were selected according to their title and abstract, and then by reading them in full. After choosing the papers, the gathered information was organized into categories and put into context in a way to enable a clear and simplified approach to the topic. The study of chapters 7, 10 and 20 of the book Clinical Periodontology and Implant Dentistry was useful to gather information about the periodontal disease. The study of part II - A of the book Enfermedad de Alzheimer y otras Demencias allowed us to gather information about the pathogenesis, neuropathology, genetic factors, cognitive and functional manifestations, symptoms and signs of Alzheimer's disease.

Alzheimer's disease

The Alzheimer's disease was first described in 1906 by the German psychiatrist and neuropathologist Alois Alzheimer. It's a neurodegenerative disorder characterized by a gradual and progressive destruction of nervous tissue, starting on an undetermined moment of adult life. It's a brain disease, and macroscopically this translates into an atrophy of the cerebral cortex resulting from the process of neuronal loss.

Research carried out in the last few years in the field of Genetics has allowed to identify a considerable number of metabolic changes or genetic errors which take part, directly or indirectly, in the pathophysiology of Alzheimer's. Nowadays, two subgroups of the disease are being considered: the autosomal dominant forms, also known as early onset familial Alzheimer's; and the sporadic or late onset familial forms, caused by genetic and epigenetic physiopathogenic determinants, as well as environmental determinants, that are common of the physiological ageing process. In early familial forms, the disease occurs by genetic transmission, that is, the disease is triggered by a genetic mutation transmitted by a carrier parent. Such mutations are linked to three genes: the amyloid precursor protein (APP) gene on chromosome 21; the presenilin 1 gene on chromosome 14; and the presenilin 2 gene on chromosome 1. Individuals with early familial forms of the disease (FAD) develop early (usually before age 55) a picture of cognitive deterioration and histological changes typical of Alzheimer's disease. These are rare clinical situations with a marked family history. In the sporadic and/or late onset familial forms, the associated gene does not act as a causal agent but as a susceptible one. Some studies suggest a genetic association to the *locus* of the apolipoprotein E (ApoE), with one of its three alleles, ApoE-E4, being regarded as an important risk factor and predictor of sporadic and/or late onset familial forms of the disease.

The processes that induce the manifestation of Alzheimer's disease in its different forms are not yet fully known; however, it has been suggested that some risk factors can play a part on the appearance of sporadic and/or late onset familial forms of the disease [20,21].

The signs and symptoms include memory lapses, disorientation, language changes, difficulty solving problems, personality changes and mood swings. In the most advanced stages, there is an aggravation of these signs and symptoms, with patients manifesting apraxia, agnosia, aphasia, distorted perception, delusion, irregular sleep-wake rhythm, and death [21,22]. These signs and symptoms appear to have worsened with the COVID-19 pandemic [23,24].

The clinical and histological characteristics constitute the key elements for its diagnosis, and they're represented in table 1.

Characteristics of Alzheimer's disease
Clinical Alterations of memory and of other cognitive functions; psychiatric manifestations (depression, anxiety, psychosis) and behavioural changes (apathy, agitation, escape, aggressiveness). Progressive and chronic profile. Absence of focal neurologic signs.
Likely clinical diagnosis Confirmation of the presence and functional impact of the referred changes. Confirmation, trough a neuropsychological study, of the compromised state of memory and other upper nervous functions (dementia syndrome): Absence of focal neurologic signs. Exclusion of other causes of dementia or depression major (with appropriate laboratory and imaging study).
Neuropathological changes (definitive diagnosis) Cerebral atrophy (more marked at a parietal-temporal level) Histological markers - selective neuronal death, neurofibrillary trances and senile plaques.

Table 1: Clinical and histological characteristics of Alzheimer's disease [21].

Neuropathology, neurotransmission and neuroinflammation changes

The study of abnormal and pathological functions associated with Alzheimer's allows us to characterize this disease as being the result of a triad of neuronal changes that are responsible for the criteria that define it. Such triad includes cortical and subcortical atrophy, the accumulation of amyloid plaques in the brain and neurofibrillary tangles of the tau protein.

Nowadays, researchers believe that there's an association between the accumulation of amyloid plaques and neurofibrillary tangles; it's consider that the former may lead to the latter and, later on, to cerebral atrophy. Both amyloid plaques and neurofibrillary degenerations result from the pathological accumulation of malformed proteins: the amyloid protein, responsible for amyloid plaques, and the tau protein, responsible for neurofibrillary degenerations [21].

Soluble amyloid protein exists in its alpha or random configuration under healthy physiological conditions; however, its shape can undergo some changes, starting to adopt an insoluble beta configuration capable of aggregating and forming agglomerates of insoluble proteins, which are referred to as "amyloid plaques" or "senile plaques". The biochemical analysis allows us to understand that the basal protein of these agglomerates is an abnormal protein made of 42 amino acids: the beta-amyloid peptide. In its free form, the beta-amyloid peptide can be degraded by the glial cells and eliminated from the nervous system; however, when the rhythm of formation and aggregation of these peptides is superior to the capacity of eliminating them via glial cells, an amyloid cascade may be spread, i.e., a succession of biological reactions capable of leading to neuronal death and consequent atrophy of the nervous tissue. The beta-amyloid protein seems to be determinant in the disease, acting directly on the degeneration of synaptic terminals through cytotoxic mechanisms. Other polypeptides identified in the central nucleus of the plaques are ApoE, proteoglycans, alpha-1 chymotrypsin and other inflammatory proteins, which allows some speculation on an eventual contribution of inflammatory processes to the degenerative process. According to this "amyloid hypothesis", the excessive production, rapid deposit or abhorrent metabolism of Aβ results in the formation of toxic Aβ aggregates, which, in its turn, results in neuronal injuries, neuronal death and cognitive dysfunction [25,26].

Nowadays, The deposition of amyloid plaques is considered to be at the origin of neurofibrillary degeneratio. Neurofibrillary tangles are aggregates of neurofilaments made of tau protein in its hyperphosphorylated form. Physiologically, the tau protein contributes to the normal functioning of neurons, taking part in the constitution of microtubules; however, its hyperphosphorylated form causes disorders in the neurotransmission processes, making neurons unable to transport their synthesis products. The biochemical alterations that occur in association with morphological changes on neurons result in rigidity and neurofibrillary tangles, which lead to the apoptosis of nervous cells. The mechanisms that lead to the hyperphosphorylation of the tau protein and to the formation of PHF (Paired Helical Filaments) are not yet fully clear. The disorder induced by the neurotransmission capacity may play an important role in the pathophysiology of the disease, in a way that it conditions the transport of growth factors, essential to the survival of cholinergic neurons, and may alter the metabolism of the β-amyloid protein, thus contributing decisively to the genesis of senile or amyloid plaques.

The Alzheimer's disease is characterized by a state of ongoing neuroinflammation, with such state designating the inflammation of the nervous tissue resulting from infection, tissue injury, toxic metabolites or autoimmune mechanisms. Microglia are the main immune cells of the central nervous system which includes the brain and the spinal cord. These cells perform an active surveillance of the brain, confirming, among others, if communication between neurons is working properly, or identifying pathological changes or infections caused by microorganisms. When damage is detected, the microglial cells are activated and start to function as innate immune cells, eliminating pathogenic microorganisms and cellular waste and promoting the reestablishment of tissue balance. However, the prolonged action of microglia, as observed in Alzheimer's, may spread or accelerate irreversible neuronal damage [21].

Periodontal disease

The periodontal disease is an inflammatory disease which results from the bacterial colonization of the oral biofilm. The accumulation of dental plaque and tartar causes the gradual and progressive destruction of tissues that support the teeth. Its signs are gingival inflammation, loss of bone structure, dental mobility and tooth loss.

The periodontal tissue disease can be seen as a disruption of homeostasis between the host's tissues and the resident microbiota. The disturbance of this internal balance at the oral cavity is responsible for the emergence of the periodontal disease. The inflammatory process associated with the progression of this disease activates local or systemic immune mechanisms capable of sustaining an ongoing inflammatory state in the organism [27-30].

The periodontal disease is a condition that can be prevented and treated through surgical and non-surgical procedures. The prevention is relatively simple, involving motivation and information on oral hygiene care, as well as regular dental check-ups to control the accumulation of dental plaque [28]. The current knowledge on the discipline of periodontology and the simplicity of the prevention and/or treatment procedures are in contrast to the lack of information on Alzheimer's disease and to the inexistence of a cure to this disease. For this reason, the confirmation of risk factors associated with Alzheimer's disease is essential to treat or to stop the progression of this neurologic disease [6].

Possible association

The most recent scientific publications are considering an association between Alzheimer's disease and periodontitis, in the sense that the induction of a chronic inflammatory state by the periodontal disease seems to develop or aggravate neuroinflammatory processes present in Alzheimer's disease, namely in its sporadic and/or late onset familial forms.

The hypothesis is that there is an association between Alzheimer's disease and peripheral inflammation, being suggested that this peripheral chronic inflammation may aggravate the brain's inflammatory processes. Since chronic periodontitis is a generalized peripheral immunoinflammatory condition, it was suggested that it plays a significant role in the aggravation of Alzheimer's disease.

The bacterial load and the inflammatory response associated with periodontitis may aggravate the neuro-inflammatory process present in Alzheimer's disease due to the increased levels of proinflammatory mediators in the blood stream, namely Interleucine-1, Interleucin-6 and TNF-α, which are believed to be capable of trespassing the blood-brain barrier and cause the activation of microglial cells, accelerating the neurodegenerative process.

As such, some research has been conducted in order to try to prove a possible association between both diseases, and how the inflammation caused by periodontitis may affect Alzheimer's disease. In effect, the hypothesis that peripheral inflammation may alter the neurological inflammatory state seems to be evidence-based. Some preliminary studies revealed that the presence of peripheral infections might accelerate the manifestation and progression of Alzheimer's disease.

Currently, two hypotheses are being laid out to justify the contribution of periodontal disease in the emergence and progression of Alzheimer's disease. The first one lies on the possibility of activation of the brain's microglial cells and on the intensification of the senile plaques formation process following the migration of pro-inflammatory molecules from the intraoral environment and resulting from the body's immune response to the bacterial load of the oral biofilm in case of periodontitis. According to this hypothesis, the existence of Pro-inflammatory molecules in systemic circulation interferes with neuroinflammation in the brain. Another hypothesis is that bacteria from the intraoral biofilm are able to migrate to the brain tissue, crossing the blood-brain barrier and

causing inflammation in these tissues. The presence of these bacteria would result in the activation of immune mechanisms and of microglial cells. Such mechanism can cause or intensify neuronal destruction and the formation of senile plaques that is typical of Alzheimer's disease. The cytokines released during the immune response include the IL family, TNF-α, transforming growth factor-β, and chemokines (monocyte chemoattractant protein, IL-8, macrophage migration inhibitory factor and monokines induced by interferon γ). The cytokines released during the immune response play an important role in the neurodegenerative disease, particularly TNF-α, which enhances the inflammatory process causing gliosis, demilienization, deterioration of the blood-brain barrier and cellular death.

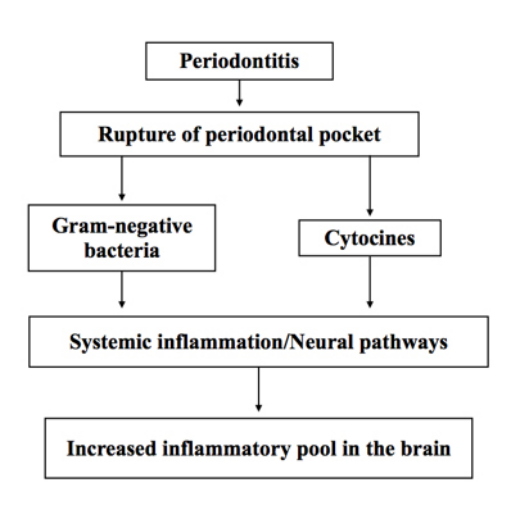

Figure 1: Association mechanisms between periodontitis and Alzheimer's disease [6,31,38].

The association between periodontal disease and Alzheimer's disease appears to be bilateral and published epidemiological studies have shown evidence of a high prevalence rate of periodontal disease in patients diagnosed with dementia. However, it is important to bear in mind the confusion factors associated with this topic, as well as the difficulties inherent to the conduction of studies amongst this usually fragile and not very cooperative population. Confounding factors increase the risk of bias in published studies and are the result of loss of autonomy and inability to collaborate in the performance of oral hygiene by patients with dementia. Still, despite these limitations, it is believed that the prevalence rate of periodontal disease among patients with Alzheimer's is high, Even so, despite the limitations presented, it is considered true that the prevalence rate of periodontal disease in Alzheimer's patients is high; without having been able to access epidemiological studies that demonstrate the incidence rate [31-39].

Importance of the association between periodontitis and Alzheimer's

Alzheimer's disease is a disease whose etiology and treatment pose a real challenge to the scientific and medical community, with recognized risk factors that are thought to play a part in the manifestation and progression of the disease.

Periodontitis can be prevented and treated, which may reduce the risk profile of diagnosed patients or of those that are likely to develop Alzheimer's. The importance of investigating the possible association between these pathologies becomes even more relevant because, despite the intense clinical and biochemical research carried out in recent years on Alzheimer's disease, its etiology and pathophysiology are partially unknown, and there is no curative treatment. With this in mind, the high incidence and prevalence rates associated with the gravity of the consequences of dementia require a conjugated effort to prevent and improve the quality of life of those who bear the disease. As such, it is fundamental to establish all the risk factors that might be associated and prevent the emergence and/or aggravation of Alzheimer's disease.

More longitudinal and multicenter studies should be developed, with larger samples, in order to test the possibility of a practical and biological association between these diseases [40-43].

Conclusion

Alzheimer's disease represents a major challenge for health professionals with regard to the development of prevention, promotion and intervention strategies that ensure a guided and well-assisted aging population. This need requires the recognition of risk factors and the adequacy of health measures aimed at the prevention and adequate monitoring of patients at risk in order to reduce the incidence rate of Alzheimer's disease and periodontal disease, promoting health and population's quality of life. The supposed association between these two conditions may give new hope for therapeutic interventions that can prevent the progression and worsening of both pathologies.

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