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REVIEW ARTICLE

Porphyromonas gingivalis in relation to Alzheimer's disease

Porphyromonas gingivalis en relación con el Alzheimer

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ABSTRACT

Introduction: periodontal disease is a multifactorial and inflammatory condition and in recent years one of these bacteria has been linked to the development of Alzheimer's disease.
Objective: to describe the relationship between periodontal disease, Porphyromonas gingivalis and Alzheimer's disease.
Methods: a bibliographic, documentary, exploratory, non-experimental, qualitative, qualitative research was carried out by searching for articles in pages such as: Pubmed, Scielo through the Google Scholar search engine. The PRISMA method for systematic reviews was used, with MeSH terms, accompanied by Boolean terms (And, Or, Not). The documents found through the search in digital databases are selected by inclusion and exclusion criteria from 2010 to 2023 because the information was scarce on the subject.
Development: porphyromona gingivalis present in periodontal disease has the ability to be transported with saliva to a more subgingival location, this in turn can directly invade the brain through the bloodstream or via cranial nerves, secreting gingipains which are toxins that cause precursor proteins of Alzheimer's disease to be produced. Porphyromonas gingivalis produces high levels of cytokines, chemokines and systemic tumor necrosis factor, which in turn leads to overproduction and ultimately neurotoxicity.
Conclusions: despite all available scientific evidence indicating that periodontal disease is related to Alzheimer's disease, it has not been possible to date to determine the mechanisms involved.

Keywords: Periodontal Disease; Alzheimer's; Porphyromonas Gingivalis; Oral Pathology.

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RESUMEN

Introducción: la enfermedad periodontal es una afección multifactorial e inflamatoria que en los últimos años se ha relacionado una de estas bacterias con el desarrollo de la enfermedad de Alzheimer.
Objetivo: describir la relación existente entre la enfermedad periodontal, la *Porphyromonas gingivalis* y el Alzheimer.
Métodos: Se realizó una investigación tipo bibliográfica, documental, exploratoria, no experimental, cualitativa mediante la búsqueda de artículos en páginas como: Pubmed, Scielo a través del motor de búsqueda Google Scholar. El método PRISMA para revisiones sistemáticas fue usado, con términos MeSH, acompañados de términos booleanos (And, Or, Not). Los documentos que se encuentren a través de la búsqueda en bases de datos digitales se seleccionan mediante criterios de inclusión y exclusión desde 2010 al 2023 debido a que la información fue escasa sobre el tema.
Desarrollo: la *Porphyromona gingivalis* presente en la enfermedad periodontal tiene la capacidad de transportarse con la saliva hacia una ubicación más subgingival, esta a su vez puede invadir directamente el cerebro a través del flujo sanguíneo o por medio de los nervios craneales, secretando gingipaínas que son toxinas que hacen que se produzcan proteínas precursoras de la enfermedad de Alzheimer. *Porphyromonas gingivalis* produce altos niveles de citocinas, quimiocinas y factor de necrosis tumoral sistémico, lo que a su vez conduce a la sobreproducción y finalmente a la neurotoxicidad.
Conclusiones: A pesar de toda la evidencia científica disponible indica que la enfermedad periodontal está relacionada con la enfermedad Alzheimer, no ha sido posible hasta la actualidad determinar los mecanismos involucrados.

Palabras clave: Enfermedad Periodontal; Alzheimer; Porphyromonas Gingivalis; Patología Bucal.

INTRODUCTION

Periodontitis is a chronic oral disease of multifactorial etiology that affects 50 % of the population worldwide. This pathology can cause low-grade systemic inflammation through the release of proinflammatory cytokines and the invasion of bacteria. Porphyromonas gingivaliswhich affects the development of neuroinflammation, in turn has become a prominent common feature among neurodegenerative disorders, thus causing a significant progression of Alzheimer's disease.[1,2,3]

Currently, numerous studies have been carried out to determine the relationship between periodontitis and neurodegenerative pathology (Alzheimer's). Patients who suffer from this disease normally have poor oral hygiene, which is why, as the disease progresses, the oral condition worsens rapidly, resulting in periodontal disease one of the main bacteria present is Porphyromona gingivalis, which passes through the periodontal pockets into the bloodstream and later into the brain. It is currently known that this bacteria secretes gingipains, toxins that cause precursor proteins of Alzheimer's disease to be produced.[4,5,6]

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Gingipains are enzymes produced by microorganisms called microbial proteases. These enzymes have been observed to be found together with tau and ubiquitin proteins in the context of Alzheimer's disease, which are typical features of this disease. Interestingly, it has been noted that the levels of Porphyromona gingivalis in the cerebrospinal fluid (the fluid surrounding the brain and spinal cord) have an inverse relationship with saliva samples taken from the same patients. This suggests that microorganisms could migrate from the periphery of the body to the central nervous system. This phenomenon could explain why microbial species are found in the brains of patients suffering from Alzheimer's disease.[4]

In patients at risk, such as those with certain pre-existing medical conditions or specific risk factors, the toxins produced by the bacteria present in dental plaque can have a more significant impact and accelerate the progress of periodontal disease, since situations such as an exacerbated inflammatory response, the response may be more intense and less controlled, contributing to rapid progression of periodontal disease, alterations in the immune response as some medical conditions and risk factors may affect the function of the immune system, may A microbial imbalance may also occur in at-risk patients. The imbalance in the composition of the oral microbiota can favor the proliferation of pathogenic bacteria associated with periodontal disease.[5]

The present bibliographic review is oriented on periodontal disease related to Alzheimer's, in which, through the review of high-impact scientific articles, this relationship and the factors involved in its development will be described.

METHODS

A bibliographic, documentary, exploratory, non-experimental, qualitative type of research was carried out by searching for articles on pages such as: Pubmed, Scielo through the Google Scholar search engine.

The PRISMA method for systematic reviews was used, using advanced searches with the use of keywords and MeSH terms accompanied by Boolean terms (And, Or, Not) in the PubMed and Scielo databases as shown in the table. The documents found through the search in digital databases are selected using inclusion and exclusion criteria from 2010 to 2023 because the information was scarce on the topic.

Inclusion Criteria

- Types of documents analyzed: Original articles, randomized clinical trials, observational studies, review articles
- Free access articles
- Language: English and Spanish
- Animal studies
- Studies from 2010 to 2023.

Exclusion Criteria

- Document type: Theses, books, review articles.
- Duplicate documents
- Private access documents
- Content: information other than the topic
- Time: Outside the established range.

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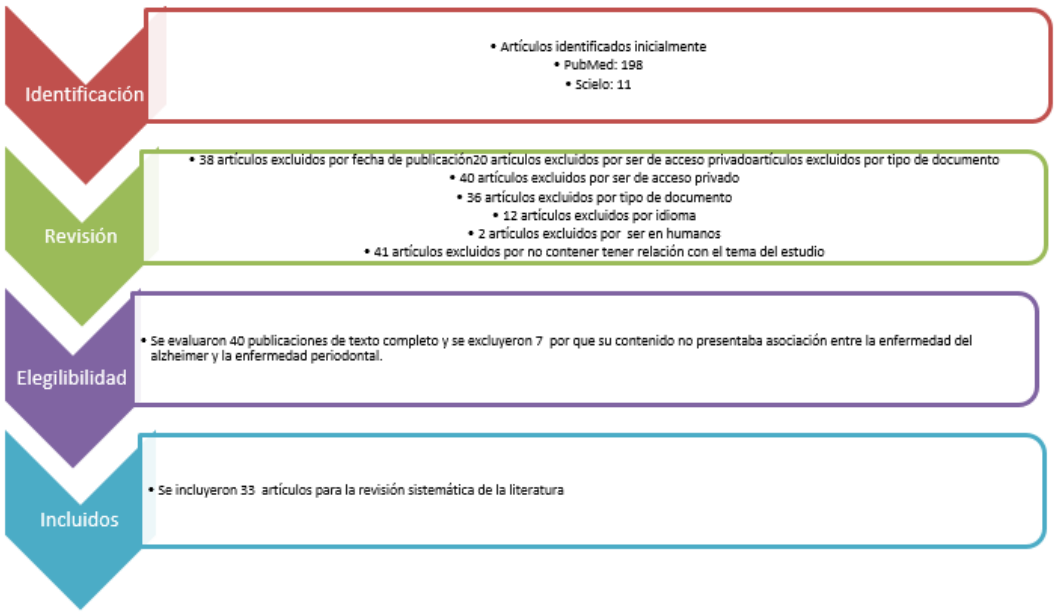
Table 1. PRISMA Summary

Section	Item
Eligibility criteria	Inclusion and exclusion criteria
Information sources	Scopus, SCIELO
Search strings	((ALZHEIMER) AND (Porphyromona gyngivalis)) AND (periodontal diseases))
Selection process	Discard duplicates and no access free. Summary reading. Complete reading for selection of results.
MeSH Terms	Periodontal diseases, Alzheimer's, gingipains, Porphyromona gyngivalis

Own elaboration. 2023



Elaboración propia. 2023

Fig. 1 Item selection diagram.

DEVELOPMENT

Periodontal Disease

Periodontal disease is considered as a set of inflammatory pathologies of multifactorial origin, which will affect the supporting tissues of the tooth (epithelia, connective tissue, bone, root cementum and periodontal ligament) resulting in inflammation of the gums, imbalance in The immunological interaction of the host and the flora of the dental plaque that is lodged in the gingival sulcus, these will be strongly related to the origin of one of the main periodontal diseases such as gingivitis, which if not treated will evolve into periodontitis, which is more destructive.[4,5]

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In several epidemiological studies it has been recorded that the prevalence of this disease increases in adolescents, due to the lack of oral hygiene, it is also related to hormonal changes in puberty, since there is an increase in them such as progesterone and estrogen.[5,6]

It should be kept in mind that periodontitis always begins with gingivitis, which, if left untreated, develops and ends in periodontal disease. In addition to the aforementioned, this pathology has been related to other diseases at a systemic level such as: diabetes mellitus,metabolic syndrome, high blood pressure, obesity, kidney, respiratory and atherosclerotic diseases. On the other hand, it is associated with the development of Alzheimer's, whose relationship will be described later.[4,7]

Alzheimer's

Alzheimer's disease is the most common cause of dementia and has been associated with many risk factors: age, sex, apolipoprotein E4 (related to hypercholesterolemia), parental age at birth, cerebrovascular disease, traumatic brain injury, heart attack to the myocardium, immunological defects, genetic factors such as chromosomal defects (Down Syndrome), and environmental factors such as infectious agents, toxins, education, and occupation. This is defined as a clinical syndrome characterized by a persistent and progressive deterioration of higher brain functions such as memory, language, orientation, calculation or spatial perception. Cases of dementia increase exponentially with age, constituting one of the main causes of dependency and disability in the elderly population.[1,8]

Increased levels of aggregated Aβ peptide and phosphorylated tau protein (a polypeptide that undergoes a series of changes in Alzheimer's disease, and is deposited in neurons instead of axons) lead to the deposition of tangled extracellular amyloid and intracellular neurofibrillary plaques in the brain of patients with AD, making it a hallmark of AD neuropathology. The main description of tau modification is its phosphorylation. The phosphorylation state of the protein depends on the balance between the activities of different protein kinases and phosphatase.[9]

The second basic factor in tau assembly or aggregation is its tendency to form a β secondary structure. In this regard, it should be noted that tau is part of a group of proteins that cause amyloid brain diseases and has a conformation rich in β4 structure in its characteristics. Another member of this group is the Aβ peptide.[9]

In tautomerism, including AD, tau is hyperphosphorylated and has a more folded conformation, which is more likely to aggregate than non-phosphorylated tau. Highly phosphorylated tau protein can self-assemble or self-aggregate even in vitro.[10]

NFTs (neurofibrillar tangles) contain tau and to be generated they assemble directly from free tau monomers and/or tau oligomers in the cytosol. In fact, the oligomerization of this protein has been seen on the surface of microtubules, which can generate tau oligomers, which constitute the nucleation site of the protein, leading to NFTs.[10]

Tau protein can promote and stabilize NFTs, and its hyperphosphorylation can cause changes in microtubules, which can cause some of the cellular dysfunctions observed in AD. Both Aβ and hyperphosphorylated tau are characterized by their ability to aggregate, thereby forming insoluble clumps. The ability to self-aggregate is given by the advantage of transforming the α-helical conformation into the β-sheet structure.[9]

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In the process leading to the formation of amyloid plaques and NFTs, soluble oligomers of different sizes are produced, which are considered the more toxic form of the two molecules. Although Aβ appears to be more involved in AD pathology, both molecules are involved in AD pathogenesis. The effects of extracellular Aβ peptide and intracellular tau protein are likely to be closely linked through a series of processes and events.[9]

Periodontal Disease and Alzheimer's

Oral diseases play a very important role in the patient's general health, since these diseases can be a source of infection for the development of systemic diseases, which is why dentists as health professionals must treat patients as an integral unit. Currently, after several articles, periodontal disease and Alzheimer's have been linked.[11,12]

Among the main unknowns that arise in this field of research, it is considered a priority to determine if neurodegenerative diseases are inflammatory-based processes, if they have a possible infectious etiology and if an independent association between oral infectious diseases and neurodegenerative diseases is plausible. Likewise, progress is being made in clarifying other doubts of interest, such as whether the oral microbiota can reach the central nervous system or whether there is experimental evidence of the connection between the mouth and the central nervous system. And, most importantly, it remains to be determined what the health implications of the association of both diseases could be.[13]

Periodontitis and Alzheimer's are very prevalent diseases in elderly people. According to the population survey of oral health in Spain in 2015, 10,8 % of the adult population between 65-74 years old presents deep periodontal pockets, and 17,7 % of this population cohort shows a clinical attachment loss of 6 mm or greater. The prevalence rates of dementia in Spain are between 5,2-16,3 % of the population over 65 years of age, reaching between 22-30 % in patients aged 85 years or older.[13,14]

In scientific evidence, it has been suggested that one of the main causes is the bacteria Porphyromona gingivalis, a gram-negative anaerobic bacteria, which is present in periodontal disease and causes neuroinflammation, since it secretes proinflammatory cytokines that generate systemic inflammation. These neurotoxins are known as gingipains can suppress the deposition of opsonins on the surface of the bacterial cell, thereby limiting the stimulation in the phagocytosis process, which does not stimulate exocytosis, thus ceasing to produce oxygen free radicals, giving rise to infections. pyogenic bacteria such as periodontitis.[15,16]

Periodontal disease plays an important role in vascular changes, because when periodontal pathogens are found (such as Porphyromonas gingivalis and Streptococcus sanguis), they increase the expression of platelet agglomerates and form atherosclerotic plaques. The plaque forms a thrombus, which promotes cerebrovascular events. Gingivitis regulates inflammasome activity, so the formation of atherosclerotic plaques in Alzheimer's disease is related to the activation of NLRP39 inflammasomes and innate immune responses.[2,3.11]

Inflammasomes fight against the activation of innate intracellular defenses. The intracellular IL interleukin-1 pathogen, IL-8, causes cell death by apoptosis. Furthermore, the inflammation caused by these pathogenic stages produces endothelial dysfunction and contributes to the formation of atherosclerotic plaques, which have a risk of developing cognitive impairment in Alzheimer's disease. [3]

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Porphyromonas gingivalis DNA was also found in the cortex of the brain of mice, in a region that participates in conceptual thinking, generally in patients with Alzheimer's disease. Residues of Porphyromonas gingivalis and accumulation of beta amyloid were also found in some healthy patients suffering from periodontitis, but at a low level. This is the reason why there is an assumption that Porphyromona gingivalis enters the brain due to Alzheimer's Disease.[16]

It was further demonstrated that when chewing or oral hygiene procedures, periodontal pathogens and their products are stimulated, proinflammatory cytokines (interleukin 1, IL 6) and tumor necrosis factor alpha are produced. After repeated exposure to bacteria, they become saturated and enter the systemic circulation through the mouth. In advanced periodontal disease, these pathogens and their products can affect these defense barriers, which in turn leads to saturation of proinflammatory cytokines reaching the brain, leading to neuroinflammation, neuronal death, which eventually leads to a Cognitive dysfunction in Alzheimer's disease.[17]

Another pathophysiological mechanism is the entry of microorganisms found in dental plaque through direct invasion of the tissue or through the blood circulation or peripheral nerves to enter the brain tissue. Pathogenic bacteria such as Actinobacillus, Porphyromonas gingivalis, Chlorella intermedius, Treponem have been found. These pathogens cross the blood-brain barrier and reach the brain tissue producing mediators and inflammatory products, where they will produce a series of reactions that cause the dissolution of the brain tissue.[16]

Hashioka S et al.[18] state that periodontitis is a chronic oral multifactorial infection that affects almost 50 % of the world's population. In addition, they mention that periodontitis accelerates other chronic systemic inflammations such as cardiovascular diseases, diabetes and Alzheimer's. In this last pathology, neuroinflammation will occur, which causes chronic inflammation associated with the activation of microglia, the immune cells of the brain, thus being associated with neurodegenerative disorders at present, in agreement with the article by Aguayo S et al.[19] mentions that periodontal disease is maintained by the biofilm that is on the tooth in which gram-negative anaerobic bacteria such as Porphyromonas gingivalis, Prevotella, Fusobacterium nucleatum and Treponema denticola are harbored, which if not controlled can lead to tooth loss and potentially to the development of other diseases.

Singhrao S et al.,[20] describe that Porphyromonas gingivalis remains in low quantities in the gingival sulcus, since this bacteria is highly resistant, therefore, the dentist must provide adequate treatment; non-surgical treatment and Surgical, since scaling and planing does not reach all spaces of the tooth, with periodontal surgery you can remove most of the bacteria and completely eliminate periodontal disease. Cuha P et al.,[21] establish that periodontitis induces chronic systemic inflammation, which stimulates the production of inflammatory cytokines, including interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha. (TNF-α) and contributes to an increase in neuroinflammatory.

Schnaider L et al.,[22] describe that in a 2019 publication it was evidenced that Porphyromonas gingivalis is the key pathogen in periodontitis and the development of Alzheimer's, it also mentions that evidence in the last 5 years has increased on the correlation of these two diseases, when chronic periodontitis occurs more than 10 years it is associated with double the risk of developing Alzheimer's disease. Leira Y.,[10] mentions that the invasion of the bacteria is through blood flow or through the peripheral nerves and thus accelerates neuroinflammation. In addition, the cytokines derived from periodontitis can reach the brain through systemic or neural routes.

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Harding A et al.,[23] argue that periodontitis constitutes a peripheral oral infection whose pathogenic components can result in infecting the brain and thus exposing it to immunogenic and inflammatory virulence factors. The risk factors for periodontal disease to occur in patients with Alzheimer's are poor oral hygiene, since their condition does not allow them to perform adequate oral hygiene. Leblhuber F et al.,[24] indicate that periodontal disease should be prevented with adequate management of these patients. The dentist is primarily responsible for instructing family members about oral hygiene measures in these patients in order to prevent the development of periodontitis.

Olsen I et al [25] assure that the etiological role of bacteria in periodontal disease related to the development of Alzheimer's disease is still in doubt. The pathogens adopt and adapt to the survival and utilization of long-standing inflammatory environments as demonstrated by the presence of P. gingivalis in the subgingival sulcus (as a commensal and pathogen) and at distant sites (heart, placenta and perhaps brain) with sites inflammatory components for the development of systemic diseases. Sheng N et al.,[26] indicate that patients with chronic periodontitis and gingivitis have a higher risk of developing Alzheimer's.

CONCLUSIONS

Porphyromonas gingivalis is one of the bacteria of periodontal disease that can produce systemic inflammation and consequently alteration in the blood-brain bar, causing neuroinflammation having important repercussions on the development of Alzheimer's disease. It is also known what the path of these bacteria is. to the brain, which can be directed through blood flow or nerves, on the other hand, it has been shown in several articles that elderly patients who suffer from Alzheimer's disease have a higher level of presenting periodontal disease due to lack of hygiene. oral hygiene of the patient due to his condition, which is why it is recommended to instruct relatives or the person in charge of the person who suffers from Alzheimer's about oral hygiene.

Conflicts of interest
There are no conflicts of interest.

Authorship contribution

GLVA: original idea, conceptualization,drafting of the article, final review and approval of the final report.
ÁFVT: conceptualization,drafting of the article and approval of the final report.
SLÁVB: drafting of the article and approval of the final report.
YVSB: final review and approval of the final report.

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