



Cognitive Decline and Oral Microbiota. Pro-Inflammatory Conditions Become Risk Factors in Neurodegenerative Disease

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Abstract

The growing scientific interest in the correlation between systemic pathologies and periodontal pathologies, shows how chronic infectious-inflammatory diseases, such as periodontitis, have implications with neurodegenerative pathologies, cause of cognitive decline and deprivation of self-sufficiency in the affected subjects.

Numerous studies in literature show that pathogenic microorganisms implicated in periodontal disease play an important role in the onset or more likely in the progression of neuro-degenerative diseases.

The increase in the average age of the population requires increasing commitment in the management of the needs of the "Aging Society".

The appropriateness of clinical management in preventing and removing universally known periodontal pathogens is fully part of the prevention of systemic diseases that impact on social and public health.

The minimally invasive "flapless" techniques performed with new-generation instruments represent the preferred approach also for patients presenting polytherapy, guaranteeing them an adequate reduction of the microbial load, a factor which is decisive for oral and systemic health.

Keywords: Oral Microbiota; Alzheimer Disease; Porphyromonas Gingivalis; Gingipain Inhibitor

Introduction

The correlation between low bacterial load in the oral cavity and systemic health is universally recognized. Conversely, a high proportion of supragingival and subgingival microbial biofilm is associated with numerous pathologies not only of the periodontal type.

Clinical and experimental studies have shown the correlation between periodontal disease and some systemic diseases such as Diabetes Mellitus, Preterm Birth, Cardiovascular Disease, Lung Disease and Colorectal cancer.

The dissemination, via the bloodstream, of oral pathogenic microorganisms, can determine a systemic inflammatory process and direct contact with vital organs such as the heart and lungs.

Recent studies also focus attention on the interest of the brain with respect to invasion by oral bacteria. An anaerobic Gram negative bacterium in particular, could be implicated in the formation of amyloid plaques in Alzheimer's Disease (AD), it is Porphyromonas gingivalis (Pg) [1].

PG is a late colonizer, it is found in mature dental plaque and lives in ecological niches with little oxygen, preferring sub-gingival

areas and determining with its numerous virulence factors serious tissue damage at the level of deep periodontal tissues. It also appears to be highly responsible in the formation of the sulphurated volatile compounds responsible for halitosis.

Professional Oral Hygiene Maintenance interventions and non-surgical or surgical Periodontal Therapy, aimed at correcting the consequences of periodontal disease damage, are important for the health of the whole organism.

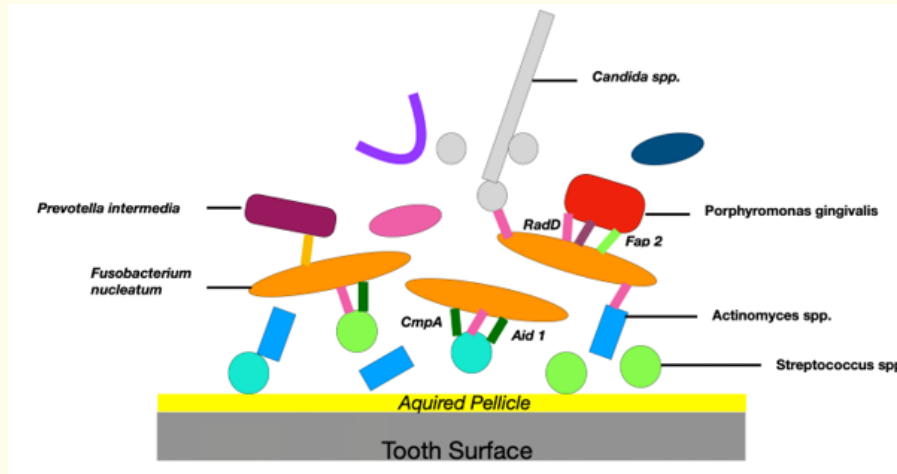


Figure 1

Oral bacterial spread in the circulatory stream

The oral cavity and intestine represent the areas of the human body with the greatest representation and number of microorganisms.

From the oral cavity, there are four ways of diffusion towards other body areas.

blood: through it, microorganisms (bacteria, viruses, fungi) can reach vital organs such as the heart and brain.

The blood-brain barrier (BBB) is a semipermeable membrane that separates the circulating blood from the cerebral extracellular fluid in the central nervous system. The BBB has protective functions of the brain and prevents substances present in the arterial blood from passing into the extracellular fluid of the brain and therefore from reaching the nervous tissue. BBB is a very selective barrier, allowing only necessary substances or metabolites to pass through, blocking all other substances by reflex.

It is important to preserve the integrity of the BBB, it becomes more permeable when an inflammatory process is present.

Periodontal disease subjects show higher values of systemic inflammatory parameters, such as C-reactive protein, than periodontally healthy subjects.

The weakening of the BBB can allow bacteria and their endotoxins to have access to the brain, modifying brain function and initiating neuropathologies [2].

- saliva: the daily production is about two liters, microorganisms can move to the intestine from saliva.
- The *Fusobacterium nucleatum* (Fn) is an important subject in the bacterial community of the oral biofilm as it acts as a "bridge" between early colonizers and late colonizers.
- Fn is a symbiont bacterium, opportunist and oncobacterium. It has virulence factors that can increase the proliferation of cancer cells, it can localize in cancer cells by blocking the anti-tumor immune responses of Natural Killer cells.

Various studies in the literature highlight the association between Fn and colorectal cancer (CRC).

When colorectal cancer is identified and treated, the presence of Fn is associated with an increased risk of recurrence and chemoresistance [3].

Some studies show that the origin of intestinal Fn comes from the oral cavity of those affected by CRC [4]:

- **Respiratory:** Subjects with dysfunctional swallowing, often elderly patients with polypathologies including neurodegenerative, have a high rate of microbial populations in the oral cavity following insufficient home oral hygiene. A share of bacteria present in their saliva originates from the tongue coating and is ingested with saliva.

Aspiration of oral contents can lead to lung infections. Aspiration pneumonia is a major cause of death among the elderly with dysfunctional swallowing [5].

Lymphatic: Recent studies show the correlation between periodontal disease and a significant increase in breast cancer of 1.22 times [6].

When breast cancer has occurred, the therapies administered can affect the oral health of patients. There is an increased risk of tooth decay, mucositis, dysgeusia and alterations of the oral microbiome [7].

Cognitive decline and oral microbiota

From 1990 to 2016, the incidence of dementia, including Alzheimer's Disease (AD), increased by 117% (The Lancet Neurology).

In 2016, 43.8 million people with dementia worldwide. Dementia forms represent the second leading cause of death for people over 70, preceded by ischemic heart disease, chronic obstructive pulmonary disease, cerebral hemorrhage, stroke.

Recent research shows that *Porphyromonas gingivalis* (Pg), an oral biofilm bacterium that lives mainly in the subgingival environment, is actively implicated in Alzheimer's Disease. Pg DNA was found in the cerebrospinal fluid of patients with AD.

In mouse models, the presence of oral Pg infection caused brain infiltration by bacteria, and was accompanied by an increase in the production of beta-amyloid (A β) 1-42, a component of the amyloid plaques involved in the AD.

One of the virulence factors of Pg is represented by gingipain, they are proteases that the bacterium uses to fragment the host proteins as nourishment.

Brain gingipain damage the Tau protein, necessary for normal neuronal function and whose disintegration is implicated in AD.

Small gingipain inhibitory molecules administered to mice reduced the bacterial load of Pg in the brain, blocked the production of A β 1-42 and reduced neuroinflammation [1].

A recent study in dogs with oral periodontal disease caused by *Porphyromonas gulae* has been treated with COR388, a gingipain inhibitor and is currently undergoing a phase 2/3 clinical trial for Alzheimer's Disease.

Dogs were administered orally for a maximum of 90 days.

In a 28-day dose-response study, COR388 inhibited the gingipain target and reduced the load of *P. gulae* in saliva, vestibular epithelial cells and gingival crevicular fluid.

Histologically, the dog's brain tissue showed evidence of the presence of *Porphyromonas gulae* and neuronal gingipain DNA, showing that *P. gulae* infection is systemic and spreads beyond its oral reservoir, similar to recent observations of Pg in humans [8].

The relationship between periodontal disease and Alzheimer's disease appears to be two-way. When periodontal disease is cured, it improves the memory of AD patients. Periodontal disease persisting for 10 years or more, doubles the risk for AD.

Studies show that if periodontal disease is present in AD patients and is not cured, further cognitive decline ensues [9].

There are three mechanisms that can explain the association between periodontal disease and neurodegenerative pathology or vascular dementia pathology:

- Increase in inflammatory markers.
- Direct invasion of bacteria
- Induction of atherosclerotic plaques [10].

Reduction of the bacterial load through Professional Oral Hygiene interventions

Periodontal disease is an infectious-inflammatory pathology with implications for systemic health, as a result of which its therapy is a real medical act.

The instruments used in this therapy are constantly evolving and allow increasingly conservative approaches, targeted in the removal of microbial biofilm from both hard and soft tissues.

Non-surgical therapy can be used with the use of manual, ultrasonic instruments and low abrasiveness powders.

The “flapless” techniques can be indicated and lead to predictable results considering some factors such as the patient’s diagnosis, the anatomy of the bone defect, the root anatomy, the lifestyle (smoking, alcohol), the correct home control of the biofilm microbial.

The management of pathogenic noxa requires careful removal above and below the gums, including ecological niches (e.g. lingual back surface). Low abrasive powders showed the smallest tissue impact at soft tissue level [11].

The reduction of the pocket depth is subordinated not only to the operator’s ability and the quality and avant-garde of the instruments, but also to some fundamental factors.

- They can influence the short-term clinical outcome of non-surgical periodontal treatment.
- These factors are:
- Presence / absence of a smoking habit.
- Periodontal probing depth compared to the presence / absence of dental plaque at the treated site level.
- Dental element to be treated if single rooted or multi rooted [12].

Conclusion

The removal of the microbial biofilm is still the gold standard in the treatment of periodontal infections.

The new frontiers of clinical and laboratory research show how much some bacteria of the oral cavity can contribute in determining serious systemic diseases.

Certainly good oral health and the reduction of the load of *Porphyromonas gingivalis* especially at a young age, should be taken more seriously than is currently the case [1].

Maintaining a healthy oral microbiota and managing periodontal disease with regular surveillance and good oral hygiene throughout life is likely to reduce Alzheimer’s Disease in some individuals [13].

Conflict of Interest

Nil.

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