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Aggregatibacter actinomycetemcomitans: A scoping review

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Abstract
Introduction: Periodontal pathogens, such as Aggregatibacter actinomycetemcomitans are involved in the etiology and pathophysiology of many neurodegenerative diseases and neuropsychiatric disorders, as well as in systemic diseases and cardiovascular diseases, as they generate in the immune system a dysregulation.
Objective: To analyze the literature on A. actinomycetemcomitans, with a focus on the dental field, analyzing its epidemiology, diagnostic methods, treatments and oral manifestations.
Methodology: Information from articles published in PubMed, Scopus and Google Scholar was analyzed with emphasis on the last 5 years. It was performed with the words ""Aggregatibacter actinomycetemcomitans", "periodontal disease", "epidemiology", "oral manifestations", "diagnosis", "treatment".
Results: A. actinomycetemcomitans is found approximately 90% in cases of aggressive periodontitis, and 21% in patients with chronic periodontitis. The common diagnostic method for periodontopathogenic bacteria is by quantitative PCR. Treatment is based on a combination of mechanical and antibiotic therapy for best results. Clinical evaluation shows clinical attachment loss, severe bone destruction at an early age with rapid progression, causing mobility and tooth loss.
Conclusions: The presence of this pathogen generates an environment that requires mechanical, chemical and antimicrobial procedures for its long-term control, so a timely diagnosis leads to the early establishment of therapies for the management of the infection.

Keywords: Aggregatibacter actinomycetemcomitans, periodontal disease, epidemiology, oral manifestations, diagnosis, treatment.

1. Introduction

Periodontal pathogens are involved in the etiology and pathophysiology of many neurodegenerative diseases and neuropsychiatric disorders, as well as in systemic diseases such as diabetes mellitus and cardiovascular diseases, as they generate a dysregulation of the immune system [1].

Research on the human microbiome in recent years has provided a clear focus that has generated an understanding of microorganisms and how they influence host physiology [2]. The role of the oral microbiome in health and disease states has many directions as it can modify or induce metabolic, autoimmunogenic or neurodegenerative diseases, as well as regulate the host immune response and modulate drug interactions [3].

The oral cavity is composed of approximately 700 species of bacteria. It is considered a unique and diverse ecosystem of microorganisms that interact with each other physically and metabolically; their interaction generates biofilm communities that create distinct niches for microorganisms with different metabolic needs [4]. When this biofilm goes into a dysbiotic state, there is a total absence of a homeostatic balance of the host, generating pathological processes in a wide range of oral cavity, intestinal, neurological and systemic diseases [5].

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Periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*, have been studied for a long time, because it shows a clear participation in the onset and progression of periodontal disease [6]. *Aggregatibacter actinomycetemcomitans* is considered the causative agent of aggressive periodontitis and is the microorganism that promotes the development of alliances of different specific microorganisms that cause symptoms of the disease. It produces a protein endotoxin called leukotoxin, which directly attacks white blood cells, limiting the ability of the entire host to respond to infection [7].

An analysis of the literature allows us to detect the lack of updated information about *Aggregatibacter actinomycetem-comitans* with dental relevance, so the aim of this article is to analyze the literature about *Aggregatibacter actinomycetem-comitans*, with a focus on the dental field, analyzing its epidemiology, diagnostic methods, treatments and oral manifestations.

2. Materials and Methods

Information from articles published in PubMed, Scopus and Google Scholar was analyzed with emphasis on the last 5 years. The quality of the articles was evaluated based on the standard guidelines, i.e., identification, review, choice and inclusion. The quality of the review was assessed using the measurement instrument for evaluating systemic reviews. The search was performed using the Boolean logical operators AND, OR and NOT. It was performed with the words "Aggregatibacter actinomycetemcomitans", "periodontal disease", "epidemiology", "oral manifestations", "treatment". The keywords were used individually, as well as each of them related to each other.

3. Results and Discussion

3.1 Epidemiology

The group of pathogens called HACEK, are a small group, composed of gram-negative bacteria that are part of the oral microbiota and colonize also the upper respiratory tract[8]. The acronym HACEK corresponds to the initials of the pathogen species involved, i.e., the genus of *Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens* and *Kingella*. Nowadays *Aggregatibacter spp*, is considered dominant etiological factor of infective endocarditis [9].

Aggregatibacter actinomycetemcomitans is a gram-negative, facultative anaerobic, non-motile, bacterial pathogen, considered the most prevalent microorganism in patients with periodontitis. It is strongly associated with aggressive periodontitis, with a prevalence in young individuals and adolescents [10]. She is found in approximately 90% of cases of aggressive periodontitis, and in 21% of patients with chronic periodontitis[11]. She is also associated with serious non-oral diseases, such as endocarditis and brain abscesses, rheumatoid arthritis, and Alzheimer's disease. Serotypes a, b and c are globally more predominant [10].

In 2019, the prevalence of patients with aggressive periodontitis in Africa was reported to be 4.2%, in South America 4.0%, Europe 0.1%, Asia 1.2%, and North America 0.8% [12].

Aggregatibacter actinomycetemcomitans, *Tannerella forsythia* and *Porphyromonas gingivalis* since 1996 have been designated as etiological agents of periodontitis [13].

A. actinomycetemcomitans plays a critical role in the pathogenesis of a specific form of periodontitis, in the new 2018 classification it corresponds to grade C, and in the 1999 Armitage classification it was recognized as aggressive periodontitis[14]. Serotype b is present in the microbiota of the oral cavity, and in severe periodontal disease. It is capable of producing toxins and virulence factors that make it a periodontal pathogen [15]. Its mechanism of action provokes through leukocytes a release of pro-inflammatory mediators that favor the progression of periodontal disease. This inflammatory response generates systemic effects leading to chronic generalized hyperinflammation, altering the entire innate and adaptive system, thus aggravating the overall immune system [16].

The prevalence we found of *A. actinomycetemcomitans* in cases of aggressive periodontitis corresponds to 90%, it is considered a rare and severe form, which shows a deficient response of the host associated with an exaggerated destructive response. The epidemiology of this disease is found with a higher frequency of occurrence in patients aged 14 to 17 years, however its prevalence is less than 1% and varies according to race, country and region.

3.2 Diagnostic Methods

A variety of techniques are used with methodology based on specific bacterial DNA sequence since they show high specificity, sensitivity and rapid determination of specific oral pathogens [17]. Methods for bacterial identification in clinical samples are: polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), fluorescence in situ hybridization (FISH), checkerboard hybridization and microarray cloning and sequencing [18].

The most common method used for the diagnosis of periodontopathogenic bacteria is quantitative PCR, which is effective in quantifying and differentiating the bacterial species of the periodontium by means of a sample of saliva or gingival crevicular fluid from the patient [19, 20].

PCR has the advantage of contributing accurately to the identification and characterization of *A. actinomycetemcomitans*. This test is the most suitable for periodontal pathogen recognition, as it establishes a more accurate quantification of pathogens in a complex plaque biofilm [21].

A study analyzed the diagnostic accuracy of the multiplex PCR technique compared to the culture technique, within the endopathogenic microbiota within which *A. actinomycetemcomitans* was present and concluded that with real-time multiplex PCR has a higher sensitivity and specificity when compared to the culture technique [22, 23].

Another accurate and successful diagnostic tool currently reported is mRNA and circ RNA technology that allows the identification of pathogen mechanisms, as well as new target genes and protective compounds that lead to an improvement in the therapeutic and prognostic protocol. These RNA techniques accurately detect periodontal bacteria [24].

Samples that are analyzed by culture and PCR are obtained by taking subgingival plaque samples from patients [25]. Periodontal pockets are also an idea site to obtain a sample of *A. actinomycetemcomitans* from oral cavity, the technique for collection consists of using sterile paper tips that are inserted into the periodontal pocket, as well as scraping with a cotton swab on mucosa and collecting stimulated saliva in test tubes [26].

The currently most accepted method for the diagnosis of bacteria present in the oral cavity is by quantitative PCR, and the sample can be taken from saliva, gingival crevicular fluid or even by taking a sample of subgingival plaque from the tooth. It is obtained by means of sterile paper tips, scraping

with swabs or collecting saliva in test tubes.

3.3 Treatment

The first phase of periodontal therapy consists of non-surgical mechanical removal combined with oral physiotherapy by the patient. If clinical signs persist subsequent to performing non-surgical therapy, a surgical therapeutic approach with adjuvant systemic antimicrobials should be indicated to the patient to reduce the pathogen load [26, 27].

The combination of a mechanical therapy with antibiotic therapy shows better results. Studies indicate that moxifloxacin, amoxicillin or amoxicillin in conjunction with clavulanic acid and doxycycline show superior benefit compared to any other antibiotic administered in aggressive periodontitis [28].

A combination of amoxicillin and metronidazole and periodontal therapy generates a healthier long-term periodontal clinical condition and reduces pathogen levels, especially *A. actinomycetemcomitans* which achieves a significant reduction with antibiotic administration compared to only mechanical therapy [29, 30].

The American Academy of Periodontology observed that scaling and root planning in conjunction with an antimicrobial photodynamic treatment developed for inactivation of microorganisms showed significant short-term decrease of *A. actinomycetemcomitans* compared to patients who were only treated with mechanical therapy [31]. Likewise, the use of photoactivated disinfection has shown significant reductions in *Aggregatibacter actinomycetemcomitans* fimA gene expression, as well as a decrease in the ability to form biofilms and its metabolic activity. This therapy can serve as an adjunct for non-surgical treatment of periodontitis and peri-implantitis [32].

Studies have revealed the use of ethanolic extracts of the plants *Punica granatum*, *Commiphora molmol* and *Azadirachta indica* as antibacterial compounds. Their use creates a synergy with antibiotics and generates an enhanced activity. A high synergism was reported in *Punica granatum* with Amoxicillin against *Aggregatibacter actinomycetem-comitans*, followed by *Azadirachta indica* with tetracycline against *Aggregatibacter actinomycetemcomitans*, however like any study, more research is needed to know in depth the synergistic effects [33].

Ethanolic extracts of *Salvadora persica* and *Cinnamomum zeylanicum* trees have also shown inhibition of the proliferation and growth of periodontal strains. A combination of herbal extracts with different antibiotics has revealed a synergistic antibacterial effect, *Salvadora persica* with metronidazole against *Aggregatibacter actinomycetem-comitans* has shown the best synergism among the studies [34].

Periodontal therapy aims to stop the progression of periodontal disease and maintain the patient in a state of periodontal health this therapy, in conjunction with systemic antibiotics in patients with periodontitis stage ll and lV, grade B and C showing better results in disease remission and low disease activity thus decreasing the presence of *Aggregatibacter actinomycetemcomitans*.

3.4 Oral Manifestations

Aggregatibacter actinomycetemcomitans acts by first colonizing the subgingival surface of the gingiva, deepening the periodontal pocket. It acts silently but aggressively, evading the defense mechanism of the immune system. The suppressed host response promotes bacterial overgrowth leading to dysbiosis and leaves the host susceptible to further infection [35].

The clinical aspects of periodontal disease include gingival inflammation and bleeding, pain, halitosis, mobility and tooth migration. There is loss of attachment of periodontal tissues by apical migration of the junctional epithelium forming periodontal pockets and this generates horizontal bone loss with alveolar destruction [13]. The virulence mechanisms of *Aggregatibacter actinomycetemcomitans* establishes an early and rapid form of this disease [36]. The RTX toxins presented by this bacterium are linked to increased pocket depth at probing and disease progression [37].

The specific form of periodontitis associated with *A. actinomycetemcomitans* is what was previously known as localized aggressive periodontitis and is now known as molar incisor pattern periodontitis (Periodontitis, grade C) [38]. It is an inflammatory disease that affects the periodontium of molars and incisors, causing clinical attachment loss and severe bone destruction at an early age and has a rapid progression, causing mobility and tooth loss [39]. *A. actinomycetemcomitans* shows an increased association with peri-implantitis. The presence of this pathogen leads to destruction of the attachment apparatus and bone loss around a tooth or dental implant [40].

The virulence factors presented by *A. actinomycetemcomitans* generate an evasion of the host immune system causing a rapid and silent destruction of periodontal tissues causing clinical attachment loss and severe bone destruction at an early age resulting in tooth mobility and loss. It is important to remember that its progress is not only limited to the oral cavity, as it can trigger systemic pathological processes.

4. Conclusions

Aggregatibacter actinomycetemcomitans plays a critical role in the pathogenesis of a specific form of periodontitis. A 2020 study shows that it is present in 90% of cases of aggressive periodontitis and in 21% of patients with chronic periodontitis. This disease causes clinical attachment loss and severe bone destruction at an early age with rapid progression resulting in tooth mobility and loss. PCR is the effective diagnostic method to quantify and differentiate bacterial species in the periodontium and can be obtained from saliva, gingival crevicular fluid or subgingival plaque. It requires mechanical, chemical and antimicrobial procedures for long-term control.

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