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Literature Review Article

Localized aggressive periodontitis – clinical, radiographic, microbiological and immunological findings

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Abstract

Introduction: Localized Aggressive Periodontitis (LAP) is characterized by a disease with rapid progression and loss of bone support specifically in the region of the permanent first molars and incisors teeth, and may lead to loss of dental elements. **Objective:** The aim of this study was to conduct a brief literature review on LAP, and present the clinical, radiographic, microbiological and immunological aspects of this rare form of periodontal disease. **Literature review:** Epidemiological studies in different populations showed a higher incidence in non-white population, and non-industrialized countries, there is also a predilection for female gender, manifested between puberty and 25 to 30 years of age. **Conclusion:** LAP is a disease with low prevalence, mainly caused by *Aa*, and radiographically manifested by extensive destruction of periodontal tissue supporting of permanent first molars and incisors. In contrast, clinically, the affected teeth not presented significant amount of dental biofilm or gingival inflammation. The early diagnosis is important to establish an effective treatment, including antibiotic therapy, and favor prognosis.

Introduction

The Localized Aggressive Periodontitis (LAP) is a type periodontal disease with low prevalence, characterized by rapid loss of bone support specifically in the region of the permanent first molars and incisors. The concepts about the etiology, treatment and prognosis of this disease have undergone considerable changes since its first description as a diffuse atrophy of the alveolar bone by Gottlieb, in 1923. After this first description a theory of non-inflammatory, degenerative disease of the periodontium was suggested, by Orban and Weinmann in 1942, who called this process "periodontosis". In 1971, Baer cleared its clinical features and described as a "rapid destruction of the alveolar bone, not commensurate with the local irritants, around more than one permanent tooth in otherwise healthy adolescents". The term Localized Juvenile Periodontitis was proposed by Lehner and his coworkers in 1974, as a selective, cell-mediated immunodeficiency condition [*apud* 43], and was widely employed until 1999.

The American Academy of Periodontology (1999) instituted the term Localized Aggressive Periodontitis, aiming not restrict the classification of the disease with the age of onset. The term prepubertal periodontitis was separated, as distinct category of periodontal disease, manifested as consequence of a systemic disease. The prepubescent child with periodontitis without any modifying systemic conditions was fitted under the chronic or aggressive disease categories [23]. According to American Academy of Pediatric Dentistry (13/14) patients with LAP have insertion loss of interproximal in at least two permanent first molars and incisors [3].

The aim of this study was to conduct a brief literature review on the LAP, presenting the clinical, radiographic, microbiological and immunological aspects of this rare form of periodontal disease and emphasizing the importance of early treatment.

Literature review

Etiology and epidemiology

The main etiologic agent associated with LAP etiology and pathogenesis is the *Actinobacillus actinomycetemcomitans* (*Aggregatibacter actinomycetemcomitans*) (*Aa*). This microorganism is an aerobic, facultative anaerobic, capnophilic, Gram-negative coccobacillus, found in LAP patients in higher prevalence than other periodontal pathologies [17, 32, 38, 45, 57]. It is found in supra and subgingival space and is highly independent and self-sufficient. A peculiar characteristic that makes it important and that hinders its elimination is its high capacity for tissues invasion. If *Aa* penetrates through the junctional epithelium and underlying connective tissue, it can reach the root cementum surface and bone tissue and install in these locations, which makes difficult its eradication through mechanical means. The *Aa* is also known as *Haemophillus actimycetemcomitans*, and is also responsible for a series of systemic infections, including the bacterial endocarditis, the brain and skin abscesses and the urinary tract [39, 47, 48].

The incidence of LAP varies from 0.1 to 3 %, of adolescent children depending on the specific form of disease and the population studied [28, 37]. Epidemiological studies in different populations have found higher incidence in non-white population, and non-industrialized countries, there is also a predilection for female gender [Dalberto]. Most reports suggest a low prevalence (0.2%), which is markedly greater in African American populations (2.5%) [3]. The prevalence of this disease among 15-18 year-old school children was 0.13% in Iran [41]. A study at a dental school in southern Brazil showed that 1.8% of patients had LAP at 15-36 years [21]. According to the American Academy of Periodontology, LAP is manifested between puberty and 25 to 30 years of age [9, 16, 17, 20, 60], all of these studies show a wide variation in age of onset for the disease, showing that it usually occurs in adolescence.

Some evidences about the heredity, such as the possibility of genetic predisposition for the occurrence of this disease and the possibility of intrafamilial transmission are present in the literature [36, 43, 46]. The family relationship is a common occurrence in LAP, and this explanation is the transmission of genetic polymorphisms that alter the host susceptibility to disease, exacerbating the inflammatory response. Another typical feature of LAP is the abnormal presentation of neutrophils, the first line of defense against foreign agents [34].

According to literature review carried out in 2010, correlating the occurrence of periodontal changes and systemically-compromised patients, it was observed that there is high frequency of periodontal changes in children and adolescents and that the manifestations may vary from a gingival inflammation to the most destructive forms, such as LAP, leading, in some cases, to the early loss of teeth [58].

Some genetic aspects also have been associated with LAP since immune- inflammatory host response may be amended from genetic polymorphisms of cytokines. During the inflammatory defensive response of the body with migration of neutrophils occurs; however, birth defects in neutrophils can cause injury in the chemotaxis of polymorphonuclear cells [19]. There is heterogeneity within the aggressive periodontitis classification with regard to neutrophil abnormalities: in USA studies, there is a decreased neutrophil chemotaxis trait about 60-70% of LAP patients [11, 54, 55]; while in northern Europe and Finland it is lower [24, 42]. Some studies present a co-segregation of the neutrophil trait with clinical disease in African-American populations and in certain African-American families [52].

Among the neutrophilic changes in these families, it is included the decreased chemotaxis to a number of chemotactic factors associated with reduced receptor expression on the neutrophil surface for those chemotactic factors [53], reduced calcium transport in LAP neutrophils [1], increased diacylglycerols levels in stimulated LAP neutrophils, and decreased protein kinase C activity [25].

LAP is linked to human chromosome 1q25, certain forms of this disease show a simple Mendelian pattern of transmission, but no single gene has been identified as being responsible for the disease phenotype. Subjects affected by LAP, received clinical and laboratory diagnosis to define a homogeneous phenotype. A connection with a DNA marker, D1S492 was observed. The association with D1S492 indicated that LAP locus is located between D1S196 and D1S533 on chromosome 1 [27].

Microbiological and immunological aspects

The development of LAP involves the participation of immune an inflammatory response and the release of some cytokines, such as IL-1β, IL-6 and TNFα which promotes degradation of collagen tissue and resorption of alveolar bone surrounding affected teeth [19, 35, 51]. The *Aa* also has potentially destructive mechanisms as production of endotoxin, proteolytic enzymes (collagenase and hyaluronidase), leucotoxins, that can destroy polymorphonuclear cells and monocytes and compromise the ability of the organism defense, inhibiting chemotaxis and phagocytosis of polymorphonuclear leukocytes, inhibiting factor of fibroblasts, which interferes with the synthesis and production of collagen, thereby impairing the tissue repair. The production of strata soluble may alter the lymphocytes function, producing a polyclonal activation of B lymphocytes, induced by bacterial factors, resulting in the production of antibodies with determinants not related with the activator agent [13, 15, 22, 26].

The *Aa* may also exists intracellularly within human gingival fibroblasts, suggesting that the attachment and invasion of *Aa* in human gingival fibroblasts play a direct role in periodontal tissue damage and can also be a method of bacterial evasion of host immunity [5].

There are several methods for detecting periodontal pathogens, such as dark-field microscopy and phase contrast, microbial culture, enzymatic assay, biochemical markers, immunofluorescence, ELISA, flow cytometry and analysis of DNA and RNA. The polymerase chain reaction (PCR) methodology applied is widely used for periodontal microbiology analysis [12]. During identification of microorganisms involved in PAL by microbiologic culture, the samples shall be taken from periodontal pockets by collection supragingival biofilm through sterile cotton balls and the periodontal pocket through insertion of sterile absorbent paper points, until it found resistance and maintained on site for 10 seconds [45]. For detection of pathogens by PCR, the samples may be collected by sterile absorbent paper points, without specifying the time of contact between the paper point and the sample and maintained at -70ºC until they were analyzed by means of probe for analysis of microorganisms and PCR, it was found that based on microarray analysis with 16S rRNA, the *Aa* was strongly associated and specific sites in LAP [44].

A recent analysis [14] performed by real time PCR related that Human β-defensins (HBDs) are frequently expressed in the crevicular fluid in both healthy and LAP subjects. In this study the sample was collected and maintained similarly to that of Shaddox *et al.* [45]; however, the time of contact of the paper point was 30 seconds and the points were immersed in distilled water.

Recent researches reported an association of apoptotic biomarkers in gingival crevicular fluid (GCF) and periodontal destruction in four cases of localized aggressive periodontitis (LAP). A total of 62 samples of GCF were collected from diseased sites and from contralateral healthy sites and the samples were assayed for apoptotic markers, including Fas/FasL, DNA fragmentation, and nitric oxide. The DNA fragments and nitric oxide levels were analyzed by enzyme-linked immunosorbent assays, and Western blotting was used for Fas/FasL analyses. A significant increase in the apoptotic

markers Fas/FasL and DNA fragmentation was reported in patients with LAP when comparing GCF from diseased versus non-diseased sites [31].

Aa is a Gram-negative microorganism that have Lipopolysaccharide (LPS) in cell wall, this LPS induce a significant macrophage production of nitric oxide (NO). The increased of nitric oxide synthase (NOS) activity, cannot have a positive correlation with neutrophil chemotaxis. This study aimed to determine the occurrence and distribution of inducible NOS (iNOS) in human gingival tissue from LAP patients, by monoclonal antibody against iNOS. The immunostaining revealed the presence of iNOS in inflamed compared to non-inflamed gingival tissues and macrophages expressed high levels of iNOS that may cause some damage to the periodontal tissues. The iNOS activity in macrophages may modify abnormalities of neutrophil function [18].

Clinical and radiographic findings

The aggressive periodontal diseases are clinically heterogeneous and include forms of disease clinically indistinguishable from other forms of periodontitis, and several forms of disease with a uniquely localized clinical presentation with significant destruction at a very early age [2].

Maciel *et al.* [31] suggests that the dentists play a fundamental role in the diagnosis of LAP, because they are the professionals who have the first contact with these patients and may thus prevent the early loss of the deciduous dentition, and also establish an adequate treatment, according to the degree of disease development.

Clinically and radiographically, LAP is manifested by rapid attachment loss and bone destruction localized in first molar and incisor teeth with interproximal attachment loss on at least two permanent teeth [2, 50].

Although in these areas deep periodontal pockets, mobility and migration, with formation of dental diastema are detected, the gingival tissue often presents an appearance of normality, with absence of any inflammatory alteration. After the advance of the disease, other signs and symptoms such as an increase in clinical crown and consequent sensitivity to different agents, pain when chewing, inflammatory changes and periodontal abscesses may appear [59].

LAP patients have small amount of dental biofilm, little or no deposit of calculation and low incidence of tooth decay when compared to patients with chronic periodontal disease. The presence of irritant local factors is not sufficient to trigger or justify the emergence of the disease [40].

In accordance with the "World Workshop", conducted by the American Academy of Periodontology, LAP is manifested between puberty and 25 to 30 years of age [9, 16, 17, 20, 60], presents familial tendency and absence of evident etiological factors in the affected areas. Clinically all individuals affected by LAP have a bone loss ≥ 4mm and usually the most affected teeth are the permanent first molars and incisors. At least the first molar must necessarily be compromised [6, 9]. According to the American Academy of Pediatric Dentistry (13/14) patients with LAP have interproximal insertion loss in at least two permanent first molars and incisors.

Diagnosis, treatment and prognosis

LAP diagnosis is based on clinical, radiographic, and historical data [4]. Because LAP is a disease with very rapid progression and possess some difficulty to be controlled, it should be treated by a specialized periodontist. However, one should not overlook the importance of general practitioners to perform early diagnosis of LAP. For an accurate diagnosis is necessary that the general practitioner has data on medical, family and social history of the patient [49].

The aim of LAP treatment is to eliminate the infection and prevent its recurrence, allowing the healing of gingival tissue and bone neoformation. According to the American Academy of Periodontology (1999), it is necessary to inhibit the progression of the disease. In this way, initially the patient should receive guidance on oral hygiene and biofilm control, which should be constantly evaluated. Following, supra and sub gingival scaling, dental polishing, and (basic) periodontal treatment should be performed, and if necessary, occlusal restoration.

Due to the complexity of LAP, that involves systemic and immune defense aspects, its control may not be possible in all cases. Some studies [29, 32, 33], reported that the basic periodontal treatment may not be sufficient to eliminate all microorganisms, which can be housed in retentive areas of difficult access and in the periodontal pocket. Considering that supragingival biofilm is a niche for *Aa*, these remaining microorganisms may penetrate in the gingival sulcus and re-emerge in the connective tissue causing reinfection.

Thus, the surgical treatment may be necessary after the basic periodontal treatment, aiming to

obtain a direct access to deeper regions. In this case, through full thickness mucoperiosteal flap, the gingival tissue, alveolar mucosa and periosteum are separated from the root surface and bone, enabling that the granulation tissue on the internal walls of the periodontal pocket covering the bone defects can be removed to decrease inflammatory response.

According Machtei *et al.* [30], the surgical step should use the Widman modified flap for better tissue curettage, or even the apically positioned flap without bone resection. On the other hand, Mandell *et al.* [33] recommend the full-thickness flap with inverted bevel.

Considering that the primary LAP cause is bacterial infection, an antibiotic therapy should be prescribed concomitant to preventive and surgical procedures. The effectiveness of local or systemic tetracycline has been widely reported in the literature [7, 32, 40, 45, 56]. This agent is indispensable, due its substantivity and slow release to dentin tissue, which may reduce the activity of collagenase in the tissue affected by periodontal disease. Thus, tissue destruction can be reduced, allowing the connection of fibronectin to the root surface, stimulating growth and chemotaxis of fibroblasts and at the same time preventing the migration of epithelial cells by facilitating the formation of a new insertion, in addition to inhibiting bone resorption mediated by osteoclasts, due to their affinity to bone tissue.

Aim to reduce gastrointestinal effects the doxycycline, a semi-synthetic tetracycline, can be used to replace tetracycline, at a dosage of 100 mg/day for 14 days [33]. In refractory cases to tetracycline treatment, the administration of metronidazole 250 mg, 3 times a day, associated with amoxicillin 250 mg, 3 times a day, for 8 days is recommend [10].

Another clinical study, evaluated patients submitted to surgical periodontal treatment and treated by antibiotic therapy immediately after the surgical procedure, and recommended the dosage of metronidazole 750 mg daily and amoxicillin 1500mg daily for 8 days. The clinical parameters were measured after 12 months of treatment. The results showed an improvement of the clinical parameters in all patients, although half of them were infected by *Aa* one year after treatment. However, the infected group by the microorganism was not significantly worse than the non-infected group [56].

LAP treatment is more satisfactory for patients who receive systemic antibiotics immediately after the local treatment, resulting in a greater improvement in clinical parameters and local inflammatory response when compared with the late use of antibiotics, after 6 months [7]. In contrast, the systemic use of azithromycin 500 mg, once a day, for 3 days, was ineffective in reducing the levels of important subgingival periodontal pathogens in individuals with LAP [20].

For these reasons the knowledge of this disease is extremely important for an early diagnosis and instruction of appropriate treatment. The prognosis depends on biofilm control.

Thus, the prognosis of LAP depends on the awareness of the patient regarding to the importance of oral hygiene and also of a periodic control, through monthly visits that can become quarterly. If the deciduous dentition is affected, the eruption of permanent teeth should be monitored for early detection of bone loss [30].

According to Saba-Chujfi and Zanatto [41], there are many perspectives regarding the treatment of LAP in the future. The inhibition that the *Streptococcus mitis* causes in *Aa* could lead to the development of some serum, capable of controlling the activity of these bacteria. The increased concentrations of lysozyme in gingival fluid of patients with LAP, causing lysis of *Aa*, would represent an alternative to be better studied. Still, the high levels of IgA, IgG and IgM serum for the microorganism mentioned above could be an important factor in preventive therapy of this disease.

Conclusion

LAP is a disease with low prevalence, mainly caused by *Aa*, manifested clinically and radiographically by rapidly progressive form of periodontitis that affects the permanent dentition during the pubertal stage. This results in loss of attachment of 4 mm or more in at least 2 permanent first molars and incisors. Gingival tissue around the teeth can have normal texture and color, subgingival calculus is not frequent, and the periodontal destruction is not consonant with the presence of local irritating agents. The early diagnosis is important to establish an effective treatment and thus to offer the patient a favorable prognosis.

Collaborators

All authors participated in the conception, data collection and composition of the article.

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