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Host Response and Immune Regulation in Aggressive Periodontitis

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Abstract: *A paradigm shift several decades ago explicated that aggressive periodontitis was not a degenerative disorder but a rapid progressive form of plaque-induced inflammatory periodontal disease. Present years of research have led to linkage analysis identification of specific genetic defects and host responsible for Aggressive Periodontitis in some families and to the finding that subgingival detection of A. actinomycetemcomitans. Recent advances are leading to a new paradigm shift, with the realization that genetically-driven dysbiotic changes in the subgingival microbiota may predispose to a cascade of events leading to the rapid periodontal tissue destruction seen in Aggressive Periodontitis. This review tries to dissect the existing literature on the host response-microbial axis of Aggressive Periodontitis and to propose possible pathogenic pathways in line with current theories.*

KEYWORDS: *Aggressive Periodontitis, Host response, Aggregatibacter actinomycetemcomitans, Neutrophil, Periodontitis.*

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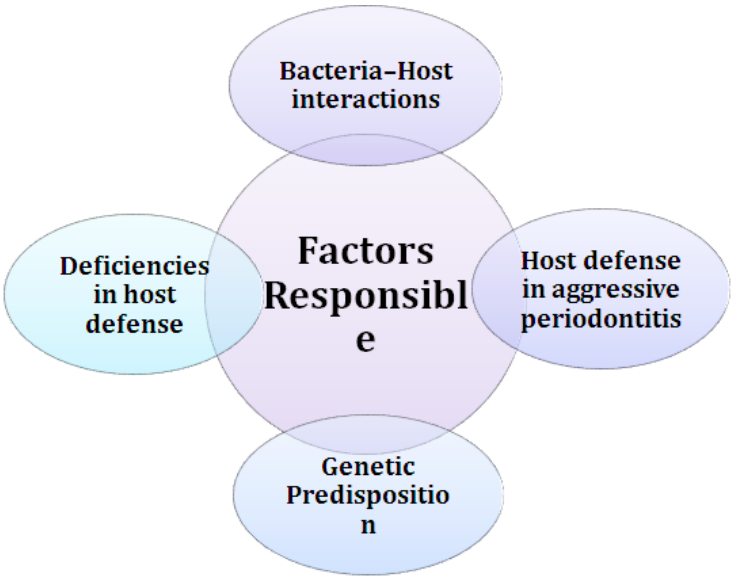
I. Introduction

A substantial body of evidence has accumulated to suggest large inter-individual variations in the response to dental plaque accumulation, leading to different degrees of gingival inflammation. [(1)] In aggressive periodontitis, the following four factors play distinct role in the susceptibility of the host and thus in the manifestation of disease:

1. bacteria-host interactions
2. host defenses in aggressive periodontitis
3. deficiencies in host defenses
4. genetic predisposition



The first line of periodontal defence is provided by the innate immune response, in the form of neutrophils and macrophages, fibroblasts, epithelial and dendritic cells, which are normally continuously engaged in responses to bacterial plaque in a state of pre-clinical 'physiological' inflammation. When this response is not able to control microbial accumulation, complex inflammatory cascades are activated and an adaptive immune response is called upon by antigen presenting cells, with a progressive shift from a predominantly T-cell lesion to a B-cell dominated lesion typical of periodontitis. [(2)] As evidence of presence of neutrophils in gingival lesions and in root surfaces of Aggressive Periodontitis cases, it emerged that neutrophils in AgP patients could be responsible for disease predisposition due to an array of suspected malfunctions, including increased adhesion, reduced chemotaxis, increased superoxide and nitric oxide production and reduced phagocytosis.[(3-8)] These neutrophil features would make individuals more susceptible to periodontitis upon subgingival microbial colonization.

NEUTROPHIL CHEMOTAXIS AND FUNCTION

Neutrophils represent the first line of defence against infection and are an essential component of the human innate immune system. Neutrophils are attracted to the site of infection in an attempt to eliminate or reduce the infectious load, and they kill bacteria by oxidative bursts and phagocytose bacteria and antigens. In an early study, **Suzuki et al.** studied neutrophil functions in subjects with different forms of aggressive periodontitis and in controls. In addition to uncovering abnormalities in peripheral blood neutrophil chemotaxis in more than half of the subjects with aggressive periodontitis, they also found abnormalities in other neutrophil functions in significant numbers of the subjects with aggressive periodontitis.

These studies suggest that defects in neutrophil chemotaxis and function may be key etiological factors in the pathogenesis of aggressive periodontitis because these defects impede the host immune response and contribute to pronounced loss of periodontal tissue. Formyl peptide receptors on the cell surface of leukocytes are involved in mediating immune-cell responses to infection. The bacteria derived N-formyl-methionyl peptides have high affinity to the N-formyl-methionyl peptide cell receptor, and after binding to the neutrophil receptor the neutrophils become activated, thus triggering them to migrate to the site of infection. Early studies suggested that neutrophils from the serum of patients with aggressive periodontitis show impaired chemotaxis to these antigens.

The 1999 Workshop also suggested among secondary features of AgP 'Hyperresponsive macrophage phenotype, including elevated levels of prostaglandin E2 (PGE2) and interleukin Host response in aggressive periodontitis 55 (IL)-1β'.5 Recently, reports of an excessive local and systemic inflammatory response has been reported in AgP cases, specific to macrophage inflammatory protein (MIP)-1α 50 and to response to bacterial endotoxin in LAP.

CYTOKINES

Interleukin-4 and interleukin-13 are closely related cytokines and have similar functions and anti-inflammatory properties. It has been shown in several studies that patients with aggressive periodontitis produce higher concentrations of interleukin-4 in activated CD4+ cells. A study found an association between the IL13-1113 CC genotype and a higher frequency of aggressive periodontitis. Furthermore, it has been shown that T-helper 1 cells from patients homozygous for the 34T and 590T alleles show higher interferon-c and interleukin-2 expression and significantly increased interleukin-13 production.

The cytokine interleukin-6 is encoded by the IL6 gene and has pro-inflammatory as well as anti-inflammatory functions. **Nibali et al.** concluded that IL6 polymorphisms and haplotypes are moderately associated with periodontitis and that this association was stronger for the localized form of aggressive periodontitis than for generalized aggressive periodontitis or chronic periodontitis.

The cytokine interleukin-17 is a central player in the immune system in complex diseases that integrate innate and adaptive immune mechanisms. This cytokine is secreted by a variety of innate cells and it has been shown that it exerts a hostdefense role in many infectious diseases, but also promotes inflammation and tissue loss in autoimmune diseases.

A study in 102 patients with aggressive periodontitis and 67 periodontally healthy controls showed that interleukin-17 was present at significantly higher concentrations in the patients and was barely detectable in the controlled individuals. The study concluded that interleukin-17 may play a role in the pathogenesis of aggressive periodontitis. Another study, however, found that the concentration of interleukin-17 in the gingival crevicular fluid was significantly lower in the group of patients with aggressive periodontitis than in the healthy control group.[(9)]

VITAMIN D

Vitamin D plays an important role in bone metabolism and in calcium and phosphorus homeostasis, and also regulates the expression of a large number of genes. The blood concentration of the prehormone calcifediol (calcidiol) is considered as the best indicator of a subject's level of vitamin D. A study found higher

plasma levels of calcifediol and osteocalcin and lower serum levels of inorganic phosphorus in subjects with aggressive periodontitis than in healthy controls.[10]

Although host factors can also play an enormous role in the progression of disease, polymorphonuclear neutrophil dysfunction does not appear to be a cause for aggressive periodontitis in non-syndromic individuals. Interestingly, even treated AgP cases exhibited an enhanced inflammatory response in an experimental gingivitis model, suggesting a possible constitutive hyper-inflammatory status. These clues lead to the understanding that, if chronically activated by certain microbial triggers, the host response could contribute to the extensive rapid tissue damage to the periodontium seen in these cases. Genetic studies investigating heritable AgP traits have focused on putative host response genotypes, which would cause constitutive neutrophil abnormalities or dysfunctions in other inflammatory/immune response pathways.

IMMUNE REGULATION IN AGGRESSIVE PERIODONTITIS

The immune response in periodontal disease is governed by the net effect of T-helper 1 (Th1) and T-helper 2 (Th2) cytokines. Th1 cytokines include interleukin-2 and interferon-gamma and promote cell-mediated immunity, while the Th2 cytokine, interleukin-4, suppresses cellmediated responses and enhances humoral immunity. Recently, a new subset of T-helper cells, Th17 cells, characterized by the production of interleukin-17, has been described. This subset may have both destructive and protective effects in periodontal diseases.[11]

The early/stable lesion of chronic periodontitis is dominated by macrophages and Tcells, suggesting that Th1 cytokines are important in the development of this response, while the advanced/progressive lesion of chronic periodontitis, which is characterized by B-cells and plasma cells, is dependent upon Th2 cytokines. Interferon-gamma, produced by the Th1 cells in the early lesion, would act to limit the infection by enhancing the phagocytic activity of neutrophils and macrophages. Owing to the persistence of the bacterial antigens in the plaque biofilm, however, the lesion cannot resolve. Progression from a stable lesion to progressive periodontitis is characterized by a change in the nature of the inflammatory infiltrate and an increase in the number of B-cells and plasma cells. This may occur as a result of the continued presence of pathogens and the existence of an ineffective Th1 response.

The production of interleukin-4, possibly as a result of mast cell stimulation, causes a Th2 response with B-cell activation and the production of antibodies. Protective antibodies are likely to be effective in containing the infection, but non protective antibodies may also be produced, leading to persistence of the infection and high levels of interleukin-1 with resultant tissue destruction. A reduced Th1 response has been shown in chronic periodontitis, where peripheral blood mononuclear cells obtained from patients with chronic periodontitis and then stimulated with mitogens, P. gingivalis and Fusobacterium nucleatum showed lower levels of Th1 cytokines. Additionally, increased levels of Th2 cytokines have been reported in the gingival crevicular fluid, gingival tissue and peripheral blood of patients with chronic periodontitis.

These studies support the concept that in chronic periodontitis the early/stable lesion is characterized by a Th1 response and that the advanced ⁄ progressive lesion is associated with a Th2 response. Because of the B-cell/plasma-cell nature of the aggressive periodontitis lesion it is likely that aggressive periodontitis is also a Th2-mediated lesion. Interleukin-10 has been implicated in the pathogenesis of chronic periodontitis. By stimulating B-cell immunity, while at the same time suppressing innate immunity and antigen-specific T-cell responses, in particular Th1-mediated responses, the role of interleukin-10 in human chronic infections is both complex and critical. Indeed, interleukin-10 may be critical in controlling the balance between Th1 cells and Th2 cells in chronic periodontitis, whereby an excess of interleukin-10 may shift the balance in favour of a Th2 response and progressive disease, whereas a shortage of interleukin-10 may lead to increased interleukin-1 production and increased tissue destruction.

COMPARISON OF NEUTROPHIL FUNCTION IN CHRONIC AND AGGRESSIVE PERIODONTITIS

In the study of aggressive vs. chronic periodontitis, one of the most significant paradigm shifts has centered on the role of alterations in neutrophil function, either due to inherent changes, external factors or a combination of both, in the pathogenesis of these two broad disease categories. The earliest pioneering work on neutrophil functions and periodontal diseases in general and aggressive periodontitis in particular indicated an impairment of neutrophil functions responsible for host protection.

In the absence of a specific stimulus such as microbial colonization in the gingival crevice/periodontal pocket, neutrophils flow within the terminal circulation system in the periodontal tissue, with a proportion of these neutrophils rolling along the endothelial lining. This rolling motion along the endothelial lining is facilitated through weaker binding of selectins on the neutrophil surface to lectins on the endothelial lining. Neutrophils respond to binding of microbial products or antigens resulting from microbial colonization of the tooth surface, such as the small bacterial chemotactic peptide N-formylmethionyl-leucyl-phenylalanine (referred to here as f-Met-Leu-Phe), and binding of these peptides or antigens to specific receptors or neutrophil binding at a variety of inflammatory mediators released in response to the microbiota to neutrophil receptors. One of the first responses to such binding is shedding of the selectins on the neutrophil surface, with a concomitant

increased expression of integrins of the CD11/CD18 (cluster determinant 11/18) family on the neutrophil cell surface. These integrins enable the neutrophil to adhere more tightly to intercellular adhesion molecules on the surface of endothelial cells, and facilitate migration of neutrophils through the endothelial lining and into the lamina propria of the periodontal tissues. The actual movement of neutrophils into the tissue is driven by an actin filament motor through polymerization and depolymerization of intracellular actin filaments. Neutrophils then move out of the lamina propria into the gingival crevice / periodontal pocket, where they attempt to engulf/phagocytose and kill the bacteria on the tooth surface. This process of engulfing the bacteria via phagocytosis and eliminating them by intracellular killing is facilitated by two neutrophil processes:

(i) release of enzymes such as myeloperoxidase and a variety of proteolytic enzymes from lysosomal granules, and
(ii) the oxidative burst, which entails the synthesis and release of superoxide and hydroxyl radicals, and subsequent conversion of these products to hydrogen peroxide. In addition, as part of this first line of defense against microbial colonization in the periodontal pocket, neutrophils secrete other bactericidal substances such as calprotectins and cathelicidins as part of the innate immune system.

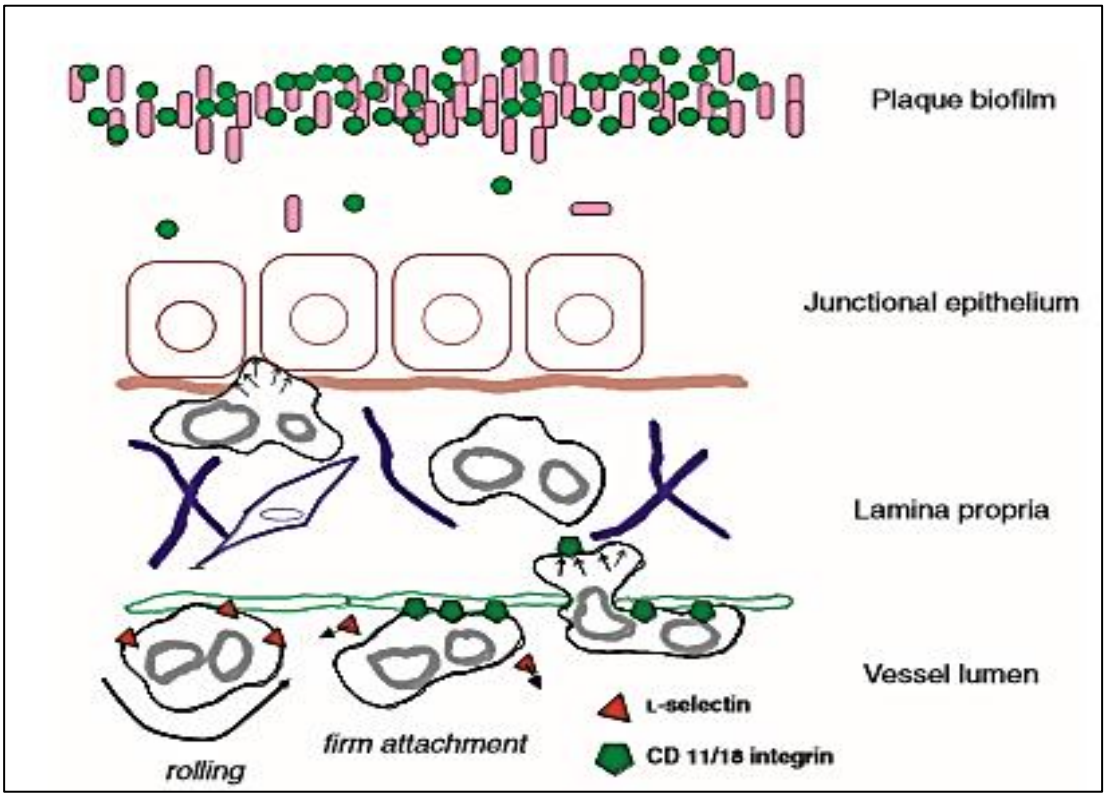


Figure 1: Early events of neutrophil chemotaxis in periodontal tissues.

Neutrophils attach to, and roll along, the endothelial cells in the terminal circulation via relatively weak selectin-mediated binding. In response to a microbial and/or pro-inflammatory stimulus, selectins are shed and surface integrins are up-regulated to create a firm attachment to the endothelial lining of the blood vessel and to promote migration of neutrophils from the blood vessel into the lamina propria of the gingiva. This migration is facilitated by polymerization and depolymerization of actin filaments (Arrows). **(Figure 1)**[12]

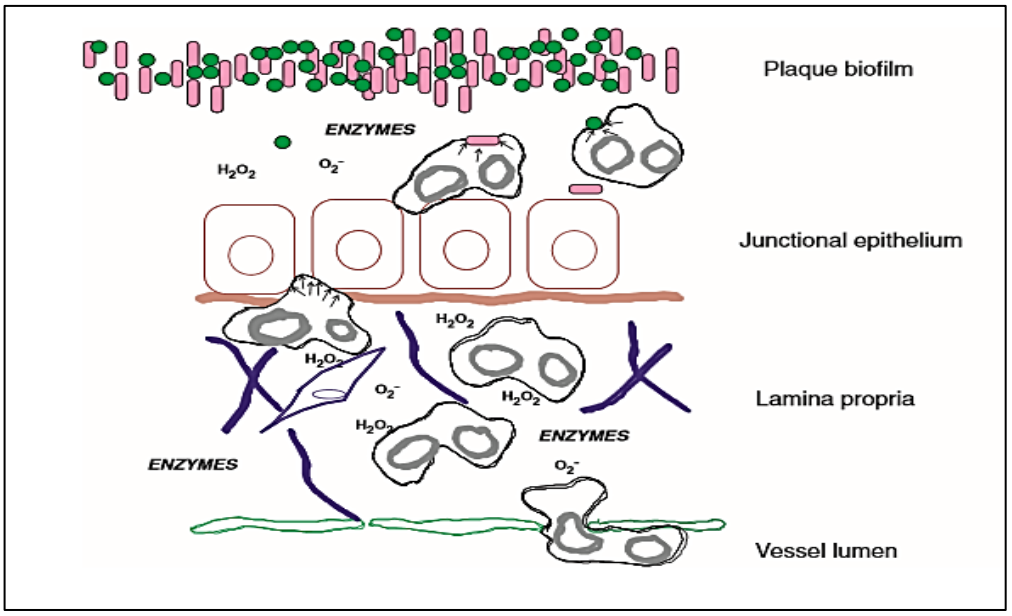


Figure 2: Later stages of the neutrophil response.

In an attempt to isolate and ⁄ or kill bacterial plaque in both the plaque biofilm and the overlying planktonic suspension, neutrophils attempt to phagocytose individual bacteria, release superoxide (O2) as part of the oxidative burst process, which is converted to hydrogen peroxide (H2O2), and release a series of enzymes that may have antimicrobial and/or tissue-destructive effects. **(Figure 2)**

THE IMPAIRED NEUTROPHIL MODEL IN AGGRESSIVE PERIODONTITIS

Before considering impairment of neutrophil function as an underlying mechanism for the pathogenesis of aggressive forms of periodontitis, it is necessary to address the question of whether there is a reduced number of neutrophils or proportion of neutrophils in the whole leukocyte population that may in turn impair the host response to the subgingival microbiota. There is clear evidence that patients who have low counts of circulating neutrophils due to rare conditions such as cyclic neutropenia present with a pattern and progression of loss of periodontal attachment that is similar to that of aggressive forms of periodontitis.[13] However, low neutrophil counts have not been demonstrated in either chronic or aggressive forms of periodontitis. Some authors have reported elevated neutrophil counts in patients with generalized aggressive periodontitis.[14] Others found that the numbers and proportions of neutrophils in serum are similar in aggressive and chronic forms of periodontitis. Thus the relevance of neutrophil counts in aggressive periodontal diseases remains unresolved.

In addition to impaired chemotaxis, some early studies demonstrated impaired phagocytosis and killing in patients with localized or generalized aggressive periodontitis compared to individuals with chronic periodontits. In one study, a proportion of patients with localized aggressive periodontitis (53%) and generalized aggressive periodontitis (46%) showed consistently lower percentages of neutrophils with phagocytosed particles and lower numbers of phagocytosed particles per neutrophil compared to chronic periodontitis patients. This reduced function had not altered after treatment, implying an inherent defect that is not affected by changes in serum factors that could be altered after periodontal treatment.[15]

In another study, the number of phagocytosing cells obtained from generalized aggressive periodontitis patients did not differ from that obtained from periodontally healthy controls. However, when challenged in vitro with one strain of Porphyromonas gingivalis and two strains of Aggregatibacter actinomycetemcomitans, crevicular phagocytes harvested from healthy individuals ingested significantly more bacteria than phagocytes obtained from affected sites in patients with generalized aggressive periodontitis. In addition, intracellular killing of P. gingivalis and both strains of A. actinomycetemcomitans was decreased in the periodontitis group.[16]

Evidence also began to emerge indicating that, in some patients with aggressive periodontitis, the chemotaxis defects were genetically inherent and could not be reversed by treatment.[17] However, in other patients with aggressive periodontal diseases, these defects were acquired through exposure to inflammatory mediators in the serum and/or microbiota, and were subsequently fully or partially resolved by periodontal treatment. For example, one early study demonstrated that 86% of localized aggressive periodontitis patients showed impaired neutrophil chemotaxis due to an intrinsic abnormality, while 48% of generalized aggressive periodontitis patients showed an abnormality related to the composition of their serum.

EMERGENCE OF THE CONCEPT OF A HYPERACTIVE OR PRIMED NEUTROPHIL

Evidence for increased enzyme activity is supported by studies of neutrophils from patients with aggressive forms of periodontitis who have increased intracellular levels of ***beta-glucuronidase***, an enzyme characteristic of ***azurophil lysosomes***.[16] Patients with generalized aggressive periodontitis had greater beta-glucuronidase activity in crevicular fluid than individuals with localized aggressive periodontitis, whose levels were in turn greater than found in periodontally healthy controls. These higher levels of beta-glucuronidase could lead to increased periodontal breakdown in aggressive periodontal diseases.[18]

Myeloperoxidase is another enzyme secreted by neutrophils that may play a central role in the activation of neutrophil proteases, and in inactivating constitutive tissue and serum inhibitors of protease activity, particularly matrix metalloproteinases. This would tilt the balance of tissue homeostasis toward a situation favouring tissue breakdown or resorption. In patients with aggressive periodontitis, baseline levels of myeloperoxidase were highly correlated with the presence of bleeding and suppurating sites, although no specific comparisons were made between aggressive and chronic periodontitis patients. On the other hand, studies that examined the activities of selected neutrophil-derived matrix metalloproteinases such as MMP-8 found no difference in tissue or crevicular fluid levels of this enzyme between chronic and aggressive periodontitis patients. In addition, the levels of MMP-25 and MMP-26, two newly identified neutrophil matrix metalloproteinases involved in extracellular matrix breakdown and turnover, were comparable between aggressive and chronic periodontitis patients.[19]

Perhaps the most characteristic event in neutrophil priming or hyperactivity is an increase in the synthesis and release of oxidative burst products, such as superoxide, hydroxyl radicals and hydrogen peroxide, from both resting and stimulated cells. As in other neutrophil function studies in aggressive and/or chronic periodontitis, there is no clear consensus as to whether the oxidative burst is increased, decreased or unchanged in unstimulated, stimulated or both unstimulated and stimulated neutrophils than in individual patients.

RELEVANCE OF THE HOST RESPONSE IN DIAGNOSIS AND THERAPY

Clinical diagnosis is the primary method by which aggressive periodontitis is recognized but may be supplemented with microbiological and family segregation analysis. A thorough periodontal examination is necessary for the diagnosis of aggressive periodontitis. Because of the rarity of the condition, it is not practical to complete a thorough periodontal examination for every child or adolescent.[20] However, patients should be routinely screened for periodontal disease and a more comprehensive periodontal examination would be warranted if screening suggests that periodontal disease could be present. In many cases of aggressive periodontitis there is a disproportionate amount of disease progression in comparison with the amount of localized microbial deposits. Consequently, there may be little clinically visible sign of disease, particularly in the early stages. Bitewing radiographs are routinely taken in children and adolescents and may be used for initial screening purposes. Once aggressive periodontitis is suspected a comprehensive periodontal examination should be completed. Given the high incidence of aggressive periodontitis in families, all siblings, parents and offspring should also be screened for the condition, as there is 50% likelihood that the disease will be present. Although the disease may not be identical, it is important to follow patients who show even minor levels of involvement as this may represent the early stages of disease. Treatment of aggressive periodontitis can be challenging. Successful treatment is associated with early diagnosis, elimination of the infectious organism and maintenance. Treatment with conventional debridement alone has not been shown to be effective in the long-term elimination of aggressive periodontitis. Antibiotic as an adjunct to debridement has been suggested for treatment.[21] Treatment may be empiric, or microbiological testing may be used for selection of appropriate antibiotics. Evidence in the literature suggests that the use of metronidazole plus amoxicillin, in combination with mechanical debridement, is very effective in chronic periodontitis and would also be useful in aggressive periodontitis in most cases. Other regimens have been tested, including the use of tetracycline, but this was based on the poorly supported contention that this disease was predominantly caused by A. actinomycetemycomitans, a facultative anaerobe that would need an antibiotic capable of killing aerobes and anaerobes.

II. Conclusion

Aggressive periodontitis affects a small, but significant, percentage of the population. Because of the rapidly progressing and aggressive nature of the disease process these patients require early diagnosis and treatment in order to prevent further tissue damage and tooth loss. The role of the practitioner is not only to treat those who already present with significant disease but to prevent and educate those who are at high risk.

Numerous factors play a role in aggressive periodontitis. Bacterial factors are well recognized as a key factor in the pathology of periodontitis; however, as described previously in this article, evidence to prove that a single pathogen, A. actinomycetemycomitans, is the universial primary etiology for disease is unsupported. Similarly, although host factors can also play an enormous role in the progression of disease,

polymorphonuclear neutrophil dysfunction does not appear to be a cause for aggressive periodontitis in nonsyndromic individuals.

The knowledge of genetic factors may be one of the most important aspects in the early detection of disease. Because of the high level of familial aggregation, it behoves the practitioner to screen all siblings and family members of an affected individual.

References

[1]. Trombelli L. Susceptibility to gingivitis: a way to predict periodontal disease? Oral Health Prev Dent 2004;2;1:265-269.
[2]. Van Assche N, Van Essche M, Pauwels M, Teughels W, Quirynen M. Do periodontopathogens disappear after full-mouth tooth extraction? J Clin Periodontol 2009: 36: 1043-1047.
[3]. Slots J, Rosling BG. Suppression of the periodontopathic microflora in localized juvenile periodontitis by systemic tetracycline. J Clin Periodontol 1983: 10: 465-486.
[4]. Kornman KS, Robertson PB. Clinical and microbiological evaluation of therapy for juvenile periodontitis. J Periodontol 1985: 56: 443-446.
[5]. Califano JV. Position paper: periodontal diseases of children and adolescents. J Periodontol 2003;74: 1696-1704.
[6]. Mombelli A. Heresy? Treatment of chronic periodontitis with systemic antibiotics only. J Clin Periodontol 2006;33: 661-662.
[7]. Kornman KS, Robertson PB. Clinical and microbiological evaluation of therapy for juvenile periodontitis. J Periodontol 1985;56: 443-446.
[8]. Saxen L, Asikainen S. Metronidazole in the treatment of localized juvenile periodontitis. J Clin Periodontol 1993;20: 166-171.
[9]. Schenkein HA, Koertge TE, Brooks CN, Sabatini R, Purkall DE, Tew JG. IL-17 in sera from patients with aggressive periodontitis. J Dent Res 2010;89: 943-947.
[10]. Ryder MI. Comparison of neutrophil functions in aggressive and chronic periodontitis. 2010;53: 124-137.
[11]. Genco RJ. Current view of risk factors for periodontal diseases. J Periodontol 1996;67: 1041–1049.
[12]. Buchmann R, Hasilik A, Van Dyke TE, Lange DE. Amplified crevicular leukocyte activity in aggressive periodontal disease. J Dent Res 2002;81: 716-721.
[13]. Kimura S, Yonemura T, Hiraga T, Okada H. Flow cytometric evaluation of phagocytosis by peripheral blood polymorphonuclear leucocytes in human periodontal diseases. Arch Oral Biol 1992: 37: 495-501.
[14]. Eick S, Pfister W, Sigusch B, Straube E. Phagocytosis of periodontopathogenic bacteria by crevicular granulocytes is depressed in progressive periodontitis. Infection 2000;28: 301-304.
[15]. Meng H, Xu L, Li Q, Han J, Zhao Y. Determinants of host susceptibility in aggressive periodontitis. Periodontol 2000 2007;43: 133-159.
[16]. Kimura S, Yonemura T, Kaya H. Increased oxidative product formation by peripheral blood polymorphonuclear leukocytes in human periodontal diseases. J Periodontal Res 1993;28: 197-203.
[17]. Mouynet P, Delamaire M, Legoff MC, Genetet B, Yardin M, Michel JF. Ex vivo studies of polymorphonuclear neutrophils from patients with early-onset-periodontitis (II) Chemiluminescence response analysis. J Clin Periodontol 1994;21: 533-539.
[18]. Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 198;320: 365-376.
[19]. Makariou S, Liberopoulos EN, Elisaf M, Challa A. Novel roles of vitamin D in disease: what is new in 2011? Eur J Intern Med 2011;22: 355-362.
[20]. Gaffen SL, Hajishengallis G. A new inflammatory cytokine on the block: re-thinking periodontal disease and the Th1 /Th2 paradigm in the context of Th17 cells and IL-17. J Dent Res 2008;87: 817–828.
[21]. Albandar JM. Aggressive periodontitis: case definition and diagnostic criteria. Periodontol 2000 2014;65: 13-26.

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