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Aggressive Periodontitis

Aysan Lektemur Alpan

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Abstract

Aggressive periodontitis (AgP) is a disease characterized by rapid loss of periodontal tissues affecting systemically healthy individuals under age of 30 years. AgP classified into two categories named localized and generalized aggressive periodontitis. It differs from chronic periodontitis (CP) depending on age of onset of the disease, rate of progression of the disease, structure and composition of the associated subgingival microflora, changes in host response and familial predisposition. Tissue destruction in patients with AgP is not directly related to bacterial deposits also personal immune response plays a major role in severity of destruction. Surgical and non-surgical techniques can be applied in the treatment of AgP. It is important to treat and obtain frequent controls of individuals with AgP. The main purpose of the treatment is to create a clinical condition that can hold the largest number of teeth in the mouth. After the treatment performed and provided the health of periodontal tissues, patient should be included in the maintenance program.
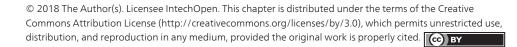
Keywords: aggressive periodontitis, generalized aggressive periodontitis, genetics, familial predisposition, localized aggressive periodontitis

1. Introduction

Aggressive periodontitis (AgP) is a disease characterized by rapid loss of periodontal tissues affecting systemically healthy individuals during adolescence and adulthood, and forms a group of periodontal diseases [1]. It differs from chronic periodontitis (CP) depending on age of onset of the disease, rate of progression of the disease, structure and composition of the associated subgingival microflora, changes in host response and familial predisposition.

AgP classified into two categories named localized and generalized aggressive periodontitis [2] and took place prepubertal, juvenile, rapidly progressive periodontitis in the group that

was defined as early onset periodontitis in 1999 International Workshop for a Classification of Periodontal Disease and Conditions [1]. This report defined some characteristic features of the AgP [2, 3].

- Patients are clinically healthy, except for the presence of periodontitis.

- Rapid attachment loss and bone destruction.

- Familial aggregation.

Secondary features that are often, but not always, present include the following:

- The amounts of microbial deposits are inconsistent with the severity of periodontal tissue destruction.

- Elevated proportions of *Actinobacillus actinomycetemcomitans* (*A. actinomycetemcomitans*) which is now termed *Aggregatibacter actinomycetemcomitans.*

- Elevated proportions of *Porphyromonas gingivalis* (*P. gingivalis*) in some populations.

- Phagocyte abnormalities.

- A hyper-responsive macrophage phenotype, including elevated levels of prostaglandin E2 and interleukin-1β.

2. Localized aggressive periodontitis (LAgP)

2.1. Clinical features

LAgP starts at a much earlier age than CP, but it is not right to go to a certain age limit. The age of onset of the disease can help us diagnose the disease [4]. There is no significant sub-gingival and supragingival calculus in patients with LAgP. Lesions are mostly associated with the biofilm layer. In the form of LAgP there is little or no inflammation of the gums [5, 6]. During this period gingival hyperplasia depending on dental plaque and/or calculus rarely appears [6]. It is characterized by rapid bone loss in the first molar and incisors [7]. In this disease, there are at least two permanent teeth involvement, one of them must be the first molar, and involving no more than two teeth other than first molars and incisors [8]. Powerful serum antibody response to infecting agents and circumpubertal onset are among disease features [3]. According to the workshop in 1999, if the involvement is less than 30%, the disease is localized, if it is not, considered as generalize [1]. During the disease bone loss in the first molar region is symmetric [9]. Patients with LAgP between the ages of 21–35 are those who have not been diagnosed and treated before, depending on the severity of the disease and previous treatments, tooth loss, bone defects and gingival recessions are observed [6, 7].

The following reasons have been proposed regarding the limited localization of lesions in AgP [8].

Figure 1. LAgP patient; (a)-clinical view of the LAgP patient, (b) 7 mm probing depth at distal of the incisor tooth, (c) radiographic view of the LAgP patient.

1. *A. actinomycetemcomitans* affects the host response in many ways after colonization in first molars and incisors:

   - *A actinomycetemcomitans* secretes a factor that inhibits Polymorphonuclear leukocytes (PMNL) chemotaxis.

   - *A actinomycetemcomitans* secretes some factors such as endotoxin, collagenase and leukotoxin to facilitate the colonization of bacteria in the periodontal pocket and cause destruction of periodontal tissues.

2. Antagonistic bacteria against to *A. actinomycetemcomitans*. Colonize the periodontal tissues and prevent the colonization of *A. actinomycetemcomitans* in other areas of the mouth. This situation leads the localization of infection and tissue destruction.

3. For unknown reasons, *A. actinomycetemcomitans* may lose its ability to produce leukotoxin. In this case, the disease progression slows down and colonization of new areas is prevented.

4. The possibility that the cement formation is defective and may also cause the lesions to be localized. The hypoplasia or aplastic cement formation was seen in the examinations performed on teeth withdrawn from patients with LAgP.

LAgP progresses rapidly and bone loss is three to four times greater than CP. Other clinical features of LAgP are distolabial migrations of the upper incisor teeth and consequent diestema formation, increased mobility in the first molars, tenderness on the uncovered root surfaces, deep pain spreading in every direction during chewing that does not last so long. In this phase, periodontal abscess and regional lymphadenopathy may occur [8].

2.2. Radiographic features

The classic feature of LAgP is the vertical bone loss seen in alveolar bone in the first molar and incisor teeth in healthy teenagers. Radiographic finding may include an arc shaped alveolar bone loss extending from the distal surface of the premolar to the mesial surface of the second molar. In this disease bone loss usually wider than CP [8] (**Figure 1**).

3. Generalized aggressive periodontitis (GAgP)

3.1. Clinical features

GAgP; is characterized by diffuse attachment and bone loss affecting at least three permanent teeth other than first molar and incisor teeth, usually seen in young adults, where poor serum antibody responses to infectious agents occur [10]. The GAgP may begin as localized and become more generalized as more teeth are affected over time. The disease remained active and passive periods. The rate of attachment and bone loss is not the same at these times. Dark red and ulcerated areas are characterized by severe acute inflammatory disease table is detected during the active phase. The condition is accompanied by bleeding which usually occurs with light stimulation and discharge of the pus. Severe attachment and bone loss occur during this period of the disease [10, 11]. GAgP sometimes accompanied by systemic findings such as weight loss, mental depression and fatigue [12]. Also, GAgP has been implicated in the pathogenesis of systemic diseases such as uncontrolled diabetes mellitus, AIDS, leukemia, neutropenia, histiocytosis X, syndromes such as Papillon-Lefevre or Cheidak-Higashi, rare inherited diseases such as hypophosphatasia and intraoral symptom of acquired disorders such as granulocytopenia [13]. In the passive period, the clinical image is especially similar to that of healthy individuals in terms of color, shape and consistency. However, deep periodontal pockets are encountered in the probing. It has been stated that Gram(−) microorganisms play a role mostly in microbial dental plaque (MDP). Pathogenic microorganisms, especially *P. gingivalis* and *Tannerella forsythensis* (*T. forsythensis*) are related to disease progression [10, 11]. Patients also had increased antibody response against *A. Actinomycetemcomitans, Prevotella intermedia* (*P. intermedia*) and *Campylobacter rectus* (*C. rectus*) [14].

Figure 2. GAgP patient; (a) clinical view of the GAgP patient, (b, c) increased probing depth around the teeth, (d) radiographic view of the GAgP patient.

3.2. Radiographic features

The radiographic image of GAgP, characterized by severe horizontal and vertical alveolar bone loss especially in the first molar and incisors. This severe destruction can affect only a few teeth as well as the majority of the teeth in the mouth. The disease can progress so quickly that the aggressive nature, radiographs taken at different times, bone loss is easily recognizable [8]. Page et al. [12] reported that in patients with GAgP, the loss of alveolar bone in regions where periodontal destruction is more severe is increased from 25–60% over 9 weeks (**Figure 2**).

4. Epidemiology of AgP

The prevalence of AgP changes significantly different between geographical regions and between different racial/ethnic origins. For this reason, the prevalence of the disease in a given population can be determined by the distribution of the population according to the type and proportion of the race and ethnic group. In the studies, the methods which have been used to diagnosis of disease such as; whether radiographies is taken or not, differences in diagnostic equipment, different indexing systems etc. varies. According an epidemiologic

study performed by Susin et al. [15] prevalence of AgP in Africa is between 1–5%, in North and mid-Europe Caucasians 0.1%, in South European ~0.5%, in North America ~0.1–0.2% of Caucasians, 0.5–1.0% of Hispanics and 2.6% of Black people, in South America 0.3–2.0%, in Asia 0.2–1.0%. According these results, AgP can be a health problem in some populations and/or races. In a national survey which include US school children aged 13–19 years, the prevalence of AgP was found 0.40% in 13–15 years, 0.80% in 16–19 years, 0.06% in whites, 2.60% in blacks and 0.50% in Hispanics [16]. Haubek et al. [17] found a high prevalence of AgP as 7.6% in Moroccan children aged 14–19 years. Also Albandar et al. [18] found AgP with a high prevalence 6.5%, in Uganda. Given the prevalence of AgP in Asia; it found 1.8% in Iraq, 0.86% in Israel, 0.47% in Japan and 0.42% in Saudi Arabia [19]. In South America, the prevalence of disease was vary among the countries: 0.32–2.6% in Brazil, 0.32% in Chile [19]. In Europe it has relatively low prevalence been observed; 0.1% in Denmark, 0.1% in Finland, 0.5% in Italy, 0.1–0.3% in Netherlands, 0% in Norway, 0.11–0.13% in Switzerland, 0.02–0.8% in United Kingdom [19]. The disease is most commonly seen in African-Caribbean (80%) and least Norwegian (0.2%) [20]. In terms of the prevalence of racial attachment, it was found that AgP was higher in black people (2.6%) than white people (0.17%) [21]. Most studies show comparable disease prevalence in both male and female patients. Gender factor and its role in development of AgP have not become clear. In some studies AgP was found to be more common in women than men with 3: 1 ratio [22–25]. However, researches are also available that indicates AgP more common in men than women [18, 21].

5. Pathogenesis of AgP

Periodontal destruction in AgP occurs pathogenic microorganisms and host immune system interaction [14, 26] and this interaction is influenced by many local and systemic factors [27]. Four basic factors play role in the pathogenesis of AgP [26].

- Microbial factors.

- Host factors.

- Environmental factors.

- Genetic factors.

5.1. Microbial factors

The presence of microorganisms is essential for the initiation of the inflammatory process in periodontal diseases and the factors related to the host are involved in the progress of the disease. The appearance of severe tissue destruction with a small amount of plaque in AgP suggests that microorganisms with high virulence in the etiology of the disease may play a role. *A. actinomycetemcomitans* is considered to be the most effective etiologic agent in AgP for about 30 years [28]. *A. actinomycetemcomitans*, short (0.4–1 μm), facultative anaerobic,

immobile, Gram(−) rod. The virulence factor is serotypically variable and some serotypes are known to be invasive epithelial cells and gingival tissue. Tonetti and Mombelli (1999) listed the findings of *A. actinomycetemcomitans* in relation to LAgP [11].

1. In areas where periodontal tissue destruction occurs in aggressive periodontitis patients, 90% of *A. actinomycetemcomitans* are found.

2. In the areas where the destruction proceeds and continues, in high amounts, *A. actinomycetemcomitans* were detected.

3. High serum antibody levels against *A. actinomycetemcomitans* were observed in the majority of locally aggressive periodontitis patients.

4. Clinical trials have shown that improvement in clinical parameters with treatment is associated with a decrease in the level of *A. actinomycetemcomitans* in subgingival floras.

5. It is known that *A. actinomycetemcomitans* has virulence factors that can play a role in the development of the disease such as leukotoxin.

A. actinomycetemcomitans has been suggested to play a role in the onset of AgP by interacting with facultative anaerobic and capnophilic species such as the locally useful Capnocytophaga species and *Eikenella corrodens* (*E. corrodens*) [29]. Today, the microbiological profile of AgP has changed from the presence of specific microorganisms to the presence of more complex microbiota [30]. Some of the bacteria found in periodontal pockets related to gingivitis, while some are related to periodontitis. Dental plaque biofilm is a dynamic structure and changes over time. Different bacterial groups are complexed at different times in biofilm. Among these, orange complex bacteria: *P. intermedia, Prevotella nigrescense* (*P. nigrescense*), *Parvimonas micra* (*P. micra*), *Fusobacterium nucleatum* (*F. nucleatum*), *C. rectus, Eubacterium nodatum* (*E. nodatum*) and *Campylobacter showae* (*C. showae*) build a bridge between the pathogens seen in the early period of periodontal disease named red complex bacteria. Red complex bacteria named *P. gingivalis, T. forsythia* and *Treponema denticola* (*T. denticola*) were associated with periodontal tissue destruction [31]. In some studies, *P. gingivalis* and *T. Forsythia* have been shown to be an etiological agent for AgP [10, 11]. Patients also had increased antibody response against *A. Actinomycetemcomitans, P. intermedia* and *C. rectus* [14]. Electron microscopic studies performed on LAgP demonstrates that bacteria found in the connective tissue to the extending bone surface. When examined by more advanced techniques, the presence of *A. Actinomycetemcomitans, Capnocytophaga sputigena* (*C. sputigena*), mycoplasma strains and spirochetes has been defined [8]. In the extracted teeth affected by LAgP, electron microscopic observations showed that in the biofilm layer on the root surface formed Gram(−) cocci bacteria and other microorganisms [5]. In some studies, it has been reported that spirochetes are rarely or not present in LAgP lesions [32, 33], in contrast some authors reported that there is a high number of spirochetes in lesions [34, 35]. In a study performed in population of Chilean patients with GAgP and CP, *P. gingivalis, P. micra* and *C. rectus* isolated from subgingival plaque and found to be related to disease progression [36]. In a recent study performed with patients who affected by GAgP, the authors concluded that existence of a complex cooperative interaction

promoted by *Herpes Simplex Virus Type-1* (HSV-1) infection, involving *Staphylococcus aureus* (*S. aureus*) and the periodontopathogens *P. gingivalis*, *T. forsythia*, and *Fusobacterium periodonticum* (*F. periodonticum*), that could promote an accelerate progression of lesions of GAgP [37]. Dogan et al. [38] compared subgingival flora in LAgP, GAgP, CP and healthy controls in 69 Turkish people. *T. forsythensis* and *C. rectus* found the lowest frequency in LAgP. *A. actinomycetemcomitans*, *P. gingivalis*, and *C. rectus* were higher in GAgP than in healthy controls. Yeasts also were found in samples. Lee et al. [39] found the bacteria in diseased sites in Korean AgP patients, descending percentages; *Fusobacterium sp.*, *P. gingivalis*, *Treponema sp.*, *T. forsythensis*, *P. intermedia and A. actinomycetemcomitans*. They also concluded *P. intermedia* was associated with GAgP. In a study red complex bacteria found in that of Generalized CP and GAgP. No significant differences found in term of 40 bacteria species in Generalized CP and GAgP [40]. *Human cytomegalovirus*, *Epstein–Barr virus type-1* and *HSV-1* are also involved in the progression of the disease [41, 42]. These differences may be related to variations in the societies living in the various regions of the world, as well as the difficulties in grouping diseases.

5.2. Host factors

AgP is a disease that shows significant differences from other periodontal diseases in terms of severity of destruction, rate of progression, response to treatment, etiologic factors and genetic susceptibility criteria. Defects of host defense system and complex factors like microbial flora play a role together in hostility and disease formation affecting severity of destruction, speed of disease progress and response to treatment. In the response to dental plaque accumulation, which leads to gingivitis, substantial evidence has been collected to propose large differences between individuals. In line with this concept, it has been shown from the initial research attempts on early-onset periodontitis forms that affected individuals, suffer from metabolic imbalance or hereditary host response defects.

The first step of periodontal defense is inflammation in innate immune response that provided a respond to bacterial plaque by neutrophils, macrophages, fibroblasts, epithelial and dendritic cells [43]. If this immune response is not capable to control the inflammation process, complex inflammatory cascades are activated. Second stage which is called adaptive immune response that resumed by antigen-presenting cells and predominantly B-cell lesions composed in periodontitis [43]. Tissue destruction in patients with AgP is not directly related to bacteria accumulation in root surface. Personal immune response plays a major role in severity of destruction [44].

PMNL is an important component of the immune system and found in gingival lesions and in root surfaces of AgP cases [45]. Some of neutrophil malfunctions such as increased adhesion, reduced chemotaxis, increased superoxide and nitric oxide production and reduced phagocytosis were thought to be responsible for disease progression [46–48]. Hyper-responsive macrophage phenotype including elevated prostaglandin E2 and interleukin-1β levels took place among the features of AgP in the 1999 Workshop [49]. According to Kantarci et al. [50] LAgP has been associated with various abnormalities of host cell function such as; neutrophil abnormalities, reduced chemotaxis, increased superoxide production, reduced receptor expression, reduced phagocytosis and killing of *A. Actinomycetemcomitans*, impaired leukotriene B$_4$ and signal transduction abnormalities. They suggest the PMNL is not hypofunctional or deficient,

but it is hyperfunctional and excessed activity is responsible of the tissue damage. A constantly uncontrolled periodontal infection activates neutrophils and make them more effectively stimulated to counteract microbial episodes. Thus, differences in neutrophil functions in AgP are thought to be a combination of genetic and acquired properties of person [51]. Human leukocyte antigens (HLA) are antigens that regulate the immune response. HLA-9 and HLA-15 antigens have been shown to be associated with AgP [8, 52]. Another study has shown that HLA class I, HLA class II antigens are associated with periodontal disease [53] but no significant associations were found between HLA class II antigens and AgP. There is a positive association with HLA-A9 and negative relationship with HLA-A2 and HLA-B5 have shown in patients with AgP [54]. HLA class II antigens are capable bind peptides derived from bacterial antigens and present them to T cells while HLA class I antigens generally present peptides derived from viruses and self-antigens to cytotoxic T cells. In a theory, viral peptide binding and presentation to T cells via HLA-A9 or HLA-B15 is not sufficient for activating immune response properly resulting AgP with severe periodontal destruction [53]. IgA plays an important role in the host defense system and, locally dominant in saliva. IgA is important because of its antiinflammatory function and reduces inflammation by inhibiting IgG and IgM production. Studies have shown that the IgA ratio decreases significantly in AgP subjects [55]. Hwang et al. provides evidence against the 1999 Workshop's decision of weak serum antibody response in AgP. In their study, serum IgG levels to *A. Actinomycetemcomitans* in GAgP patients is not differ from LAgP, Localized CP and Generalized CP but it is significantly increased to several species, including *P. gingivalis, T. denticola*, and *C. rectus* [56]. CRP is an acute phase response molecule and increases in an inflammatory condition such as heat, infection, hypoxia and tissue damage. Elevated fibrinogen levels can activate the inflammatory cascades. Chandy et al. [57] investigated these two molecules in AgP patients. Elevated CRP and fibrinogen levels found in CP patients not in AgP and healthy controls. These results may explain the severity of the lesions by delaying the immunological response against to AgP. In some studies platelet size and function found to decrease in GAgP patients due to the consumption of large platelets at sites of periodontal inflammation. Platelets may play active role in host response in GAgP patients [58, 59].

5.3. Environmental factors

Environmental factors such as oral hygiene/bacterial plaque, smoking, stress and systemic factors may exacerbate the inflammation and play an important role in the periodontitis progression. Studies have shown that there is a positive correlation between AgP and stress [60]. In a controlled study patients in the GAgP group were significantly more depressed and lonely than patients in the CP and control groups [60]. Existing dental plaque is also very important to develop the periodontal disease. A positive correlation found between the amount of plaque and GAgP, but not in LAgP [61]. Smoking is also a risk factor for AgP [54]. In a study smoking found to related disease activity and progression in GAgP but it is not associated with LAgP [62]. Also smoking affects the cytokine profiles of patients with AgP and disturbs the host–parasite relationship [63]. AgP patients who are smoking showed poor clinical respond the periodontal treatment [64].

According to the 1999 workshop, the main feature in diagnosing of AgP is that the individual should be medically healthy [1]. However symptoms of the gum in some systemic diseases/

conditions may resemble AgP. This group of diseases includes; neutropenia, hypophosphatasia, leukemias, Cheidak-Higashi syndrome, leukocyte adhesion deficiency, Papillon-Lefevre syndrome, trisomy 21, histiocytosis and agranulocytosis [1].

5.4. Genetic factors

AgP is a multifactorial disease and many etiological factors are required for clinical presentation. Bacterial content and host defense clearly play an important role in the disease. Genetic variations may affect the host response to the disease. Once diagnosed, the sibling of the child or adolescent must also be investigated for the AgP. The genetic factors that may be involved in the pathogenesis of AgP, have been investigated by considering the immune system regulated by genetic factors and that certain genetic polymorphisms may disrupt the defense system against the agent that infects the immune system.

Interleukin-1 (IL-1) is a potent pro-inflammatory mediator that is mainly released by monocytes, macrophages and dendritic cells and genetic polymorphisms of IL1 have been studied in association with AgP. Three studies have reported no association between the carriage rates of the IL1A − 889 (+4845) C → T gene and AgP [65–67], but one study have found an association with this gene and AgP in Chinese Population [68]. IL1B + 3954 (+3953) C → T gene polymorphisms and carriage rate of the rare (R) allele in Caucasians found associated with AgP in a study [65]. In studies involving IL-4 which have anti-inflammatory properties, no association was found between AgP and genotype encoding this cytokine [69]. In a meta-analysis that conducted the evaluating IL-6 polymorphisms, there was concluded an associated with AgP and IL-6 polymorphisms [70]. IL-10 is an anti-inflammatory cytokine which down-regulates the pro-inflammatory immune response of monocytes and macrophages. The results of the studies investigating polymorphism on the gene that encoded IL-10 were not significant [71, 72]. IL-17 plays an important role in natural and acquired immune response; there is a study in mice demonstrating that IL-17 receptor trigger bone loss in infectious conditions [73]. In a recent metaanalysis authors concluded that there is no significant association between the polymorphisms rs2275913 and rs763780 in interleukins 17A and 17F genes and CP and AgP in the allelic evaluation [74]. IL-23 is a pro-inflammatory cytokine and found positively correlated with CP but existing studies how that there is no significant association of IL-23 polymorphisms with AgP [75]. IL-8 is a chemokine and plays role of chemoattractant for the neutrophils. Insufficient studies exist that correlate IL-8 polymorphisms with AgP. Existing studies in literature demonstrated that there is no significant association between IL-8 polymorphisms and AgP [75].

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine which has the potential to stimulate the production of secondary mediators, including chemokines or cyclo-oxygenase products, amplifying the degree of inflammation. No associations between the TNFA polymorphisms and AgP in a meta-analysis [72]. An Fc receptor is a protein found on the surface of certain cells and part of immunoglobulin (FcγR) link cellular and humoral parts of the immune system that contribute to the protective functions of the immune system [76]. A Japanese study reported an association for a composite genotype of the Fc cRIIIa N allele and the Fc cRIIIb +141 R allele in AgP [77] in contrast in a stud performed with Caucasian population there is no association found in term of this gene [78]. There is limited information about

polymorphism of FcγR and AgP. The vitamin D receptor was included various biological processes such as bone metabolism and the immune response to microbial infections. Nibali et al. [79] and Park et al. [80] found an association with AgP but Bret et al. [65] could not find any accociation.CD14 and Tolllike receptors (TLRs) are extra and intracellular receptors such as recognize pathogen-associated molecules on Gram(+) and Gram(−) bacteria and mediate the production of cytokines required for effective immune response. In studies that performed to find a relationship CD14 polymorphism and AgP received no association [81, 82]. About TLRs, there is limited information and studies are available.

Most studies performed about polymorphisms were limited by sample size and had variations in case inclusion criteria. Genetic studies can also be limited by geographic and ethnical differences. To understand the pathogenesis of this complex disease multicenter studies and large sample sizes are required.

6. General treatment strategy

AgP is a complex periodontal disease that causes rapid destruction of the periodonticum and even causes tooth loss. Complex pathogens are involved in the etiology of AgP. Therefore, it is important for clinicians to treat the disease and maintain periodontal health [83]. The treatment protocols are based on studies so far. Physicians can achieve very effective results if they are working with microbial tests during and after treatment. People with the same clinical characteristics may have different bacterial flora, or people with different clinical characteristics may have the same bacterial flora. In clinical trials, the success of treatment is assessed by considering the probing depth (PD), clinical attachment level (CAL) and bleeding on probing (BOP) using conventional periodontal instruments. All parameters for the patients should be assessed and the treatment decision should be given. Surgical and non-surgical techniques are applied in the treatment of AgP [84]. It is important to treat and obtain frequent controls of individuals with AgP which is seen in younger patients coexistent rapid attachment and alveolar bone loss. There are studies demonstrated that the post-treatment attachment level can be maintained despite the risk of recurrence of the disease [85, 86]. A study of 40-year follow-ups from patients with GAgP shows that even the most aggressive and most advanced periodontitis cases are treatable [87]. The motivation and adaptation of the patient is very important in order to control the disease. In this phase, the patient should be informed by the doctor about the role of the patient, the severity of the illness and the risk factors. The main purpose of the treatment is to create a clinical condition that can hold the largest number of teeth in the mouth for as long as possible. Periodontal treatment is considered in four main phases. First phase; initial therapy or non-surgical periodontal treatment. The second periodontal treatment phase is surgical periodontal treatment, third phase prosthetic treatment and fourth phase maintenance periodontal treatment.

6.1. Non-surgical treatment of AgP

Removal of agents causing periodontal disease, providing good oral hygiene to the patient, and reducing pre-existing gingival inflammation and periodontal pocket depths in advance

of future phases are among the goals of non-surgical periodontal treatment. Mechanical treatment involves removal of plaque and its products from dental surfaces (supra/subgingival), as well as dental and other plaque-retaining local agents by hand or ultrasonic instruments. Root planning are also included. The responses of patients with LAgP to initial periodontal care vary in studies. In general, the least amount of work on this issue and it is not long to observe the final results. Based on the literature GAgP responds good clinical results to scaling and root planning (SRP) in the short term (up to 6 months). However, after 6 months despite frequent visits to the physician and strengthening oral hygiene, relapses and disease progression have been reported [88].

Studies have shown that the total supragingival and subgingival plaque mass is reduced by mechanical treatment. However, because some pathogens can invade into the tissue, or because periodontal instruments are not effective in deep and complex pockets, mechanical treatment is sometimes ineffective [89]. The success of periodontal treatment depends on the removal of dental plaque and therefore pathogenic microorganisms in the dental plaque. The anti-infective treatments applied in this context directly affect the success of the treatment. Anti-infective treatment includes both mechanical and chemotherapeutic approaches and aims to destroy or reduce the microbial dental plaque biofilm which is primary etiological agent of periodontal infections. The use of therapeutic agents especially systemic antibiotics have been widespread to be able to obtain predictable treatment responses due to conventional periodontal treatment and to support treatment for the specific microbial structure of the disease.

At this time there is a clear consensus that mechanical instrumentation should always precede antimicrobial therapy. To achieve effective levels of the drug on the day of the completion of SRP [90]. The subgingival bacterial load that will be inhibited by the antimicrobial agent must be reduced by mechanical treatment. Insufficient antimicrobial agent concentrations may cause the emergence of resistant bacterial strains [88]. The tetracycline group is considered first in systemic treatment. Tetracycline and SRP found to be more effective in term of elimination *A. actinomycetemcomitans*, *Capnocytophaga* and spirochetes comparing only SRP [91]. Tetracycline is known to have beneficial effects in wound healing regarding its anticollagenase activity [92] .

Doxycycline is a semisynthetic tetracycline and is effective in the treatment of periodontitis. It is easier to take doxycycline at lower doses and use it with daily foods. In a study 60 patients were divided into a placebo group and a group that received systemic doxycycline (loading dose of 200 mg and doses of 100 mg daily for 14 days) SRP was performed to all groups over an 8-week period, systemic antibiotic or placebo was only used during the first 2 weeks of the SRP. At the end of the study no significant differences were found in term of PD, BOP [93]. It was demonstrated in many studies, biofilm showed high levels of resistance against tetracycline, minocycline, amoxicillin, doxycycline and amoxicillin/clavulanate. In addition, high-degree of antibiotic tolerance has been demonstrated in mature biofilms [94] when tetracycline was unable to suppress *A. actinomycetemcomitans,* it has been raised a combined use of antibiotics for the treatment of AgP. Metronidazole is a nitroimidazole derivative antibiotic which has a strong bactericidal effect on obligate anaerob Gram(−) bacteria. It is highly effective on periodontopathogenic bacteria such as *P. gingivalis* and *P. intermedia* which in the "red complex" [95]. The combination of 250 mg of metronidazole and 375 mg of amoxicillin, three times a day for 7 days, as an adjunct to SRP, was found to be very effective

in suppressing subgingival *A. actinomycetemcomitans* load [96]. Guerrero et al. [97] evaluated SRP plus systemic metronidazole and amoxicillin in use on clinical parameters, in total of 41 individuals with GAgP. Twenty randomly selected patients were given 500 mg metronidazole and 500 mg amoxicillin three times a day for 1 week in addition to mechanical treatment, and the remaining 21 patients were given placebo in addition to mechanical treatment. Two and six months re-evaluations were made. Additional metronidazole and amoxicillin may provide a statistically significant improvement in clinical parameters in the short term. Xajigeorgiou et al. [84] investigated metronidazole + amoxicillin, doxycycline, metronidazole efficacy in 43 GAgP patient clinically and microbiologically. Patients were randomly divided into 4 groups. First group was received SRP plus 500 mg metronidazole +500 mg amoxicillin three times a day for 1 week, second group was received 200 mg for the first day loading, 100 mg doxycycline for the following 14 days, third group was received 500 mg metronidazole three times a day for 1 week, and the fourth group was evaluated as the control group. After 6 weeks and 6 months patients were reevaluated in term of CAL, BOP, PD. Additional metronidazole + amoxicillin or metronidazole plus SRP have been effective comparing the other groups. Adjunctive use of metronidazole plus amoxicillin, metronidazole alone or clindamycin in patients with GAgP results in well clinical improvements comparing with the use of doxycycline for a similar amount of time or with SRP alone [88].

The use of azithromycin in recent years has become an issue in AgP treatment. Long half-life of and use of only once every 3 days of azithromycin, provides advantages for the patient and the physician. In a study clinical efficacy of the adjunctive use of azithromycin with SRP was investigated in AgP. Twelve months after treatment, approximately 1 mm reduction in PD and higher percentage of teeth with attachment gain was observed in test group [98]. There is no certain protocol for the use of adjunctive systemic antimicrobials with SRP, but in general suggests that antibiotic intake should start on the day of debridement completion; debridement should be completed within a short time (preferably <1 week) [94].

Local antibiotic applications may also used to complete the periodontal therapy. Several local antibiotic applications have been developed in addition to initial periodontal therapy. These include metronidazole, chlorhexidine, minocycline, doxycycline and tetracycline. The use of this systems in LAgP may be more beneficial effect in term of the nature of the disease. To achieve maximum efficacy, drugs must provide some criteria such as; the drug must reach the targeted site of action, remain at an effective concentration and last for an adequate period of time [99]. In a study, 26 patients with LAgP divided into a control group, a group receiving 1% chlorhexidine gel and a group receiving a 40% tetracycline gel. After 12 weeks, either of these antimicrobial agents provide significant additional improvement of the clinical parameters [100]. Kaner et al. compared local chlorhexidine chip and ministration and systemic amoxicillin plus metronidazole combination in addition to SRP on clinical parameters in GAgP patients. Systemic use of amoxicillin plus metronidazole combination found to be statistically significant clinical improvements comparing the local chlorhexidine chip [101]. In a similar study Purucker et al. [102] concluded that additional applied local (tetracycline fibers) and systemic (500 mg amoxicillin/clavulanic acid) antibiotics showed equally benefits in terms of clinical parameters. In conclusion, local antimicrobial adjuvant effects reported in the literature do not appear to improve on the adjunctive effect of systemic antibiotics in patients with AgP. When using such systems, cost-benefit and efficiency should be considered well.

6.2. Surgical treatment of AgP

Surgical treatment may require for the remaining pockets after initial periodontal treatment of AgP. The surgical approach has the advantages such as; reaching difficult anatomical formations of the teeth, cleaning the pocket epithelium from invaded *A. actinomycetemcomitans* and application of regenerative procedures.

Twenty-five periodontal lesions in seven patients with LAgP divided into three treatment groups: SRP; SRP plus soft tissue curettage; SRP plus modified Widman flap surgery. The microbiologic and clinical measurements were performed up to 16 weeks. At the end of the study SRP alone unable to suppress *A. actinomycetemcomitans* in periodontal lesions, in contrast SRP plus soft tissue curettage and modified Widman flap surgery succeeded [103]. Systemic antibiotic use can preferred with various surgical techniques in the treatment of AgP. Kornman and Robertson [104] found modified Widman flap surgery plus tetracycline was effective in areas where the black pigmented bacteroides and *A. actinomycetemcomitans* load was high. Lindhe and Liljenberg [105] treated 16 patients with modified Widman flAgP surgery plus tetracycline (14 days). As a result of 5-year follow-up, successful clinical results were obtained and radiological bone fill in angular bony defects. In a case series performed by Buchmann et al. [106], SRP and modified Widman flap surgery plus systemic amoxicillin/metronidazole combination provide periodontal tissue stabilization at a rate 95% over 5 years.

There are many methods to regain bone in vertical bone defects such as bone grafting, guided tissue regeneration by using membranes, the use of biologic modifiers and combinations of the above. Autografts are the gold standard and have been extensively used because of its osseoinductive, osseoconductive, and osteogenic properties but it has limitations like morbidity and mortality hence different graft materials are available in practice. Allografts (e.g. freeze-dried bone allograft), xenografts (bovine or corral derived) and alloplastic materials (e.g. bioactive glass, hydroxyapatite and beta-tricalcium phosphate) are alternatively used instead of autograft [107]. Yukna and Sepe [108] demonstrated an average defect fill (80%) in 12 LAgP patients using freeze-dried bone allografts. In a study different graft materials were evaluated in 10 patients with LAgP. 4:1 ratio combination of beta-tricalcium phosphate/tetracycline, hydroxyapatite/tetracycline or freeze-dried bone allograft/tetracycline were applied into these groups. Each graft material showed a decrease in defect and pocket depth although no significant differences between the different grafting materials were found in terms of hard-tissue or soft-tissue changes. But hydroxyapatite/tetracycline showed a greater percentage of defect fill was comparing with beta-tricalcium phosphate/tetracycline [109].

Membranes have been grouped into two major categories: nonresorbable (high-density polytetrafluoroethylene (PTFE) membranes reinforced or not with a titanium framework (e.g. Cytoplast ® TXT-200; Osteogenics Biomedical, Lubbock, Tex., USA) and resorbable membranes (polylactic acid (PLA) and its copolymers, tissue-derived collagen membranes) [110]. Nonresorbable membranes serve as a space maintenance which is needed for tissue regeneration and inert also biocompatible. Unfortunately, second surgery for removal or membrane exposure take place among its disadvantages. Although resorbable membranes show lack of sufficient strength, unpredictable degradation rate and cause a greater inflammatory response [110]. Usage of nonresorbable or resorbable membranes for treating intrabony defects in AgP has been shown to be effective in many studies [86, 111].

6.3. Other treatment modalities

Photodynamic antimicrobial therapy that photosensitizers (toluidine blue, methylene blue, malachite green) are used inside periodontal pockets for increasing the cytotoxic potential of laser light to potential periodontal pathogens. In a metaanalysis authors concluded that photodynamic antimicrobial therapy cannot be suggested as routine with nonsurgical treatment of patients with AgP according to lack of evidence based on the literature [112].

Enamel matrix proteins (amelogenin) which provides new cementum and the formation of new attachment in periodontal defects and growth factors/differentiation factors (platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, bone morphogenetic protein, transforming growth factor-beta) which play an import role in tissue development and healing are tools for gaining attachment. Their effectiveness on periodontium were demonstrated in many studies with CP but studies with AgP, mostly exist as case reports [113, 114]. Yılmaz et al. [115] treated patients with GAgP with a total of 12 intrabony defects with the combination of platelet rich plasma +bovine derived xenograft combination. PD, marginal recession, relative attachment, probing bone and radiographic bone levels were measured at the beginning and at 12 months reentry. The researchers noted that the combination of platelet rich plasma and bovine derived xenograft for the treatment of GAgP, provided successful clinical results in large intrabony defects and that prognosis was affected positively even for teeth that were thought to have hopeless prognosis.

Dental implants are a widely used treatment edentulism and provides functional and esthetic resolutions. Since tooth loss is frequently seen in AgP patients, dental implant applications can be applied. However, marginal bone loss and implant survival rates in AgP patients significantly higher than those of CP and healthy subjects [113, 114]. Care should be taken when considering dental implant in AgP patients. Frequent follow-ups should not be neglected in these patients.

6.4. Maintenance therapy

After the treatment performed and provided the health of periodontal tissues, patient should be included in the maintenance program. Due to the recurrence nature of AgP, maintenance is given to for prevention of additional tooth loss and disease recurrence. Regular controls are useful for controlling the progression of the disease. These controls should be lifelong, but there is no definitive protocol for frequency. Some researchers suggested monthly checks during the first 6 months after the treatment finished. Some researchers stated that 3–4 controls per year would suffice. In every control session; PD and CAL should be assessed. Also, when necessary, SRP should be performed. Radiographs should be taken separately from each tooth or area affected by the disease once a year. Local antibiotic administration may be preferred to risky areas [116]. The prognosis of teeth that affected AgP depends on many factors such as the amount of missing bone, the presence or absence of furcation region, the morphology of bone defects, the degree of mobility, crown/root ratio, occlusal contacts, oral hygiene and general health. Treatment should be evaluated according to the initial condition. It is also important to perform microbial testing at every control session whenever possible. Thus, the physician may be an idea about the activation of the disease.

7. Conclusion

AgP is a complex disease and has multifactorial etiology. While bacterial plaque is essential for initiation of disease, it is generally accepted that genetic factors and host immune response play a large role in the disease susceptibility. Also environmental and behavioral factors determine the final clinical outcome. The outcome of rapid and severe alveolar bone loss; gingival recession, pathological migration of teeth, mobility and eventual loss of teeth occur. Because of the clinical results, AgP patients suffer social problems due to esthetic, phonetic and nutritional problems and their quality of life diminishes. The treatment of these patients is quite challenging, due to the absence of a standard treatment protocol for this disease which its etiology is not fully understood, but also because of the rapid progression, severe periodontal tissue loss and recurrence of the disease. Non-surgical and surgical periodontal treatments combined with systemic antibiotics are recommended for the complete eradication of deep periodontal pockets. In long term, active periodontal treatment must followed by maintenance periodontal treatment for preventing attachment and tooth loss.

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