Aggressive periodontitis: A review

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ABSTRACT

The purpose of this review is to highlight the current etiological and therapeutic concepts of aggressive periodontitis which is rapidly progressing and aggressive in nature. It leads to destruction of periodontal tissues and loss of teeth. We need advanced diagnostic techniques to learn about current disease activity and rate of progression. We also require strategies to keep the disease under control with proper maintenance regime and prevent tooth loss, because it can result into complicated prosthetic rehabilitation in a very young patient. The evidence suggests that aggressive periodontitis is influenced by microbiological, genetic, and host factors. This paper reviews clinical, microbiological, immunological, and genetic aspects of pathogenesis of aggressive periodontitis, as well as diagnostic criteria of the disease and appropriate nonsurgical and surgical treatment options.

Key words: Aggressive, genetic, host factors, microbiologic, periodontitis

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INTRODUCTION

Aggressive periodontitis generally affects systemically healthy individuals less than 30 years of age, though patients may be older. Aggressive periodontitis is distinguished from chronic periodontitis by the age of onset, the rapid rate of destruction, composition of the subgingival microflora, alteration in the host immune response, familial aggregation of diseased individuals, and a strong racial influence.

HISTORY

Black in the year 1886,[1] used the terms phagedenic pericementitis and chronic suppurative pericementitis to describe patients who suffered from a rapid destruction of alveolar bone. Gottlieb in the year 1923 described an unusual form of periodontal disease that involved some or all of the permanent incisors and first molars of young individuals. Based on histological observations on extracted teeth from affected sites, he believed that the disease was due to defective deposition of cementum or cementopathia. Gottlieb in the year 1928 applied the principles of classical pathology, which stated that all human nonneoplastic diseases could be classified as either inflammatory or noninflammatory and used the term diffuse atrophy of the alveolar bone[2] to describe a condition in which adolescent patients did not exhibit the intense gingival inflammation ordinarily seen in other adult patients with periodontitis, he believed that the disease was a noninflammatory or degenerative condition. In the year 1942, Orban and Weinmann introduced the term periodontosis to describe the periodontal destruction in young individuals.[3] At the 1966 World Workshop in Periodontics, it was concluded that there is no evidence for the existence of noninflammatory degenerative periodontal disease and the term periodontosis should be eliminated from periodontal nomenclature. In the late 1970s and early 1980s, it was believed that the condition was an infection that could be treated by therapy based on excellent plaque control and the idea that the disease may be due to degeneration of cementum, or any other components of the periodontium, was laid to rest. As a reflection of this changing opinion regarding the etiology of the disease in 1969 Butler[4] used the term juvenile periodontitis andreplaced periodontosis and in 1989 as early onset periodontitis[5] as the preferred term for the condition. In the1999 classification system, the name of the disease was changed to aggressive periodontitis,[6] the reason being to eliminate nonvalidated age-dependent designations.

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CASE DEFINITION AND DIAGNOSTIC CRITERIA

In 1971, Baer defined aggressive periodontitis as a disease of the periodontium occurring in an otherwise healthy adolescent,

which is characterized by a rapid loss of alveolar bone around more than one tooth of the permanent dentition.[7]

Definition: Disease of the periodontium occurring in an otherwise healthy adolescent, which is characterized by rapid loss of alveolar bone about more than one tooth of the permanent dentition. The amount of destruction is not commensurate with the amount of local irritants.

A contemporary case definition of aggressive periodontitis is presented by Albandar in 2014.[8]

Key diagnostic criteria of this disease include an:

- Early age of onset,
- Involvement of multiple teeth with a distinctive pattern of clinical attachment loss and radiographic bone loss, and
- A relatively high rate of disease progression and the absence of systemic diseases that compromise the host's response to infection.
- Although in some patients the disease may start before puberty, in most patients the age of onset is during, or somewhat after, the circumpubertal period. A typical patient shows disease onset at an early age (i.e., before 25 years of age), although identification of the affected patient usually occurs after disease commencement.
- Initially, the periodontal lesions show a distinctive pattern, depicted radiographically as vertical bone loss at the proximal surfaces of posterior teeth, and the bone loss usually occurs bilaterally. In advanced cases of aggressive periodontitis the periodontal lesions may be depicted radiographically as a horizontal loss of bone. The primary teeth may also be affected, although early exfoliation of these teeth is not common.
- Aggressive periodontitis may be localized or generalized, in localized aggressive periodontitis (LAP), tissue loss usually starts at the permanent first molars and incisors, and with increasing patient age the disease may progress to involve the adjacent teeth. The generalized form of aggressive periodontitis involves most or all of the permanent teeth.

CLASSIFICATION

1. Localized aggressive periodontitis (LAP): Localized to first molar/incisor interproximal attachment loss
2. Generalized aggressive periodontitis (GAP): Generalized interproximal attachment loss affecting at least three permanent teeth other than incisors and first molar.

EPIDEMIOLOGY

The prevalence of LAP varies considerably between continents, and differences in race/ethnicity seem to be a major contributing factor.

Estimates of the disease prevalence are 1-5% in the African population and in groups of African descent, 2.6% in African-Americans, 0.5-1.0% in Hispanics in North America, 0.3-2.0% in South America, and 0.2-1.0% in Asia.

Among Caucasians, the disease prevalence is 0.1% in northern and in central Europe, 0.5% in southern Europe, and0.1-0.2% in North America.

The prevalence of LAP is less than 1% and that of GAP is 0.13%. Blacks are at higher risk than whites, males are at higher risk of GAP than females. In Asia the prevalence rate of 1.2% for LAP and 0.6% for GAP in Baghdad and Iran population, and 0.47% in Japanese population.[9]

CLINICAL FEATURES

LAP starts at circumpubertal age, involving interproximal attachment loss of first molar, and or incisors, there will be lack of inflammation with presence of deep periodontal pocket and advanced bone loss. Amount of plaque is minimal which is inconsistent with the amount of destruction, and rarely mineralizes to form calculus, but the plaque is highly pathogenic due to the presence elevated levels of bacteria like *Aggregatibacter actinomycetumcomitans* (A.a) and *Porphyromonas gingivalis* (P.g). Secondary clinical features like distolabial migration of incisors with diastema formation, mobility of the involved teeth, sensitivity of the denuded root, deep dull radiating pain to the jaw, and periodontal abscess lymph node enlargement may occur.[10]

GAP has generalized interproximal attachment loss affecting at least three permanent teeth other than incisors and first molar involving individuals under age 30 with destruction appears to occur episodically. There will be presence of minimal plaque which is inconsistent with destruction and presence of bacteria like P.g, A.a, and *Tannerella forsythia* are detected in plaque.[10]

Two kinds of gingival responses are seen in GAP patients. First response is severe acutely inflamed tissue which is ulcerated and red in color with spontaneous bleeding indicating destructive stage and the other one with pink gingiva free of inflammation, with some degree of stippling and deep periodontal pockets are present representing quiescence stage.[10]

HISTOPATHOLOGY

Histopathology of aggressive periodontitis is not well-documented as compared to chronic periodontitis because of less numbers of aggressive periodontitis patients, changing the definition of disease entity, and variations in the timing of the biopsies.

However, Stambolieva and Bourkova[11] found increase in the numbers of acid phosphatase positive macrophages (phagocytic macrophages) in aggressive periodontitis patients. In the pretreatment biopsies of LAP, there was predominant plasma cell inflammatory infiltration,[12] and the root surfaces of individuals with aggressive periodontitis were observed to beheavily covered by neutrophils.[13] A fully developed lesion consists ofplasma cell dominated infiltration in the connective tissue with neutrophils migrating through the pocket lining epithelium and creating a layer between the plaque and tissues.

MICROBIOLOGY

Use of advanced microbiological methods has improved our knowledge regarding the composition of bacteria in subgingival deposits which can cause different forms of periodontitis. There are geographic and ethnic variations in relation to periodontitis associated microorganisms.

Since long time A.a has been considered the primary pathogen for aggressive periodontitis, especially in its localized form. Six serotypes of A.a (a, b, c, d, e, and f) are described based on the composition of O polysaccharide of their lipopolysaccharide and there are phenotypically nonserotypeable strains of A.a which lack expression of serotype-specific polysaccharideantigen.[14] A highly leukotoxic clonal type of A. A serotype b was first isolated, in the early 1980s, from an 8-year-old male child with localized aggressive periodontitis.[14] Prevalence of A.a in LAP varies from 70 to 90%,[15,16] but there are studies which states there is no association between A.a and the periodontal diseaserather prevalence of levels of P.g, *T.denticola*, and *P.intermedia* are significantly associated withaggressive periodontitis. In a study done by Takeuchi for detection of microorganisms in sub gingival flora of Japanese population using polymerase chain reaction (PCR) it was found that the prevalence of A.a was less in patients with LAP whereas elevated levels of P.g, Tannerella forsythia, *T.denticola*, *P.intermedia*, and *Campylobacterrectus* was detected.[17] Albander found elevated levels of IgG and IgA to P.g and A.a and IgA to *P.intermedia* in subjects with GAP than LAP and no difference was found at the antibody levels of *C.rectus*, *E. corridens*, *F.nucleatum*.[18] *Filifactor alocis* is gram positive anaerobic rod which has the potential of being periodontal pathogen and the levels of these bacteria is elevated in aggressive periodontitis patients.[19] *Treponema lecithinolyticum*and *Treponema socranskii* are elevated in GAP.[20] Sulfate reducing bacteria, *Desulfomicrobium orale*, has been suggested to be involved in various categories of periodontal destruction, possibly synergistically with the red complex periodontal pathogens.[21] Yamabe suggested Archaea a methanogenic organism, especially *Methanobrevibacter oralis*as putative periodontal pathogen for aggressive periodontitis.[14] Herpes viruses, especially Epstein-Barr virus (EBV) and human cytomegalovirus, have been suggested to play a role in the onset of aggressive periodontitis by interacting with periodontitis-associated bacteria, such as A.a, P.g, *T. forsythia*, *C. rectus*, *Dialister pneumosintes*.[22]

ROLE OF GENETICS IN AGGRESSIVE PERIODONTITIS

In periodontitis, the host-activated inflammatory and immunological cascades responding to predominantly gram-negative microorganisms that result in the destruction of connective tissue and bone are under genetic control. Genetic and environmental factors play a crucial role in the development of aggressive periodontitis. Here are few gene polymorphism and their associations with aggressive periodontitis.

A strong association was found between interleukin (IL)-1a (889)[23] and IL-1a 3954allele 2 polymorphism[24] and aggressive periodontitis. IL-1 gene cluster was not associated with AP according to Fiebig in caucasians.[25] IL-4-590 T/T, IL-4-34 T/T genotype are associated with AP.[26] IL-6-174G allele increased the risk of AP and IL-6-572 C/G polymorphism is associated with pathogenesis.[27] Nibali found link between IL-6-1363,-1480 polymorphism and LAP susceptability.[28].IL-10 promoter polymorphisms at positions -1082 G-A,-819C-T, and -590C-A showed that haplotype ATA is a putative risk indicator for GAP.[29] FPR348 T-C gene polymorphism showed association with AP in African American subjects.[30] Fc gamma RIIIb-NA2 allele and Fc gamma RIIIb-NA2/NA2 genotype and composite genotype FcaRIIIb-NA2/NA2 and FCgammaRIIIa-H/H131 may be associated with GAP.[31] FCgamma polymorphisms can lead to modulation of neutrophil superoxide production and predispose to AP.[32] VDR, FcaRIIIb composite genotype may be associated with susceptibility to generalized early onset periodontitis.[33] TLR-4 399 Ile polymorphism showed a protective effect against AP.[34] TNFA gene polymorphism (1031, 863,857, 308, and 238) was not associated with aggressive periodontitis.[35] HLA-DR4, HLA-A9, B-15 are found in high frequency in rapidly progressive periodontitis patients[36,37] and HLA-DQB1 plays a crucial role in pathogenesis of AP.[38]

Miscellaneous genes associated with aggressive periodontitis are AGT-angiotensinogen CTSC-cathepsin C, E-selectin in Iranian population, FPR-formyl peptide receptor in Asian population, NADPH-NADPH oxidase, PAII-plasminogen activator inhibitor 1, and S100A8-calprotectin in Asians, TIMP2-tissue inhibitor of matrix metalloproteinase 2 in Asians, and t-PA-tissue plasminogen activator in Caucasian.

HOST RESPONSE

Aggressive periodontitis should be present in a healthy individual; multiple systemic conditions may be associated

with attachment loss which needs to be ruled out before giving the diagnosis as aggressive periodontitis because in conditions like leukocyte adhesion deficiency syndrome and Papillon-Lefevre syndrome the oral picture resembles aggressive periodontitis. Polymorphonuclear neutrophils (PMNs) play an important role in host immune response, qualitative and quantitative deficiency in PMNs can lead to increased periodontal destruction, and this does not mean aggressive periodontitis is caused by dysfunctional PMNs. Although host factors can also play an enormous role in the progression of disease, PMN dysfunction does not appear to be a cause for aggressive periodontitis in nonsyndromic individuals.[39]

TREATMENT

The overall treatment concepts and goals in patients with aggressive periodontitis are not markedly different from those in patients with chronic periodontitis. Therefore, the different treatment phases (systemic, initial, reevaluation, surgical, maintenance, and restorative) are similar for both types of periodontitis. However, the considerable amount of bone loss relative to the young age of the patient and the high rate of bone loss warrants a well-thought-through treatment plan and an often more aggressive treatment approach, in order to halt further periodontal destruction and regains as much periodontal attachment as possible.[40]

NONSURGICAL PERIODONTAL THERAPY

Scaling and root planing

Scaling and root planing in patients with LAP improves the clinical parameters, but with the limited data present it is unclear to know the predictability and long-term stability of scaling and root planing (SRP) in LAP. The effect of SRP is well-documented in patients with GAP. Patients with GAP respond well to SRP in short term (6 months), after 6 months, relapse, and disease progression is reported despite frequent recall visits and oral hygiene reinforcements.[40]

Systemic antibiotics

Treating patients with aggressive periodontitis is challenging. The disease responds less predictably to conventional mechanical periodontal therapy, hence scientists have been exploring adjunctive treatment to improve the outcome, predictability of the conventional mechanical therapy. In view of the specific microbial nature of aggressive periodontal disease, the use of systemic antibiotics can play an important role in the treatment of these diseases.

Systemic antibiotics like tetracycline, metronidazole, combination of metronidazole and amoxicillin, clindamycin, and azithromycin are also used as adjunct in the treatment of aggressive periodontitis. Slots and Rosling, Kornman and Robertson, Asikainen, Palmer, and Tinoco, did studieson SRP in combination withantibiotics in LAP patients. Sigush, Guerrera, Hass, Yek, Mestnik, and Aimetti did studies on SRP in combination with antibiotics in GAP patients. The studies concluded that using antibiotics as an adjunct to SRP is beneficial when compared to SRP alone in treating aggressive periodontitis. Combination of amoxicillin and metronidazole with SRP is effective in treating GAP.[40]

Local antimicrobials

Agents like 1% chlorhexidine gel, 40% tetracycline gel, tetracycline fibers, and chlorhexidine chip have been used as local antimicrobials in the treatment of LAP and GAP. Unsal, Purucker, Kaner, and Sakellari have done studies on treating aggressive periodontitis using local antimicrobials. The studies concluded that the adjunct effect of local antimicrobial is not clear and do not seem to improve on the adjunct effect of systemic antibiotics. Therefore, it seems reasonable that the decision to use this type of treatment modality should be made on an individual basis rather than be evidence-based.[40]

SURGICAL THERAPY

Access surgery

Modified Widman flap surgery alone or in combination with tetracycline is effective in reducing the pocket depths and pathological microbial load. Modified Widman flap with systemic administration of amoxicillin and metronidazole combination is also beneficial in treating aggressive periodontitis. Christersson, Lindhe and Liljenberg, Mandell and Socransky, and Buchman have done extensive research on access surgery alone or in combination with antibiotics in treating aggressive periodontitis and concluded that access surgery in combination with systemic antibiotics was effective than access surgery alone.[40]

Teeth used as abutments for fixed constructions in aggressive periodontitis patients are more prone for extractions during follow-up period of 10 years (Yi *et al*., 1995 and Lulic *et al*., 2007). Pretzel indicated double rate of tooth loss used as abutments in fixed constructions over 10 years than teeth that are not used as abutments. The reason might be because of decreased accessibility for cleaning leading to risk for reinfection and progression of disease.[41]

IMPLANTS

According to short-term studies, the survival rate of implants in GAP patients is around 97.4-100%; whereas that of long-term studies, survival ranges from 83.3 to 96%. Therefore, implant treatment in patients with GAP is not contraindicated, provided that adequate infection control and an individualized maintenance program is assured.[42]

AGGRESSIVE PERIODONTITIS IN INDIAN POPULATION

In a cross-sectional survey done to know the prevalence of aggressive periodontitis in Moradabad population with their systemic manifestations, it was concluded that the frequency of systemic manifestations such as fatigue, weight loss, and loss of appetite was significantly greater in aggressive periodontitis and a significant correlation between anxiety/depression and aggressive periodontitis was observed.[43] In a study done by Rahul *et al*., neutrophil functions like chemotaxis, phagocytosis, and microbicidal activity, are deficient in LAP patients. These abnormal neutrophil functions may predispose to increased susceptibility for LAP.[44]

The incidence of A.a along with P.g and *T. forsythia* was high in aggressive periodontitis patients in subgingival plaque in south Indian population.[45] Viruses like herpes simplex virus (HSV)-1 and EBV were found to be significantly associated with destructive periodontal disease, including chronic and aggressive periodontitis. Further, HSV-1 was found to be associated with severity and progression of destructive periodontal disease.[46]

FcγRIIIa V/V genotype and/or V allele, as well as the FcγRIIIb NA2/NA2 and/or NA2 allele, along with the FcγRIIa-R allele, may be risk factors for generalized aggressive periodontitits (GAgP) in the population of South India.[47] In a study done by Shete *et al*., there was no gene polymorphism found in patients with aggressive periodontitis.[48] In Malayalam speaking Dravidian population, IL-4 + 33C/T loci appears to be an important risk factor for periodontal disease with a leaning towards aggressive periodontitis.[49] The association between IL-17F at 7383A/G and 7488A/G loci with either chronic or an aggressive periodontitis could not be ascertained.[49] In a study to know the clinical and genetic aspects of GAP in families of Tumkur district in Karnataka, it was concluded that the disorder may not be segregating as an autosomal recessive trait and could have been misled by consanguinity in the family and it could be a multifactorial trait, or still segregating as an autosomal recessive trait, but the region of homozygosity could be small.[50]

Systemic administration of doxycycline with full mouth SRP resulted in a better improvement of periodontal parameters and elimination/suppression of putative periodontal pathogens such as A.a, P.g, and *T. forsythia*, than amoxicillin plus metronidazole in patients with LAP.[51]

CONCLUSION

Aggressive periodontitis affects smaller percentage of population, which is influenced by specific bacterial etiology, host response, and genetic factors. As the disease is rapidly progressing and aggressive in nature, these patients require early diagnosis and treatment to prevent further progression of the disease and tissue damage.

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