Review Article

AGGRESSIVE PERIODONTITIS: A LITERATURE 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: Periodontitis.

Introduction

Mankind has known periodontitis as a disease entity for more than 5000 years.[1] Aggressive periodontitis refers to the multifactorial, severe, and rapidly progressive form of periodontitis, which primarily but not exclusively affects younger patients.[2] Aggressive periodontitis generally affects systemically healthy individuals less than 30 years of age, though patients may be older.[3] The term aggressive periodontitis does not refer to a new disease, but is used to describe the rare, but extremely progressive forms of periodontitis, which in most cases manifest themselves clinically during youth. This was replaced by the terms "*juvenile*" or "*early onset periodontitis (EOP)*". The presence of systemic diseases, resulting in an impaired immune system of the host and thereby causing severe periodontal diseases and premature tooth loss, must be excluded.[4,5] Aggressive periodontitis as the name suggest is a rapidly progressing type of periodontitis. It is an extreme variant type of infective-inflammatory periodontal disease *[chronic plaque induced periodontits]* and is believed to be caused by specific microorganisms. Certain immune defects in the patient are believed to play major role in etiopathogenesis of aggressive periodontitis. It is generally seen in 'seemingly' healthy [systemically] individuals.

HISTORY

A variety of names have been given to a form of periodontal disease characterized by deep pockets and advanced alveolar bone loss in the young children, adolescents and adults, without any associated systemic diseases.[3,4]

YEAR	AUTHOR	TERMS
1923	**Gottlieb**	***Diffuse Atrophy Of The Alveolar Bone***
1928	**Gottlieb**	***Deep cementopathia***
1938	**Wannenmacher**	***Parodontitis marginalis progressive***
1940	**Thoma, Goldman**	***Paradontosis***
1942	**Orban, Weinmann**	***Periodontosis***
1966	**World Workshop**	**Periodontics**
1967	**Chaput**	***Juvenile periodontitis***
1969	**Butler**	***Juvenile periodontitis***
1985	**Page, Baab**	***Early onset periodontitis (EOP)***
1989	**World Workshop in Clinical Periodontics**	***Localized juvenile periodontitis (LJP)***
1923	**Gottlieb**	***Diffuse Atrophy Of The Alveolar Bone***
1928	**Gottlieb**	***Deep cementopathia***

DIAGNOSTIC CRITERIA

- **The key diagnostic criteria of this disease includes:[5]**

- Early age of onset
- Involvement of multiple teeth with a distinctive pattern of clinical attachment loss and radiographic bone loss.

- 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.
- Although the current classification is no longer principally based on the age of the patient, the evaluation of the loss of periodontal supporting tissue can be helpful in the evaluation of progression of the disease.
- The specific distribution of the periodontal lesions (molars/incisors or generalized occurrence) permits the identification of localized and generalized aggressive periodontitis.

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.[11]

PREVALENCE

The prevalence of AP varies considerably between continents, and differences in race/ ethnicity seem to be a major contributing factor.[12]

Europe

5 surveys using representative samples comprising predominantly Caucasian subjects have been conducted in European populations. 4 of these surveys targeted 14-17 year old school children in Norway, the Netherlands, Finland and Switzerland.[12]

AGE	PLACE	PREVALENCE
14 years	Norway	-
14-17 years	Netherland	0.1-0.2%
16 years	Finland	0.1%
16 years	Switzerland	0.1%
19-20 years	Switzerland	0,13%

❖ **North America**

- The National Survey of Oral Health of US has undertaken school children during 1986/1987 and represented the most comprehensive dental survey to date of school-age children in the world.
- Study estimated that 0.66% of 14-17 years subjects in the US population have AP, including 0.53% of children with LAP and 0.13% children with GAP.

Second report assessed in the US population:[12]

AGE	PLACE	PREVALENCE
13-15 years	US	0.4%
16-19 years	US	0.8%

❖ **South America**

- Two surveys were conducted:

1. First survey studied 15-19 years school children in Santiago, Chile, using an initial clinical examination to screen the probing depth at 1st molars and incisors, and then used clinical and radiographic examinations of subjects identified as possibly having AP to validate the diagnosis of the disease.
2. Second survey was in Porto Alegre, Brazil and was household-based. It clinically examined 14-29 years individuals and found a disease prevalence of 5.5%

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❖ **Asia**

- 3 Asian populations were studied using probability samples:[13]

AGE	PLACE	PREVALENCE
13-19 years	Ankara, Turkey	0.6%
15-18 years	Tehran, Iran	0.13%
18-19 years	Israeli	0.86%

- In Asia, prevalence rate of 1.2% for LAP and 0.6% for GAP in Baghdad and Iran population, and 0.47% in Japanese population.

❖ **Africa**

- Only one study using a representative sample was found for African populations.[13]

AGE	PLACE	PREVALENCE
13-19 years	Khartoum, Sudan	3.4%

- The prevalence of LAP is <1% and GAP is 0.13%.

❖ **Prevalence of aggressive periodontitis by demographics:**[12]

➢ **Age**

- AP is detected more frequently among older children and young adults than in younger children.
- Albandar et al. estimated the prevalence of AP in US school children to be 0.4% among 13-15 years children and 0.8% among 16-19 years children.

➢ **Race/ethnicity**

- In 1986/1987 National Survey of US school children, 2 studies assessed the prevalence of AP:
-

Black Americans (2.6% and 2.64%) > Hispanic Americans (0.5% and 1.08%) > White Americans (0.06% and 0.17%)

- A study in US military recruits found a higher disease prevalence in Black people (2.9%) compared with Caucasians (0.09%).
- In the UK the reported prevalence is 0.02% in Caucasians, 0.2% in Asians and 0.8% in Afro-Caribbeans.
- In Brazil, AP was found in 2.4% of white people Vs. 6.1% of non-white people
- In Israel AP was detected in 3.2% of European compared with 10.4% of Africans.

A study in Sudan found a significantly higher prevalence in children of African tribes (6%) compared with those of Afro-Arab tribes (2.3%).

➢ **Gender**

PLACE	MALE	FEMALE
US (National Survey)	0.78%	0.52%
Porto Alegre, Brazil	5.7%	5.3%
US (Military Recruits)	0.73%	0.81%
Denmark	0.1%	0.1%
UK	0.1%	0.1%
Khartoum, Sudan	4.9%	2.0%

SCHOOL CHILDREN	MALE	FEMALE
Brazil	5%	2.7%
Iraq	0.4%	1.4%

- Black male school children were 2.9 times more likely to have LAP compared with black female school children, whereas white female school children were 2.5 times more likely to have the disease compared with white male school children.
- Another study conducted a longitudinal investigation of a group of 13 year old Brazilian at baseline and 3 years later and found that 1.3% and 1.8% of children had AP at 13 and 16 years respectively.
- Loe & Brown estimated that the odds ratio for detecting localized aggressive periodontitis in 17 years US children compared with those of 14 years was 3.8.
- Similarly, a study of US military recruits reported a higher disease prevalence in black male subjects than female subjects (3.81% vs. 1.99%), whereas in Caucasians and in other ethnic groups the prevalence was higher in female than in male.
- The study reported the following female:male ratios of disease prevalence: 0.52:1 in Black people; 4.3:1 in Caucasians; and 3:1 in other races.

❖ **Prevalence of aggressive periodontitis in India:**[14]

- A study was done to know the prevalence of aggressive periodontitis among teenagers and young adults.
- The prevalence of aggressive periodontitis in district Yamunanagar in a population attending schools and colleges in the age group of 15–30 years was 0.15% which was in accordance with the earlier epidemiological studies worldwide.

CLASSIFICATION

1. Localized aggressive periodontitis (LAP)
2. Generalized aggressive periodontitis (GAP)

Localised Aggressive Periodontitis:

- Localised Aggressive Periodontitis is localized in nature and doesn't involve all teeth in the dentition.
- It is confined to the incisors and first molars or at least two permanent teeth one of which is a molar and not more than two teeth other than molars and incisors.

- There is a lack of local factors such as plaque and calculus.
- Clinically there is lack of inflammation. But it presents with deep periodontal pockets.
- Distolabial migrations of the maxillary incisors with diastema formation are also present.
- There is an increased mobility of the maxillary and mandibular incisors and first molars.
- Dentinal hypersensitivity of denuded root surfaces is observed to thermal and tactile stimuli if present.
- Deep, dull, radiating pain during mastication probably caused by irritation of the supporting structures by mobile teeth and impacted food are present.
- Periodontal abscesses formation can be seen in the localized areas in such cases.
- Regional lymph node enlargement are also common in some cases. Rate is 3 to 4 times more and severe than in Chronic Periodontitis.
- Blacks are more prone to suffer from LAP. Among whites, females are more prone and among blacks, men are prone more to have LAP.
- It has been seen that in Localized Periodontitis Robust serum antibody response to infecting agents
- It usually occurs at puberty to 30 years of age.

Generalized Aggressive Periodontitis:

- Generalized aggressive periodontitis is characterized by "generalized interproximal attachment loss affecting at least 3 permanent teeth other than first molars and incisors.
- It is a multifactorial disease where interplay of microbiologic, genetic, immunologic, and environmental/behavioral risk factors decides the onset, course, and severity.
- The pathogenic bacteria in the dental plaque especially *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* have an indispensable role which elicits an aggravated host response which in turn is determined by the genetic and immunologic profile of the patient modified by environmental risk factors like smoking.
- Patients may complain of halitosis and pus discharge from gums in some cases.
- Pronounced episodic nature of the destruction of attachment and alveolar bone can be seen
- In generalized periodontitis poor serum antibody response to infecting agents.
- Mobility of the affected teeth will be seen towards the later stages of the infection. Patients will be otherwise systemically healthy.
- Severe pain is rarely experienced by the patients except in situations where a periodontal abscess develops or a periodontal-endodontic infection occurs via accessory canals or tooth apex.

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 colour 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]

RADIOLOGICAL FEATURES

Radiographic findings in aggressive periodontitis show bilateral, usually symmetrical bone resorption is seen in relation to the first molars and /or incisors.[11] The extent of bone loss depends upon the stage of the disease at the time of diagnosis, whether early or advanced. Bone loss starts usually on the mesial aspects of molars, while buccal and lingual or palatal plates resorbs last, leading to furcation involvement only in advanced cases. Periapical radiographs may show a cupped out (arc shaped) bony defect extending from the distal surface of the second premolar to the mesial aspect of the second molar.[11] The rate of bone destruction is very rapid and radiographic evidence of a three-fourths loss of bony support of involved teeth can be achieved in a 5-years interval or even less. This progression rate is about four times as much as for adult periodontitis.[15]

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, an increase in the numbers of acid phosphatase positive macrophages (phagocytic macrophages) in aggressive

periodontitis patients. In the pre-treatment biopsies of LAP, there was predominant plasma cell inflammatory infiltration, and the root surfaces of individuals with aggressive periodontitis were observed to be heavily covered by neutrophils.[16] A fully developed lesion consists of plasma 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 non serotypeable strains of A.a which lack expression of serotype-specific polysaccharideantigen.[17] 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.[17] Prevalence of A.a in LAP varies from 70 to 90%,but there are studies which states there is no association between A.a and the periodontal disease rather prevalence of levels of P.g, *T.denticola*, and *P.intermedia* are significantly associated with aggressive periodontitis.[18,19] 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.[20] 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*.[21] *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.[22] *Treponema lecithinolyticum*and *Treponema socranskii* are elevated in GAP.[23] 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.[24] Yamabe suggested Archaea a methanogenic organism, especially *Methanobrevibacter oralis*as putative periodontal pathogen for aggressive periodontitis.[17] 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*.[25]

META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES OF AGGRESSIVE PERIODONTITIS

Periodontitis has been widely classified into the widespread moderate form chronic periodontitis (CP) and the rare early-onset and severe phenotype aggressive periodontitis (AgP). These different disease manifestations are thought to share risk alleles and predisposing environmental factors. Both forms have an estimated heritability of 50%, with aggressive periodontitis having a stronger and better established heritable component compared to chronic periodontitis.[26] Chronic periodontitis and aggressive periodontitis have a similar etiology and histopathology and can be considered as parts of the same disease spectrum.

To obtain novel insights into the shared genetic etiology and the underlying molecular mechanisms of both forms, a study was done by Matthias et al where they performed a two step-wise meta-analysis approach using genome-wide association studies of both phenotypes. Genotypes from imputed genome-wide association studies (GWAS) of aggressive periodontitis and chronic periodontitis comprising 5,095 cases and 9,908 controls of North-West European genetic background were included.[27]

Two loci were associated with periodontitis at a genome-wide significance level. They located within the pseudogene MTND1P5 on chromosome 8 (rs16870060-G, $P=3.69\times10-9$, OR=1.36, 95% CI= [1.23–1.51]) and intronic of the long intergenic noncoding RNA LOC107984137 on chromosome 16, downstream of the gene SHISA9 (rs729876-T, $P=9.77\times10-9$, OR= 1.24, 95% CI= [1.15–1.34]). This study by Matthias et al identified novel risk loci of periodontitis, adding to the genetic basis of Aggressive periodontitis and chronic periodontitis.[27]

HERPES VIRUSES IN ETIOPATHOGENESIS OF AGGRESSIVE PERIODONTITIS.

Previous studies have found that herpes viruses are associated with aggressive periodontitis (AgP). However, these findings are controversial. A meta-analysis based on a case control study by Fei et al was conducted which aimed at clarifying the association between herpes viruses and aggressive periodontitis.[28]

The etiopathogenesis of aggressive periodontitis involves complex interaction between multifarious microorganisms and the host immune system.[29] Bacteria have long been proposed as the causative and most important agents in the course of periodontal disease. However, the periodontal tissue destruction in AgP is usually site-specific, bilaterally symmetrical, occasionally breakout, and self-limited. These typical clinical manifestations of AgP cannot be well explained by bacterial infection alone.[30] Hence, many scholars thought that pure bacterial aetiology of AgP may have been over-emphasised.[31]

Herpes viruses have been implicated in the etiopathogenesis of human periodontal disease since 1990s.[32] The etiopathogenesis of aggressive periodontitis

differs from chronic periodontitis and the association between herpesviruses and aggressive periodontitis is still unclear. Numerous studies have investigated the association between herpesviruses and aggressive periodontitis.[33,34] However, the results of these studies remained controversial. Some researchers believed that herpesviruses do play a role in the etiopathogenesis of AgP, whereas others do not. Nibali et al failed to detect herpesviruses in any of the subgingival plaque samples from patients with AgP.[35] Saygunetal reported no significant difference in copy numbers of herpes viruses between patients with AgP and periodontally healthy individuals.[36]

The typical clinical manifestation of AgP like little plaque formation at sites with rapid periodontium destruction could be better explained by alteration between active and latent periods of herpes virus infection.[37] Some research scholars have reported weak connection even opposite results between aggressive periodontitis and herpes viruses. Therefore, it is necessary to give overall estimations on the association between herpes viruses and aggressive periodontitis based on existing research data.

Several recent reviews have summarized the published findings on interaction between herpes viruses and aggressive periodontitis.[36,37] Hence, the different meta-analysis studies by different research scholars may help to provide more convincible evidence.

Periodontopathic bacteria might activate periodontal herpesviruses through inflammation-inducing factors. Recent studies found that *Porphyromonas gingivalis* has the potential to trigger EBV by increasing the activity of the BZLF1 gene, which encodes the key protein for the transition from latency to the lytic replication cycle.[38,39] Another study found that the co-infection of *Porphyromonas gingivalis* and EBV increase the gingival crevicular fluid visfatin levels, which might stimulate the expression of matrix-degrading enzymes and the breakdown of periodontal tissues.[40]

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. However more extensive researches and studies are required to be able to efficiently and effectively diagnose and manage AP

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