

ETIOPATHOGENESIS OF AGGRESSIVE PERIODONTITIS: PIECING THE PUZZLE!

Snehal P. Deotale, Deepti R. Gattani², Shiva charan Yadav³, Sachin Gaikwad⁴

1. Post Graduate student, Department of Periodontology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur

2. Head of Department and Professor, Department of Periodontology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur

3. Post Graduate student, Department of Periodontology, College of Dental Sciences, Davangere

4. Post Graduate student, Department of Periodontology, YMT Dental College, Navi Mumbai

ABSTRACT:

Aggressive Periodontitis is a group of periodontal diseases characterized by localized or generalized loss of alveolar bone usually affecting individuals under 30 years of age. In the past few decades, the retrospective analysis of the possible etiological factors responsible for Aggressive periodontitis has magnified to its brink. The necessity lies in segregating the evidences and acknowledging their potential role in the pathogenesis of Aggressive periodontitis.

In this paper, an attempt has been made to summarize recent views on various etiological agents involved in the pathogenesis and progression of aggressive forms of periodontitis. Data was identified by searches of the Medline and Pubmed. Articles published in English were selected and most up-to-date or relevant references were chosen.

Keywords: Aggressive periodontitis, etiological factors, pathogenesis



INTRODUCTION:

Over the years, the etiopathogenesis of Aggressive Periodontitis (AgP) has jumped up several milestones identifying various factors that could possibly be responsible for acquiring this disease entity. On behalf of the apposite evidence, there has been a growing necessity to categorize the various etiological factors and evaluate their contribution in the causation of AgP. The current piece of exposition attempts to fulfill this long awaited need of the hour.

The inception of the term AgP took place in the 1999 consensus workshop, thus sidelining the pre-existing terminologies like early-onset periodontitis. However much before its universal acceptance, Baer in 1971 had proposed a case definition for the same.

He defined AgP 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.” Also, to support his description he proposed classical criteria that encircled certain clinical and radiographic features. ^[1] His efforts to acknowledge AgP as a distinct entity laid the foundation for further research to define the disease elaborately.

Consequently, a subcommittee at the American Academy of Periodontology workshop 1999 adopted the terminology ‘Aggressive Periodontitis’ and proposed a case definition and diagnostic criteria to supplement the same. Firstly, the report presented by

the committee described various features that were synchronous to both localized and generalized forms of AgP comprising of:

A. Primary features:

- Occurrence of periodontitis in otherwise healthy individuals.
- Rapid rate of periodontal destruction and disease progression.
- Familial aggregation.

B. Secondary features that are seldomly present include the following.

- Local etiologic factors are not in accordance with diseases severity
- Elevated proportions of Aggregatibacter actinomycetemcomitans (A.a) and /or Porphyromonas gingivalis (P.g) in some populations.
- Phagocyte abnormalities.
- A hyper-responsive macrophage phenotype, including elevated levels of prostaglandin E2 and interleukin-1b.

The committee firmly believed that, age at the time of disease presentation should be used as a descriptor in the subtypes of AgP rather than a criterion for the case definition of this disease. Nonetheless, the committee penned down certain findings that are characteristic to the two subtypes individually which included:

A. Localized aggressive periodontitis.

- Circumpubertal onset.

- Localized first molar / incisor presentation with interproximal attachment loss on at least two permanent teeth (one of which is a first molar) and involving no more than two teeth other than first molars and incisors.
- Robust serum antibody response to infecting agents.

B. Generalized aggressive periodontitis.

- Usually affecting persons under 30 years of age, but patients may be older.
- Generalized interproximal attachment loss affecting at least three permanent teeth other than first molars and incisors.
- Pronounced episodic nature of the destruction of attachment and alveolar bone.
- Poor serum antibody response to infecting agents. [2]

Advancements in the criteria for disease presentation have thrown the limelight on the necessity to categorize disease causation elaborately. In order to ameliorate the complexity lying behind the pathological basis of AgP this literature review aims to typecast the possible etiological factors systematically and briefly highlight their role in disease pathogenesis.

METHOD OF DATA ACQUISITION

A Medline and PubMed search was conducted using the keywords “aggressive periodontitis”, “etiopathogenesis”, “risk factors” and

“genetic polymorphisms”, to identify articles published until October 2015. All possible factors associating to etiopathogenesis of AgP were acknowledged and assimilated to formulate the review.

A. MICROBIOLOGY OF AgP [3]

a. Bacterial etiology:

The role of microbial plaque in the pathogenesis of AgP was vividly emphasized in the 1999 consensus report. The two dominant microbes in disease causation were narrowed down to A.a and P.g. Their pathological vivacity is attributable to the several virulence factors that these microorganisms exhibit to maintain their presence in the close proximity to the periodontium. The virulence factor of prime importance secreted by A.a is leukotoxin which destroys the innate immune cells and hampers the immune response. Bacteriocin on the other hand, prevents the growth of beneficial species. Collagenases, secreted by most of the pathogens cause degradation of collagen, the foundation of the attachment apparatus of the periodontium. Various other enzymes secreted by P.g include hyaluronidase, nuclease, gelatinase which weaken the host immune response.

C. ROLE OF CULTURAL AND ENVIRONMENTAL FACTORS [3- 5]

Several factors are known to alter the microbial environment and host

Cortelli et al 2012, has noted that the symbiotic association of microbial colour complexes justifies the subsistence of other species like *Campylobacter rectus*, *Tannerella forsythia*, *Prevotella intermedia* etc.

b. Viral etiology:

Numerous studies have proved that Epstein Barr virus (EBV) and Human Cytomegalovirus (HCMV) are the two most commonly associated viruses with AgP. Their mechanism of action was justified using Novel Infectious Disease model by Slots and Contreas 2000, that highlights the bidirectional viral-bacterial interaction to suppress the host immune response. They explained that, plaque induced gingival inflammation facilitated viral ingress causing subgingival upgrowth of pathogenic bacteria which in turn mediated a re-activation of the nascent virus. The resultant vicious cycle favoured rapid attachment loss. Viral etiology was confirmed by several DNA studies conducted on EBV and HCMV which were all of the opinion that, there was a correlation between levels of the former and altered pocket probing depth, clinical attachment loss and bleeding on probing.

B. ROLE OF LOCAL ETIOLOGIC FACTORS [4]

immune response thus dictating the direction of disease progression. These include:

a. Ethnicity:

Research on disease prevalence in socially defined groups have shown that each group presents with a unique genetic configuration that separates it from the others in prevalence of specific serotypes of bacterial species, their virulence factors and host immune response. These peculiar features separate the races in rate of disease acquisition and evolution

Socio- demographic status:

Paolantonio et al 2000 conducted an Italian based cultural study to determine the carriage rates of A.a and clinical conditions of children and adolescents in the rural versus the urban populations. His study drew a conclusion that the former group had an increased susceptibility to carry the disease as they were socio- economically pauperized and lacked efficiency in maintaining their oral hygiene irrespective of their gender and age. The reasoning for such discrepancies was that the greater amount of supragingival plaque in rural subjects may have affected subgingival colonization by A. a.

c.Smoking:

The adverse effects of smoking is the vasoconstriction caused by nicotine which facilitates decreased oral neutrophil function, diminished oxygen supply promoting growth of anaerobic organisms and depressed host immune response. These

factors have lead smoking to be an important factor for AgP disease severity and progression.

d.Role of Stress in AgP:

Literature emphasizes on the behavioral changes that occur as a result of increased psychosocial stress leading to smoking, poor oral hygiene, obesity which have already been linked with periodontal disease.

A possible link between AgP, psychosocial stress and loss of appetite was first investigated by Page RC et al 1983. [6] Monterio Da Silva et al 2003 added his valuable contribution by conducting a case control study on the psychophysiological responses in 1196 AgP cases and concluded that increased stress lead to rise in the levels of prostaglandins and proteases simultaneously depressing the host immune response, increasing host susceptibility to microbial attack all in all leading to rapid periodontal destruction. Also, the test group subjects were more depressed and socially introvert than the subjects in the chronic periodontitis control group. [7]

Kamma JJ et al 2003 evaluated the clinical and microbiological parameters of AgP subjects in maintenance follow up study over 5 years after active periodontal treatment and highlighted that

stress was responsible for disease progression in some cases. [8]

e.Diabetes Mellitus (DM) and AgP:

Increased blood glucose levels and the accumulation of advanced glycation end products in the oral cavity provide nutrition for the growth of periodontal pathogens. A frail immune system in diabetic patients also causes a diminished host response towards bacterial attack and hence periodontal destruction is accelerated.

A case control study by Nibali et al 2007 brought into the limelight, the prevalence of high random blood glucose levels in AgP subjects. [9] A pilot study conducted by Davies RC et al 2011 managed to determine the association between DM and AgP by successfully demonstrating altered serum levels of inflammatory mediators, lipids and adipokines in the test groups over healthy controls. [10]

D.HOST RESPONSE IN AgP [11, 12]

It is evident that a case of gingivitis transforms into periodontitis due to a diminished host immune and inflammatory response. Hence it is of utmost importance to focus on the host-related aspects and their vital role in the etiopathogenesis of AgP.

a.Bacterial- host interactions:

A microbial insult to the periodontium initially activates a locally occurring early host response which on full establishment activates the delayed host response.

b.Host defenses in AgP:

The early response is mediated through the activation of innate immune cells like fibroblasts, dendritic cells, macrophages and intracellular or transmembrane pathogen recognition receptors. There are a series of intracellular events that occur resulting in the increased production of inflammatory mediators. The role of a polymorphonuclear neutrophil (PMN) is of great importance in the phase. The cell is activated by the virulence factors released by the bacteria and any defect in its chemotactic or phagocytic activity can encourage a debilitated innate immune response. Common causes of the same are altered surface receptors for identifying chemotactic mediators or polymorphisms in membrane receptors for the Fc gamma receptor fragment of antibody to evoke a future delayed host response.

An impaired neutrophil transforms into a hyperactive or primed one, with the release of several noxious enzymes and free oxygen radicals. This functional metamorphosis proves to be a lethal reaction to the

diseased as well as the surrounding healthy periodontal structures.

As the severity and duration of disease progress, there is a distinct shift from innate to adaptive host immune response. Primarily, a T-cell mediated lesion overtaken by a B-cell mediated one, is commonly encountered. Lucisano et al 1991 stated that IgG2 was the most abundant subgroup of IgG antibody which demonstrated a specific antibody response to both A.a and P.g.

c. Deficiencies in host response:

Paradoxical but rare forms of AgP, are those cases that occur as oral manifestations of systemic diseases. Although AgP should ideally be associated with systemically healthy subjects, underlying leucocyte deficiencies can be an indication of medical problems. Examples of such ailments demonstrating an oral picture influenced by leucocyte dysfunction are Leucocyte adhesion deficiency, Papillon Lefevre syndrome, Leukemia, etc.

d. Role of Genetic factors:

The early stages of inflammation show a predominance of proinflammatory cytokines secreted by inflammatory cells. Cytokine genes play a very significant role in orchestrating the immune response. Genetic variations that modify immunological reactions identify the

disease susceptibility in various individuals. The growing awareness of these allelic variants has made them potential therapeutic targets.

Boughman et al 1986 stated that familial aggregation reflected exposure to common environmental factors thus showing genetic similarities amongst individuals who shared the same. The acknowledgement of familial tendency of AgP has led researchers to investigate the genetic predisposition aspect of AgP as a separate etiological factor. Studies on pedigree analysis, segregation analysis, linkage analysis and association analysis are of the opinion that AgP is an X-linked autosomal dominant disorder with a major located on chromosome 4q. Twin model studies have drawn a conclusion that it is commonly rendered in monozygous than in dizygous twins. [13]

These findings have led to speculation that a major gene defect is responsible for the spread of AgP, but such a gene that is generalized to the population has not been found yet. However, several gene polymorphisms associated with high disease risk have been enlisted in Table 1. [13, 14]

Such polymorphisms show variations in different population groups and geographic locations in AgP patients, making it a formidable

task to attain any conclusive results from the published data.

FUTURE CONSIDERATIONS

Each etiological factor playing a role in the etiopathogenesis of AgP is symbiotically related to the other and incapable of causing the disease individually. Hence, it is apt to consider aggressive forms of periodontitis as multifactorial disease entities. The need to discover advanced diagnostic tools for its optimum evaluation will significantly enhance the predictive value and detect Agp cases before significant tooth loss sets in. [4]

REFERENCES:

1. Baer PN. The case for periodontosis as a clinical entity. *J Periodontol* 1971; 42: 516–520.
2. Lang N, Bartold PM, Cullinan M, Jeffcoat M, Mombelli A, Murakami S, Page R, Papapanou P, Tonetti M, Van Dyke T. Consensus report – aggressive periodontitis. *Ann Periodontol* 1999; 4: 53
3. Könönen E, Müller PH. Microbiology of aggressive periodontitis. *Periodontology* 2000, 2014; 65:46–78
4. Albandar JM. Aggressive periodontitis: case definition and diagnostic criteria. *Periodontology* 2000, 2014; 65: 13–26
5. Schnkein H, Van Dyke TE. Early onset periodontitis: systemic aspects of etiology and pathogenesis. *Periodontology* 2000, 1994; 6: 7- 25
6. Page RC, Altman LC, Ebersole JL, Vandesteen GE, Dahlberg WH, Williams BL, et al. Rapidly progressive periodontitis. A distinct clinical condition. *J Periodontol* 1983;54:197–209.
7. Monterio Da Silva A, Oakley D, Newmann H, Nohl F, Lloyd H. Psychosocial factors and adult onset rapidly progressive periodontitis. *J Clin Periodontol* 2003; 30: 562–72.
8. Kamma JJ, Baehni PC. Five-year maintenance follow-up of early-onset periodontitis patients. *J*

CONCLUSION:

Aggressive Periodontitis as a disease entity demonstrates a great deal of etiological heterogeneity. Hence, until the various pathologic processes that are involved in disease causation are defined, logical categorization and appropriate preventive and therapeutic measures may not become available. The future considerations are expected to curtail these insufficiencies. A thorough understanding of all the etiological aspects will enhance the diagnosis and treatment planning thus facilitating betterment of the diseased.

Clin Periodontol 2003; 30: 562–72.

9. Nibali L, D_Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS. Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. J Clin Periodontol 2007; 34: 931–937.

10. Davies RC, Jaedicke KM, Barksby HE, Jitprasertwong P, Al-Shahwani RM, Taylor JJ, Preshaw PM. Do patients with aggressive periodontitis have evidence of diabetes? A pilot study. J Periodont Res 2011; 46: 663–672

11. Ryder MI. Comparison of neutrophil functions in aggressive and chronic periodontitis. Periodontology 2000, 2010; 53: 124–137

12. Kulkarni C , Kinane DF. Host response in aggressive periodontitis. Periodontology 2000, 2014; 65: 79–91

13. Bali D, Pandit N, Kathuria R, Bali A. Genetics and Aggressive Periodontal Disease: An Update Review. J Oral Health Comm Dent 2012; 6: 97-101

14. Maney P, Owens JL. Interleukin polymorphisms in aggressive periodontitis: A literature review. J Ind Soc Periodontol 2015; 19: 131-41

TABLES:

TABLE 1: [13, 14]

| GENE POLYMORPHISMS ASSOCIATED WITH AGP | |
|--|---|
| GENE | POLYMORPHISM |
| 1. Interleukin (IL) group: - IL- 1 - IL- 2 - IL- 4 - IL- 6 | IL-1A(+4845,)IL-1B(+3954) IL-2–330T/G IL-4 promoter and introns polymorphism IL-6–174 |
| 1. Fc̄RIIIb-NA2 allele 2. Fc̄RIIIa-158F | Fc receptor gene polymorphism |
| 3. FMLP receptor | N-FMLP polymorphism |
| 4. VDR polymorphism | Vit-D receptor polymorphism |