

REVIEWS

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Localized Aggressive Periodontitis – Diagnostics, Epidemiology, Etiopathogenesis

Umiejscowione agresywne zapalenie przyzębia – diagnostyka, występowanie, etiopatogeneza

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A – koncepcja i projekt badania; B – gromadzenie i/lub zestawianie danych; C – opracowanie statystyczne;
D – interpretacja danych; E – przygotowanie tekstu; F – zebranie piśmiennictwa

Abstract

Localized aggressive periodontitis (LAGP) is a very characteristic clinical entity. Numerous changes in the classification and naming of this periodontal disease over the last 35 years have not fundamentally changed its diagnostic criteria. Most of the research confirms the important role of *Aggregatibacter actinomycetemcomitans* in the etiopathogenesis of LAGP, especially the JP2 clone. Family history of the disease and racial differences suggest the influence of genetic factors. Research on the effects of the individual polymorphisms of genes involved in the regulation of the immune system does not give a clear answer on the relationship between polymorphisms of genes encoding various types of protein-modifying immune processes and the initiation and course of localized aggressive periodontitis. What is certain is that there is impaired chemotaxis and phagocytosis. The question remains whether these abnormalities are primary or are caused by the influence of an infectious agent. Nowadays, it is suspected that reduced production of defensins by the epithelial cells of the gingival sulcus plays a crucial role in the formation of LAGP. The aim of this study was to gather information on the diagnosis, prevalence and etiology of localized aggressive periodontitis based on the state of the art (**Dent. Med. Probl. 2012, 49, 4, 567–575**).

Key words: localized aggressive periodontitis, diagnosis, prevalence, etiology.

Streszczenie

Umiejscowione agresywne zapalenie przyzębia (LAGP) jest bardzo charakterystyczną jednostką kliniczną. Liczne przekształcenia klasyfikacji i nazewnictwa chorób przyzębia w okresie ostatnich 35 lat nie zmieniły zasadniczo kryteriów diagnostycznych dla tej jednostki chorobowej. Większość badań potwierdza istotną rolę *Aggregatibacter actinomycetemcomitans* w etiopatogenezie LAGP, zwłaszcza jego klonu JP2. Rodzinne występowanie choroby i różnice rasowe przemawiają za wpływem czynników genetycznych. Badania nad wpływem polimorfizmu pojedynczych genów związanych z regulacją czynności układu immunologicznego nie dają jednoznacznej odpowiedzi na temat związku polimorfizmu genów kodujących poszczególne rodzaje białek modyfikujących procesy immunologiczne z powstawaniem i przebiegiem umiejscowionego agresywnego zapalenia przyzębia. Zjawiskami pewnymi są zaburzenia chemotaksji i fagocytozy. Przedmiotem dyskusji pozostaje fakt, czy zaburzenia te mają charakter pierwotny, czy są wywołane wpływem czynnika infekcyjnego. Pewną rolę w powstawaniu LAGP przypisuje się obecnie zmniejszonemu wydzielaniu defensyw, wytwarzanych przez komórki nabłonka kieszonki dziąsłowej. Celem pracy było zebranie informacji na temat diagnostyki, częstości występowania i etiopatogenezy umiejscowionego agresywnego zapalenia przyzębia na podstawie współczesnego stanu wiedzy (**Dent. Med. Probl. 2012, 49, 4, 567–575**).

Słowa kluczowe: agresywne umiejscowione zapalenie przyzębia, diagnostyka, występowanie, etiopatogeneza.

Localized aggressive periodontitis is a very specific disease which occurs in young people. It is characterized by a heavy destruction of periodontal tissues and hard to discern gingival inflammation. The differences of this condition from other periodontal diseases were first noticed in the first decades of the last century. In 1967, the International Society for the Study of Periodontal Diseases – ARPA Internationale titled it Desmodontosis. In 1975 the Council of the German Dental Association changed its name to parodontosis localisata. In 1988 the condition was named localized juvenile periodontitis (LJP), which in American nomenclature has been described as juvenile periodontitis (JP) since 1977. In 1982, Page and Schroeder proposed a division of periodontitis into 4 groups: generalized and localized prepubertal periodontitis (occurring in children before puberty), juvenile periodontitis (JP) in systemically healthy young people and beginning at the onset of puberty, rapidly progressing periodontitis (RPP) occurring in adults, and adult periodontitis (AP), a chronic inflammation of the periodontal tissues also occurring in adults [1]. Another classification was proposed by Ranney. In this framework, the forms of early-onset periodontitis were: early-onset localized periodontitis, generalized early-onset periodontitis, early-onset periodontitis related to systemic disease and early-onset periodontitis associated with unknown systemic diseases [2]. The current classification of periodontal diseases was accepted in 1999 at an International Workshop in Illinois (USA), where the condition was described as „localized aggressive periodontitis” (LAgP or LAP). The current diagnostic criteria for it were set out as well [3].

Diagnosics

Primary symptoms are rapid loss of connective tissue and alveolar bone, familiar aggregation of the diseased. Patients are considered systemically healthy. In turn the secondary symptoms are: the amount of bacterial plaque seems inconsistent with the progression of the disease, presence of large amounts of microorganisms such as *Aggregatibacter actinomycetemcomitans* (*A.a*) and *Porphyromonas gingivalis* (*Pg*) in the subgingival biofilm, impaired phagocytosis, probably the occurrence of macrophages in a state of excessive activity, showing an increased secretion of certain inflammatory mediators such as prostaglandin-2 (PGE2) and interleukin-1 beta (IL-1 β), the progression of attachment and bone loss may be spontaneously self-arresting.

To identify localized aggressive periodontitis, additional criteria should be adopted which, in ac-

cordance with the provisions of the International Workshop of Periodontics in 1999, are as follows: onset occurs in puberty, very high levels of antibodies against pathogenic bacteria in periodontal tissues, loss of epithelial-connective tissue attachment in the interdental spaces including the first molars and/or central incisors, amount of bacterial plaque is inconsistent with the progression of the disease. Although the name of this aforementioned condition has changed over time, the diagnostic criteria have not changed but have only been extended with any subsequent knowledge. This has meant that the scientific community has been able to analyze and compare the results of observations from various periods.

Epidemiology

Most of the very large number of epidemiological studies of periodontal disease is based on indicators: CPITN (Community Periodontal Index of Treatment Needs) and its abbreviated form of CPI (Community Periodontal Index). Their analysis makes it possible to determine the population status and treatment needs in the given territory. Unfortunately, due to the methodology of research, this data cannot be directly applied to the frequency of LAgP. The research carried out by Saxby [4, 5] about localized juvenile periodontitis (LJP), conducted over 30 years on 7266 students aged 15–19 years, showed significant differences in prevalence between the races: Caucasians (0.02%), Afro-Caribbean (0.8%) and Asian (0.2%). Contemporary studies do not always confirm these figures but all agree on strong racial diversity in the prevalence of LAgP. Among 5590 Iranian high school students in Tehran (aged 15–18 years), the incidence was 0.13% [6]. A study among Turkish young people (3056 persons, aged 13–19 years) showed a LAgP prevalence of 0.6% with the ratio of female to male 1.25:1 [7].

In Uganda, localized aggressive periodontitis was observed in up to 4.2% of surveyed adolescents and young adults (aged 12–25 years), but this disease occurred more frequently in young males than females (1.50:1), and its incidence was independent of age, economic status and area of residence [8]. In multi-ethnic Sudan (1200 persons aged 13–19 years), the frequency of aggressive periodontitis was 3.4% and was not differentiated through age groups (13–16 years old/17–19 years old), but was statistically higher in Africans (6%) than in those of Arab origin (2.3%) [9]. Eickholz [10] states that in Germany in 1000 16 year olds surveyed, there should be at least one case of aggressive periodontitis (0.1%).

Etiopathogenesis

Plaque

The development of new molecular biology techniques allows the detection, identification and quantification of a growing number of microorganisms. Of the hundreds of species that inhabit the human oral environment, about 40 have been fully characterized. They have been grouped into bacterial complexes by Socransky based on their metabolic connections. The presence of complexes depends largely on the depth of periodontal pockets. These complexes include: groups of *Actinomyces* – *Actinomyces naeslundii* 1, 2, *Actinomyces israeli*, *Actinomyces gerencseriae*; purple complex – *Actinomyces odontolyticus*, *Veillonella parvula*; yellow complex: *Streptococcus Gordon*, *Streptococcus intermedius*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguis*; green complex: *Aggregatibacter actinomycetemcomitans*, *Capnocytophaga gingivalis*, *Capnocytophaga ochracea*, *Capnocytophaga sputigena*, *Eikenella corrodens*; orange complex: *Campylobacter gracilis*, *Campylobacter rectus*, *Campylobacter showae*, *Eubacterium nodatum*, *Fusobacterium* ssp. *nucleatum*, *Fusobacterium nucleatum polymorphicum* spp., *Fusobacterium nucleatum* ssp. *vincenti*, *Fusobacterium periodonticum*, *Parvimonas micra* (formerly *Peptostreptococcus micros*, *Porphyromonas micros*), *Prevotella intermedia*, *Prevotella nigrescens*, *Streptococcus constellatus*, red complex: *Tannerella forsythia*, *Porphyromonas gingivalis*, *Treponema denticola* and other bacteria – *Eubacterium saburreum*, *Gemella morbillorum*, *Leptotrichia buccalis*, *Propionibacterium acnes*, *Prevotella melaninogenica*, *Streptococcus anginosus*, *Selenomonas noxia*, *Treponema socranskii* [11, 12]. Modern microbiological tests show the presence of all these microbes, in individuals with healthy periodontium as well as in individuals with periodontitis. It has been shown that the essence of periodontal disease is not the difference in spectrum of the bacteria in the biofilm but the disruption in ratio of the bacterial plaque composition [13–15]. It is believed that the development of LAgP is related to the presence of Gram-negative anaerobic rods or *Aggregatibacter actinomycetemcomitans*. This microorganism inhabits the oral cavity in more than one-third of the human population [16]. It produces a number of factors that trigger the host's immune system; adhesins, lipopolysaccharides (LPS) and toxins: *cytolethal* distending toxin (CTD) and the well-known leukotoxin (LtxA) which was first described in 1979 by Tsai [17]. It is a protein produced by many Gram-negative bacteria. It acts against the cell membranes of host leukocytes.

A. actinomycetemcomitans occurs in two different phenotypes – a clone (strain) of 625 and JP2. The difference between them is the scale of leukotoxin production *in vitro*. The JP2 clone is phylogenetically a very ancient organism. It is estimated that it has inhibited the human body for over 2400 years [18]. This bacteria probably comes from Africans living in the Mediterranean, and then was carried to other continents. This is supported by the fact that there is a selective and sustained colonization of periodontal tissues in those of African descent. It should also be emphasized that the increased risk of aggressive periodontitis is mainly in people with a constant colonization of the JP2 clone. For this reason, individuals of Afro-American descent are at greater risk of aggressive periodontitis of up to 10–15 times more than Caucasian-Americans. It is understood that the special virulence of JP2 is due to higher leukotoxin production compared to other strains of *A. actinomycetemcomitans*. It is still unknown why JP2 strains produce more leukotoxin. Initially it was thought that leukotoxin is associated with the outer part of the bacteria cell membrane. Subsequent studies have shown that it is also actively transported to the outside of the bacteria and can affect all cells of the host immune system [19]. However, physical access primarily occurs in neutrophils and monocytes. The primary role of LtxA is to protect bacterial cells from the immune system of the host. The first immune response is mobilization of neutrophils (PMNs) in order to eliminate the bacteria. The cell membrane of neutrophils has a receptor called LFA-1, which is activated by cytokines. This results in the adhesion of neutrophils to the blood vessel wall and diapedesis. A non-operating receptor of LFA-1 is directed into the cell and is expressed only as a result of ongoing inflammation. The role of leukotoxin is to combine with the receptor LFA-1 and its inactivation. LtxA may have a strong effect by binding to another bacterial protein, superoxide dismutase, that causes detoxification of any free radicals generated by the host cells during the respiratory burst [20–22]. In large doses LtxA destroys leukocytes by increasing the calcium concentration inside the cell and in smaller quantities induces their apoptosis [23, 24]. This mechanism, however, is poorly understood. LtxA production is regulated by the level of fermentable sugar. Increased levels of glucose inhibit the production of LtxA [25]. The clone of *A. actinomycetemcomitans* called 625 is insulated from individuals with healthy periodontium but the clone JP2 (mainly serotype b) is detected mainly in people with periodontitis. It has been shown that its presence in subgingival plaque increases the risk of aggressive periodontitis markedly in Moroccan

adolescents [26, 27]. However, Fine et al. [28], after studying American Afro-American and Hispanics youths, reported large individual differences in the bone destruction of people who did not have the JP2 clone, during the entire period of study. A reasonable explanation for this phenomenon may be, according to Fine, that the role of LtxA is exaggerated or microorganisms having the minimum LtxA secretion in the laboratory may in a natural environment produce the same amount as JP2 strains. These doubts can only be explained by measuring the level of LtxA in gingival fluid [29].

Most work carried out on localized aggressive periodontitis over the last 35 years confirms the essential role of *A. actinomycetemcomitans* in this pathology. Faveri et al. [13] studied 120 generally healthy Brazilians: 15 people (12–20 years old) with localized aggressive periodontitis, 25 (aged: 20–29) with generalized aggressive periodontitis, 30 (30–49 years old) with chronic periodontitis, 30 healthy adults (aged 18–40) and 20 healthy adolescents (aged 13–19 years). An analysis of subgingival plaque in the presence of 38 previously mentioned microorganisms revealed the presence of all species, regardless of periodontal status. However, the number and frequency of microorganisms in each group was varied. In the group with localized aggressive periodontitis *T. fosythia* and *P. gingivalis* were observed most frequently. The number of these pathogens and *C. gracilis*, *E. nodatum* and *P. intermedia* in patients with LAgP was significantly higher than in the group of young people with a healthy periodontium. In healthy periodontium, *A. naeslundii* and bacteria from purple, yellow and green complexes were found most frequently. With the increasing depth of periodontal pockets in cases with LAgP, a growing proportion of pathogenic bacteria was found from red complex and a decreasing number of bacteria from purple (*V. parvula*, *A. odontolyticus*), yellow (*S. mitis*, *S. oralis*, *S. sanquis*, *S. Gordini*, *S. intermedius*) and green (*E. corrodens*, *C. gingivalis*, *C. ochracea*, *C. sputigena*, *A. actinomycetemcomitans*) complexes and *Actinomyces* species. *A. actinomycetemcomitans* was proportionately in greater numbers in patients with LAgP. A comparison of the number of bacteria between groups of people with periodontitis showed significantly higher levels of *A. actinomycetemcomitans* in patients with LAgP, and *Fusobacterium nucleatum* spp and *P. gingivalis* in a group of GAgP, and *A. naeslundii* in patients with CP. A comparison of bacterial flora depending on the depth of periodontal pockets showed no difference between groups of individuals with periodontitis except a higher level of *P. gingivalis* in medium pockets (4–6 mm) in patients with GAgP and *A. actinomycetemcomitans*

in shallow (less than 3 mm) and medium pockets in patients with LAgP compared to those of GAgP and CP [13].

Bacterial flora of deep pockets (greater than 7 mm) did not differentiate in groups of patients with periodontitis. The data may confirm the dominant role of *A. actinomycetemcomitans* in the etiology of localized aggressive periodontitis. However, there are studies that contradict such an association [30–32]. Observations of 24 generally healthy children performed by Høglund et al. [30] for 19 years showed that only 3 out of 13 people with the initial presence of *A. actinomycetemcomitans* presented later symptoms of localized loss of epithelial-connective tissue attachment. Detected microorganisms had serotype a, c and e. None of the children were positive for the highly leukotoxic JP2 clone, although in one case there was clone detected possessing the gene coding for another strong toxin called CDT (cytolethal distending toxin), which causes eukaryotic cell cycle arrest in the G2 phase and leads to their death. Also, Mroz and Berghlund [31], after 14–19 years of follow-up of children screened for the first time at age 7–13 years showed a lack of a connection between the presence of *A. a* JP2 strains and localized aggressive periodontitis.

15 years of observations of young generally healthy Jamaicans who were diagnosed with localized aggressive periodontitis (80% of the respondents were women) showed that the most common subgingival bacteria were *Enterobacter* spp. (40.5%), followed by *Klebsiella* spp. (19%) and *Acinetobacter* spp. (10.8%). The key bacterium of LAgP, *Aggregatibacter actinomycetemcomitans*, was only detected in 5.4% of cases (2/37 patients at baseline). The authors emphasize the racial differences present in the periodontal flora and its pathogenic effects on the development of periodontal disease [32].

The sole presence of bacteria is not a sufficient condition for the prediction of the development of aggressive periodontitis. It is well known that the disease is the result of interaction between the disturbances between the host organism and the pathogen. It is therefore necessary to consider the factors of internal origin, which predispose some individuals to the disease.

Disorders of Chemotaxis of Neutrophils

Disorders of the number and function of neutrophils and their impact on the rapidly progressive periodontal inflammation have been well known for over 110 years. This was initially associated with congenital and acquired diseases such

as systemic hypophosphatasia, Chediak-Higashi syndrome, lazy leukocyte syndrome, Down syndrome, Job syndrome, chronic granulomatous disease, Crohn's disease, type II diabetes, agranulocytosis and neutropenia. In 1977, Cianciola et al. [33] showed that impaired chemotaxis and phagocytosis also occur in generally healthy people with periodontitis. This report set a new direction in the research of the causes of aggressive periodontitis, and resulted in a number of ongoing studies on the role of innate immune responses in periodontal diseases. Konopka [34] in 2002 and Ryde [35] in 2010 reviewed the literature on functional disorders of neutrophils. They showed that the disorder of chemotaxis was observed in 70–86% of people with LAgP. The question of whether these abnormalities are primary or secondary is discussed. Initially it was thought that neutrophil dysfunction is permanent and genetically determined. Van Dyke [36] (based on the assumption that the mechanisms of innate immunity are regulated at the genetic level) showed that the cause of the reduced chemotaxis may be a genetically determined reduction in the amount of receptors on the cell membrane or their defect (bacterial antigen receptors for f-Met-Leu-Phe and/or co-receptor for receptor f-Met-Leu-Phe, such as glycoprotein 110 – GP110).

This theory is also supported by other studies, which have demonstrated that some patients with aggressive periodontitis have a defect of neutrophil chemotaxis even after removal of the pathogen and elimination of inflammation [37, 38].

Not all researchers agree with this statement [39–41]. The secondary nature of the described pathology is evident by the fact that the function of neutrophils in gingival fluid and peripheral blood can return to its original condition after periodontal treatment [39, 40]. It is known that the function of micro- and macrophages can be altered by plaque microorganisms such as *A. actinomycetemcomitans*, *P. gingivalis* and *Capnocytophaga* sp. Even very low concentrations of proinflammatory cytokines (IL- β , TNF- α) in serum may alter neutrophil function, particularly their chemotaxis. What is more, cytokines in the serum of patients with LAgP change the neutrophils function taken from completely healthy people [41]. Studies on the protein expression of co-receptor CD38 on the cell membrane of neutrophils (which is one of the intermediaries of signal transduction into the cell), showed no differences between people with a healthy periodontium and LAgP, but only when the leukocytes were unstimulated. After the stimulation of neutrophils with bacterial antigen f-Met-Leu-Phe, the activity of leukocytes in patients with localized aggressive periodontitis was significantly lower than in subjects with healthy periodontium [42].

Disorders of Phagocytosis

As in the case of abnormal chemotaxis, impaired phagocytosis is clearly observed in patients with LAgP. There is no consensus about the primary or secondary nature of this pathology. In the study of Kimura et al. [43], the interference of phagocytosis was observed in 53% of patients with LAgP, and reduced capacity for phagocytosis did not change after treatment. Konopka and Ziętek [44–47] showed that the phagocytosis ability of peripheral blood neutrophils against *Staphylococcus aureus* and latex particles is impaired but this defect disappears after treatment. The essence of such a reaction is the reduction of pathogenic bacteria and the reduction or resolution of inflammation.

Disorders of Diapedesis of Neutrophils

There are other facts supporting the theory of secondary mechanisms in the development of disturbances in immune response in some cases of LAgP. In the cell membrane of neutrophils (PMN) there is a receptor called LFA-1 (Lymphocyte function-associated antigen 1) which consists of two proteins, CD11a and CD18. This provides species specificity of the receptor [48]. Non-operating receptor LFA1 is directed into the cell and is expressed only as a result of ongoing tissue inflammation. Its activation occurs under the influence of proinflammatory cytokines. The natural ligand for LFA-1 is the ICAM-1 (Intercellular Adhesion Molecule 1) receptor on the surface of endothelial cells of blood vessels. Activated LFA-1 connects with ICAM-1 and this combination results in the migration of neutrophils from the blood vessel into infected tissue. Leukotoxin secreted by *Aggregatibacter actinomycetemcomitans* binds with the neutrophil LFA-1 receptor and inactivates its function. This results in a reduction of cytokine secretion and reduced neutrophil diapedesis through the blood vessels [20–22].

Dysfunction of Epithelial Cells in Periodontal Pockets

Epithelial cells produce defensins, which are non-specific, phylogenetically very old, small antimicrobial proteins (consisting of 38–42 amino acids) [49]. They contain six cysteine residues linked with three disulfide bridges. In the early 1990s, studies on the human β defensin discovered that these peptides have the nonspecific ability to destroy Gram-negative bacteria, Gram-positive bacteria and yeasts of *Candida albicans* and *Candida*

tropicalis. Their activity is greater against aerobic than anaerobic bacteria [50]. A study by Laube et al. [51] has shown that epithelial cells taken from the pockets of people with a healthy periodontium stimulated by *Aggregatibacter actinomycetemcomitans* produce large amounts (4–30 times more than without stimulation) of interleukin- β and defensin-8. *Lipopolysaccharides* alone did not stimulate epithelial cells to increased production of defensins. Pocket epithelial cells taken from individuals with localized aggressive periodontitis did not produce a larger amount of defensin β or IL-8. It has also been proved that the JP2 of *Aggregatibacter actinomycetemcomitans* clone may increase the activity of 15 of 84 genes regulating the immune response of epithelial cells in a gingival pocket after 24 hours of infection. The effect of this phenomenon is the increased production of granulocyte-macrophage colony stimulating factor (CSF2/GM-CSF) and tumor necrosis factor (TNF- α) and also increased concentration of adhesion molecules ICAM-1 [52].

Genetic Factors

The frequent occurrence in families is one of the most important diagnostic criteria of localized aggressive periodontitis [3]. Efforts in the past 20 years have not given a definite answer on the impact of specific combinations of genes on the formation of LAgP. The specific model of inheritance of localized aggressive periodontitis is also still unknown [53]. Research on genetic factors in LAgP is concentrated around the study of single nucleotide polymorphism encoding proteins regulating certain types of host immune responses to inflammatory factors, including genes encoding proteins of IL-1, IL-6, IL-10, TNF, E-selectin, Fc-gamma receptors, CD14 and innate immune receptors (TLR – toll-like receptors). Among the factors examined in different ethnic groups, at the present state of knowledge, only the polymorphism of genes encoding proteins Fc-gamma receptors can only be proved, wherein it is present in patients with all forms of periodontitis both in patients with chronic and with aggressive periodontitis [54–56]. A meta-analysis of 17 studies involving 1,650 people with aggressive forms of periodontitis and 1570 patients with chronic periodontitis showed that the gene polymorphism of Fc-gamma RIII F158V is not crucial in the development of aggressive periodontitis and the polymorphism of genes for Fc gamma RIIIb in NA1/NA2 is equally associated with chronic and aggressive periodontitis in Asians and Caucasians [57]. Aggressive forms of periodontitis are most likely due to a number of genes whose expression is dependent

on environmental factors (polygenic inheritance). Carvalho and colleagues [58] have segregated 74 families with a total of 475 members. LAgP only occurred in 13 families, generalized aggressive periodontitis-GAgP – in 42 only, and early GAgP and LAgP in the other 19. The data obtained in the first two groups supports the hypothesis that LAgP and GAgP and can be caused by different genetic factors. However, for families that include various forms of aggressive periodontitis, it is not so clear.

Conclusions

Unambiguous identification of factors and mechanisms in the *etiopathogenesis* of localized aggressive periodontitis is difficult due to the low incidence of this disease. Most of the research carried out in the last 35 years confirms the important role of *Aggregatibacter actinomycetemcomitans* in the formation of localized aggressive periodontitis. But it is not indifferent with which serotype and clone of *A. a* periodontium is infected. Currently, a particularly virulent clone of *A. actinomycetemcomitans* is JP2, which includes mainly serotype b. An important factor is the racial sensitivity, which is associated with periodontal tissue's highly leukotoxic JP2 clone in people of African race. The high prevalence of LAgP in families suggests the existence of genetic factors. However, the studies of individual gene polymorphism relating to the regulation of the immune system do not give a definite answer on the relation between the polymorphisms of genes encoding these proteins and aggressive localized periodontitis. The elevated levels of proinflammatory cytokines or the distorted ratio between them occurs both in chronic and aggressive periodontitis. It has been proven that elevated levels of pro-inflammatory cytokines or impaired balance between them is in both chronic and aggressive periodontitis, and the increased production of cytokines is not associated with the form of periodontitis but with the progression of the disease. LAgP is not special in this respect. It is certain that in LAgP there is impaired chemotaxis and phagocytosis. However, it remains the subject of debate whether the dysfunction of neutrophils and macrophages is primary (genetically determined) or secondary as an effect caused by certain bacteria present in deep periodontal pockets. The results of available studies show that periodontal treatment can eliminate these defects.

The elimination of inflammatory agents, particularly *A. a* which has the ability to penetrate the tissues, is effective through combination therapy. The use of general antibiotics

and *mechanotherapy* returns the normal function of neutrophils in some patients. *Photodisinfection* in periodontal pockets may prove to be an effective means of reducing the microorganism in question in periodontal tissues [59]. In some patients, even with the highly leukotoxic *Aggregatibacter actinomycetemcomitans* JP2 clone, the development of periodontitis does not occur. A large role in the formation of localized aggressive periodontitis is attributed to the reduced pro-

duction of antimicrobial proteins, defensins, produced by the epithelial cells of the gingival pocket. It is worth noting that, due to the rarity of this disease, most research is based on laboratory models, which each include only part of the pathogenesis of the disease. The results are very valuable, however do not fully explain the mechanisms of initiation of the disease, its progression and the specific location of the lesions.

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