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THE REGULARITIES OF IMMUNOLOGICAL DISORDERS IN PATIENTS WITH THE RAPIDLY PROGRESSING GENERALIZED PARODONTITIS WITH THE DRUG-SENSITIVE AND DRUG-RESISTANT PERIODONTOPATHOGENIC BACTERIA

ABSTRACT

Generalized periodontitis is one of the most common d ental diseases and is one of the main causes of tooth loss in young and mature people. Recently, the etiology and pathogenesis of this disease, which is prone to a persistent and aggressive course with unstable results of complex treatment, have become a priority in the study of the problem of rapidly progressive generalized periodontitis. The results of the study are based on a comprehensive clinical and immunological examination of 59 patients with a diagnosis of rapidly progressive generalized periodontitis of I-II and II-III severity, aged 30 to 52 years (the average age was 35.4 ± 1.4 years on average), among they were observed 31 (53%) women and 28 (47%) men who did not have other general somatic diseases that could affect the immunological status during

the examination.
It was found that in patients with rapidly progressive generalized periodontitis, between violations of the local production of basic immunoglobulins (SIgA, IgA, IgG and IgM), cytokines (IL-1β, TNF-α, IL-4) and bacteria inhabiting periodontal tissues with different drug sensitivity to antibacterial drugs, there is a close relationship. It has been proved that in patients with rapidly progressive generalized periodontitis against the background of colonization of periodontal tissues with resistant strains of periodontopathogenic bacteria to protocol antibacterial therapy, the level of production of pro-inflammatory mediators of the immune response increases more significantly, simultaneously with a decrease in the synthesis of the oral mucosa SIgA, IgM, INF-γ-α, INF-γ and phagocytic activity of blood neutrophils than when detecting drug-sensitive bacteria.
Key words: *rapidly progressive generalized periodontitis, bacterial resistance, system of mononuclear phagocytes, immunity.*

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ЗАКОНОМЕРНОСТИ ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ У БОЛЬНЫХ БЫСТРОПРОГРЕССИРУЮЩИМ ГЕНЕРАЛИЗОВАННЫМ ПАРОДОНТИТОМ С ЛЕКАРСТВЕННО-ЧУВСТВИТЕЛЬНЫМИ И ЛЕКАРСТВЕННО-РЕЗИСТЕНТНЫМИ ПАРОДОНТОПАТОГЕННЫМИ БАКТЕРИЯМИ

Генерализованный пародонтит относится к числу наиболее распространенных стоматологических заболеваний и является одной из главных причин потери зубов у лиц молодого и зрелого возраста . В последнее время приоритетным направлением в изучении проблемы быстропрогрессирующего генерализованного пародонтита стали вопросы этиологии и патогенеза этого заболевания, склонного к упорному и агрессивному течению с нестойкими результатами комплексного лечения. Результаты исследования базируются на комплексном клинико-иммунологическом обследовании 59 больных с диагнозом быстропрогрессирующий генерализованный пародонтит I-II и II-III степени тяжести, в возрасте от 30 до 52 лет (средний возраст составил в среднем 35,4±1,4 лет), среди них наблюдались 31 (53%) женщина и 28 (47%) мужчин, которые не имели других общесоматических заболеваний, которые могли бы влиять на иммунологический статус в процессе обследования.
Установлено, что у больных быстропрогрессирующим генерализованным пародонтитом, между нарушениями локальной продукции основных иммуноглобулинов (SIgA, IgA, IgG и IgM), цитокинов (ИЛ-1β, ФНО-α, ИЛ-4) и заселяющими пародонтальные ткани бактериями с различной лекарственной чувствительностью к антибактериальным препаратам, существует тесная взаимосвязь. Доказано, что у больных быстропрогрессирующим генерализованным пародонтитом на фоне заселения пародонтальных тканей резистентными штаммами пародонтопатогенных бактерий к протокольной антибактериальной терапии, более значительно возрастает уровень продукции провоспалительных медиаторов иммунного ответа, одновременно со снижением синтеза слизистой полости рта SIgA, IgM, ИНФ-α, ИНФ-γ и фагоцитарной активности нейтрофилов крови, чем при выявлении лекарственно-чувствительных бактерий.
Ключевые слова: *быстропрогрессирующий генерализованный пародонтит, бактериальная резистентность, система мононуклеарных фагоцитов, иммунитет.*

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ЗАКОНОМІРНОСТІ ІМУНОЛОГІЧНИХ ПОРУШЕНЬ У ХВОРИХ ШВИДКОПРОГРЕСУЮЧИМ ГЕНЕРАЛІЗОВАНИМ ПАРОДОНТИТОМ З ЛІКАРСЬКО-ЧУТЛИВИМИ І ЛІКАРСЬКО-РЕЗИСТЕНТНИМИ ПАРОДОНТОПАТОГЕННИМИ БАКТЕРІЯМИ

Генералізований пародонтит відноситься до числа найбільш поширених стоматологічних захворювань і є однією з головних причин втрати зубів у осіб молодого і зрілого віку . Останнім часом пріоритетним напрямком у вивченні проблеми бистропрогрессирующего генералізованого пародонтиту стали питання етіології і патогенезу цього захворювання, схильного до наполегливого і агресивного перебігу з нестійкими результатами комплексного лікування. Результати дослідження базуються на комплексному клініко-імунологічному обстеженні 59 хворих з діагнозом Швидкопрогресуючий генералізований пародонтит I-II і II-III ступеня тяжкості, у віці від 30 до 52 років (середній вік склав в середньому 35,4±1,4 років), серед них спостерігалися 31 (53%) жінка і 28 (47%) чоловіків, які не мали інших загальносоматичних захворювань, які могли б впливати на імунологічний статус в процесі обстеження.
Встановлено, що у хворих бистропрогрессирующим генералізованим пародонтитом, між порушеннями локальної продукції основних імуноглобулінів (SIgA, IgA, IgG і IgM), цитокінів (ІЛ-1β, ФНП-α, ІЛ-4) і заселяють пародонтальні тканини бактеріями з різною лікарською чутливістю до антибактеріальних препаратів, існує тісний взаємозв'язок. Доведено, що у хворих швидкопрогресуючим генералізованим пародонтитом на тлі заселення пародонтальних тканин резистентними штамами пародонтопатогенних бактерій до протокольної антибактеріальної терапії, більш значно зростає рівень продукції прозапальних медіаторів імунної відповіді, одночасно зі зниженням синтезу слизової порожнини рота SIgA, IgM, ІНФ-α, ІНФ-γ і фагоцитарної активності нейтрофілів крові, ніж при виявленні лікарсько-чутливих бактерій.
Ключові слова: *швидко прогресуючий генералізований пародонтит, бактеріальна резистентність, система мононуклеарних фагоцитів, імунітет.*

The generalized parodontitis relates to the number of the most widespread dental diseases and is one of the main reasons of tooth loss in persons of young and adult age [1].

Recently, the questions of etiology and pathogenesis of this disease, which is inclined to a persistent and aggressive course with unstable results of the combined treatment, became as the priority area in the study of a problem of the rapidly progressing generalized parodontitis [2-5].

According to the modern concepts, the leading role in the aetiopathogenesis of the rapidly progressing inflammatory-destructive process in the alveolar tissues is assigned to the infectious factors and immunological disorders [6-9]. In this respect, interesting are those researches, which are dedicated to the integrated study of the immunologic reactivity and response to antigens of the causative agents.

According to present knowledge, the persistence of the periodontopathogenic causative agents comes against the background of immunodeficiency of the humoral and cellular immunity. In turn, the virulent microorganisms can also lead to a breakdown of the immunological response to the side of more profound disorders [10-12, 4].

Herewith, it is necessary to count, that under the action of the treatment medicines, especially of the antibiotics, which are most widely and empirically used in the practical dentistry, there is often an adaptation of the periodontopathogenic microflora of the alveolar tissues and the appearance of strains, which are stable to the protocol antibacterial therapy [13-17]. It should be noted that the evaluation of their significance in the formation of disorders of the immune mechanisms of defense wasn't carried out. This circumstance served as a motive for the study of abnormalities of the immunologic condition of the cellular and humoral immunity, depending on the changed character of the main parodontal bacteria: by colonization of the alveolar tissues with the drug-sensitive or drug-resistant causative agents of the rapidly progressing generalized parodontitis. The absence of such data, from the one hand, doesn't allow the clarification of the immunopathogenesis of different bacteria by the drug-sensitivity, and from the other hand, it complicates the development of the adequate and necessary schemes of the rational immunoreabilitation in patients with the rapidly progressing generalized parodontitis.

All mentioned circumstances determine the timeliness of the topic of these researches.

Goal of research. The study of the main regularities of the immunological disorders in patients with the rapidly progressing generalized parodontitis by colonization of the alveolar tissues with the drug-sensitive or drug-resistant periodontopathogenic bacteria.

Materials and methods of research. The research included 59 patients with the diagnosis – the rapidly progressing generalized parodontitis of the I-II and II-III severity levels, at the age from 30 to 52 years (the average age was 35.4±1.4 years) and there were among them 31 (53 %) woman and 28 (47 %) men.

The patients with the rapidly progressing generalized parodontitis didn't have other general somatic diseases, which could affect the immunological status in the process of research.

The group of control, which is comparable by age (average age is 33.6±1.8) and sex, was created to standardize the immunological results, it consists of 24 apparently healthy blood donors, without the clinical signs of dental pathology. All patients, at admission to the clinic, after the close insight into the plan of the further clinical and laboratory studies and their goals, signed an informational consent and liabilities for the strict implementation of medical recommendations.

By formation of groups for the advanced clinical and laboratorial research, the data obtained during the microbiological examination of sensitivity of the dominant activators to the protocol generally accepted antibacterial therapy was taken into account.

The first group included 29 patients with the colonization of the alveolar tissues by strains of the drug-sensitive bacteria. The second group included 30 patients, who were characterized by the presence of drug-resistant periodontopathogenic microflora in the periodontal structures.

Upon admission to the clinic, all patients and persons of the control group had standard common clinical researches, which include clarification of complaints, medical history, visual and instrumental assessment of the oral health status and of the alveolar tissues. The number of extracted teeth, denture defects was determined.

Along with it, it was paid attention to the nature of pain, bleeding intensity, the severity and prevalence of hyperemia and edema and gingival tissues, and it was established the depth of periodontal pockets and the degree of tooth mobility.

For an objective assessment of the periodontal condition, the digital diagnostic system «Florida Probe» and paraclinical examination methods were used:

1. Standard Hygiene Index according to Green-Vermillion (1964);
2. The sulcus bleeding index of the gingival tissue according to Muhlemann in modification of Cowell (1975);
3. Papillary marginal alveolar index according to Parma (1960);
4. Dental plaque index according to Russel A. (1956).

It was made to all patients with rapidly progressive generalized periodontitis the roentgenologic orthopantomographic with the use of Planmeca Pro ONE device (Finland).

Special laboratory studies were carried out according to a unified plan, which provided the levels detection of the content in the oral liquid of immunoglobulins sIgA, IgA, IgG and IgM, cytokines IL-1β, FNO-α, IL-4, interferon α and γ, of the neutrophil phagocytic rate.

Determination of the concentration of imunoglobulins was carried out by ELISA technique with the use of monospecific conventional antiserum contra immunoglobulins sIgA, IgA, IgG и IgM with test systems «Biopharm» (Ukraine) according to the developer's method.

The quantitative detection of the content of cytokines in the oral fluid was carried out with the use of Pro-con reagents "Protein Contour" and «Polignost» (city of Saint Petersburg) with ELISA technique with the use of Horse radish Peroxidase, according to recommendations of the developers of test systems.

The phagocytic activity of blood macrophages was found after incubation at the temperature 37°C during 30 minutes with the use of the killed suspension Staphylococcus aureus. There were calculated the number of phagocytosed cells from 100 neutrophils (Neutrophil phagocytic rate – NPR %), the number of microbial bodies, absorbed on average by one cell (phagocytic index – PI, unit), the percent of the digested microorganisms (phagocytic activity – PA %) in the stained smears.

The statistical processing of the research findings was conducted with the use of computer programs Microsoft Excel 2015 and Statistica for Windows v.12.0. The statistical analyses of the obtained data was carried out by the variation statistics methods with calculation of the arithmetic average means (M), standard deviations (t), standard error of the mean (m). In the case of confirmation of the normal law of distribution by comparison of the quantitative indicators between the groups, we used the parametric techniques – t- Student criterion. The differences between the compared indicators were taken as significant when the significance level $p < 0.05$ was reached.

Results of researches and their discussions. During initial presentation, the patients of both groups presented complaints, which are typical enough for the rapidly progressing generalized parodontitis: about expressed tenderness of gingivals when eating the solid food, the difficulties in chewing, hematostaxic, redness and edema of the gingival tissues, periodical appearance of the plethorical pyorrhea from the periodontal pockets, and it was noted the teeth dislodgement and their motility. The generalized analysis of the data by the index evaluation confirmed the presence of the similar in prevalence activity and severity of the inflammatory-destructive process in the alveolar tissues.

It was detected in the radiological way the destruction of the bone alveolar tissue and the decrease of interdental septas from ⅓ to ⅔ of the dental roots length. The bone defects were formed, mainly, due to the system vertical and horizontal resorption. The destruction of bone tissues had the generalized character.

It was registered the disappearance of the closing cortical plate, the availability of active focuses of the bone osteoporosis.

The identity of clinical and radiological signs in patients of the I. and II. groups was confirmed by the received data through the research of the dental plaque index, which hadn't statistically significant intergroup differences (respectively in patients of the I. group – 5,64±0,4mm, and in patients of the II. group – 5,7±0,4 mm; $p<0,05$).

The obtained results of the immunology research allowed detecting the interrelation with different sensitivity of the main periodontopathogenic bacteria to the protocol antibacterial therapy.

It was noted a significant decrease of the products sIgA and IgM and a moderate increase in the synthesis of IgA and IgG by the study of concentration levels of the main classes of salivary immunoglobulins in patients with the rapidly progressing generalized parodontitis against a background of colonization of the alveolar tissues with the drug-resistant disease causative agents. The signs of suppression of products sIgA and IgM in patients, excreting drug-sensitive bacteria to protocol antibacterial medicines (chlorohexidine, lincomycin, metronidazole), were less significant (Table 1).

Moreover, it was found during statistical analyses conduction, that the more characteristic, by development of the drug resistance, is a deep decrease of the average cumulative percentage of phagocytizing neutrophils, phagocytic activity and phagocytosis completeness (respectively 32.8±1.7 %; 2.18±0.13 and 26.2±2.2 % against 44.7±1.2 %; 3.44±0.22 and 38.1±1.7 % in patients with microorganisms, which are sensitive to antibacterial medicines).

Moreover, a significant decrease in phagocytic activity occurs against the background of the expressed suppression of the metabolic activity of neutrophils, determined by NBT test (Table)

Summarizing the obtained data through the research of the content of the main classes of immunoglobulins and phagocytic activity of monocytes, we can conclude that the simultaneous reduction of products sIgA and IgM and of the phagocytic function leads to the more significant reduction of

blood bactericidal activity and of oral liquid in patients with the rapidly progressing parodontitis in the condition of colonization of the alveolar tissues with the drug-resistant precursors of disease than drug-sensitive. Most probably, it promotes not only the saving of pathogenic flora in the parodontium tissues, but also it makes a mutual influence on the functioning of the defense immune mechanisms.

Table 1

The indicators of the immunological status in patients with the rapidly progressing generalized parodontitis with the drug-sensitive and drug-resistant precursors of disease

Immune status indicators	Testing groups		
	Control group (n=24)	The first group (n=29)	The second group (n=30)
sIgA (g/l)	1,48±0,2	0,37±0,02*,**	0,64±0,03*
IgA (g/l)	0,61±0,03	0,69±0,02*,**	0,86±0,02*
IgG (g/l)	10,8±0,3	13,5±0,3*,**	12,2±0,4*
IgM (g/l)	0,51±0,02	0,22±0,01*,**	1,01±0,3*
NPR (%)	68,4±1,4	32,1±0,9*,**	46,0±1,1*
PA (abs.num.)	6,0±0,4	2,1±0,3*,**	3,29±0,3*
PI (%)	57,9±3,4	25,8±2,1*,**	39,4±1,8*
IL-1β(pg/ml)	70,9±3,4	478,7±4,12*,**	201±6,0*
FNO (pg/ml)	44,3±3,1	212,0±6,2*,**	108,4±4,2*
IL-4 (pg/ml)	82,8±6,4	25,5±6,1*,**	49,3±5,4*
INF-α (pg/ml)	13,4±0,9	8,0±0,8*,**	10,9±0,7*
INF- γ (pg/ml)	27,8±1,9	16,6±0,2*,**	23,2±2,6*

N o t e : * the difference is significant (p < 0,05) in comparison with the healthy group;
** the difference is significant (p < 0,05) in comparison with the second group of patients.

It was detected the increase of the content of these cytokines in all groups during the study of concentration of IL-1β and FNO-α in the oral liquid. When conducting a comparative analysis, it was noted that the local production of IL-1β and FNO-α in patients with the rapidly progressing parodontitis, who have in their alveolar tissues the drug-resistant strains of periodontopathogens to the common antibacterial therapy, increased, to a greater extent, in comparison with the group of carriers of drug-sensitive periodontal bacteria. At the same time, it was observed more significant exhaustion of synthesis of IL-4 in patients of the first group, than in patients of the second group (Table 1).

The obtained results of immunological examination, on the one hand, can be interpreted as protective, adaptive reactions to periodontal pathogenic bacteria with different drug sensitivity, and on the other hand – it should be recognized the aggravating role of the resistant precursor of disease to the protocol antibacterial agents of complex therapy of the generalized periodontitis on the state of immune response.

Conclusions. 1. There is a strong correlation in patients with the rapidly generalized periodontitis, between abnormalities of the local products of the main immunoglobulins (sIgA, IgA, IgG и IgM), cytokines (IL-1β, FNO-α, IL-4) and bacteria, which colonize alveolar tissues, with different drug-sensibility to the antibacterial medicines.

2. The level of products of pro-inflammatory mediators of the immune response increases more significantly in patients with rapidly progressive generalized periodontitis against the background of colonization of the alveolar tissues with resistant strains of the periodontal pathogenic bacteria to protocol antibacterial therapy, simultaneously with a decrease in the synthesis of the oral mucosa sIgA, IgM, INF-α, INF-γ and phagocytic activity of blood neutrophils than when detecting drug-sensitive bacteria.

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