

REVIEW ARTICLE

FEATURES OF DEVELOPMENT OF GENERALIZED PERIODONTITIS IN PERSONS WITH SECRETORY IMMUNOGLOBULIN A DEFICIENCY AND ITS TREATMENT (LITERATURE REVIEW)

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ABSTRACT

The aim: To present data on the possibility of occurrence and active progression of generalized periodontitis in persons with secretory immunoglobulin A deficiency and possible methods of its correction.

Materials and methods: Analytical elaboration of scientific and medical literature based on the immunological aspect of generalized periodontitis.

Conclusions: The deficiency of secretory immunoglobulin A may occur in cases of primary or secondary insufficiency of the immune system. Selective IgA deficiency is an example of primary insufficiency of the immune system. Secondary immunodeficiency disorders is a clinical and immunological syndrome that develops against the background of a previously normally functioning immune system, characterized by a steady decrease in quantitative or functional indicators of specific or(and) nonspecific factors of immunoresistance. Insufficient awareness of dentists about certain aspects of the etiology and pathogenesis of generalized periodontitis leads to deterioration of treatment results.

KEY WORDS: periodontitis, secretory immunoglobulin A, immunotropic drugs

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INTRODUCTION

According to various estimates, the prevalence of generalized periodontitis (GP) in different regions of the world reaches 88-100% in the adult population. According to statistics, periodontal disease ranks fourth among non-communicable diseases, giving way to cardiovascular disease, cancer and diabetes. The issues of atypical forms of periodontitis are relevant, as the inflammatory process leads to rapid and profound bone loss in people aged from 17 to 30 years, and by the age of 45, patients already lose up to 80% of their teeth. Destructive changes of the periodontium in chronic generalized periodontitis (CGP) are often irreversible, and, in combination with the weakened function of the dental apparatus and premature tooth loss, they reduce the quality of life of patients and impair their social adaptation [1, 2, 3].

THE AIM

The aim of the research is to consider the modern views of various authors on the peculiarities of the occurrence and course of generalized periodontitis in persons with the deficiency of secretory immunoglobulin A (sIgA) based on the study of scientific and medical literature.

MATERIALS AND METHODS

The study relies on the analytical processing of scientific and medical literature on chronic generalized periodontitis in persons with the deficiency of secretory immunoglobulin A.

REVIEW AND DISCUSSION

It is a well-known fact that one of the most important etiological causes of the disease is a microbial factor. The oral cavity is a unique bacterial ecosystem of the organism, which includes more than 400 species of microorganisms [4, 5, 6]. According to various authors, the number of bacteria in the oral fluid ranges from 40 million to 5.5 billion in 1 ml. The microbial concentration in plaques and gingival sulcus is almost by 100 times higher: it is about 200 million cells per 1 g. [5, 7]. The development of periodontitis is most often associated with the persistence of periodontopathogenic microflora in the periodontal tissues. The pathogenic significance of its representatives is different and, depending on the severity, there are two groups. The first group includes microflora that has a pronounced virulence, mechanisms of adhesion to periodontal tissues and a pronounced aggressive and destructive effect (Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and Tanerella forsythia). Microorganisms of the second group, Treponemad denticola and Prevotella intermedia, are less virulent, but they form microbial associations with members of the first group. Microbial endotoxins and exotoxins possess high proteolytic activity and easily penetrate the thin epithelium of the gingival attachment, and when the dynamic "microbes – local defense system" balance is disturbed, they cause a cascade of immunopathological reactions – inhibition of antibody production and phagocytic activity of macrophages and neutrophils, resulting in the development of inflammatory destruction in the periodontal tissues and formation of foci of a chronic infectious process [8, 9, 10].

The role of microflora in the initiation of periodontal disease is obvious, but the severity of the inflammatory reaction is largely determined by the ability of the macroorganism to resist the action of pathogens. According to the studies [11], in cases of IgA and IgG2 deficiency, stable microbial mutualism of periodontal pathogens is formed. As is known, life dictates its rules, and atypical reactions to antibacterial drugs are already registered in the typical pathogenic microorganisms, due to the widespread and uncontrolled use of antibiotics. Increased virulence and aggressiveness of microflora sets a new rhythm in finding effective and safe methods of control. According to recommendations of the American Academy of Periodontology, the correction of the body's immune response during the development of periodontal diseases, along with the control of etiologically significant bacteria, should form the basis for the modern concept of periodontitis treatment [2].

SIgA is the most important immunoglobulin of external secretions, it is a product of cooperation of the two types of cells - plasma and epithelial cells of the salivary glands. The oral fluid contains much more secretory IgA than other immunoglobulins: for example, in the saliva secreted by the parotid salivary glands, the ratio of IgA / IgG is by 400 times higher than in the serum. Functions of sIgA embrace: agglutination of bacteria, change of the metabolism of bacteria, delay of colonization by microorganisms, neutralization of viruses, bacterial toxins, enzymes, decreasing virulence of pathogens and increasing opsonization of microorganisms. Receptors of slgA molecules are related to some pathogenic proteins and, thus, provide the formation of passive immunity to bacterial and viral infections [1, 2].

According to some scientists, the trigger for the development of GP, especially its aggressive forms, is the disruption of the immune response to a foreign agent of the microbial flora of the oral cavity. Particular attention is paid to patients with immune system deficiency and existing congenital defects of the immune system, including patients with impaired synthesis of immunoglobulins [1, 3].

Numerous studies have revealed a number of disorders in local immunity at the level of the gingival mucosa in patients with CGP in the form of reduced quantitative and functional indicators of phagocytosis, leukocyte chemotaxis, immunoglobulin production [2, 3, 12]. Furthermore, in the interaction of the pathogen with the human immune system during a chronic infectious process, microbiocenoses of different types and with different properties form, including the effect of suppression of the immune response, which also causes variability and survival of pathogenic microorganisms [13]. The immunosuppressive potential of bacteria is achieved through a number of effects, including the production of exotoxins that disrupt the cells of the macroorganism; synthesis of pathogenic enzymes (in particular proteinases that break down immunoglobulins and components of the complement system); blockade of phagocytosis due to the disruption of the phagolysosomal fusion mechanism; infection of phagocytic cells, which leads to the suppression of oxygen-dependent microbicidal mechanisms; expression of superantigens that disrupt the specificity of the immune response and induce excessive secretion of proinflammatory cytokines [14].

Primary immunodeficiency disorders (PIDD) are pathological conditions that are based on changes in immune mechanisms associated with genetic defects. The relevance of the issue of immune system insufficiency is currently highly significant as about 150 clinical forms of PIDD have already been described [1]. General IgA deficiency is associated with anomalies in monomer synthesis, which leads to a decrease in both serum and secretory IgA. In some cases, the defect can be manifested at the level of synthesis and the stage of joining the J-chain, and then only sIgA is absent. Isolated deficiency of secretory IgA at normal serum IgA levels is rare.

Selective IgA deficiency (SD IgA) (ICD-10 code D80.2) is one of the options for primary immunodeficiency. Although most cases of SD IgA are sporadic [15], there are familial cases of the disease. Inheritance in these cases occurs by autosomal recessive, autosomal dominant, multifactorial modes [15]. Studies conducted by V. Giambra and H. Suzuki convincingly prove that the genetic defect, which leads to the development of selective IgA deficiency, is determined at the level of the HLA system of human histocompatibility, causing the disruption of the terminal stage of differentiation of B-lymphocytes to IgA-secreting plasma cells or the maturation of these cells is blocked. Patients with congenital IgA deficiency often have A1, B8 and DR3 HLA haplotypes [13, 14]. In addition, it is observed that IgA deficiency is a possible component of some other primary immunodeficiencies, including general variable immunodeficiency (GVID), IgG subclasses deficiency, ataxia without telangiectasia and Bruton's agammaglobulinemia [14, 15, 16].

The inability to differentiate B cells into IgA-secreting plasma cells can also be caused by a deficiency of cytokines such as IL-4, IL-6, IL-7 and IL-10 [17].

L. Hummelshoj and co-authors claim that a possible variant of the disease development is TGF-β deficiency, which is a major factor in the induction of IgA synthesis [16]. Moreover, there is evidence that a genetic defect is caused by the mutation in members of the tumor necrosis factor receptor family, the transmembrane activator, calcium modulator inhibitor and the cyclophilin ligand (TACI), whose function is to facilitate isotype switching in B cells. Such a mutation is also observed in some patients with GVID, which may explain why some cases of SD IgA may progress to general variable immunodeficiency [3, 16].

In infants, sIgA appears 3 months after birth, and the optimal concentration is reached by 2-4 years [1]. Serum IgA levels reach a maximum up to 10-12 years. Average levels of sIgA in oral fluid are as follows: in adults - 115.3-299.7 mg / l; in children from birth to three years of age - 370-670 mg / l, in the elderly - 24.7 ± 14.4 mg / l. The half-life of sIgA is 5 days [18, 19].

Out of all primary immunodeficiency conditions, SD IgA is much more common in Caucasians than in Asian and Negroid representatives [17]. The prevalence of sIgA deficiency in Europe varies between 1:160 and 1:870 [20]. This diagnosis is made in the following cases: if IgA is not detected after 10 months of age; in children above the age of 1 year with serum IgA concentration <0.5 g / l in the absence of signs of other immunodeficiency conditions (e.g., ataxia-telangiectasia); in children above the age of four years, in whom other causes of hypogammaglobulinemia are excluded. SD IgA is defined as a serum IgA level below 7 mg / l with normal serum IgG and

IgM levels. Partial IgA deficiency is defined as having serum IgA levels greater than two standard deviations below the mean for one's age but above 7 mg / l [20]. This disease is often associated with IgG2 deficiency, whereas the incidence of infectious bacterial diseases increases. SD IgA is equally common in men and women [17].

It is impossible to cure selective IgA deficiency. The asymptomatic course of the disease does not require therapy. Treatment is pathogenetic and symptomatic, aimed at eliminating infectious, allergic and autoimmune syndrome. Replacement immunotherapy is required for patients with infectious syndrome and is conducted using immunoglobulin IgA-free medications, as there is a high risk of an allergic anaphylactic reaction, and is performed only after the laboratory confirmation of the absence of anti-IgA antibodies [13, 17, 20, 21].

Secondary IgA deficiency (SIDD) is a clinical and immunological syndrome that develops against the background of a previously normally functioning immune system and is characterized by a steady decrease in quantitative or functional indicators of antibody production, which is a risk for chronic infectious diseases, autoimmune pathology and tumors [3]. In addition to somatic and infectious diseases, common for people, the human body is negatively affected by socio-economic, environmental factors, medical measures (surgery, stress, etc.), which primarily affects the immune system [1, 14, 22]. A number of medications, such as D-penicillamine, sulfasalazine, captopril, carbamazepine, valproic acid, phenytoin, gold compounds, hydroxychloroquine, ACE inhibitors, NSAIDs, and thyroxine can lead to a reverse decrease in IgA concentration; treatment with cyclosporine A causes permanent IgA deficiency. In addition, some diseases induce a decrease in IgA (cytomegalovirus infection, toxoplasmosis, rubella, bacterial infections: staphylococcal, pneumococcal, meningococcal, fungal, tuberculosis, etc.) [15].

In order to form the resistance of periodontal tissues to alternating effects, the following immunotropic drugs are successfully used: Tactivin, Thymogen, Thymalin, Vilon, Imunofan, Polyoxidonium, Imudon, Galavit, Derinat, Myelopid, Licopid, Hepon, phytoconcentrates and others.

Thymomimetics have taken a prominent place in dentistry and possess numerous positive properties. They include Tactivin, Thymogen, Thymalin, Vilon. Tactivin normalizes the functions of T cells, stimulates the synthesis of lymphokines, interferons, restores the activity of T-killers, as well as the functioning of stem hemocytoblasts, normalizes other indicators of immunity. Its prescription in moderate and severe forms of CGP allows us to achieve long-term clinical remission exceeding 12 months [22].

Thymogen stimulates the proliferation and differentiation of T-lymphocytes, affects the processes of replication, transcription and repair of DNA, inducing the expression of genes of protective systems of cells and mitochondria. It has an antimutagenic action, reducing the level of chromosomal aberrations in lymphocytes under the influence of radiation and toxicochemical factors. The medication normalizes the number of CD3, CD4 and CD8 lymphocytes. It has a regulatory effect on the production of IgA, IgG, IgM and IgE. According to the studies [23], it is more effective in young patients (up to 37 years of age).

Thymalin regulates the number and ratio of T- and B-lymphocytes and their subpopulations, it enhances phagocytosis, stimulates cellular immune responses, regeneration and hematopoiesis in the case of their suppression, and improves the course of cellular metabolism [22]. It has been proven to be effective over the age of 37.

B-Activin (Myelopid) is used to activate the humoral part of the immune system, it also restores cellular immunity, enhances the synthesis of antibacterial antibodies against the background of the inflammatory process and is therefore effective in the exacerbation period [21], whereas in the periods of remission its use is not effective.

Vilon, the synthesized peptide bioregulator of the thymus, is used in dentistry to enhance regeneration of the mucous membrane of the gingival margin and the epithelial dentogingival attachment, as well as to correct the function of the immune system [22]. It is shown that the use of Vilon contributes to the normalization of the depth of periodontal pockets and the condition of periodontal tissues in elderly and senile patients with CGP [24].

Periodontitis involves the accumulation of exo- and endotoxins of pathological microflora, as well as its negative impact on the periodontal tissues and the entire body. Therefore, in recent years much effort has been made to develop new immunomodulators with detoxifying effect. One of these efforts resulted in the application of Polyoxidonium. A distinctive feature of Polyoxidonium is its effect on the immune system depending on its initial state, i.e., an increase of the initially reduced or a decrease in the initially elevated levels. It also has membrane-protective, detoxifying and antioxidant properties, as confirmed by experimental and clinical studies. When using the drug, one can correct the moderate degree of immunodeficiency after the traditional treatment of periodontitis. In severe immunodeficiency, the effectiveness of Polyoxidonium is insignificant, which should be taken into account in the comprehensive treatment of GP [25].

The study by L.V. Lukina [26] proposed to use of the immunological drug Hepon, which has immunomodulatory properties due to the changes in cellular synthesis of cytokines, immunoglobulins, and increases the functional activity of phagocytes and epithelial cells by increasing the ability of tissues to regenerate.

The immunocorrective drug Imudon is frequently used to increase the level of local immunity [21]. This drug is an immunomodulator of microbial origin by its chemical composition, derived from the microbes that are usually present in chronic viral and bacterial infections of the oral cavity. The drug is a so-called mucosal vaccine for topical use, which enables the anti-infective and anti-inflammatory immunotherapy of oral diseases. Its anti-inflammatory action is associated with increased phagocytic activity and lysozyme activity, normalization of proinflammatory cytokine synthesis, while its anti-relapse activity is associated with an increase in the number and activity of immunocompetent cells, antibodies and sIgA production.

Licopid activates the first phase of the immune response (phagocytosis, synthesis of IL-1, TNF, etc.), and thereby

stimulates T cells and the synthesis of antibodies to common bacteria (staphylococci, pneumococci, etc.). According to clinical data, Licopid reduced the frequency of exacerbations by 2-3 times, and it accelerated recovery in combination with antibacterial drugs. It has the properties of a polypotent vaccine, as it activates the immune response to main glycopeptides of the bacterial wall, and on the other hand, it acts as an immunomodulator, and normalizes the reduced capacity of the immune system [27].

Imunofan has an immunoregulatory, detoxifying and hepatoprotective effect; it causes inactivation of free radical and peroxide compounds. The effect of the drug develops within 2-3 hours and lasts up to 4 months. In 2-3 days, it enhances phagocytosis. The immunocorrective effect of the drug is manifested in 7-10 days, it enhances the proliferation of T-lymphocytes, increases the production of IL-2, synthesis of immunoglobulins, increases the production of sIgA, even in cases of congenital deficiency. Its use gives positive results in the treatment of moderate and severe CGP [12].

Antibody response and phagocytosis are the main targets of Galavit. This drug at a dose of 200 mg increases the titer of low-affinity immunoglobulins (IgG). It is prescribed primarily in the acute period of the disease in combination with antibacterial drugs. Galavit at a dose of 100 mg enhances the synthesis of class G immunoglobulins with increasing their affinity for pathogen epitopes [21].

Derinat is a drug based on a high-molecular physiologically active natural compound - an extract from the sturgeon or salmon milk, namely the sodium salt of highly purified depolymerized native deoxyribonucleic acid. The immunomodulatory effect of the drug is due to its ability to stimulate B-lymphocytes, activate T-helpers and cells of the monocyte-macrophage system. The drug accelerates energy metabolism inside cells, RNA and DNA synthesis. It has high reparative and regenerative capabilities. Derinat has potent anti-inflammatory effects, antitumor, antiallergic and detoxifying effects, as well as antioxidant and membrane stabilizing properties. It positively affects the anabolic processes and stimulates hematopoiesis [21]. Derinat is used in secondary immunodeficiency conditions.

Due to the microbial antagonism, associated with the presence of normal bacterial flora of the human oral cavity, the growth of a number of pathogenic bacteria and fungi is inhibited. Therefore, the question of the possibility of using probiotics as immunotropic drugs can be considered proven. Immunoregulation is carried out through the interaction of probiotic bacteria and their metabolites with the lymphoid tissue of mucous membranes [10, 21, 28]. The ability to adjust microbiological and immune parameters with the introduction of probiotic bacteria can qualitatively supplement the comprehensive therapeutic treatment of inflammatory diseases of the periodontal tissues. There is also an anti-inflammatory effect of bifidumbacteria, associated with the induction of interleukin-10 synthesis, lactobacilli transfer the dendritic cells of the oral mucosa to a mature state, reducing the production of proinflammatory cytokines and increasing the population of regulatory T cells. The study by E.V. Fomenko proved that when using Acylact, Bifidumbacterin and Lactobacterin, the sensitivity to antibiotics is restored in mild periodontitis in 90%, in moderate periodontitis in 75%, and in severe periodontitis in 50% of cases. The use of Lactobacterin, the active principle of which are strains of Lactobacillus casei, in contrast to antiseptics, can significantly improve not only the composition of the oral microflora, but also the local immunity, increasing the lysozyme activity and normalizing sIgA levels [29].

CONCLUSIONS

The analysis of literature sources and our researches demonstrated that in cases of aggressive and rapid developing forms of generalized periodontitis there is a decrease in the main factor of humoral protection of mucous membranes – secretory immunoglobulin A. This can be one of the causes of the disease and can be a serious consequence of chronic inflammation in the periodontal tissues. If patients with generalized periodontitis have a deficiency of secretory immunoglobulin A (young age of patients, the course of the disease is more progressive with severe destruction, characterized by frequent recurrences and unstable remissions), it is necessary to conduct the analysis to determine its level in oral fluid. If a decrease in the concentration of sIgA in the oral fluid is confirmed, it would be necessary to include an immunomodulatory drug in the scheme of comprehensive treatment. This will increase the level of humoral immunity of the oral cavity and will promote a faster onset and a longer period of remission.

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