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The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(11): 101-104

www.thepharmajournal.com
Received: 25-09-2019
Accepted: 27-10-2019

Timokhina Tetiana
OO Bogomolets National Medical University (NMU), Kyiv, Ukraine

Corresponding Author:
Timokhina Tetiana
OO Bogomolets National Medical University (NMU), Kyiv, Ukraine

Features of local oral immunity in patients with generalized periodontitis and bronchial asthma

Timokhina Tetiana

Abstract
The object of the work is to determine the indicators of local immunity in patients with generalized periodontitis (GP) with concomitant BA. To achieve this goal were examined 86 patients with GP aged from 42 to 60 years old. First (1) group (main group) were consisted of 44 people with GP second (II) stage who had a concomitant disease - persistent BA of mild or moderate severity and received as the basic therapy inhaled glucocorticosteroids (ICS), and second (2) group (comparison group) - 42 people with GP on second (II) stage without signs of BA. All patients underwent an immunological examination to determine the level of pro- and anti-inflammatory cytokines by the enzyme immunoassay according to the method of the manufacturer «Pro Con» (Russia) in blood and saliva, the level of circulating immune complexes (CICs) of various molecular weights in serum and saliva, the concentration of IgG, IgA, IgM, IgE immunoglobulins in blood serum and secretory sIgA in saliva, as well as the phagocytic activity of peripheral blood neutrophils and phagocytes in saliva. In patients with GP with concomitant BA were detected a pro-inflammatory changes in the humoral link of the immune system and a decrease in the phagocytic activity of peripheral blood neutrophils.In patients with GP with concomitant BA, changes in the indices of local immunity of the oral fluid are deeper and more specific and are manifested by a pronounced imbalance in the level of T-helper 1 and T-helper 2 derived cytokines, with a predominant content of pro-inflammatory against a significant deficiency of IFN-γ and reduced concentration of SIgA.

Keywords: Generalized periodontitis, bronchial asthma, local immunity, circulating immune complexes, cytokines, oral fluid

Introduction
Bronchial asthma (BA) is one of the most important medical and social problems. The disease affects all age groups of the population and, with ineffective control, leads to a significant violation of the quality of life, and in some cases to the death of patients. The prevalence of BA is increasing from year to year in most countries of the world, leading to significant losses, not only in terms of the cost of treatment and medical services, but also to loss of productivity and reduced participation in public life. BA is one of the widespread diseases that have a tendency to increase, acquire a progressive and malignant course: the number of people who are receiving corticosteroid therapy treatment (mainly hospitalized for asthmatic status) is increasing, and mortality rate from this disease has increased [4, 6].

The specific gravity of BA is 0.6% to 2% of all respiratory tract pathology. According to the literature data science, bronchial asthma affects between 1% and 10% of the population in different countries of the world, and it is generally believed that at least 2% of the entire population suffers from bronchial asthma. In Ukraine, in 2017, the prevalence of asthma was 515.9 patients per 100,000 adults (in 2010 - 506.6, in 2009 - 501.9). Official statistics shows very low indicators, which do not reflect the real picture. In the analysis of figures in the dynamics, we can speak of a tendency to some increase in the incidence [4, 6].

The purpose of BA treatment is: achieving and maintaining disease control; maintaining a normal level of daily activity, including physical activity, maintaining breathing function as close to normal as possible; prevention exacerbations of BA; avoid side effects of anti-asthma medications; prevention of mortality from BA. For this purpose, inhaled glucocorticosteroids (ICS) are used, which have a basic anti-inflammatory effect. The main pharmacological properties of ICS is a pronounced local anti-inflammatory, anti-exudative, anti-allergic and anti-proliferative effect; stabilization of cell membranes by blocking all molecular mechanisms of inflammation based on the regulation of the cell genome, the synthesis of new anti-inflammatory proteins that directly inhibit phospholipase A2, that responsible for the production of leukotrienes, prostaglandins, platelet aggregation factor, decrease in the number

of mast cells, release of inflammatory mediators, and suppression of migration eosinophils into the mucous membrane of the bronchi, blocking the production of T-lymphocytes and transcription factors of cytokines secreted by the epithelial cells; a decrease in mucus secretion, as well as a restoration of the sensitivity of β2-adrenergic receptors of the bronchi to β2-agonists and a decrease in bronchial hyperreactivity [4, 6].

However, the incorrect technique of inhalation or non-washing away of residues of the substance from the oral cavity after inhalation of the drug leads to secondary lesions of the mucous membrane of the oropharynx with the development of candidiasis in the oral cavity or to increased manifestations of generalized periodontitis (GP).

Year by year periodontal disease is becoming more widespread among the population of Ukraine and is not only a general medical, but also a social problem, accompanied by significant tooth loss in the working-age population [1, 2].

Source of infection in the oral cavity has an adverse effect on the body. As a result of the formation and changes in the biofilm, mainly due to an increase in the number of facultative anaerobic microorganisms in the periodontium, vascular changes occur associated with exudation and migration of phagocytes (neutrophils, monocytes, and macrophages) into the connective epithelium and gingival sulcus, which leads to primary inflammation of the gum tissue [8]. Therefore, the participation of the immune system and factors of local immunity, primarily in the development and progression of generalized periodontitis (GP) is not in doubt [10].

The object of the work is to determine the indicators of local immunity in patients with GP with concomitant BA.

Material and Research Methods:

To achieve this goal were examined 86 patients with GP aged from 42 to 60 years old (average age was 52.7 ± 4.6 years). First (1) group (main group) were consisted of 44 people with GP second (II) stage who had a concomitant disease - persistent BA of mild or moderate severity and received as the basic therapy ICS, and second (2) group (comparison group) - 42 people with GP on second (II) stage without signs of BA. Groups of patients were randomized by age and gender; all patients gave voluntary informed consent to participate in the study. The control group consisted of 35 healthy individuals randomized by age and gender, without signs of GP. The diagnosis and severity of GP was established in accordance with the classification of M.F. Danilevsky 1994 [3]. Dental status was determined by conventional dental methods with mandatory questioning and examination of patients. In the course of the survey, an index assessment of the condition of periodontal tissues was carried out: hygiene index - (HI) according to Fedorov-Volodkina, papillary-marginal-alveolar index - (PMA) in the modification of Parma (1960), sulcus bleeding index – SBI according to H.R. Muhlemann and S. Son (1971) [3]. The diagnosis of BA was established in accordance with the unified clinical protocol of primary, secondary (specialized) medical care for patients with bronchial asthma (Order of the Ministry of Health of Ukraine dated October 8, 2013 No. 868) [6]. Patients of first (1) group as a basic therapy for BA received ICS (salmeterol 50 μg / fluticasone 250 μg), 1 breath 2 times a day. All patients underwent an immunological examination to determine the level of pro- and anti-inflammatory cytokines by the enzyme immunoassay according to the method of the manufacturer «Pro Con» (Russia) in blood and saliva, the level of circulating immune complexes (CICs) of various molecular weights in serum and saliva [7], the concentration of IgG, IgA, IgM, IgE immunoglobulins in blood serum and secretory sIgA in saliva [9], as well as the phagocytic activity of peripheral blood neutrophils and phagocytes in saliva. [5]. Statistical data processing was carried out by methods of variation statistics using the Microsoft XP «Excel» application package, as well as using the special program «STATGRAPHICS Plus version 2.1».

Results and Discussion

Evaluation of dental status indicators did not reveal significant differences between the values of the hygiene index and the PMA index between groups of patients. At the same time, the bleeding index in patients of first (1) group were significantly higher, which may be associated with the pharmacological effects of ICS.

Table 1: Evaluation of index indicators of dental status in patients with GP (m ± m)

Indicator	Patients of first (I) group (n=44)	Patients of second (II) group (n=42)	The probability of a difference in the index
HI index, %	2,62±0,11	2,71±0,12	p>0,05
PMA index, %	63,6±1,4	65,7±1,6	p>0,05
SBI index,%	2,9±0,08	2,5±0,09	p<0,05

Also were conducted an assessment of indicators of systemic immunity in patients with GP with concomitant BA. These indicators are presented in Table 2.

Table 2: Indicators of systemic immunity in patients with GP with concomitant BA (m ± m)

Indicator	Patients of first (I) group (n=44)	Patients of second (II) group (n=42)	Control group (n=35)
Ig E, IU/ml	145,9±12,7	62,4±3,75*	65,9±8,3
Ig G, g/L	14.8±0,62	13,75 ± 0,78	13,85±1,42
Ig A, g/L	1,26±0,07	1,29 ± 0,08	1,52±0,19
Ig M, g/L	1,01±0,02	0,96 ± 0,03	0,96±0,08
CICs large (>19S), c.u	35,24±2,13	33,08 ± 2,21	52,5±4,02
CICs medium (11-19S), c.u.	45,11±1,96	42,26 ± 2,16	30,98±3,52
CICs small (<11 S), c.u	55,16±1,31	32,22 ± 1,82 *	15,23±1,07
TNF-α, pg/mL	81,4±2,1	62,6 ±1,3*	45,13±3,2
IL-1β, pg/mL	80,6±2,5	61,2±1,9 *	40,93±3,5
IL-4, pg/mL	57,1±2,4	19,2±1,8 *	20,51±1,9
IFN-γ, pg/mL	41,9±2,1	76,1±1,2*	79,36±2,7
Phagocytic number	4,75±0,22	4,91±0,19	6,50 ± 0,60
Phagocytic index, %	53,71±2,36	55,21±2,68	69,80 ± 7,20
HCT-test,%	36,63±1,42	34,20±2,5	21,69±2,4

Note * - significance of differences between groups (p <0.05) n- number of patients

Analysis of systemic immunity in patients with GP with concomitant BA showed that the concentration in the blood serum Ig A, Ig G, Ig M did not have significant differences between the groups of patients, at the same time, in patients of the main group, was found a reliable higher serum concentration of Ig E, which indicator exceeded the level in the comparison group by 2.34 times (p <0.05), that is associated with the development of eosinophilic inflammation as the main pathogenetic mechanism for the development of BA.

It should be noted that in both groups of patients there were an imbalance in the level of CICs in the blood serum, which was manifested by an increase in the content of pathogenic medium and small molecular weight with a significant decrease in physiological CICs of large size. However, in the main group of patients, a significantly higher content of small molecular weight CICs was found to be 71.21% (p <0.05) relative to the comparison group. This is primarily due to the fact that with concomitant BA a large number of immune complexes are formed both as a result of stimulation of the immune system by microbial flora and various allergens.

More highly sensitive to the manifestation of various mechanisms of inflammation were serum concentrations of cytokines. In the main group of patients, was found a significantly higher serum level of pro-inflammatory cytokines. Thus, the concentration in the blood serum of TNF-α was higher by 30.03% (p <0.05), IL-1β - by 31.69% (p <0.05), and IL-4 - by 2.97 times (p <0.05). At the same time, in the blood serum of patients with GP with concomitant BA were observed a significant decrease in the concentration of IFN-γ by 44.94% (p <0.05) compared with patients of second (II) group.

A study of the phagocytic activity of peripheral blood neutrophils in both groups of patients revealed a decrease in phagocytic numbers and phagocytic index with an increased HCT test, which indicates prolonged persistence and antigenic stimulation of various pathogenic bacterial microflora and is manifested by a significant increase in the metabolic activity of neutrophils [10].

Thus, in patients with GP with concomitant BA were revealed the following changes in the humoral link of the immune system, which were manifested by hyperproduction of serum immunoglobulin E, increased levels of pro-inflammatory cytokines TNF-α and IL1-β and T-helper 2 of the IL-4 derivative at a low concentration of T -helper 1 of IFN-γ derivative and pronounced signs of immunotoxicosis. At the same time, these changes were combined with a significant decrease in the phagocytic activity of peripheral blood neutrophils.

An analysis of literary sources showed the leading role of local immunity of the oral cavity and respiratory tract in the pathogenesis of both diseases: BA and GP. Factors of local nonspecific immunity include the absorbing activity of alveolar macrophages, bactericidal, bacteriostatic and virus-neutralizing activities of various substances, primarily cytokines, which are present in secret. Local specific immunity is provided by the B and T-system of lymphocytes.

It is known that with BA there are changes in all parts of the local immunity of the respiratory system. The material basis of nonspecific local immunity of the respiratory system are interferon, lysozyme, various inhibitors and cellular elements (epithelium and macrophages). Phagocytosis is an important mechanism for the resistance of the respiratory system to various bacterial infections, and alveolar macrophages play an important role in the removal of pathogenic microorganisms from the bronchial pathways.

As evidenced by numerous literature data science, suppression of alveolar macrophage activity is the main pathogenesis link of many infectious pathological processes developing in the respiratory system, due to which bronchospasm occurs, which are characteristic of an infectious-allergic form of BA. Under the influence of microbial antigens and immune complexes, macrophages secrete: acid hydrolases, neutral proteases (collagenases, plasminogen activator, lysozyme), pyrogen, prostaglandins, as well as factors that suppress the blast transformation of T-lymphocytes and stimulate the function of B-cells [4].

As is known from the literature data science [2, 8, 10], TNF-α is considered as the main mediator that determines the development and progression of inflammation in periodontal tissues. An increase in its content in the oral fluid or in periodontal tissues during inflammation of the latter is a marker of the duration and activity of the disease, and some studies indicate that the level of this cytokine in periodontal tissues increases even before the appearance of clinically significant manifestations of the disease and can serve as its indicator. In addition, it is TNF-α that plays a key role in the pathogenesis of inflammatory-induced bone loss in patients with GP.

Based on the above-mentioned, an assessment was made of indicators of the cytokine status, CICs, the concentration of immunoglobulins and the activity of phagocytes in the oral fluid of patients with GP with concomitant BA (Table 3).

Table 3: Indices of local immunity in the oral fluid of patients with GP with concomitant BA (m ± m)

Indicator	Patients of first (I) group (n=44)	Patients of second (II) group (n=42)	Control group (n=35)
Ig G, g/L	3,75 ± 0,22	2,96±0,42*	1,03±0,04
SIg A, g/L	0,16 ±0,01	0,31 ± 0,02 *	1,52±0,09
CICs large (>19S), c. u.	24,43±1,18	33,08 ± 1,15*	43,5±3,13
CICs medium (11-19S), c. u.	55,46±2,31	43,36± 1,84*	35,61±3,28
CICs small (<11 S), c. u.	41,42±2,06	25,29 ± 1,74*	14,97±1,21
TNF-α, pg/mL	88,6 ±3,7	63,9±3,1*	42,3±4,9
IL-1β, pg/mL	87,6±2,6	62,1±2,4 *	39,42±4,5
IL-4, pg/mL	37,2±1,6	16,5±0,9 *	25,42±3,3
IFN-γ, pg/mL	17,1±1,2	58,7±1,5*	65,1±3,7
Phagocytic number	5,08±0,22	4,97±0,17	9,53 ± 0,56
Phagocytic index, %	38,71±2,36	41,21±1,43	52,82 ± 2,21

Note* - significance of differences between groups (p <0.05)n- number of patients

An analysis of the data presented in Table 3 showed that in patients with GP with concomitant BA in the oral fluid were revealed a significant increase level of Ig G (by 19.95%), as well as a probable decrease in the concentration of SIg A by 48.39%. Changes in the concentration of CICs were manifested by a significant increase in the level of pathogenic small and medium molecular weight CICs with a probable decrease in the concentration of physiological large CICs relative to the comparison group. A significant imbalance of pro- and anti-inflammatory cytokines in the oral fluid was found in all patients with GP. It was found that in patients with GP were a significant increase in the level of pro-inflammatory TNF-α, IL-1β in the oral fluid. However, in the main group of patients in the oral fluid was also found significantly higher relative to the comparison group, the level of IL-4 with a significantly reduced concentration of IFN-γ. The increased concentration of IL-4 in the oral fluid, obviously, due to both the local influence of CICs, which have a local anti-inflammatory effect, and the predominance of T-helper 2 units of the immune response as a key link in BA pathogenesis. At the same time, of course, a negative side effect of ICS is a decrease in the level of IFN-γ in the oral fluid, which can contribute to more severe manifestations of the course of GP.

A study of the phagocytic activity of phagocytes in the oral fluid established significant inhibition of this function in both groups of patients.

Conclusions

1. In patients with generalized periodontitis with concomitant bronchial asthma were detected a pro-inflammatory changes in the humoral link of the immune system and a decrease in the phagocytic activity of peripheral blood neutrophils.
2. In patients with generalized periodontitis with concomitant bronchial asthma, changes in the indices of local immunity of the oral fluid are deeper and more specific and are manifested by a pronounced imbalance in the level of T-helper 1 and T-helper 2 derived cytokines, with a predominant content of pro-inflammatory against a significant deficiency of IFN-γ and reduced concentration of SIgA.

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