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Influence of fungal colonization of the respiratory tract of patients on the course of the mild and moderate bronchial asthma

micromycetes role in the course of bronchial asthma (BA) continues to be actively investigated and discussed in scientific literature, due to a lack of understanding of the participation of these microorganisms in the pathogenesis of asthma. Strong evidence is provided that micromycetes can be triggers of allergic diseases and asthma, when sensitivity to mold is observed in 80% of patients, the most often to *Alternaria, Aspergillus, Cladosporium, Helminthosporium, Epicoccum, Aureobasidium* and *Penicillium* [18]. However, in the majority of patients there is registered a polyvalent sensitization to fungal allergens, the cause of which is not fully elucidated [16].

It was also established that severe persistent asthma in adults is often associated with sensitization to *Aspergillus fumigatus*, which can manifest itself as a severe asthma fungal sensitization and allergic bronchopulmonary aspergillosis [11, 12]. Involvement of these *Aspergillus fungi* in the formation of allergic bronchopulmonary aspergillosis is confirmed by positive outcomes of the treatment using antifungal agents (improved lung function, clinical symptoms, decreasing the frequency of exacerbations) [9, 19].

There are reports that, in addition to these fungi, in the development of allergic diseases and asthma are involved also other micromycetes, including *Curvularia, Bipolaris, Drechslera, Exserohilum* and *Aspergillus* species, as well as fungal infections of the skin [14].The study of G. Carpagnano et al. (2016) on the bronchial condensate of exhaled air, in 70% of patients with asthma (47 patients examined) there were microbiologically (using Dichloran Rose-Bengal Chloramphenicol Agar) identified various fungi (*Cladosporium, Penicillium*, etc.) (In control – 0% of patients in healthy persons) [8].

Thus, the evidence of involvement of fungi that colonize the surface of the human body, including respiratory tract mucosa, in the pathogenesis of asthma continues to be studied [13]. But the difficulty of such studies is related to their heterogeneity, problems of standardization of applied methods, drugs and chemicals.

The **purpose** of this study was to establish how the clinical, anamnestic, functional, allergological and laboratory characteristics of patients with mild and moderate asthma are influenced by fungal colonization of the lower respiratory tract.

Materials and methods

at the Kiev hospital «Feofania» there was conducted a prospective open-label study of clinical, functional, laboratory and allergological survey of 106 patients with asthma in remission from 18 to 81 years, mean age (52,7 ± 1,2) years, 80 women (75,5%). The criteria for inclusion were: mild and moderate asthma in remission (diagnosis exhibited under the order № 868 (10/10/2013) of the MOH of Ukraine), the presence of written informed consent to participate in the study. Exclusion criteria: presence of other serious diseases (tuberculosis, AIDS, decompensated hepatic, renal failure, etc.) and pregnancy in patients.

There were 28 patients (26,4%) with mild persistent asthma and 78 persons (73,6%) with moderate one. Disease duration was (11,8 ± 1,5) years, the incidence of asthma exacerbations – (2,3 ± 0,3) times / year. Forced expiratory volume in 1 second was on average (76,2 ± 2,1)%, forced vital capacity of the lungs – (78,6 ± 2,0)%, peak expiratory flow rate – (74,3 ± 2,1)%. 71 patients (67,0%) were treated with inhaled glucocorticoid drugs. There were 54 patients (50,9%) with well controlled asthma, 33 persons (31,1%) with partial control and 19 persons (17,9%) with uncontrolled asthma.

In order to study the influence of Micromycetes on features of asthma, patients were divided into groups: «C +» group of patients with *Candida* yeast Micromycetes in sputum (34 patients); «C-» group of patients without *Candida* (72 patients); «P +» group of patients with mold Micromycetes in sputum (8 patients) and «P-» group of patients without mold Micromycetes (98 patients / 25 patients). Taking into account the patients disparity of the distinct groups P+ (n = 8) and P- (n = 98), in order

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to reduce the quantative inequality of the groups of patients, P- sample was reduced to 25 people (excess stratified sample) [2]. To reduce systematic errors and to equalize with the P+ group according to age and disease duration of patients, P- sample size was reduced by older patients with greater disease duration.

Patients filled in a questionnaire asthma control ACQ-5 (symptoms only, in 2005, Ukrainian version modified june 2007), the results of which determined the degree of asthma control.

Measurement of respiratory function were carried out with the apparatus «Pulmovind», Ukraine. Bronchodilatory test was performed 30 minutes after inhalation of 400 mcg of salbutamol.

Allergological study was conducted by setting skin tests (prick test) with fungal mixed allergens (mixture of household mold) of interior rooms (*Aspergillus fumigatus, Aspergillus niger, Penicillium sp., Mucor sp., Rhizopus sp.*) (Production Sevafarma, Czech Republic) and a mixture of allergens of mites, allergens from house dust, animal dander (cats, dogs, sheep) (produced by «Immunologist», Ukraine) with the test-controlled fluid and positive histamine controls. Evaluation of skin tests was performed in 15–20 minutes (immediate type reactions). The response was assessed by measuring 3 mm papules or more.

In order to evaluate cellular characteristics of sputum composition (spontaneous or induced), its microscopic examination was conducted by staining smears after Gram.

Microbiological studies were conducted for patients, whose sputum smears showed a small number of epithelial cells (less than 10) when viewing 8–10 visual fields with 100-fold magnification. To study the respiratory tract microflora, there were used methods of sputum seeding on nutrient media (Columbia agar, chocolate agar agar McConkie, yolk-salt agar, medium Saburo, wort-agar, et al.). To saprophytic bacteria were included: Gram-negative (Gram-) cocci *Neisseria spp.*, Gram-positive (Gram +) cocci: *Staphylococcus (St.) epidermidis*, *St. saprophiticus* and *Streptococcus (S.) sanguis*, *S. oralis, S. intermedius, S. viridans, S. haemoliticus, S. hominis, S. pyogenes* and others. [3, 4]. To opportunistic microflora were included: Gram-positive cocci *S. pneumoniae*, *St. aureus*; Gram-negative coccus bacterium *Haemophilus influenzae* and diplococci *Moraxella catarrhalis*, Gram-negative bacteria of the *E.coli* group – *Klebsiella spp.*, *Esherichia coli*, *Citrobakter spp., Proteus spp., Pseudomonas aeruginosa* and others, micromyceta – yeast *Candida spp.* and mold ones (*Aspergillus spp., Penicillus spp.*, etc.). In the statistical analysis there was taken into account the number of bacterial strains in the sputum, logarithm of concentration of bacteria (the number of microorganisms in 1 mL of sputum) in conventional units (conv. units).

The presence of antifungal Ig E-antibodies (to *Aspergillus fumigatus, Aspergillus niger, Penicillium sp., Mucor sp., Rhizopus sp.*) in the serum of patients was determined by chemiluminescence CLIA-IM on the basis of the analyzer Immulitte 2000 Siemens using test kits «Simens» (USA). Measurement of levels of total immunoglobulin in serum (Ig) E and interleukin 4 was performed by ELISA using kits «Simens», USA. The level of IgA, IgM, IgG in serum was determined using ELISA kits «Vector-Best», Russia.

Storage of research results and their mathematical processing was carried out using licensed software products included in the package of Microsoft Office Professional 2007 license Russian Academic OPEN No Level № 43437596. There were determined the average arithmetic indicator (M), standard deviation (σ), error of the arithmetic mean (m), number of studies (n), and in the proportions and percentages indicating the confidence interval (CI). Comparison of average group values and evaluation of the reliability of differences was made by parametric and nonparametric methods of variation and rank statistics using Student's t-test, U-criterion of Uilkoksona-Mann-Whitney. If the analyzed values were equal to or less than 5, Fisher»s accurate test was used. As the level of statistical significance there were adopted values of the likelihood difference between groups (p) equal or less than 0,05.

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Results and discussion

it was found that *Candida* in the airways of patients with mild to moderate asthma were determined in 34 patients (32,1%). Patients with asthma with the presence of *Candida* in sputum were older (Table. 1). Their sputum contained more white blood cells, which probably was due to the large number of its bacterial content (strain amount and concentration of bacteria) by saprophytic bacteria and opportunistic Gram + bacteria in the sputum (including – *Str. Viridians*).

Thus, the presence of *Candida* in the airways of 32,1% of patients with asthma was associated with moderate leukocytosis and increased colonization of airways by saprophytic and opportunistic Gram + bacteria (including – *Str. Viridians*).

Among surveyed 106 patients with mild to moderate asthma there were 8 patients (7,5%) with the colonization

Table 1

Distinctive features of patients with asthma in remission depending on the infection of lower respiratory tract of patients with Candida (M±m), (n = 106) (p <0,05 between groups of patients).

Index	Group of patients	
	C+ (n = 34)	C– (n = 72)
Age (years)	56,4 ± 1,1	50,9 ± 1,6
WBC sputum (the number in sight)	29,5 ± 1,7	22,6 ± 1,5
Number of strains of bacteria in the sputum (units)	1,7 ± 0,6	0,4 ± 0,1
Total logarithm of concentration of bacteria in the sputum (conv. units)	9,2 ± 1,3	2,0 ± 0,5
Total logarithm of concentration of saprophytic bacteria in the sputum (conv. units)	3,6 ± 1,1	0,8 ± 0,3
Total logarithm of concentration of opportunistic Gram + bacteria in the sputum (conv. units)	5,1 ± 1,0	1,2 ± 0,3
Logarithm of concentration of Str. viridans in sputum (conv. units)	3,8 ± 1,0	0,9 ± 0,2

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of the airways by Micromycetes mold. These patients were younger, with shorter disease duration (tab. 2). In stratified samples (excluding the factors of age and duration of asthma) patients of the group P + differed in great experience of smoking, among them there were more patients with other allergic diseases and tonsillectomy in history. It is possible that smoking against the background of atopy facilitated colonization of the airways by Micromycetes mold.

At the same time, patients from group P + had the best indicators of respiratory function (FVC) and a greater increase in FEV_1 under the bronchodilatory test, which correspond to some data about the presence of atopy (Table. 3). This fact was also confirmed by a severe skin sensitivity to histamine prick test. Characteristically, their skin sensitivity to allergens in mixed fungi-prick test was more severe and likely was linked to airway colonization by fungi. As for sensitivity to other allergens (mites, house dust, wool, cats, dogs, sheep), such differences between groups has not been established.

It is characteristic that the group P + patients had lower levels of hemoglobin (see. Table. 3). Their sputum contained more strains of microorganisms, mainly due to opportunistic Gram + bacteria (Str. Viridians) and Candida spp., whose concentration was higher.

Note that in the total sample P- (n = 98) all aforementioned differences between groups were kept, but indicators

Table 2

Distinctive features of the medical history of patients with asthma in remission depending on the infection of lower respiratory tract of patients by Micromycetes mold (M± m), (n = 33, stratified sampling).

Index	Group of patients			
	P+ (n = 8)		P– (n = 25)	
Age (years) (n = 106 total sample)	49,0 ± 1,2* (n = 8)		52,9 ± 1,3 (n = 98)	
Disease duration (years) (n = 106 total sample)	5,9 ± 1,2* (n = 8)		12,3 ± 0,9 (n = 98)	
Age (years) (n = 33, stratified sample)	49,0 ± 1,2		48,5 ± 1,5	
Disease duration (years) (n = 33, stratified sampling)	5,9 ± 1,2		5,7 ± 0,5	
Smoking (pack-years)	6,9 ± 1,9*		2,0 ± 1,2	
	% of patients (CI)	n	% of patients (CI)	n
% of patients with allergic diseases in history	100,0* (100,0–68,8)	8	68,0 (46,5–85,1)	17
% of patients with a history of tonsillectomy	100,0* (100,0–68,8)	8	52,0 (31,3–72,2)	13

Note. * – statistically confirmed difference of the corresponding figures in the two groups (p <0.05)

Table 3

Some distinctive features of patients with asthma in remission depending on the infection of lower respiratory tract of patients with Micromycetes mold (M ± m), (n = 33, stratified sampling)

Index	Group of patients	
	P+ (n = 8)	P– (n = 25)
FVC (forced vital capacity)% to proper size	91,6 ± 1,5*	80,7 ± 3,8
Bronchodilatory test: by modifying FEV_1 (forced expiratory volume in 1 second),% of increase	20,1 ± 1,3*	16,2 ± 0,6
Skin sensitivity to histamine prick test (size of papules, mm)	9,0 ± 0,6*	7,2 ± 0,4
Skin sensitivity to allergens in mixed mushroom-prick test (size of papules, mm)	7,6 ± 0,6*	5,6 ± 0,7
The level of hemoglobin in blood (g / L)	121,3 ± 3,9*	136,1 ± 2,3
Number of microorganisms (bacteria and fungi) in sputum (units)	3,5 ± 0,3*	1,0 ± 0,3
Logarithm of concentration *Str. viridans* in sputum (conv. units)	4,8 ± 0,8*	1,4 ± 0,5
Logarithm concentrations of Candida spp. in the sputum (conv. units)	4,1 ± 0,7*	1,1 ± 0,4

Note. * – statistically confirmed difference of the corresponding figures in the two groups (p <0,05).

of respiratory function (including FEV1 and peak expiratory flow rate) were significantly worse.

Thus, the colonization of airways of patients with mild to moderate asthma by mold Micromycetes was observed in 7,5% of cases, prevalent among younger patients with shorter disease duration, due to smoking and atopic status, consistent with the best indicator of respiratory function (FVC) with greater growth of FEV1 in the bronchodslatory test and with more severe skin sensitivity to allergen histamine and mushroom mixed in prick-test against the background of lower levels of hemoglobin in the blood. There was also an increase in airway colonization by microorganisms of such patients, mainly due to opportunistic Gram + bacteria (Str. Viridians) and Candida spp.

No reliable difference was found between the groups of patients with C+ and C -, P +and P- and by other studied indicators, including: content of antifungal IgE-antibodies (to Aspergillus fumigatus, Aspergillus niger, Penicillium sp., Mucor sp., Rhizopus sp.) in the blood serum, levels of serum total IgE, IgA, IgM, IgG and interleukin-4.

It is well known that the colonization of the respiratory tract by Candida is mainly due to the use of inhaled glucocorticoids [17]. It was established that the presence of Candida in one third of the patients with mild and severe asthma was not associated with worsening of clinical status, respiratory function, additional allergization of the human body (according to skin sensitivity to histamine, the level

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of total IgE, the level of asthma control and other features). The presence of Candida in the airways of these patients was accompanied by an increase in airway colonization by saprophytic bacteria and opportunistic Gram + bacteria. Taking into account that, according to our previous studies, it was a stimulus for the activation of proinflammatory immune response to activation of phagocytosis, CD3+-lymphocytes [1] and moderate sensitization of the organism to Candida (according to the level of anti-Candida IgE) [6] and was accompanied by a relatively favorable course of the disease, it can not be excluded that the presence of Candida, within certain limits, helps to maintain airway microbiota, formed in patients with mild to moderate asthma, and has not expressed negative impact on the course of asthma. The complex relationship between microbiota and the immune response in patients with asthma needs a comprehensive analysis that will give rise to the development of new therapeutic strategies in patients with asthma [10].

According to various studies, in various forms of asthma, including severe ones, mold in the airways may be determined in 10% [5] to 70% of patients [7, 8], with a prevalence of different types of Micromycetes depending on the terrain. In most studies, the presence of mold Micromycetes in the airways of patients with asthma is connected with more severe diseases [8, 11, 12, 15].

In this study there were established a connection of airway colonization by mold Micromycetes with more mild course of disease (in lung function parameters) and the presence of atopy, which may be due to the peculiarities of the investigated sample of patients without severe asthma and patients with light to moderate asthma had a relatively low disease duration. These patients also had the experience of smoking, which probably contributed to negative changes in local defense mechanisms and mucosal colonization by fungi and bacteria [1].

The presence of more severe skin sensitivity to allergens of mixed molds in these patients showed the formation of distinct fungal sensitization, which probably reflected the influence of mold in airways of patients on the course of mild and severe asthma, despite the absence of connection with the level of serum antifungal IgE-antibodies.

Conclusions

1. in patients with mild to moderate asthma (BA) Candida colonization of the respiratory tract was observed in 32% of cases, mold Micromycetes one – in 7,5% of cases.
2. The presence of Candida in the airways of patients with mild to moderate asthma is linked with increased airway colonization by saprophytic and opportunistic Gram + bacteria and, within certain limits, and has not expressive negative impact on the course of asthma.
3. Micromycetes mold colonization of the respiratory tract in patients with mild to moderate asthma was observed among younger patients with shorter disease duration, with better lung function parameters and the presence of atopy, with the experience of smoking.
4. Micromycetes mold colonization of the respiratory tract of patients with mild to moderate asthma contributes expressive fungal sensitization to mold (manifested as increased skin sensitivity to allergens mixed fungi) and is associated with increased airway colonization by other microorganisms (mainly, opportunistic Gram + bacteria and Candida spp.).

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