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INVESTIGATION OF THE FREQUENCY OF CONTAMINATION OF THE ORAL CAVITY WITH CANDIDA FUNGI AND THEIR SENSITIVITY TO ANTIFUNGAL DRUGS IN CHILDREN WITH BRONCHIAL ASTHMA WHO USE INHALED GLUCOCORTICOSTEROIDS FOR A LONG TIME

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Abstract

Bronchial asthma is a chronic inflammatory disease of the respiratory tract that causes the development of bronchial hyperreactivity, which leads to repeated episodes of wheezing, expiratory shortness of breath, chest congestion and coughing, increasing at night or early in the morning. The main groups of drugs for the basic therapy of bronchial asthma are inhaled glucocorticosteroids in the form of individual drugs or in combination with anticholinergic or B-2 agonists. Preparations of inhaled glucocorticosteroids have a number of side effects, one of which is oropharyngeal candidiasis, which often occurs according to a number of instructions (>1/100,<1/10). This is due to the fact that inhaled glucocorticosteroids create favorable conditions for the growth of yeast-like fungi of the genus Candida in the oral cavity and pharynx, due to the suppression of the protective functions of macrophages, neutrophils and T-lymphocytes on the surface of the oral mucosa, as well as due to the appearance of dryness of the oral cavity. In this connection, IGCS preparations have instructions for use. Namely, taking into account the risk of oropharyngeal candidiasis, the patient should thoroughly rinse his mouth with water after each inhalation of the drug. The purpose of the study is to study the awareness of patients about the prevention and risks of fungal infections of the oral cavity arising from the use of inhaled glucocorticosteroids.

Keywords: bronchial asthma, inhaled glucocorticosteroids, Candida, Pulmicort

1. Introduction

Bronchial asthma is a chronic inflammatory disease of the respiratory tract, in which many cells and cellular elements are involved. Chronic inflammation causes the development of bronchial hyperreactivity, which leads to repeated episodes of wheezing, shortness of breath, chest congestion and coughing, especially at night or early in the morning. These episodes are associated with widespread variable airway obstruction in the lungs, which is often reversible spontaneously or under the influence of treatment. According to WHO, bronchial asthma (BA) affects up to 235 million people worldwide and the annual death rate from asthma, according to world experts, is 250 thousand people. The main international document regulating asthma is GINA (Global Strategy for Managing and Preventing Asthma). According to GINA experts, the incidence of AD varies from 1-18% in various countries of the world. In Russia, the prevalence of asthma among adults is 3 – 5-7%, among children – 5-12%. Sexual prevalence – boys are more likely to get sick before the age of 14, and women predominate in adulthood. The frequency of AD is steadily increasing in all age groups. The incidence of AD is traditionally higher in developed countries, and mortality is higher in third World countries. The main causes of death are the lack of adequate anti–inflammatory therapy and failure to provide emergency care during an attack. In our country, mortality rates are low (less than 1:100,000), although in recent years there has been an increase in these indicators in large cities.

Bronchial asthma (BA) is a global medical problem. This is due to the high prevalence, risk of death, significant cost of treatment and pronounced negative impact on the quality of life of patients and their loved ones. Severe uncontrolled asthma is the most difficult and least predictable in its course. Today, sensitization is considered one of the leading pathogenetic mechanisms of the occurrence and severe course of asthma. Currently, the incidence of polyvalent

sensitization to bacterial, food and fungal allergens has increased in patients with asthma, which is clinically expressed by the uncontrolled course of the disease and a decrease in the effectiveness of basic drug therapy.
BA is a hereditary burden, the presence of atopic diseases in the anamnesis, contact with aeroallergens, occupational allergization (latex for medical workers, flour, pollen, mold, etc.), tobacco smoke, obesity, low social status, diet. AD is a heterogeneous disease, the key factor of which is chronic inflammation, manifested in the cooperation of macrophages, dendritic cells, Tlymphocytes, eosinophils, neutrophils, and plasma cells. In 70% of cases, this is an allergic IgE–dependent process, in other cases - eosinophilic, non-IgE-associated inflammation or neutrophilic inflammation. After the initial ingestion of the antigen into the body, primary sensitization occurs, with the participation of Th2 helpers, activation of B lymphocytes, formation of memory cells and the formation of specific IgE antibodies. Specific IgE interact with a receptor on the surface of mast cells. Upon repeated ingestion of hypertension, histamine, IL5, IL9, IL13 are released, which leads to activation of effector cells in the bronchial wall: mucus hyperproduction, bronchoconstriction, fibroblast activation and wall remodeling at the end of the process.
Inhaled corticosteroids (ICS) are currently most often used as drugs that control the course of persistent bronchial asthma (BA), since they have high anti-inflammatory activity combined with low systemic bioavailability. Among the local side effects, oropharyngeal candidiasis is noted, associated with the deposition of the drug in the oropharynx, the frequency of which varies widely from 1% to 77% in the treatment of ICS, probably due to the method used to detect the pathogen. However, yeast-like fungi are commensals and can often be found in the throat of healthy people. Some exogenous and endogenous factors contribute to the expanded colonization of the pharyngeal mucosa, such as diabetes mellitus, oncological diseases, immunosuppression, including those associated with taking GCS, taking antibacterial drugs. At the same time, in a few studies concerning the study of the fungal landscape of the pharynx in patients with asthma using X, it has been shown that daily long—term (more than 1 year) intake of X in high dosages contributes to an increase in oropharyngeal colonization of Candida, and the reduction of local side effects and a decrease in the risk of candidiasis is the use of X with spacers, rinsing mouth and throat with water [1,4,8]. Nevertheless, studies on the pharyngeal mycobiota in patients with bronchial asthma who have been using X for a long time are few, the properties of fungal strains obtained from patients undergoing X treatment have not been sufficiently studied, it is relevant to develop diagnostic methods that allow differentiating candidiasis with the transition to the active stage of infection.
Despite the high incidence rates, most patients who suffer from bronchial asthma respond well to basic therapy and have disease control. The achievement of disease control is achieved thanks to inhaled glucocorticosteroids (IGCS), which have good efficacy and a lower frequency of side effects than systemic GCS. But like other medications, IGCS have a number of side effects, one of which is oropharyngeal candidiasis. This is due to the fact that IGCS create favorable conditions for the growth of yeast-like fungi of the genus Candida in the oral cavity and pharynx due to the suppression of the protective functions of macrophages, neutrophils and T-lymphocytes on the surface of the oral mucosa, as well as due to the appearance of dry mouth. In this regard, IGCS preparations have indications for use. Namely, taking into account the risk of developing oropharyngeal candidiasis, the patient should thoroughly rinse his mouth with water after each inhalation of the drug. In the case of candidiasis, the use of appropriate antifungal agents may be required, and in some patients, the abolition of inhaled corticosteroids.

It should be noted that currently there are more than 500 species of fungi that can sensitize humans without leading to the development of mycosis. These can be both saprophytic fungi and parasitic fungi. Mushrooms are an essential component of human-inhaled air: they are found both in household dust and in street dust. Contact with fungi can cause three conditions: carrier, invasion, and/or allergic disease. Mycogenic asthma can develop as atopic or infection-dependent, when the exacerbation is associated with periodic ingestion of antigen into the body, including in connection with endogenous sensitization caused by local pulmonary or extrapulmonary infection. Fungal colonization of the mucous membrane of the respiratory tract, and even more so fungal infection, leads to an increase in manifestations of obstructive syndrome and the progression of asthma. Mycogenic asthma is characterized by a severe course and often the need for the use of systemic and inhaled corticosteroids. On the other hand, prolonged use of glucocorticosteroids may contribute to the development of mycotic infection, which can further enhance the clinical manifestations of mycogenic allergy. Treatment of a fungal infection has a positive effect on the course of asthma. The most significant fungi for AD are:

• Penicillium (one of the first fungi for which the etiological role in AD has been proven);
• Alternaria (severe and fatal asthma is associated with hypersensitivity to it);
• Aspergillus (bronchopulmonary aspergillosis may occur in parallel with AD);
Fusarium (according to some researchers, it is the most common cause of sensitization), as well as Cladosporium, Candida, Mucor, Rhizopus and others.

2. Objectives

Investigation of the frequency of contamination of the oral cavity with Candida fungi and determination of sensitivity to antifungal drugs in children with bronchial asthma who use inhaled glucocorticosteroids for a long time. Also, to investigate the awareness of patients about the prevention and risks of fungal infections of the oral cavity that occur against the background of the use of IGCS.

3. **Methods**

During the study period, which was conducted from June 2023 to September 2023, a questionnaire was conducted in the form of testing in children and their parents diagnosed with bronchial asthma and long-term use of drugs from the IGCS group as basic therapy. A throat swab was also taken to detect Candida fungi and determine sensitivity to antifungal drugs. 43 subjects aged 5 to 18 years were selected as the study group, with an average age of 13.3±2.1 years. Among those analyzed, the female subjects were 24 people, and the male ones were 19 children. As well as the survey, 30 mothers whose children suffer from bronchial asthma passed. The children were diagnosed with persistent bronchial asthma of mild (21 subjects) or moderate severity (11 children) with well-controlled or partially controlled bronchial asthma. The duration of the disease was more than 1 year. All patients used inhaled glucocorticosteroids in small and medium doses for at least a year. The main drugs used are pulmicort and budesonide. All children passed a questionnaire in the form of a test for knowledge of oral hygiene when using IGCS.
As part of the study, the subjects were divided into the following age groups: the first group — children aged 10-12 years (14 people), the second group - children aged 13-15 years (20 people), the third group - children aged 16-18 years (9 people), the fourth group – parents whose children are diagnosed with bronchial asthma (30 people).
The subjects in the main group had a confirmatory diagnosis of bronchial asthma of varying severity. All patients used inhaled glucocorticosteroids at doses of 500-1000 mcg per day for more than a year. The main drug used was Budesonide. The control group included 48 children who did not use IGCS.
The statistical analysis of the obtained data was carried out using the MS Office Excel program, with the calculation of extensive indicators. The value of $P<0.05$ was taken as the level of statistical significance of the differences.

4. **Results**

In the main study group, Candida fungi were detected in 25 patients, which amounted to 38.5±6%. In the control group, Candida fungi were detected in 9 patients (18.8±5.6% of cases). The sensitivity of Candida fungi isolated from the oral cavity to nystatin and clotrimazole was 100%, to fluconazole 96±3.9%. (1 out of 25 subjects showed resistance of the Candida strain to flucanazole). Sensitivity of fungi of the genus Candida, 18 isolated in the control group was 100% to clotrimazole, nystatin and flucanazole. Fungi of the genus Candida have sensitive strains to all studied antifungal drugs. Patients who use IGCS for a long time have a higher risk of infection with Candida fungi than children from the control group ($p = 0.0056674$).
Subjects from the age group of 10-13 years (14 people) to the question "Will you caress your mouth and wash your face after each inhalation?"4 answered "always", 4 "almost always", 3 "sometimes", 3 answered "no". Age group 13-15 years old (20 people) to the question "Is it necessary to rinse your mouth and wash your face after inhalation with pulmicort (budesonide)?" 16 answered "yes", 4 answered "no". Age group 16-18 years old (9 people) to the question "Did you know that a flat mouth reduces the risk of developing fungal infections of the oral cavity? 1 answered "no", 8 answered "yes". Group of parents (30 people) to the question "Is it necessary to rinse your mouth and wash your face after inhalation with pulmicort (budesonide)?" 24 answered "yes", 6 answered "no".

4. **Discussion**

Almost a third of children are not aware of fungal infections of the oral cavity, which can occur against the background of the use of inhaled GCS. They are not aware of the need to thoroughly rinse their mouth with water after each inhalation of the drug, which is the basis for preventing and reducing the risk of developing a fungal lesion. Only 18.3% in the first group (10-12 years old), 14.8% in the second group (13-15 years old), 13.4% in the third group (16-18).
Based on the data obtained, it should be noted that it is necessary to organize and implement health schools more actively, since they are an important part of disease prevention. Conducting an examination of the oral cavity and conducting a planned microbiological examination, as well as taking a swab from the throat during hospitalization for bronchial asthma, will reduce the risk of developing candidiasis, make a correct diagnosis in a timely manner and conduct an adequate etiotropic.

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