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CLINICAL AND SPIROGRAPHIC FEATURES OF BRONCHIAL ASTHMA IN SCHOOLCHILDREN DEPENDING ON THE DIFFERENT REGIMENS OF BASIC ANTI-INFLAMMATORY THERAPY

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ABSTRACT
The aim: To study the clinical and spirographic features persistence of the bronchial asthma in schoolchildren against the background of the alternative daily doses of inhaled corticosteroids to increase the effectiveness of anti-inflammatory therapy for this disease.
Materials and methods: A complete comprehensive clinical-paraclinical examination of 65 schoolchildren with persistent asthma was conducted. According to the average daily dose of inhaled corticosteroids (ICS) the patients were divided into two clinical groups. The first (I) group consisted of 46 children who received ICS in the regimen of low-to-medium equipotent doses (253.95±9.98 µg per day), and the second (II) comparison group was formed of 19 patients who controlled the pBA using high doses of ICS (494.74±5.56 µg per day).
Results: The patients of the I clinical group compared to patients of the II group have a higher risk of the mild bronchial obstructive syndrome during asthma attacks. In assessing the level of control of persistent bronchial asthma using the CIA-scale, it was found that in II group cases of the controlled course of the disease were observed almost two times less than in children of the I group of comparison. In conducting spirography in children of comparison groups, it was shown that the ratio of indices of bronchospasm (FEV_1/FVC) was worse in patients receiving high doses of ICS.
Conclusions: So, characteristic clinical feature of asthma controlled by high doses of ICS is more severe nature of bronchial obstructive syndrome during the period of exacerbation (OR=1.9-3.0). In the management of persistent bronchial asthma, the Gensler index which has high specificity (94.4%) and accuracy (92.2%) should be used for disease control verification.

KEY WORDS: bronchial asthma, schoolchildren, basic anti-inflammatory therapy, comprehensive clinical-paraclinical examination

INTRODUCTION

Current clinical studies prove that bronchial asthma (BA) can be well-controlled in most of the pediatric patients, but practice demonstrates that the uncontrolled course of the disease occurs every so often, and prolonged maintenance of complete control over the disease remains an unattainable goal for most of children [1]. Inhaled corticosteroids (ICS) have a leading role in the treatment of asthma both at the stage of achieving and maintaining control over the clinical symptoms of the disease. In case of an insufficient control over the clinical asthma symptoms when using low-to-medium doses of ICS [2], optimization of the therapeutic tactics can be carried out in several ways: either an addition of a leukotriene modifier or a long-acting beta-agonist, or increasing the dose of inhaled corticosteroids [3].

To date there are multiple scientific disputes with no consensus on whether the low and medium doses of ICS are capable of causing side effects similar to those of systemic corticosteroids (SCS), in particular, retardation of bone growth, changes in carbohydrate metabolism, adrenal gland supression.

In his review B. Lipworth [4] shows the dose dependence of ICS side effects. However, a comparison of the side effects of different drugs should be made cautiously, as different methods of evaluation were used in various studies. Therefore, when asthma stabilization is achieved, it is always advisable to taper glucocorticosteroids to the minimum effective dose in order to reduce the likelihood of systemic effects and optimize the benefit/risk ratio.

High doses of ICS are recommended for the treatment of patients with resistant asthma, which is poorly controlled by the medium doses of ICS even in combination with other drugs for the standart asthma therapy. However, the use of high-dose ICS is associated with the development of systemic side effects, and a number of researchers believe this thesis is not an issue for discussion anymore [5].

Therefore, as the use of ICS remains the recommended method of asthma managemen for all the patients, these drugs should always be used in the minimum effective dose in accordance with the severity of the persistent asthma, since an insufficient control and frequent exacerbations of asthma are accompanied by an increased load on the child organism of SCS, which have multiple side effects.

THE AIM

To study the clinical and spirographic peculiarities of the bronchial asthma persistence in schoolchildren against the background of the alternative daily doses of inhaled corticosteroids to increase the effectiveness of anti-inflammatory therapy for this disease.

MATERIALS AND METHODS

A cohort of 65 school-age children with persistent bronchial asthma (pBA) was created by random method at the pulmonology and allergology Department of the Municipal Medical Establishment "Chernivtsi Regional Children's Clinical Hospital". Based on the informed consent obtained from parents, patients have been subjected to a comprehensive clinical-paraclinical examination.

The average age of the patients was 11.43 ± 0.39 years, there were 81.54% of boys, and respectively – 18.46% of girls (P<0.001). The average age at which the pBA debuted was 2.09 ± 0.09 years, so most of children had an early onset of disease.

Classification and management of pBA used according to the protocol of diagnosis and treatment of the disease in children [6]. One third of children (32.31%) had severe persistent asthma, 61.54% had moderate persistent asthma, and only 6.15% of patients had mild pBA. Two thirds of patients (60.0%) had an atopic form of pBA, and the rest of the children had a mixed form of asthma.

The equipotent doses of inhaled corticosteroids (ICS) received by patients as a component of the basic asthma treatment were determined according to current international guidelines and recommendations [7], distinguishing the low-dose, medium-dose and high-dose regimen of these drugs. Thus, the fewest number of children (9.23%) received low doses of ICS, the largest number (61.54%) – medium doses of drugs, and the rest of patients (29.23%) received high doses of ICS.

According to the average daily dose of ICS received by the examined children as a part of the basic treatment, patients were divided into two clinical groups for comparison. The first (I) group consisted of 46 children who received ICS in the regimen of low-to-medium equipotent doses (253.95 ± 9.98 μg/day on average), and the second (II) comparison group was formed of 19 patients who controlled the pBA using high doses of ICS (494.74 ± 5.56 μg/day). Thus, beclomethasone in the metered dose inhaler was given to 28.3% of patients from the I group and 57.9% of children from the II group (Pφ<0.05), budesonide – to 15.2% and 15.8% of patients respectively (Pφ>0.05), fluticasone – to 56.5% and 26.2% of children from the I and II group respectively (Pφ<0.05).

Groups were comparable by the main clinical characteristics. Thus, the fraction of boys was 80.4% in the I group and 84.2% in the II group, fraction of girls – 19.6% and 15.8% respectively (Pφ>0.05 in all cases). The fraction of the urban residents among the patients of the I group was 52.2%, the villagers – 47.8%. The distribution in the II group of comparison was 63.2% (Pφ>0.05) and

36.8% (Pφ>0.05) respectively. There were no significant differences in the severity of the asthma persistence: mild persistence was observed in 6.5% of cases in the I group and in 5.3% of patients from the II group, moderate persistence was diagnosed in 63.0% and 57.9% respectively, and severe – in 30.4% and 36.8% of observations in the I and II group respectively (Pφ>0.05 in all cases). The atopic form of pBA was registered in 60.9% of the I group patients and in 57.9% of cases in the II group (Pφ>0.05), and mixed form – in 39.1% and 42.1% of cases respectively (Pφ>0.05).

The severity of the bronchial obstruction syndrome (BOS) was assessed upon arrival at the hospital during the exacerbation period of asthma using a score scale [8]. An increase in score reflected the intensification of BOS manifestations, and the difference between the initial and an actual score reflected a degree of bronchial disobstruction. The evaluation of asthma control was carried out using a clinical and instrumental assessment scale (CIA) [9], according to which 10 and below points correspond to controlled asthma, 11-16 points – to partially controlled disease, and above 17 points – to uncontrolled variant of BA.

The statistical analysis of the obtained results was performed using the Statistica 6.0 software (StatSoft, USA). Student's t-criterion (Pt) was used to measure the differences between means, and Fisher's angular transformation criterion (Pφ) was used for comparision of percentage data. Differences were considered significant with Pt/Pφ<0.05.

The evaluation of the diagnostic value of spirographic tests was conducted with the determination of sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) of the results, and posttest probability (PP) for the positive and negative results. In all cases, a 95% confidence interval was determined (95% CI). To conduct the population analysis the relative risk (RR), attributable risk (AR), and the odds ratio (OR) with the calculation of their confidence intervals (95% CI) were estimated.

RESULTS AND DISCUSSION

An analysis of the level of pBA control in children of the clinical groups did not identify the fundamental differences, and results of the estimation using the CIA-scale in general complied with the criteria of the partially controlled disease (Table 1).

Despite the absence of significant differences between the average total scores according to results of the clinical assessment of pBA control, the incidence of controlled asthma decreased 2-fold among the patients of the II group compared to children of the I group (Table 2).

Thus, in contrast to patients receiving high doses of ICS as a basic treatment of pBA, the risk of controlled pBA increased 2-fold in representatives of the I group: OR=2.1 (95% CI 0.52-8.44), RR=1.79 (95% CI 1.32-2.43), AR=0.13. Consequently, it is assumed the existence of a "difficult to treat asthma" phenotype among the patients of the II group [10].

This assumption was partly confirmed by the results of the clinical assessment of the severity of asthma exacer-

Table 1. Comparative assessment of the clinical signs of asthma control in children of the comparison groups during the period between exacerbations (M±m)

Indices of bronchial asthma control (points) I group (n=46)	Clinical groups		P value
	II group (n=19)		
Daytime symptoms of disease	2.57±0.14	2.37±0.23	>0.05
Nightime symptoms of disease	1.57±0.12	1.53±0.19	>0.05
β_2-agonists when needed	1.74±0.13	1.63±0.21	>0.05
Limitation of physical activity	2.46±0.12	2.37±0.18	>0.05
Frequency of hospitalizations	1.87±0.17	2.08±0.13	>0.05
Frequency of exacerbations	2.61±0.09	2.42±0.16	>0.05
Unplanned visit to an allergist	0.91±0.11	0.84±0.18	>0.05
Total score	13.72±0.62	12.95±1.06	>0.05

(Row label at left side: Clinical symptoms of disease)

Table 2. Frequency (%) of the levels of asthma control in children of the clinical comparison groups (P±m)

Clinical groups (number of patients)	Controlled pBA	Partially controlled pBA	Uncontrolled pBA
I group (n=46)	28.26±6.64	45.65±7.34	26.09±6.4
II group (n=19)	15.79±8.37	63.16±11.07	21.05±9.35
Pt value	>0.05	>0.05	>0.05
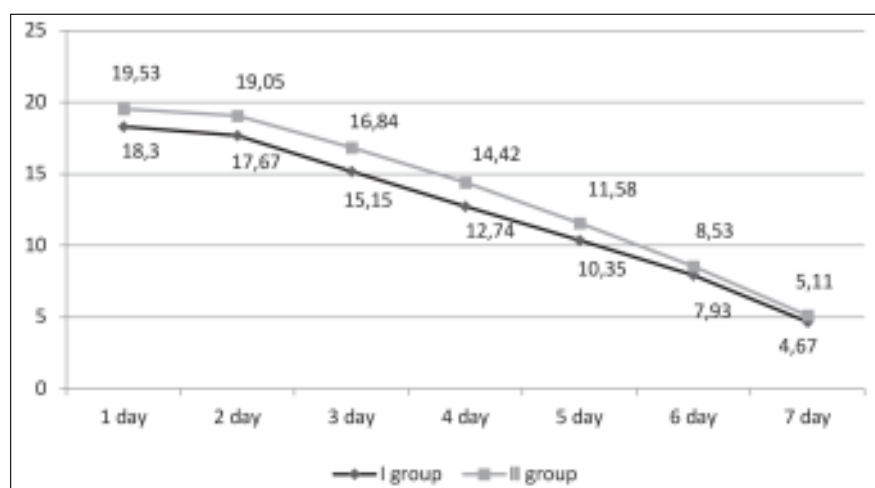
Fig. 1. Dynamics of the severity of bronchial obstruction syndrome in children of the comparison groups during hospital stay (points)

bations in children of the comparison groups, reflecting a steady tendency to more severe BOS in representatives of the II clinical group (Fig. 1).

The risks of more pronounced bronchial obstruction syndrome during the acute asthma exacerbation in patients of the II clinical group compared to patients who received low-to-medium doses of ICS as a basic anti-inflammatory therapy are presented in Table. 3

Thus, in children with pBA who received high doses of ICS as a basic therapy, the risk of the severe asthma exacerbation is increased, and, therefore, the adjuvant therapy should be provided to this patients maximally rapidly and to the fullest extent.

Accordingly, as shown in Table 4, patients of the I clinical group compared to patients of the II group have a higher risk of the mild bronchial obstructive syndrome during asthma attacks.

In our opinion, the identified patterns could be explained either by the peculiarities of the trigger factors which contributed to the asthma exacerbation or by the prevalence of the neutrophilic inflammatory process in the respiratory tract of patients from the II clinical group, which, as is known, increases asthma severity [11].

During the period between exacerbations against the background of discontinuation of drugs that may affect the results, a spirographic examination was performed. It included initial spirography, a test with dosed physical activity and inhalation of a short-acting β_2-agonist (salbutamol, 200 μg) with measurement of the forced expiratory volume in 1 s (FEV$_1$), forced vital capacity of lungs (FVC),

Table 3. Risks of persistent pronounced airway obstruction against the background of high doses of ICS compared to patients of the I group

Day of treatment (distribution point, score)	Attributable risk	Relative risk (95% CI)	Odds ratio (95% CI)
1st (> 18 points)	0.27	1.8 (1.4-2.3)	3.04 (1.7-5.5)
3rd (> 16 points)	0.17	1.4 (1.0-1.9)	1.9 (1.1-3.3)
4th (> 15 points)	0.19	1.4 (0.9-2.2)	2.1 (1.2-3.9)

Table 4. Risks of the mild bronchial obstructive syndrome against the background of low-to-medium doses of ICS compared to patients of the II group

Day of treatment (distribution point, score)	Attributable risk	Relative risk (95% CI)	Odds ratio (95% CI)
1st (< 19 points)	0.21	1.5 (1.1-2.1)	2.36 (1.3-4.2)
2nd (<19 points)	0.14	1.3 (1.0-1.7)	1.7 (1.0-3.0)
2nd (< 17 points)	0.18	1.4 (0.8-2.4)	2.1 (1.1-4.2)
3rd (< 14 points)	0.21	1.4 (0.7-2.9)	2.4 (1.1-5.2)

Table 5. Average indices of the spirographic examination in children of the comparison groups (M±m)

Spirographic index	I group (n=49)	II group (n=16)	Pt value
FEV1 (%)	84.69±2.59	81.82±6.33	>0.05
FVC (%)	90.82±2.49	97.46±4.58	>0.05
FEV1/FVC	0.93±0.03	0.82±0.02	=0.05
BSI FEV1 (%)	10.92±2.02	8.82±3.90	>0.05
BDI FEV1 (%)	14.84±2.52	14.98±4.83	>0.05
BLI FEV1 (%)	24.1±3.27	20.74±6.08	>0.05

FEV_1/FVC ratio, indices of bronchospasm (BSI) and bronchodilation (BDI), and bronchial lability index (BLI).

The comparative indices of the spirographic examination in children of the clinical comparison groups are presented in Table 5.

Despite the absence of the significant differences between the FEV_1 and FVC in the comparison groups, the FEV_1/FVC ratio was worse in patients receiving high doses of ICS. Based on the fact that the value of this ratio less than 70% indicates a marked impairment of bronchial passability [12], we have studied the peculiarities of its distribution within the clinical comparison groups. It was established that the value of the Gensler index (modified Tiffeneau index) below 70% occurred in the I group with a frequency of 5.6%, while in the II group it was observed in 27.3% of patients (Pφ<0.01). Therefore, in patients receiving high doses of ICS, there was an increased risk of impaired bronchial passability: OR=6.4 (95% CI 2.4-16.7), RR=1.9 (95% CI 0.8- 4.6), AR=0.40. Apparently, it could be explained by a more pronounced inflammatory process in bronchi with the probable development of their remodeling, which is not consistent with the assessment of asthma severity and disease control from the clinical point of view.

It should be noted that in children with uncontrolled asthma the Gensler index was below 70.0% in one-third of cases, while in patients with controlled and partially controlled pBA – only in 5.56% of observations. As a result, patients with unsatisfactory control of pBA (over 17 points according to CIA scale) had high chances of the impairment of bronchial passability even during the period of clinical well-being: OR=8.5 (95% CI 3.3-22.0), RR=2.07 (95% CI 1.0-4.9), AR=0.44.

Hence, obtaining the values of Gensler index which do not reach 70.0% can be used as an additional highly specific test for the verification of the unsatisfactory control of pBA: the sensitivity of this test is 33.3% (95% CI 24.16-43.46%), the specificity is 94.44% (95% CI 87.95-98.05%), the positive predictive value is 85.69% (95% CI 70.66-94.86%), the negative predictive value – 58.61% (95% CI 50.58-66.31%), test accuracy – 92.2% (95% CI 67.95-92.0%). With positive values, posttest probability (+) increases by 25.65%, and with a negative result – posttest probability (-) decreases by 8.61%.

CONCLUSIONS

1. A possible cause of the patients insensitivity to low and medium doses of ICS is the increased severity and neutrophilic nature of inflammation, resulting in the persistence of bronchial ventilation disturbances in the post-exacerbation period (OR=8.5).
2. Characteristic clinical feature of asthma controlled by high doses of ICS is the more severe nature of bronchial obstructive syndrome during the period of exacerbation (OR=1.9-3.0).
3. In the management of persistent bronchial asthma, the Gensler index which has high specificity (94.4%) and accuracy (92.2%) should be used for disease control verification.

4. When obtaining on the results of spirographic examination the values of the Gensler index below 70.0% the amount of the basic anti-inflammatory therapy should be reviewed using the "step up" principle.

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis,
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