International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 04, 2020
ISSN: 1475-7192

LEUKOTRIENE RECEPTORS STATE IN CHILDREN WITH BRONCHIAL ASTHMA

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Abstract---The aim of the work*is to study the level of leukotrienes C4D4E4 in children with bronchial asthma and evaluate the effectiveness of the therapy.* ***Materials and methods****. The present research work was performed at the Department of Allergology of the Tashkent Medical Academy Clinic. In total 92 children with bronchial asthma underwent examination during the disease exacerbation. The control group included 23 rather healthy children of the same age. The diagnosis of bronchial asthma is established in accordance with the International Consensus on Diagnosis and Therapy of BA.* ***Results and discussion.*** *According to the aim of our work, we researched the level of leukotrienes C4D4E4 in urine of 92 children with BA. Among them, there were 62 children with Step 1of BA (67.4%), and 30 children with Step 2 (32.6%). Comparative analysis of the initial data revealed a significant increase of LT release in 72 (78.3%) patients with cough form of BA. In 20 patients with Step 1 of BA, LT values were at the upper limit of the norm (1, 0 ± 0.01). 15 children with Step 2of BA showed an increase in the level of LT more than 5 times in comparison with the admissible norm (p < 0.05).****Conclusion.*** *The significant role of LT in the formation of allergic inflammation of the respiratory tractat BA in children has been confirmed. The prescription of cis-ALT (montelukast) is justified both as a monotherapy for mild persistent BA and in combination with IGCS in patients with moderate BA.*

Keywords---*Bronchial asthma, children, cysteinyl leukotrienes, clinic, anti-leukotriene medications.*

I. Introduction

From year to year a significant increase of allergic diseases, including bronchial asthma (BA) is observed among children[3, 7]. Bronchial asthma is the most common chronic allergic disease of respiratory tract, the debut of which comes more often in childhood age [1, 2]. Chronization of the pathological process at bronchial asthma leads to deterioration of the life quality of patients, decrease of their activity, disability and mortality [3,5]. The issues on the role of leukotrienes (LTs) in the pathogenesis of allergic diseases and the ability of their control to achieve a therapeutic effect through the prescribing of anti-leukotriene medications are discussed in the literature of recent years. It is known that the formation of mediators of allergic inflammation, including leukotrienes, occurs under the action of various stimuli: allergens, stress, non-specific factors, nonsteroidal anti-inflammatory medications (NSAIM), infections, etc. And it is

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DOI: 10.37200/IJPR/V24I4/PR201320
Received: 22 Sep 2019 | Revised: 13 Oct 2019 | Accepted: 15 Jan 2020

proved that exactly cystenyl leukotrienes C4D4E4 formed by activation of lipooxygenase way, play a leading role in bronchoconstriction and inflammation development in patients with BA [2, 10, 11, 16, 17].

The role of LT most studied at allergic rhinitis, allergic form of BA in adults [13, 15, 17], but the present issue at BA in children is not researched. BA is known to be a heterogeneous disease with many clinical phenotypes that differ significantly from each other [6]. However, it has been shown that the effectiveness of therapy depends directly on the leading mechanism of pathogenesis, and different forms of BA require a differentiated approach to the choice of treatment method [6]. Heightened LT values are an indication for the prescription of leukotriene receptor antagonists, particularly montelukast, used both in our country and abroad [2]. However, the therapy with these medications is carried out empirically without consideration of the level of leukotrienes in children. The study of the leukotrienes level in dynamics in the process of montelukast treatment has not been studied to date [2.11,16]. In accordance with the stated above, research of the LT dynamics against the background of montelukast treatment and clinical effectiveness of this type of therapy is a relevant problem which requires further study.

The aim of the work. To study the level leukotrienes C4D4E4 in children with bronchial asthma and evaluate the effectiveness of therapy.

Materials and methods. The presentresearch work was performedat the Department ofAllergology of the Tashkent Medical Academy Clinic. In total 92 childrenwere examined during the disease exacerbation. The average age of children was 6,05±0,12. The control group included 23 rather healthy children of the same age. The diagnosis of bronchial asthma is established in accordance with the International Consensus on Diagnosis and Therapy of BA. (GINA, 2015, 2018) [6]. All children underwent a complex clinical-laboratory and allergo-immunological examination. The study of the function of external respiration (FER) in BA patients was carried out on the Spirograph "MicroLab" with a computer software;the following was determined: the forced exhalation volume per second (FEV1), the peak expiratory flow rate (PEFR), the daily spread of PEFR. Clinical indicators were evaluated in scores. By the totality of clinical and functional indicators for statistical data processing, BA control was determined by scores in each patient.

All patients with BA involved into the researchwere treated with basic therapy according to the severity of the disease course. The constant intake of oral glucocorticosteroids(GCC) was a criterion for exclusion from the observation. Consultations of particular specialists (otorhinolaryngologist, neuropathologist) were held to clarify the existing concomitant diseases. Total leukotrienes C4D4E4 in urine were determined by immunoenzymatictest (IET), by the help of devices “Neogen corporation” (USA) on the base of the Central Scientific Research Laboratory (CSRL) at the Tashkent Medical Academy.

The method for determination of leukotriene receptors (C4D4E4) in urine: the device is intended for quantitative determination of leukotrienes C4/D4/E4 in samples of human biological fluids by competitive IET. Pre-preparation: extraction is required depending on the type of sample on the columns and elution of the extracted samples in methanol. Also it is possible to analyze urine samples and supernatants of tissue culture immediately after their dilution with extractory buffer without extraction. Additional equipment: nitrogen source, as it is necessary to dry eluates after extraction under a mild nitrogen current. Measuring range: 0.04-2 ng/ml. Sensitivity: 0.04 ng/ml. Mechanism: The synthesis of leukotrienes by human mast cells mainly occurs at immediate-type hypersensitivity and begins after binding the antigen withIgE fixed on the surface of these cells. Synthesis of leukotrienes is carried out as following: free

DOI: 10.37200/IJPR/V24I4/PR201320
Received: 22 Sep 2019 | Revised: 13 Oct 2019 | Accepted: 15 Jan 2020

arachidonic acid under the influence of 5- lipoxygenase (a 5- lipoxygenasepathway) turns into LTA4, of which then LTB4 is formed. At conjugation of LTB4 with glutathione, LTC4 is formed (is present in the medium for 3-5 minutes), then LTC4 is transformed into a LTD4 (prevails next 15 minutes) from which LTE4 is formed. Leukotriene C4 (LTC4) is synthesized by both mast cells and polymorphonuclear leukocytes. It prevails among lung mast cell products activated by the allergen-IgE complex.

The monoclonal antiserum in the composition of the device set recognizes LTC4, LTD4 and LTE4 and binds with them in a dependent manner.

Montelukast was prescribed depending on the age: children from 2 to 5 years took 4 mg, children from 6 to 10 years - 5 mg daily, overnight duringa month in addition to a standard basic therapy.

Statistical processing of the material was performed using the application package "Statistics 6" on the personal computer.

II. Results and discussion

Among the examined children 45.6% were girls and 54.4% were boys. The study of children anamnesis showed that the duration of the disease made in average 3,5± 0.6 years. In 65.2% of children, the main manifestation of bronchial asthma was cough, which intensified at night, after physical and emotional strain. 52.2% of children were treatedfordiagnosed chronic recurrent bronchitis during 2-3 years. On average, patients experienced 4,21±0.34 exacerbations per year, with duration up to 11,92±1.06 days. The majority of children had hotbeds of chronic infection in the respiratory tract (adenoids, tonsillitis, sinusitis, nasal polyposis, etc.) with frequent exacerbations and use of antibacterial medicines up to 3,19±0.22 courses per year. The FEV1 indicators were initially 69,30±0.90% of the proper values, the daily variation of PEFR - more than 17,21±0.67%. 2/3 of children with normal FEV1indicators had bronchial hyperactivity (BHR) for non-specific stimuli, which indicates the persistence of inflammation in the respiratory tract. According to the analysis of clinical-functional parameters, full BA control was absent in all patients. All patients underwent basic anti-inflammatory therapy, the proportion of patients who got high doses of IGCS was 41.5%, low doses of IGCS were received only by 3 patients (5.7%), average doses–by 28 (52.8%) patients.

According to the aim of our work, we performed the research of the level of leukotrienes C4D4E4 in urine of 92 children with BA. Among them, there were 62 children with step 1 of BA (67.4%), and 30 children (32.6%) with step 2. Comparative analysis of the initial data revealed a significant increase of LT release in 72 (78.3%) patients with cough form of BA. In 20 patients with step 1 of BA, LT values were at the upper limit of the norm (1, 0 ± 0.01). 15 children with step 2of BA showed an increase in the level of LT more than 5 times in comparison with the admissible norm ($p < 0.05$).

In some children with atopic form of BA, the prescription of only GCC does not lead to the complete inflammation elimination in the respiratory tract, which maintains the uncontrolled course of the disease. Children of the comparison group who did not receive anti-leukotrienemedications showed slow dynamics of symptoms of the disease, and cough reduction was observed only 15-20 days after the treatment.

Clinical effect of montelukast therapy was accompanied by positive dynamics after 7-10 days, which was manifested by reduction of symptoms such as coughing, shortness of breath, asthma attacks (Table 1).

DOI: 10.37200/IJPR/V24I4/PR201320
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Table 1. Dynamics of clinical picture of BA in children

Symptoms	Step 1 (n=62)		Step 2 (n=30)	
	Before	After	Before	After
Cough	2,83±0,03	0,5±0,01	2,23±0,04	0,4±0,01
Shortness of breath	1.8±0,07	0,2±0,05	1,92±0,05	0,5±0,08
Asthma attacks	1.1±0,05	0,06±0,002	1,4±0,08	0,08±0,003
P	*<0,001*		*<0,001*	

Note: Expressiveness of symptoms in scores:

0 – absence of symptoms *2 – persistent moderate*

1 – mild *3 – severe persistent*

The severity of BA duration decreased significantly from 2, 36 ± 0.08 to 1, 72 ± 0.09 scores ($p < 0.05$).

Besides, we studied the condition of eosinophils in peripheral blood and IgE in blood serum of examined children.Before the treatment, the average values of eosinophils in peripheral blood were 5,66±0.3%, IgE on average was 345,2±40.1IU/ml. After the treatment, a significant decrease in the amount of eosinophils (2,8±0.1%) in the peripheral blood of the patients was observed, while the IgE level tended to decrease (201,3±30.1IU/ml). In 14 children (15.2%) with Step 2 of BA the IgElevel decreased slightly after a month, while 2 children (2.2%) had a slight increase, at clinical improvement of the children 's condition.

Studying the level of leukotrienes in a month after the prescribed therapy also showed its reduction. Statistically significant results were obtained when comparing the C4D4E4 level before and after therapy in BA patients. Thus, the C4D4E4 content in children decreased in average for 1.5 times ($p < 0.05$) (3.26 ± 0.45 ng/ml to 1, 76 ± 0.45 ng/ml). In 29 children (40.3%) the level of LT reached the control values after the treatment. The individual approach revealed that 13 children (18.1%) had a tendency to reduce their C4D4E4 levels after a month, but did not reach control values.

In the process of the research, the children were separated according to the severity of BA (Table 2).

Table 2. Leukotriene valuesin patients with BA against the background of montelukast therapy

Quantity of patients (n=92)		C4D4E4, ng/ml
BA of Step 1 (n=62)	Before treatment	3,02±0,4**
	After treatment	1,46±0,45*
BA of Step 2 (n=30)	Before treatment	3,6±0,18**
	After treatment	2,14±0,3*
Healthy ones (n=23)		0,58±0,07

*Note: * - p < 0,05 reliability of distinctions before and after the treatment; ** - p < 0,05 reliability of distinctions between the BA groups and healthy.*

As shown in the Table 2, children with Step 1 BA had a reduction in LT level for 2 times after the treatment, while children with Step 2 had reduction for 1.6 times ($p < 0.05$).

These results show a positive effect of the anti-leukotriene medication in children with an intermediate and mild degree of persistent BA.

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There was a significant improvement of indicators of FEV against the background of montelukast therapy: FEV1 increased from 69.30±0.90% to 91.53±1.40% ($p<0.05$), PEFRincreased from 81.72±1.87 ml/min. to 99.02±1.34 ml/min.($p<0.05$).The daily dispersion of PEFRdecreased from 17.21±0.67ml/min to 10.91±0.41 ml/min. ($p<0.05$). Dynamics of changes corresponds to increase of BA control ($p < 0.05$). The volume of anti-inflammatory therapy after the course changed significantly: the number of patients treating with low doses of IGCS increased from 5.7% to 18.9% (10 people), the number of patients treating at high doses of IGCS decreased - from 22 (41.5%) to 16 (30.0%) patients. Clinical effectiveness of montelukast, taking into account excellent, good and satisfactory results, was 81.1% in patients with BA.

Thus, our studies have shown the pathogenetic role of cystenyl leukotrienes in the development of BA in children, especially the coughing variant.

III. Conclusions

1. The significant role of LT in the formation of allergic inflammation of the respiratory tract at BA in children has been confirmed.

2. The prescription of cis-ALT (montelukast) is justified both as a monotherapy for mild persistent BA and in combination with IGCS in patients with moderate BA.

3. ALT medications complement the anti-inflammatory effects of IGCS, as IGCS itself are unable to block the leukotrienes effects on immune system cells.

4. The positive effect of the medication is accompanied by a decrease in the manifestation of clinical symptoms of the disease, relapses frequency, improvement in pulmonary function and glucocorticosteroid therapy volume decrease.

5. High safety and easy way to take montelukast contribute to patients'commitment for treatment, especially in the childhood age group, as well as to a long-term maintenance of optimal asthma control.

6. The dynamics of leukotrienes level can serve as a biochemical marker of the effectiveness of the performed therapy.

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DOI: 10.37200/IJPR/V24I4/PR201320
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