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CHANGE OF NON-SPECIFIC FACTORS OF IMMUNITY UNDER INFLUENCE OF INTERFERON INDUCTOR (CYCLOFERON) IN BRONCHIAL ASTHMA IN CHILDREN

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The aim of the work was to evaluate the effect of immunomodulation therapy on factors of nonspecific immunity in children with bronchial asthma (BA) by including interferon (cycloferon) in a standard therapy. 120 children with BA aged from 5 to 14 were examined. The main group (n = 60) included children who, in addition to basic therapy, received an interferon inducer (cycloferon) according to the generally accepted scheme. In comparison group were children who received only basic therapy (n = 60), depending on the severity of the disease. In control group were 25 healthy children. The level of serum interferon, virus-induced interferon production (VII), mitogen-stimulated production of interferon (MSI), phagocytic activity of neutrophils, as well as spontaneous and induced activity were determined. The arithmetic mean (M) and the absolute value error (m) were statistically calculated. The reliability of the differences was determined by the t-test of the Student ($p < 0,05$). The analysis of the indices of interferon status and phagocytic activity, depending on the type of therapeutic tactics, showed that as a result of the inclusion of cycloferon in the baseline, there was a significant increase in the levels of VII ($p < 0,05$) and MSI ($p < 0,05$), spontaneous and induced neutrophil activity. It was noted that this positive effect was more noticeable in moderate and severe BA ($p < 0,05$). Activation of factors of nonspecific protection contributed to a decrease in the frequency of exacerbations of BA in children, as well as a longer-term clinical remission in this contingent of children.

KEY WORDS: bronchial asthma, children, phagocytic activity, interferon inducers

ЗМІНИ НЕСПЕЦИФІЧНИХ ФАКТОРІВ ІМУНІТЕТУ ПІД ВПЛИВОМ ІНДУКТОРА ІНТЕРФЕРОНУ (ЦИКЛОФЕРОНУ) ПРИ БРОНХІАЛЬНІЙ АСТМІ У ДІТЕЙ

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Метою роботи була оцінка впливу імуномоделюючої терапії на фактори неспецифічного імунітету у дітей з бронхіальною астмою (БА), шляхом включення до стандартної базисної схеми терапії індуктора інтерферону (циклоферону). Обстежено 120 дітей, хворих на БА, віком від 5 до 14 років. До основної групи (n = 60) увійшли діти, які до базисної терапії отримували додатково індуктор інтерферону (циклоферон) за загальноприйнятою схемою. Група порівняння – діти, які одержували тільки базисну терапію (n = 60) в залежності від ступенів тяжкості захворювання. Група контролю – 25 здорових дітей. Визначали рівень сироваткового інтерферону, вірус-індуковану продукцію інтерферону (ВІІ), мітогенстимульовану продукцію інтерферону (МСІ), фагоцитарну активність нейтрофілів, а також спонтанну і індуковану їх активність. Статистично обчислювали середню арифметичну (М), похибку абсолютної величини (m). Достовірність відмінностей визначали за t-критерієм Ст'юдента ($p < 0,05$). Аналіз показників інтерферонового статусу, а також фагоцитарної активності в залежності від виду терапевтичної тактики показав, що в результаті включення до базисної лінії терапії циклоферону відзначалося достовірне підвищення рівнів ВІІ ($p < 0,05$) і МСІ ($p < 0,05$), спонтанної і індукованої активності нейтрофілів. Відзначено, що даний позитивний ефект був більш помітний при середньому і тяжкому ступеню тяжкості БА ($p < 0,05$). Активація факторів неспецифічного захисту сприяла зменшенню частоти загострень БА у дітей, а також більш тривалій клінічній ремісії у даного контингенту дітей.

КЛЮЧОВІ СЛОВА: бронхіальна астма, діти, фагоцитарна активність, індуктори інтерферону

ИЗМЕНЕНИЕ НЕСПЕЦИФИЧЕСКИХ ФАКТОРОВ ИММУНИТЕТА ПОД ВЛИЯНИЕМ ИНДУКТОРА ИНТЕРФЕРОНА (ЦИКЛОФЕРОНА) ПРИ БРОНХИАЛЬНОЙ АСТМЕ У ДЕТЕЙ

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Целью работы была оценка влияния иммуномодулирующей терапии на факторы неспецифического иммунитета у детей с бронхиальной астмой (БА), путем включения в стандартную базисную схему терапии индуктора интерферона (циклоферона). Обследовано 120 детей, больных БА, в возрасте от 5 до 14 лет. В основную группу (n = 60) вошли дети, которые к базисной терапии получали дополнительно индуктор интерферона (циклоферон) по общепринятой схеме. Группа сравнения – дети, получавшие только базисную терапию (n = 60) в зависимости от степеней тяжести заболевания. Группу контроля – 25 здоровых детей. Определяли уровень сывороточного интерферона, вирус-индуцированную продукцию интерферона (ВИИ), митогенстимулированную продукцию интерферона (МСИ), фагоцитарную активность нейтрофилов, а также спонтанную и индуцированную их активность. Статистически вычисляли среднюю арифметическую (M), ошибку абсолютной величины (m). Достоверность отличий определяли по t-критерию Стьюдента ($p < 0,05$). Анализ показателей интерферонового статуса, а также фагоцитарной активности в зависимости от вида терапевтической тактики показал, что в результате включения к базисной линии терапии циклоферона отмечалось достоверное повышение уровней ВИИ ($p < 0,05$) и МСИ ($p < 0,05$), спонтанной и индуцированной активности нейтрофилов. Отмечено, что данный положительный эффект был более заметен при средней и тяжелой степени тяжести БА ($p < 0,05$). Активация факторов неспецифической защиты способствовала уменьшению частоты обострений БА у детей, а также более длительной клинической ремиссии у данного контингента детей.

КЛЮЧЕВЫЕ СЛОВА: бронхиальная астма, дети, фагоцитарная активность, индукторы интерферона

INTRODUCTION

Bronchial asthma (BA) remains one of the most urgent problems of modern pediatrics. The frequency of this pathology is growing every year and, according to WHO, about 300 million people in the world today suffer from BA. In addition, the increase in the frequency of BA is also a social problem, so this pathology steadily leads to deterioration in the quality of life of patients, the growth of disability and mortality [1–2]. Taking into account new approaches to the consideration of the mechanisms of formation of BA [1, 3–4] today proposed therapies of asthma, presented in the Global Strategy for the treatment and prevention of asthma (GINA 2009, 2011), which allow to some extent improve the patient's condition and pathology. However, these therapeutic methods show insufficient effectiveness in solving problems with multifaceted disorders in immune homeostasis and cannot cover the entire mosaic involvement of certain immunity units in the pathogenesis of BA. Therefore, despite the advances made in the diagnosis and treatment of this disease it has not been possible to obtain complete control over the course of BA [5–7].

OBJECTIVE

The aim of the study was to evaluate the effect of immunomodulation therapy on the state of nonspecific immunity in children with BA by including interferon (cycloferon) in a standard basal therapy.

MATERIALS AND METHODS

The study was carried out in the framework of the research theme of the I. I. Mechnikov Institute of Microbiology and Immunology of the National Academy of Medical Sciences of Ukraine «Investigation of immunological aspects of the course of chronic inflammatory processes of the upper respiratory tract». The study included 120 children with BA aged from 5 to 14 years with an average age of $11,6 \pm 1,5$ years. To establish the diagnosis the international classification of diseases in the 10th revision, the protocol for diagnosis and treatment of BA in children (Order of the Ministry of Health of Ukraine № 767 from 27.12.2005) and, in evaluating the therapeutic

effect of the prescribed therapy, the Global Initiative for Bronchial Asthma (GINA, 2011) were used. Three groups were identified. The main group (n = 60) included children who, in addition to basic therapy, received an interferon inducer (cycloferon) according to the scheme: 150 mg for 1, 2, 4, 6 and 8 days of therapy (№ 5) and then 150 mg after 72 hours (№ 5) (total 1500 mg). The comparison group included children who received only basic therapy (n = 60) depending on the severity of the disease. The control group comprised 25 healthy children.

The level of serum interferon, virus-induced production of interferon (VII), mitogen-stimulated production of interferon (MSI) was determined by the method of enzyme immunoassay (ELISA). The phagocytic activity of neutrophils was estimated by their ability to absorb inactivated cells of a one-day culture of staphylococci, as well as spontaneous and induced neutrophil activity from the chemiluminescence reaction by using the Bio-Orbit (Pribiri-Oy) chemiluminometer.

The study was carried out taking into account the main provisions and ethical and moral requirements of the Ukrainian Association for Bioethics and GCP (1992), GLP (2002), the principles of the Helsinki Declaration of Human Rights, the Convention of Council of Europe on Human Rights and Biomedicine.

In the statistical processing of the obtained data the arithmetic mean (M) and absolute value error (m) were calculated. To confirm the normality of the distribution for all studied indicators, the coefficient of asymmetry and kurtosis was calculated by the method of Lakin G. F. (1990). The reliability of the differences was determined by the t-test of the Student at a significance level of $p < 0,05$.

RESULTS AND DISCUSSION

In the development of BA in children the leading role belongs to immune disorders. It is known that the severity of the course and the frequency of development of asthma exacerbations in children depend on the phase, dynamism and severity of a number of specific and nonspecific systemic and local defense mechanisms. One of the most important factors protecting the respiratory tract from infectious agents is the interferon system, whose role in the pathogenesis of BA is noted by many researchers [8–11]. As a result of the study, it was found that the level of serum interferon, as well as VII and MSI in children receiving only basic therapy, were significantly lower compared to parameters in the main and control groups (table 1). Analysis of interferon status indicators depending on the type of therapeutic tactics showed, that using the GINA-recommended drugs significantly reduce levels of VII ($p < 0,05$) and MSI ($p < 0,05$). Moreover, in the heavier course of BA the weaker leukocyte synthesis of these interferons ($p < 0,05$ for all degrees of severity of the BA course) was determined. This agrees with the data of Kaidashev I. P., which show that weak elimination capacity and antiviral protection contribute to a greater probability to development of exacerbation of BA [3]. Similar results were noted in Khaitov M. R., where it was shown that the more severe the course of BA in more pronounced decrease in the level of these interferons [12] was noted.

In the main group of children who received an interferon inducer in addition to basic therapy, low values of serum interferon, VII and MSI relative to control were also noted in severe BA ($p < 0,05$), but despite this, the level of the last two indicators was still higher than in the comparison group ($p < 0,05$).

The addition of cycloferon to basic therapy for moderate BA was associated with the increase in the values of serum, MSI and VII and did not differ significantly from the control group, but they were significantly higher relative to the analogous course of BA in the comparison group ($p < 0,05$). With a mild course of BA the inclusion of cycloferon led to a slight increase in the values of the studied parameters, but this trend did not differ in the children of the comparison group.

Table 1

The content of factors of nonspecific immunity in children with BA on the background of therapy, depending on the severity, (M ± m)

Indicators	Control	Children receiving an interferon inducer and basic therapy			Children receiving an basic therapy		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Serum interferon, IU/ml	8,2 ± 3,3	8,0 ± 3,1	7,3 ± 1,5	6,4 ± 1,7*	7,6 ± 2,4	6,1 ± 2,2	4,4 ± 1,2*
VII, IU/ml	32,0 ± 7,8	31,6 ± 6,5	28,1 ± 4,8	17,6 ± 3,5*	22,3 ± 4,8*	16,4 ± 3,5*#	9,1 ± 1,6*#
MSI, IU/ml	38,0 ± 9,6	36,7 ± 6,4	25,6 ± 4,7*	19,7 ± 3,5*	24,8 ± 5,8*	16,7 ± 6,2*#	6,5 ± 1,8*#
Phagocytic activity of neutrophils, %	58,0 ± 6,8	57,6 ± 5,7	49,5 ± 6,3	25,7 ± 5,3*	54,8 ± 6,1	32,5 ± 4,4*#	10,3 ± 2,9*#
Spontaneous activity of neutrophils, c. u.	2,6 ± 0,80	2,5 ± 0,40	1,8 ± 0,50	1,6 ± 0,20*	2,5 ± 0,40	1,9 ± 0,30	1,4 ± 0,4*
Induced neutrophil activity, c. u.	29,7 ± 8,20	28,8 ± 6,1	24,3 ± 4,8	16,5 ± 4,2*	28,3 ± 7,1	19,6 ± 4,8*#	11,3 ± 2,8*

*Notes: * $p < 0,05$ - the differences between the indicators of the first and second comparison groups in comparison with the control group; # $P < 0,05$ - differences of the studied parameters with average and severe degrees of severity of the BA of the main group and the comparison group.*

The role of neutrophils in the course of BA and, especially in the process of development of exacerbation, is emphasized by a number of researchers [4, 13]. According to our data, the phagocytic activity of neutrophils directly depended on the severity of the course of BA and was several times lower in severe than in control and mild course ($p < 0,05$). This trend was especially noticeable in the children of the comparison group who received only basic therapy, including glucocrticosteroids. In the main group of children, the neutrophil activity indicators were close to the control group and even in the severe case the phagocyte (25,7 ± 5,3 vs 10,3 ± 2,9, $p < 0,05$) and induced (16,5 ± 4,2 vs 11,3 ± 2,8, $p < 0,05$) activity were significantly higher, which is related to the immunomodulatory property of cycloferon. The positive effect of interferon preparations is also indicated in a number of scientific works, which notes that when choosing a therapeutic approach for the treatment of BA, it is necessary to take into account the level of production of interferons with the addition of immunomodulatory therapy, in particular interferon preparations [8, 14]. Researchers note that interferon therapy is a promising direction in the complex treatment of virus-induced BA in the remission stage as one of the measures of secondary prevention of the disease, and can also be used for primary prevention of BA in children from high-risk groups of its formation. However, it should be noted that the practical application of interferon inducers both in monotherapy and in combined therapy of BA in children has advantages over the use of interferon preparations, since the synthesis of interferons when administered inducers of interferon genesis is regulated by the body itself, which prevents possible side reactions.

CONCLUSIONS

Thus, the study showed that an important aspect of increasing the effectiveness of baseline therapy of BA, proposed by GINA (2009, 2011), is the additional inclusion of inducers of interferon, in particular, cycloferon. This drug contributed to the enhancement of phagocytic activity of neutrophils, and also led to an increase in leukocyte synthesis of VII and MSI, which was particularly noticeable in moderate and severe course of BA. Considering the fact that in the exacerbation of BA the huge importance is given to infectious agents, the intensification of the activity of factors of non-specific immunity in the future will contribute to an increase in antimicrobial protection of the body, and consequently, to a decrease in relapses of asthma in children, as well as to a prolonged clinical remission in this contingent of children.

PROSPECTS FOR FUTURE STUDIES

Take into account the positive effect of the interferon inducer (cycloferon) on nonspecific defense factors, it is promising to continue the study in the direction of assessing its effect on the humoral and cellular link of immunity in children with BA.

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