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Estimation Of The Effectiveness Of Hyposensitizing Immunotherapy By Bronchial Asthma Micro-Mite Etiology In Children Of The Republic Of Uzbekistan

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ABSTRACT: This article presents the results of evaluating the therapeutic efficacy of specific allergic vaccination in 77 children with allergy of micro-mite etiology. The age of children was in the range of 7-14 years, including 7-12 years old – 29 (37.7%), 12-14 years old – 48 (62.3%).In general, of the total number of patients (77) who received specific treatment, excellent results were observed in 26 (33.7–4.2%). In this group of patients, after treatment, all the main symptoms of the disease completely disappeared. Good results were observed in 39 (50.6–4.4) patients. In this group of patients, most of the symptoms of the disease disappeared or the intensity of their severity was weakened. Satisfactory results were observed in 11.7% of patients. In this group of patients, the symptoms of the disease remained, but the intensity of their manifestation was weakened. In 3.9% of patients, the treatment effect was absent. It turned out that the therapeutic effectiveness of specific therapy lasts for 1-3 years. So, good and excellent results were achieved after 1 year – 62.8%, after 2 years – 55.4%, and after 3 years – 50.0%. The use of a new method of allergen-specific immunotherapy of children suffering from allergic diseases: the combined method (inhalation of the allergen + its electrophoresis through the skin) of immunotherapy compares favorably with the known traditional (multiple injection methods) with great therapeutic efficiency, does not cause negative side local and general reactions, does not give complications, lengthen remission.

Key words: bronchial asthma, allergen-specific immunotherapy, children

1. INTRODUCTION

Currently, bronchial asthma (BA) remains an urgent problem in pediatrics, due to the progressive prevalence of up to 19% in the structure of respiratory diseases and the growth of disability in children, amounting to 87.4% [4]. In recent years, a new scientific direction in allergology has been successfully developing - the study of regional characteristics of allergens of various nature and genesis. The fact is that even allergens of the same name from different regions differ from each other in their physicochemical and allergenic properties. The allergic reactivity of patients is also different. [7, 5]. Therefore, the WHO Allergen

Biological Standardization Unit encourages the development and commercialization of regional allergens specific to that specific region. In addition, the development and implementation of regional allergens in practical health care is also economically beneficial, since the cost of local allergens is lower than international ones.

Allergen-specific immunotherapy (ASIT) is a method of treating allergic diseases, which consists in reducing the body's sensitivity to the effects of an allergen by reintroducing an extract of this allergen, starting with minimal doses [1, 2]. Today, ASIT is the only pathogenetically justified method of treating IgE-dependent allergic reactions. Its action is focused not on the symptoms of allergy, but on the pathogenesis of the disease itself. For several decades, scientists have been closely studying the pathogenesis of ASIT.

Objective of the study: to evaluate the therapeutic efficacy of hyposensitizing immunotherapy in children with allergy of micro-mite etiology.

2. MATERIALS AND METHODS OF RESEARCH

77 children suffering from bronchial asthma of micro-mite etiology were under observation: boys – 40 (51.9%), girls – 37 (48.1%). The age of children was in the range of 7-14 years, including 7-12 years old – 29 (37.7%), 12-14 years old – 48 (62.3%).

As a control, we used 30 children suffering from bronchial asthma of micro-mite etiology, who were prescribed non-specific treatment (control No. 1) and 30 apparently healthy children (control No. 2).

In the majority of sick children, the first symptoms of bronchial asthma appeared before the age of 11 years.

The duration or duration of the disease ranged from 1 to 9 years: in most patients - 57 (74.0%) - up to 3 years.

The duration or duration of the period of exacerbation of symptoms of bronchial asthma was within wide limits, including up to 1 month – in 10 (13.0%), 2-3 months – in 16 (20.8%), 4-7 months – in 39 (50.7%), 8-11 months – in 9 (11.7%) and 12 months – in 3 (3.8%).

When assessing the severity of the clinical course of bronchial asthma in children, we were guided by the recommendation set out in the official WHO report “Bronchial asthma. Global Strategy ”(GINA project and recommendations of the International Pediatric Asthma Group (1992)).

In the etiology of bronchial asthma, allergens are of decisive importance. We have selected patients with a specific increase in sensitivity to allergens of house dust mites. According to our data, the frequency of positive reactions when performing skin scarification tests was in the range of 12.9 ± 3.8 - 81.8 ± 4.3%. The highest frequency of positive reactions was noted for the allergen G. Cadaverum (81.8 ± 4.3%) and D. Pteronyssinus (75.3 ± 4.9%). The frequency of positive reactions to other allergens was lower: D. Farinae (32.4 ± 5.3%), G. Destructor (16.8 ± 4.1%), G. Domesticus (12.9 ± 3.8). The intensity of reactions expressed for 3+ and 4+ was also higher for allergens G. Cadaverum, D. Pteronyssinus: 49.3% and 41.5%, respectively.

According to our data, only 11 (14.2 ± 4.0%) had monosensitization to one or another allergen of house dust micro mites, and polysensitization was found in 66 (85.8 ± 4.0), with 2 allergens in 29 (37.7 ± 5.5%), for 3 allergens – in 18 (23.4 ± 4.8%), for 4 allergens – in 12 (15.6 ± 4.1%), for 5 allergens – in 7 (9.1 ± 3.2%).

In sick children suffering from bronchial asthma, hypersensitization of the body is noted. The highest rates of allergometric titration were observed for the allergen from the micro mites G. Cadaverum (10^{-9}) and D. Pteronyssinus (10^{-9}). For the allergen from D. Farinae, the highest allergometric titration was 10^{-8}, and the allergens of G. Destructor and G. Domesticus, respectively, 10^{-7} and 10^{-6}.

In most (40.3%) cases, there were high titers for the G. Cadaverum allergen in titers of 10^{-6} – 10^{-8}, for the D. Pteronyssinus allergen in 35.1% of cases in titers of 10^{-6} – 10^{-8}.

For treatment, the patients were divided into two groups: the main group (77) received specific therapy, and the control group (30) received a generally accepted nonspecific treatment, which consisted of prescribing anti-inflammatory, bronchodilators, mucolytics, and vitamins. The drugs were prescribed taking into account the body weight and age of the children.

Allergens of house dust mites were used as a therapeutic agent: Glycyphagus Cadaverum, G. Destructor, G. Domesticus and Dermatophagoides Pteronyssinus. The content of protein nitrogen in allergens is 10000 PNU / ml. Allergic tests, as well as hyposensitizing immunotherapy were carried out during the period of remission of the disease. Before starting treatment, patients with symptoms of local infection underwent thorough sanitation.

Specific therapy was carried out in a new combined way. The principle of this method of treatment is that after determining the threshold (initial) dose of the allergen by allergometric titration, the treatment was started with the minimum dose and the drug was introduced into the body in gradually increasing quantities in two ways: by inhalation and electrophoresis through the skin.

For the electrophoretic method of introducing the allergen, the Potok electrophoresis apparatus was used. Allergen was injected from the cathode; 2-3 sheets of filter paper were moistened with a solution of the culprit allergen (consumption of 2.5 ml of allergen per procedure). The electrodes were placed on the interscapular region and the second on the shoulder region. The current density, depending on the individual sensitivity of the child's body, is from 0.03 to 1 мА/см^2, the duration of the procedure is 15-20 minutes. Allergen electrophoresis was combined with inhalation.

The effectiveness of treatment was assessed by comparing the data of the general condition of patients, clinical, allergic, functional and laboratory parameters before and after treatment and then after 2-3 years as follows:

• The treatment was considered excellent in the case when the symptoms of the underlying and concomitant diseases disappeared completely within 6 months показатели 1 year, the forced expiratory parameters and laboratory tests improved (conditionally 5 points).

• Good, when some of the painful symptoms of the underlying disease and concomitant diseases disappeared, and the intensity of others was significantly weakened,

the indicators of clinical and laboratory studies also improved partially, the patients did not need to take antihistamines or antispasmodic drugs (conditionally 4 points).

• Satisfactory, when the symptoms of the disease persisted, but their intensity significantly weakened (conditionally 3 points).

• Unsatisfactory, when the condition of the patients remained unchanged (conditionally 2 points).

The digital data was processed on a personal computer using the memory of Microsoft Exell-2007 application programs. The information was considered reliable if $t > 2$ and $P < 0.05$.

3. RESULTS AND DISCUSSION

The studies carried out have shown that the combined method of specific hyposensitizing therapy is effective for sick children suffering from bronchial asthma. This is evidenced by an improvement in the general condition of patients, the disappearance of asthma attacks or a weakening of the intensity of the main symptoms characteristic of bronchial asthma, as well as an improvement in clinical and laboratory parameters (Table 1).

In general, of the total number of patients (77) who received specific treatment, excellent results were observed in 26 (33.7±4.2%). In this group of patients, after treatment, all the main symptoms of the disease completely disappeared. Good results were observed in 39 (50.6±4.4) patients. In this group of patients, most of the symptoms of the disease disappeared or the intensity of their severity was weakened. The interval between relapses increased. Satisfactory results were observed in 9 (11.7 ± 2.8%) patients. In this group of patients, the symptoms of the disease remained, but the intensity of their manifestation was weakened. In 3 (3.9±1.7%) patients, the treatment effect was absent. It turned out that the result of treatment depends on the duration of the disease, the severity of the clinical course, the nature of sensitization, the number of courses of treatment and the dose of the administered therapeutic allergen (Fig. 1).

Table 1

Clinical and laboratory parameters in children with bronchial asthma with specific therapy

Indicators	Treatment				Practically healthy
	specific		non-specific		
	before	after	before	after	
Forced exhalation (l / sec)	1,32±0,22**	3,62±0,33*	1,51±0,45**	2,2±0,66	3,80±0,53

Eosinophilia (%)	12-16	5-6	11-14	7-9	4-5
Phagocytic number (%)	43,5±6,2**	67,6±5,3*	44,2±5,2**	54,3±4,6	76,6±5,4
Phagocytic index	3,3±0,3**	6,6±0,6*	3,4±0,3**	6,2±0,5	2,5±0,4
The power of phagocytosis	143,6±10,5**	446,2±13,4*	150,3±11,2**	336,7±13,4*	574,5±15,3

Note: reliability of the numerical differences ($p < 0.05$) between: indicators before and after treatment (*); before treatment in comparison with those of practically healthy people (**).

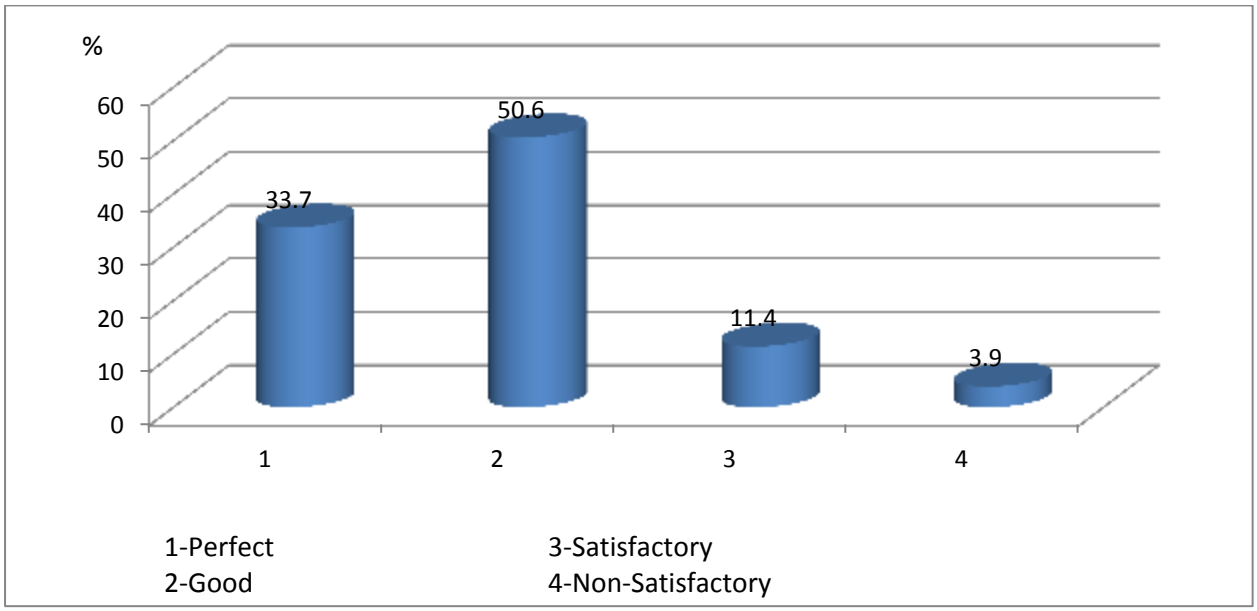

Figure: 1. Results of specific therapy of patients with bronchial asthma with house dust micro mite extract

So, for example, in children suffering from bronchial asthma, during 1 year, excellent and good treatment results were noted in 77.1% of cases. In children suffering from for 2-3 years – excellent and good results of treatment were noted in 72.7% of cases. In general, the following pattern was observed: the shorter the duration of the illness, the higher the positive results (Table 2).

Table 2

The dependence of the therapeutic effect on the duration of the disease of bronchial asthma (n = 77)

Duration diseases in years	Number of patients	Treatment results		
		Excellent and good	Satisfactory	Unsatisfactory
До 1	35 (100)	27 (77,1±4,7)*	8 (22,9±4,7) *	0 (0,0)
2-3	22 (100)	16 (72,7±5,0)	6 (27,3±5,0)	0 (0,0)
4-6	13 (100)	6 (46,2±5,6) *	4 (30±7±5,2)	3 (23,1±4,8)
7-9 and more	7 (100)	2 (28,6±5,1) *	3 (42,8±5,6) *	2 (28,6±5,1)
Total	77 (100)	51 (66,2±5,3)	21 (27,3±5,0)	5 (6,5±2,8)

It turned out that the result of specific therapy depends on the severity of the clinical course of bronchial asthma. So, with mild clinical course, excellent and good results reach 80.0 ± 4.5%, with moderate clinical course - 57.1 ± 5.6%, and with severe - 45.5 ± 5.6% (Table 3).

The result of the treatment also depended on the nature of the sensitization of the body. Thus, with monovalent sensitization, the therapeutic effect was significantly higher (72.7 ± 5.0%) than with polyvalent sensitization (48.5 ± 5.6%) (Fig. 2).

The therapeutic efficiency of specific therapy also depended on the total dose of the specific allergen received. Thus, the result of treatment was significantly higher when receiving a large total dose of a specific allergen: when receiving a total dose of 20,000 - 40,000 PNU.

Table 3

Dependence of specific therapy on the severity of the clinical course of bronchial asthma (n = 77)

The course of the	Number of	Treatment results

disease	patients	Excellent and good	Satisfactory	Unsatisfactory
Light	45 (100)	36 (80,0±4,5)*	9 (20,0±4,5)	----
Medium	21 (100)	12 (57,1±5,6)**	7 (33,3±3,3)	2 (9,5±3,3)
Heavy	11 (100)	5 (45,5±5,6)	3 (27,3±5,6)	2 (18,2±4,3)

Note: numerical differences are significant: between indicators with mild and moderately severe (*) mild and severe (**)

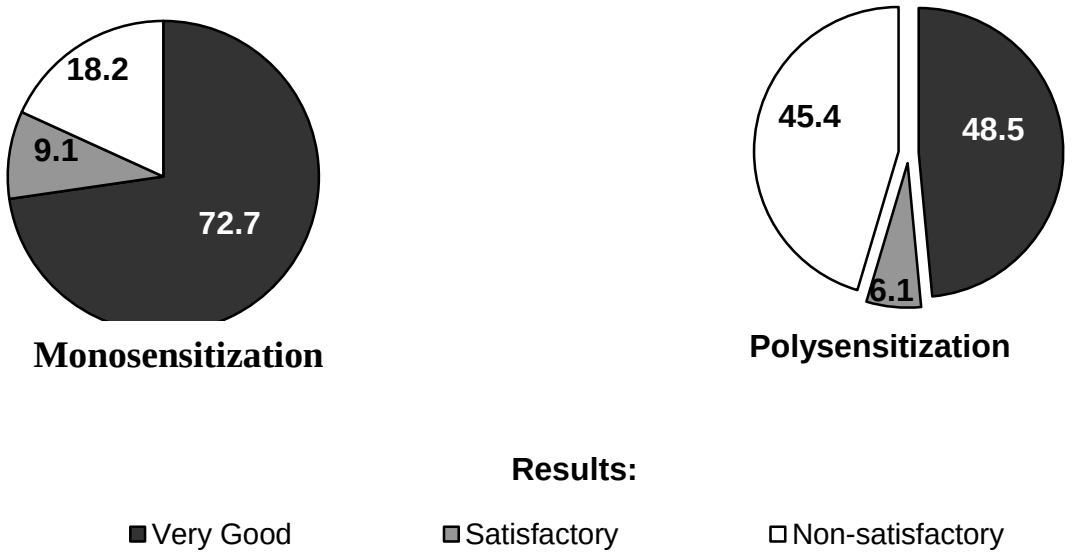

Fig. 3. The dependence of specific therapy on the nature of sensitization of the body

PNU of a specific allergen excellent and good treatment results were 48.0 ± 5.6%, upon receipt of 40,00070000 PNU –73.1 ± 5.0%, upon receipt of 70,000–100,000 PNU –92.3 ± 3.0% (Table 4).

Table 4

Results of specific therapy of patients with bronchial asthma, depending on the course dose of allergen from house dust mites

№	Total course dose of allergen in PNU	Number of patients	Treatment results		
			Excellent and good	Satisfactory	Unsatisfactory
1	20000-40000	25 (100)	12(48,0±5,6) *	8(32,0±5,3) *	5 (20,0±4,5)
2	40000-70000	26 (100)	19(73,1±5,0) *	6 (23,1±4,8)	1 (3,8±2,1)
3	70000-100000	26 (100)	24(92,3±3,0) *	2 (7,7±3,0) *	----

Note: * - reliability of numerical differences between indicators of course doses 1 and 2 ($p < 0.05$), 1 and 3 ($p < 0.01$).

It turned out that the therapeutic effectiveness of specific therapy remains in the same 1-3 years. Thus, good and excellent results were achieved after 1 year - 62.8 ± 5.7%, after 2 years - 55.4 ± 6.1%, and after 3 years - 50.0 ± 6.4%.

Results and discussion: there are different views and theories regarding the mechanisms that ensure the positive therapeutic effect of specific vaccination.

One of the most widespread and generally accepted mechanisms providing a positive therapeutic effect is the synthesis of blocking antibodies belonging to the IgG class [3, 6]. It was found that blocking antibodies do not cause tissue sensitization and have allergen binding activity. It has been determined that the allergen associated with the blocking antibody cannot bind to the specific sensitizing IgE – antibody and therefore allergic cell alteration does not develop.

Blocking antibodies are thermostable, that is, they do not break down at a temperature of + 500C, they are able to cross the placenta, they are precipitated by 30% ammonium sulfate, they are not inactivated by mercaptanium, they are rapidly cleaved by papain, the sedimentation constant 7S belongs to gamma. 2-globulins (IgG, IgGu), neutralize allergens, do not form precipitants, do not cause passive anaphylaxis, do not fix complement [8, 10].

However, there is doubt about this theory, since there is not always a correlation between clinical improvement and high antibody titer, which indicates the complexity of the problem.

There is a theory linking the therapeutic efficacy of specific therapy with the formation of anti- and idiotypic antibodies (anti - IgE antibodies). However, not all scientists agree with this theory [2, 11].

The positive therapeutic effect is associated with the synthesis of interleukins, especially interleukin 4 [3, 7, 9].

There is a theory that specific therapy switches between IgE synthesis and IgG synthesis [2, 4]. Great importance is also attached to the reactivity of mast cells, basophils and eosinophils. With specific therapy, the frequency of mast cell degranulation decreases, and the migration of eosinophils in the oral mucosa is inhibited [3, 7, 11].

The results of our research allow us to come to the following conclusion: the use of a new method of allergen-specific immunotherapy of children suffering from allergic diseases: the combined method (inhalation of an allergen + its electrophoresis through the skin) of immunotherapy compares favorably with the known traditional (multiple injection methods) with great therapeutic efficiency, does not cause negative side effects. local and general reactions, does not give complications, lengthen remission.

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Таблица 4

Результаты специфической терапии больных бронхиальной астмой в зависимости от курсовой дозы аллергена из микроклещей домашней пыли

№	Суммарная курсовая доза аллерген в PNU	К-во больных	Результаты лечения		
			Отличные и хорошие	Удовлетворительные	Не удовлетворительные
1	20000-40000	25 (100)	12(48,0±5,6) *	8(32,0±5,3) *	5 (20,0±4,5)
2	40000-70000	26 (100)	19(73,1±5,0) *	6 (23,1±4,8)	1 (3,8±2,1)
3	70000-100000	26 (100)	24(92,3±3,0) *	2 (7,7±3,0) *	----

Примечание: * - достоверность числовых различий между показателями курсовых доз 1 и 2 ($p<0,05$), 1 и 3 ($p<0,01$).

Оказалось, что лечебная эффективность специфической терапии сохраняется в том же 1-3 лет. Так, хорошие и отличные результаты достигали через 1 год – 62,8±5,7%, через 2 года – 55,4±6,1%, а через 3 года – 50,0±6,4%.

Результаты и их обсуждение: относительно, механизмов, обеспечивающих положительного лечебного действия специфической вакцинации существуют разные взгляды и теории.

Одним из самых распространенных и общепринятых механизмов, обеспечивающих положительный лечебный эффект – это синтез блокирующих антител относящихся к классу IgG [3, 6]. Установлено, что блокирующие антитела не вызывают сенсибилизацию тканей, обладают аллерген связывающей активностью. Определено, то аллерген, связанный с блокирующим антителом не может соединиться

со специфическим сенсибилизирующим IgE – антителом и поэтому не развивается аллергическая альтерация клеток.

Блокирующие антитела являются термостабильным, то есть не разрушаются при температуре $+50^0$C, способны переходит через плаценту, осаждаются 30% сульфатом аммония, не инактивируются меркаптанием, быстро расщепляются папаином, константа седиментация 7S относятся к гамма. 2-глобулинам (IgG, IgGu), нейтрализуют аллергены, не образуют преципитантов, не вызывают пассивную анафилаксию, не фиксируют комплемент [8, 10].

Тем не менее, существуют сомнение относительно этой теории, так как не всегда отмечается коррелятивная связь между клиническим улучшением и высоким титром антител, что указывает на сложность проблемы.

Существует теория, связывающая лечебную эффективность специфической терапии с образованием анти- и идиотипических антител (анти – IgE - антител). Однако не все ученые согласны с этой теорией [2, 11].

Положительный лечебный эффект связывают с синтезом интерлейкинов, особенно интерлейкином 4 [3, 7, 9].

Существует теория, утверждающая, что при специфической терапии происходит переключение синтеза IgE на синтез IgG [2, 4]. Придают большое значение также и реактивности тучных клеток, базофилов и эозинофилов. При специфической терапии уменьшается частота дегранулюции тучных клеток, тормозится миграция эозинофилов в слизистой полости рта [3, 7, 11].

Результаты наших исследований позволяют прийти к следующему **выводу**: применение нового способа аллергенспецифической иммунотерапии детей, страдающих аллергическими заболеваниями: комбинированный способ (ингаляция аллергена + его электрофорез через кожу) иммунотерапии выгодно отличаются от известных традиционных (многократных инъекционных способов) большой лечебной эффективностью, не вызывает негативных побочных местных и общих реакций, не дает осложнений, удлиняют ремиссию.

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