A NEW APPROACH TO THE TREATMENT AND PREVENTION OF ATOPIC DERMATITIS. POSSIBLE WAY OF CRISIS RESOLUTION.

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Abstract

Nowadays, in the absence of a common doctrine and conceptual schemes, both of treatment and prevention of atopic diseases, we have practically uncontrolled growth of this pathology. This dead-end situation can only be changed, if there are clinical atopy biomarkers, thus making preventive therapy possible. The article presents the program development and implementation results for primary prevention of atopic dermatitis based on identified biomarkers. A preventive treatment method, based on the correction

of intestinal microbiota through selective decontamination of opportunistic microflora using bacteriophages has been substantiated. The results of ten-year experience in secondary and primary prevention of atopic diseases are presented.

Key words: atopic diseases, intestinal microbiota, bacteriophages, primary prevention.

Introduction

The significant increase in the number of patients with allergic pathology, observed in recent decades, is becoming a serious test of healthcare systems in almost all world countries. Some ten years ago, they discussed an epidemic of allergic diseases (AD), today all the signs of a pandemic are ascertained, and, unfortunately, the reasons for this phenomenon remain unclear [1,2]. The increased morbidity rate is undoubtedly associated with the aggressive character of triggering environmental effects on humans and is closely related to climatographical and geographical features of the residence region environment, since the quantitative indicator of genetically predisposed people in the population does not change significantly [3].

Atopic dermatitis (AtD) in children is one of the most common non-transmissible inflammatory skin diseases, with incidence in the child population of economically developed countries ranging from 5% to 30.8%.Based on present modern theories, views and opinions of experts, AtD can be considered as a chronic recurrent skin inflammation, arising from a violation of the epidermal barrier and resulting in its further dysfunction, which reaches its maximum development against the background of a predisposition to IgE-mediated hypersensitivity, implemented in sensitization to surrounding allergens [4-7].

The scale of morbidity reflects the problem of absence of conceptual schemes for AtD treatment and prevention, making it, considering disease heterogeneity, an area of interaction for many specialists in related spheres [8]. It is true, that today there are no clinical biomarkers, except for a hereditary factor, that allow a pediatrician, upon first contact with a baby after discharge from a maternity hospital, to identify him as belonging to a risk group for AtD development and start preventive treatment. At the same time, it is utterly important to identify atopy biomarkers and initiate preventive correction measures before the onset of an atopic disease. The world and domestic experience of AtD research shows that the onset of clinical manifestations occurs at 1-3 months of life, in this regard, identification of biomarkers in the first week of life becomes very important. Unfortunately, currently, not a single genetic marker has been identified that would accurately predict likelihood of a particular (AD); only the possibility of inheritance has been proven [9, 10]. Primary AtD prevention, as the first stage of the "atopic march" in AD development, is the main purpose of the involved scientific community. The principal condition for the developed complex of preventive measures shall be as follows: simplicity, versatility, personalized approach and orientation towards application in primary health care. Primary prevention at the outpatient-polyclinic level shall be aimed at a “conditionally healthy child” with latent sensitization.

Many years of experience in the treatment and prevention of AtD in children,

based on more than 15,000 positive clinical outcomes, reliable statistical results, summarized at the Department of Outpatient Pediatrics, Propedeutics of Childhood Diseases and Postgraduate Training of the Federal State Budgetary Educational Institution of Higher Education "Kemerovo State Medical University" of the Ministry of Health of the Russian Federation, headed by - Doctor of Medical Sciences, Professor Perevoshchikova Nina Konstantinovna, makes it possible to present this study.

Purpose of study: identification of clinical biomarkers in children with hereditary burden of atopy complications, allowing to optimize treatment and develop a complex for the primary prevention of AtD, adapted for the pediatric area.

Materials and study methods.

The studies were performed in the city of Yurga, Kemerovo region - Kuzbass during 2006-2016. The study objects were children's polyclinics, women's consultation, the city centre for family planning and human reproduction. It is impossible to develop a program for AtD treatment and primary prevention without atopic march features in children of the region, therefore the study consisted of three stages.

At the first stage, regional features and factors of bronchial asthma (BA) formation in children were studied. Individual clinical and laboratory assessment of the state of health was performed for 60 BA patients aged 2 to 8 years (average age 5.8 ± 2.54 years), the ratio of boys and girls was 5:1. The control group was represented by 50 children of the corresponding age (average age 5.08 ± 0.64), with no predisposition to atopy, the ratio of boys and girls was 1:4.

The factors of atopic process initiation and activation in children with BA, identified at the first stage of the study, were considered at the second stage during analysis of children with AtD to develop a program to prevent AtD transformation into respiratory forms of allergy. The group of children with AD was formed from the moment of disease diagnosis (n = 60) at the age from 1 to 24 months. (The average age was 7.0 ± 4.58 months old). The control group in this case was represented by children without hereditary burden of atopy (n = 50, average age 7.34 ± 0.96 months). The follow-up observation was performed until the age of 7 years.

The third stage of the study included the program development and implementation for the primary AtD prevention in children with hereditary burden. Statistical processing of the results was performed using "STATISTICA for WINDOWS 6.1 computer program.

Study results and discussion.

Analysis of BA formation in children (index group), who were registered at the regular medical check-up and receiving basic therapy, revealed the following patterns. The children were from traditional families with average material wealth, a higher level of parental education compared to the control group, and more comfortable living

conditions (p = 0.001). In most families, children were exposed to tobacco smoke: in the index group, 61.66% of fathers smoked in and 16.66% - both parents, in the control group, 63.33% of fathers and in 5% - both parents. In every third family of children with BA, despite the this disease, pets were kept, in the control group - in every second.

All children of the index group had a hereditary atopy burden, more often - on their mother's side. Among children's relatives in the control group (n = 344), AD was not registered, except for COPD in 8 people in the third generation, working in "harmful" industries.

In most cases, children of the index group were born from the first pregnancy (83.33%), from the second - 15% and one child from the third - 1.66%. Pregnancy with urgent delivery ended in 93.33% of women and in 6.66% - with abdominal delivery. The comparison group was also dominated by children born from the first pregnancy (63.33%), from the second - 30% and two children from the third - 6.66%. Pregnancy in all women ended in term birth.

Study of records from the maternity hospital, the attention was paid to a statistically significantly higher level of eosinophils in the peripheral blood in children of the index group when taken on the first day of life in the delivery room (2.88 ± 021% versus 0.28 ± 0.10% in the control group, p = 0.011), it was regarded as a factor of intrauterine sensitization.

There was a lack of rationality in the timing and forms of feeding in children of the index group: already from the first days of life, 15% of children were artificially fed, by three months more than half were transferred to artificial feeding without sound reasons, by six months only 11.66% of babies received breast milk; 41.66% of children in this group received whole cow's milk. In the control group, 60% of children under 6 months were breastfed. In each group, the timing and products introduced as complementary foods significantly differed from the recommendations of the National Program for Feeding Children of the First Year of Life.

In all children of the index group, in the first month of life, there was an intestinal syndrome, debuted in the form of intestinal colic, pathological impurities in feces, impaired motor function in the form of stool retention for up to several days. Against intestinal dysfunction (ID) background, during the 2nd-3rd month of life a rash appeared and during the 4th month there was skin process generalization, represented by erythematous-squamous elements. In the conditions of children's clinics, the complex of therapeutic measures included adherence to a hypoallergenic diet by the mother in case of natural feeding, or transferring the baby to a hypoallergenic mixture, H_1 histamine antagonists and topical glucocorticosteroids (tGCS). Due to persisting intestinal dysfunction at the 3rd month of life, a bacteriological study of feces was performed, which revealed the presence of CPB agents in 81.66% (n-49) children (Table 1).

Table 1
Control bacterial culture tests

Microflora	Norm in children	Children with BA (n-60)		Control group (n-50)		S
		indicators		indicators	abs. (%)	
Staphylococcus aureus	$\leq 10^1$	10^7 CFU/g	26(43.33)	10^3	28(56)	**0.185**
Klebsiella pneumonieae	$\leq 10^4$	10^8 CFU/g	13(21.66)	10^3	15(30)	**0.317**
Staphylococcus aureus and *Klebsiella pneumonieae*	0	10^6 CFU/g 10^6 CFU/g	10(16.66)	10^3	7(14)	**0.700**

The presence of *Staphylococcus aureus* and *Klebsiella pneumonieae* in the control group did not initiate even minor manifestations of food allergy in any child. Intestinal colic was less prolonged and less pronounced than in the index group and was relieved by simethicone preparations.

Based on bacteriological examination results, all children of the index group were prescribed probiotic treatment for up to one month with recommendations for parallel use of simethicone preparations for intestinal colic. In 18.33% (n-11) children at the age of 3 months, probiotic treatment within one month was performed based on only clinical manifestations of intestinal dysfunction.

Against the background of ongoing therapy, exacerbations of AtD alternated with disease-free periods and by the 5th month of life 2 children suffered from obstructive bronchitis. In the first year of life, every third child of the index group had bronchial obstruction. By the age of two, skin syndrome manifestations decreased in all children, but in seven of them (11.66%) BA was diagnosed, and by the age of seven, BA was present in all children of the index group. In 16 children (26.66%) BA was combined with allergic rhinitis (AR) and in ten (16.66%) children with AtD.

The main task at the second stage of the study was to interrupt the atopic march. Analysis of the reasons for AtD formation, as in children with BA, revealed in all cases a hereditary predisposition to atopy, primarily, on mother's side (Table 2).

Table 2

Allergic diseases of relatives of children with AtD

Diseases (ICD-10)	Generations of relatives					
	abs (%)					
	I		II		III	
	sister n-5 (1)	brother n-7 (2)	mother n-60 (3)	father n-60 (4)	grandmother n-110 (5)	grandfather n-98 (6)
Urt. (L50)[1]	2(40)	4(57.14)*	40(66.66)*	32(53.33)*	61(55.45)*	34(34.69)*
Urt. (L27.0)[2]	-	2(28.57)	11(18.33)	7(11.66)	34(30.90)	18(18.36)
AP(J30.1)	-	1(14.28)	1(1.66)	6(10)	2(3.33)	1(1.02)
AtD (L20)	4(80)	-	7(11.66)	3(5)	5(4.54)	3(3.06)
BA (J45.0)	1(20)	2(28.57)	9(15)	5(8.33)	31(28.18)	12(12.24)
control group relatives (n=349)						

	n-22	n-28	n-50	n-50	n-100	n-99
	(7)	(8)	(9)	(10)	(11)	(12)
Urt. (L50)[1]	-	-	4(8.0)	1(2.0)	7(7.0)	5(5.05)
Urt. (L27.0)[2]	-	2(7.14)	3(6.0)	5(10.0)	9(9.0)	7(7.07)

*- statistically significant differences, [1] urticaria caused by a food agent, [2] urticaria caused by a drug agent.

All children were brought up in traditional families. As compared with the control group, the families of children with AtD had a statistically significantly higher educational level of parents ($p = 0.001$), more comfortable living conditions ($p = 0.01$) and income ($p = 0.005$). In every third family of children with AtD, pets were kept; children in the control group were more often exposed to tobacco smoke ($p = 0.001$). From the moment of the first visit to a doctor, the children nutrition was brought in line with the National Program for Feeding Children of the First Year of Life.

The analysis of discharge epicrisis from maternity hospitals showed that the level of eosinophils on the first day of life, as in children with bronchial asthma, was statistically significantly higher than the indicators of children in the control group ($p < 0.001$).

Every third child was diagnosed with AtD in the first 3 months of life (31.63%), from 4 to 7 months - in 25.13%, in the second half year of life - in 31.55% and from 12 to 24 months - in 11.6%. Clinical manifestations of the atopic process onset (3-4 weeks of life) in children with AtD, as in the group of BA patients, were of the same type. The pattern of intestinal dysfunction and skin syndrome depended on the presence of *Staphylococcus aureus*, *Klebsiella pneumonieae*, or a combination of both. During bacteriological research, CPB agents were isolated in increased titers: *Staphylococcus aureus* 10^7 CFU/g (35%), *Klebsiella pneumonieae* 10^8 CFU/g (18.33%), their combination - in 17% of cases.

The presence of *Staphylococcus aureus* in the first month of life was manifested by ID, accompanied by intestinal colic, pathological inclusions in the form of mucus and "spinach stool". During the 5-6th weeks, a rash appeared in typical places (on the cheeks, neck, buttocks, natural folds) with subsequent generalization and had an erythematous and erythematous-squamous character. A distinctive feature of the presence of *Klebsiella pneumonieae* in the intestine was the presence of hemocolitis from single streaks of blood to abundant discharge. A feature of the skin syndrome, which we subsequently identified as a clinical marker of the presence of *Klebsiella pneumonieae*, was areas of dermis compaction and desquamation on the lateral surface of legs and thighs. In the presence of a combination of *Staphylococcus aureus* and *Klebsiella pneumonieae*, clinical manifestations were summarized.

The presence of CPB representatives in children of the control group was recorded in a low titer (10^3 CFU/g), was accompanied by intestinal colic without dyspeptic and skin syndromes, and were relieved by taking simethicone drugs.

Initially, we began to restore the balance of intestinal microbiocenosis in children with AtD, according to clinical recommendations (2004), using probiotic preparations.

Unfortunately, their use in children with AtD did not result in the required result, besides, in 18.33% of children, the aggravation of ID and skin syndrome was observed.

The problem of intestinal microbiocenosis disorders with a predominance of CPB in children with a hereditary predisposition to atopy in the first weeks of life, inefficacy of intestinal dysbiosis treatment, using dietary measures and the appointment of probiotics questioned relevance of the drug effect. Considering genetically determined individual features of the child's intestinal microbiota, possible development of anaphylaxis to administration of a foreign protein due to hereditary predisposition, it was necessary to choose the method of the least antigenic effect.

High increase of resistance to antibacterial drugs in recent years has revived interest in bacteriophages, being high-tech biological nanoobjects of the biosphere. Selective CPB decontamination with bacteriophages is an alternative to treatment with antibiotics and probiotic drugs (if medical effect is absent) and has no side effects. Bacteriophages selectively act only on CPB agents, making it possible to preserve and accelerate the formation of a unique and individual composition of the child's intestinal microbiota, capable of immunoregulatory balance formation in the Th1/Th2 system [11-16].

We corrected the intestinal biocenosis in children by eliminating *Klebsiella pneumoniae* and *Staphylococcus aureu*s strains using bacteriophages with a preliminary determination of sensitivity.

The selective action of bacteriophages on *Klebsiella pneumoniae* and *Staphylococcus aureus* allowed us not to disturb the genetically determined diversity of the intestinal microbiota of a child in the first weeks of life and made it possible to achieve a quick clinical effect: the intensity of intestinal colic decreased on days 2-3, intestinal syndrome was stopped on days 4-5 of using bacteriophages (Table 3).

Table 3

Dynamics of CPB decontamination in children with AtD after phagotherapy (3 courses)

Microflora	Norm in children	First study (3 months)				S
		Before treatment		After treatment		
		indicators	abs. (%)	indicators	abs. (%)	
Staphylococcus aureus	$\leq 10^1$	10^7 CFU/g	21(35)	10^3 CFU/g	5(8.33)	**0.002**
Klebsiella pneumonieae	$\leq 10^4$	10^8 CFU/g	11(18.33)	10^4 CFU/g	2(3.33)	**0.020**
Staphylococcus aureus and *Klebsiella pneumonieae*	0	10^7 CFU/g 10^6 CFU/g	10(16.66)	-	-	

The frequency of phagotherapy courses was selected individually depending on the sensitivity, the degree of dysbiotic disorders and ranged from 3 to 6.In patients with AtD in children with no sensitivity to bacteriophage (staphylococcal in 20.0% and

Klebsiella in 31.7%), the clinical effect also occurred on days 2-3 of drug administration.

Intestinal colic in children of the control group, who did not have hereditary burden of atopy, were less pronounced, were well relieved by simethicone drugs and presence of *Staphylococcus aureus* and *Klebsiella pneumoniae* did not initiate the development of an atopic process during follow-up. In case of prolonged intestinal colic in children from the control group, due to presence of 10^3 CFU/g of *Staphylococcus aureus* and *Klebsiella pneumonia* 10^4 CFU/g in the bacterial cultures of intestinal contents, 1-2 courses of phagotherapy were performed for decontamination, also provided a quick clinical effect.

Use of bacteriophages, as the main link in AtD treatment, significantly affected SCORAD index. During the first visit, the skin syndrome had a generalized form in all children and amounted to P ± Me, Q1-Q3 Me-34,12.4-74.4, after full complex of phagotherapy corresponded to P ± Me, Q1-Q3 Me-15, 6.0-43.7, having statistically significant differences (p = 0.001). Dynamic observation of children, control of total IgE level and preventive treatment in case of exceeding its indicators, made it possible to achieve the absence of skin manifestations in 98% of children and SCORAD index dynamics of children in 2 years was P ± Me, Q1-Q3 Me-0.0- 17.0 (p = 0.001).

Follow-up observation of children under 7 years old revealed the complete absence of the transformation of AtD into respiratory allergy forms.

The third stage of the study was devoted to the development of primary prevention of AtD in children and its implementation in procedures of children's city polyclinics. The program included pregravid training for women with AD and hereditarily predisposed to atopy in the postnatal period. The program was based on intestinal microbiota modelling, using bacteriophages.

The main atopy markers that allow the district pediatrician and allergist-immunologist of the children's clinic to perform preventive treatment are as follows:

1. Hereditary predisposition for atopy, considering even its insignificant manifestations in relatives up to the 3rd degree of relationship.

2. An increased level of eosinophils in peripheral blood at birth is equal to or exceeding 2%, reflecting intrauterine sensitization of the fetus and possible formation of an atopic phenotype in the future.

3. Intestinal dysfunction, manifested by severe intestinal colic, the appearance of pathological impurities in the form of mucus, “spinach greenery”, blood, impaired motor functions, regarded as a manifestation of allergic enteropathy.

Practically, we often limit ourselves to presence of the first two markers. The level of eosinophils in peripheral blood in a child with a hereditary predisposition for atopy equal to or exceeding 2% is an indication for bacteriological examination of feces and subsequent phagotherapy for selective decontamination.

The program implementation for the treatment and primary prevention of atopy in children with hereditary burden according to the statistics department has made it possible to reduce the number of children with AtD over the past 10 years by 7 times and BA by 9 times. At present, 0.02% of children have manifestations of AtD and 1.11% of children with BA, who have arrived for permanent residence from other regions.

Currently, the total number of children who underwent correction of dysbiotic disorders due to presence of atopy markers is more than 15,000 - it includes both urban and children from other regions and countries. During ten years of application, we have not registered a single case of side effects of bacteriophages; it allows us safe use as monotherapy for correction of microbiocenosis disorders not only in atopy-predisposed children.

CONCLUSONS: The problem of AD rate increase in children, with all the signs of an epidemic, absence of a general concept of treatment and prevention forces us to change the vector of scientific research towards new methods.

This problem can be solved only if preventive measures are applied in children with latent sensitization, clinical biomarkers will serve as a basis.

In our opinion, the new concept of measures shall be based on the active use of phagotherapy for correction of intestinal microbiocenosis disorders in children during the first weeks of life due to high selective activity of bacteriophages, rapid clinical effect, and absence of side effects.

More than ten years of use of bacteriophages, manufactured by domestic SUE Microgen, excludes lobbying effects and financial support.

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