TEMPLATE: Original Article

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Assessment of Tolerability and Safety of Monocomponent Complementary Food Products in the Diet of Infants With Risk for Allergic Diseases

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Article received: 24.03.2016; **accepted for publication**: 26.04.2016.

***Background**: Children with burdened allergological history and/or having preliminary allergy manifestations need the effective prevention of allergy from the first months of life. **Objective**: Our aim was to assess the tolerability, safety, and efficacy of monocomponent complementary food products in the diet of infants with high risk for allergic diseases. **Methods**: Tolerability, safety, and efficacy of monocomponent complementary food products (vegetable puree, fruit juices, and after 6 months — meat sauce) were studied in a singlecentre, prospective, comparative study. The symptoms of indigestion, skin allergy symptoms were registered, the results of coprological research and immunogenicity of complementary food products were assessed. **Results**: The study included 200 children in the age from 5 months from the risk group of allergy developing. Children were divided into 4 groups of 50 people. It was found that complementary food products were well tolerated and assimilated by children, did not cause skin and gastrointestinal allergic reactions in healthy children with risk of allergy developing. Food antigens of complementary food components (pumpkin, rabbit meat, turkey meat, apples, pears, plums) were characterized by low immunogenicity: the level of specific IgE to the specified products did not change in blood serum and remained at a low level at the beginning and at the end of the study (ranging from 0.01 to 0.03 kE/l). **Conclusion**: Studied complementary food products (vegetable-, fruit- and meat-based) can be used in the diet of children with high risk for allergy.*

***Keywords:** infants, food allergy, high risk, prevention, immunogenicity, complementary food.*

*(**For citation**:* Namazova-Baranova L.S., Turti T.V., Snovskaya M.A., Lukoyanova O.L., Zimina Y.P., Bakovich Y.A., Zokirova Z.F., Gorbachyova A.A. Assessment of Tolerability and Safety of Monocomponent Complementary Food Products in the Diet of Infants With Risk for Allergic Diseases. *Current pediatrics*. 2016;15(2):154−160. (In Russ). doi:10.15690/vsp.v15i2.1533.)

FOUNDATION

Over the past two decades, the prevalence of allergic diseases in babies has doubled and even tripled in some regions of Europe [1]. A similar tendency has been noted in Russia [2]. For this reason, special attention should be granted to allergy prevention, which should be adequate to the age and health conditions of the children – especially children with atopic predisposition [3]. The relevance of prophylaxis in reducing allergic diseases morbidity has been confirmed at the highest professional level – by The European Academy of Allergy and Clinical Immunology and the World Allergy Organization, EAACI-WAO [3].

Primary prophylaxis of allergic diseases is a complex of measures that prevents the development of atopy in children. The goal of primary allergy prophylaxis is not to allow the development of

sensibility to an allergen [4]. The hereditary factor is acknowledged as the dominant atopy development risk factor, among many others [5]. The results of multiple studies allow to predict with a high probability the development of an atopic disease in a child if his/her first-line relatives (parents, siblings) have it [6, 7]. Specifically, if both parents are "atopic" with the same disease symptoms, the risk of their children being ill increases by 50-80% as compared to the population where only one parent is "atopic" (by 20-40%) [6, 7]. Thus, an aggravated hereditary allergological anamnesis is a prognostic factor for the future development of allergy and allows ascribing a newborn to the high-risk group as early as the neonatal period [8, 9]. As the child continues to develop over the first years of life, the processes of atopic disease formation may continue. The child becomes "acquainted" with a vast spectre of various antigens, and, first of all, with food allergens, which play the leading role in the formation of sensitization [9]. This is the reason why the period when supplementary foods are introduced to the child can become a turning point in the development of an allergic disease. Big attention is given to the quality of the supplemental foods. Today it is recommended to introduce industrial-produced mono-component foods with a low allergenic activity [10].

The goal of our study was to evaluate the tolerance, safety and effectiveness of mono-component supplementary feeding products in early age children with a high risk of developing allergic diseases.

METHODS

Study design

A concentric prospective comparative study has been conducted (fig. 1).

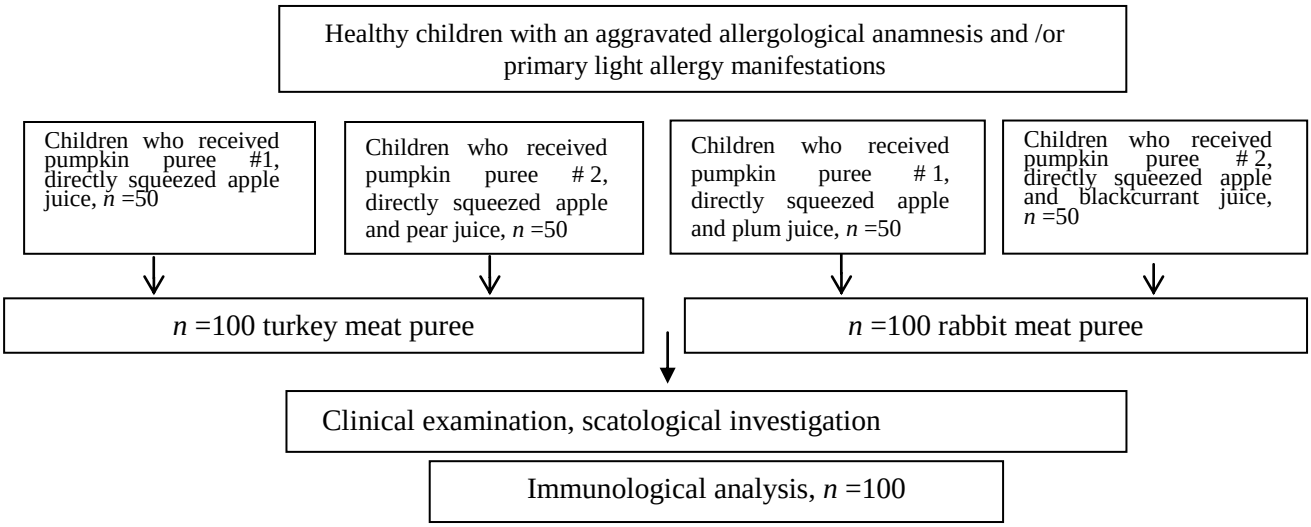

Fig. 1. Study design.

Correspondence criteria

Inclusion criteria:

- healthy children aged over 5 months;
- defined aggravated allergological anamnesis;
- presence of mild primary skin manifestations of allergy (single elements of allergic popular rash, hyperemia of skin and cheek, perineum, skin dryness etc.);
- presence of parental written informed consent to participation in the study.

Non-inclusion criteria:

- presence of the following in the ratio: industrial-made by any other brand and/or homemade meat (rabbit, turkey) puree, vegetable purees with pumpkin, fruit juices (apple, pear, plum, blackcurrant) as supplementary foods for early age children.
- contraindications to the studied supplementary foods.

Conduction conditions

The study was conducted in the Scientific Center of Children's Health (SCCH, Moscow) at the department of rehabilitative treatment for children with perinatal pathology over the period from November 2014 to January 2016.

Supplementary Foods

The studied supplementary foods were gradually introduced to the ration of children with hereditary predispositions to allergy and/or with light primary manifestations of allergy at the age of 5 months or older. The supplementary foods were: vegetable puree, fruit juices, and after reaching 6 months of age – meat puree ("FruitoNana", OAO "PROGRESS", Russia). The pumpkin puree was in two variants: recipe #1 – concentrated pumpkin puree, freshly frozen pumpkin, specially prepared drinking water; recipe #2 – freshly frozen pumpkin. The meat puree was also presented in two variants: rabbit meat puree and turkey meat puree.

Furthermore, the supplementary foods contained one of four fruit juices: directly squeezed apple juice, directly squeezed apple and pear juice, directly squeezed apple and plum juice, directly squeezed apple and blackcurrant juice.

The supplementary foods were introduced into the diet of each child corresponding to the recommended age norm: upwards 5 months – vegetable puree (10 – 150 g) and fruit juice (10 – 60 ml), upwards 6 months – turkey and rabbit puree (5 – 50 g). Puree volume were increased gradually, during 5-7 days, according to individual scheme.

Procedure of inclusion into the groups

Patients were hospitalized to the department of rehabilitative treatment of early-age children with perinatal pathology and were distributed to the attending doctor-scientist, who was offering only one of the four studied supplementary foods lines. After the legal representative received the necessary information about study and signed the informed consent, the child was included in one of the four groups.

Study outcomes and their evaluation

The tolerance to the studied foods was judged clinically: after introducing of studied food into the child's diet and during 10 days until the child will receive the whole volume of the food. The parents have been fixing the following symptoms of the functional GIT disorders in the observation diary: loss of appetite, flatulence, posseting, cramps and constipation.

For the children with the risk of allergic diseases development, safety of the studied supplementary foods was judged clinically, by the skin condition. The following allergic reactions were fixed in the observation diary: skin hyperemia, allergic papular rash.

In order to evaluate the efficiency of using studied supplementary foods we were controlling the dynamic of the physical development (weight, body length).

Scatological investigation

In order to evaluate assimilability of the studied foods a scatological investigation was conducted twice: before and after the including of the whole food volume. The investigation has been conducted in the SCCH centralized clinicodiagnostic laboratory. Consistency, shape, color and the presence of undigested foods were evaluated macroscopically while the presence of muscle fiber fragments, neutral fat, amylum (intracellular/extracellular), digested and undigested cellulose, mucus and leucocytes were evaluated microscopically.

Immunological investigation

Immunological investigations were conducted at the SCCH department of instrumental and laboratory diagnosing. Immunogenicity of the foods antigens'

Immunological research

Immunological studies are carried out in the NCCH department of instrumental and laboratory diagnostics. Immunogenicity of food antigens included in the studied supplementary foods was assessed in blood samples of about 2 ml using the ImmunoCap (Sweden) set. The concentration of specific IgE to antigens of pumpkin, rabbit and turkey meat, apples, pears, plums at the beginning and at the end of the study (not earlier than 14 days from the start of the product's introduction) was measured.

Ethical review

Study is approved by the Local independent ethics committee of NCCH (protocol of 11.12.2014)

Statistical analysis

The sample size was not calculated preliminarily. Statistical analysis of the data was made using the statistical software package STATISTICA v. 6.0 (StatSoft Inc., USA). Quantitative data are presented as median (25th, 75th percentiles). Between-group differences in quantitative variables were analyzed using the Kruskal-Wallis criteria. In case of statistically significant differences ($p < 0,05$), the pairwise comparison of independent samples was made using the Mann-Whitney's U-test. Alteration in the frequency indexes against the background of the use of supplementary foods was analyzed using the McNemar's criteria.

RESULTS

Study participants

200 healthy children in the age of 5 months of life and older [median 6 (5; 7) months] were included in the study. They had burdened allergic anamnesis, and / or a primary manifestations of mild allergies. There were 91 (45.5%) girls (Table 1). The groups were matched by sex, frequency of burdened allergic anamnesis and skin manifestations of allergy. However, the groups differed in age: the smallest age was in Group 4 (as compared to groups 1 and 2; $p = 0.008 / 0.001$, respectively).

Given the weak intensity of the allergies' skin manifestations, medication was not used. Children with skin allergy manifestations received local therapy (moisturizing ointment/cream).

Table 1. Characteristic of children included into the study.

Index	Group 1, *n* =50	Group 2, *n* =50	Group 3, *n* =50	Group 4, *n* =50	*p*
Age, months	6,2±0,7	6,4±0,5	5,9±1,2	5,5±1,45	0,045
Girls abs. (%)	22 (44)	20 (40)	20 (40)	27 (54)	0,326
Burdened allergic anamnesis, abs. (%)	22 (44)	21 (42)	18 (36)	19 (38)	0,837
Dermahemia, abs. (%)	6 (12)	8 (16)	8 (16)	6 (12)	0,816
Allergic rash, abs. (%)	12 (24)	5 (10)	10 (20)	11 (22)	0,497

Key findings

Tolerability and safety of supplementary foods

Over the entire study period (1 month), in connection with the impossibility of visiting the NCCH clinic, 10 children withdrew from the study: 4 of them from the group 2, 3 – from both groups 3 and 4.

In relation to children with known results of supplementary foods introduction, it has been established that they all tolerated the offered products well. No adverse events during the study were recorded. No refusal of taking it was fixed. Against the background of the use of supplementary foods, no new skin allergy manifestations were observed. Moreover, a significant improvement of the skin in children with skin manifestations of allergies at the start of the study was registered: 6 children of group 1 had skin hyperemia at the beginning of the study, and only 3 children had it in the end.12 and 6 children relatively had allergic papular rash. In the group 2, 8 and 2 children relatively had skin hyperemia, 5 and 3 children – allergic papular rash. In the group 3, 8 and 4 children and 10 and 8 children; in the group 4 – 6 and 2 children and 11 and 6 children relatively.

Immunogenicity of supplementary foods

Immunogenicity of supplementary was evaluated in 95 children (parents of 3 children refused to take a blood test, and 2 children had not been taken a blood test because of the difficulty in taking). It is shown that the use of supplementary foods in diet did not increase the content of specific IgE to any of its components (Table 2). Specific IgE levels remained low both in the beginning and at the end of the study.

Table 2. Dynamics of concentrations of specific IgE in children of the studied groups against the background of the use of the studied supplementary foods

Supplementary foods	**The concentration of specific IgE, KU/l**		***p***
	Initially	**Upon completion of the study**	
Group 1			
Pumpkin, *n* = 20	0,02 (0; 0,1)	0,03 (0; 0,04)	0,607
Turkey, *n* = 30	0,015 (0,01; 0,04)	0,01 (0,01; 0,04)	0,264
Apple, *n* = 20	0,02 (0,01; 0,04)	0,02 (0,01; 0,004)	0,072
Group 2			
Pumpkin, *n* = 28	0,02 (0; 0,07)	0,025 (0,01; 0,13)	0,609
Turkey, *n* = 37	0,01 (0,01; 0,05)	0,01 (0,01; 0,11)	0,115
Apple, *n* = 27	0,02 (0,00; 0,08)	0,02 (0,01; 0,03)	0,263
Pear, *n* = 50	0,01 (0,00; 0,05)	0,01 (0,00; 0,01)	0,560
Group 3			
Pumpkin, *n* = 20	0,02 (0,0; 0,08)	0,025 (0,02; 0,03)	0,886
Rabbit, *n* = 27	0,01 (0,01; 0,02)	0,01 (0,0; 0,03)	0,807
Apple, *n* = 22	0,01 (0,01; 0,06)	0,01 (0,01; 0,02)	0,350
Plum, *n* = 21	0,02 (0,015; 0,03)	0,03 (0,02; 0,04)	0,326
Group 4			
Pumpkin, *n* = 20	0,03 (0,0; 0,08)	0,03 (0,03; 0,04)	0,840
Rabbit, *n* = 10	0,01 (0,00; 0,03)	0,01 (0,01; 0,02)	0,804
Apple, *n* = 17	0,01 (0,00; 0,04)	0,02 (0,02; 0,02)	0,334

Additional findings

Weight change

Against the background of the supplementary foods introduction, physiological weight gain was observed in all groups (Table 3). No statistically significant differences in body weight values

between the groups were marked neither at the beginning nor at the end (after one month) of the study.

Table 3. Dynamics of body weight of children against the background of the use studied supplementary foods

Index	**Initially**	**After 1 month**	***p***
The change in body weight in kg			
Group 1	6,5 (6,3; 7,3)	7,5 (7,1; 8,0)	0,001
Group 2	6,9 (6,5; 7,4)	7,6 (7,2; 8,1)	0,001
Group 3	6.9 (6,2; 7,8)	7,8 (7,3; 8,3)	0,001
Group 4	7,1 (6,7; 7,2)	7,4 (7,0; 8,2)	0,001

Functional disorders of the gastrointestinal tract

At the start of the study, the prevalence of symptoms of the gastrointestinal tract functional disorders in groups was as follows: loss of appetite was observed in 6-18%, regurgitation syndrome - in 2-22%, flatulence - in 6-20%, cramps - in 2-12%, and constipation – in 6-24% of children. At the end of the study, the prevalence of some of the symptoms reduced by 2-2.5 times (Fig. 2).

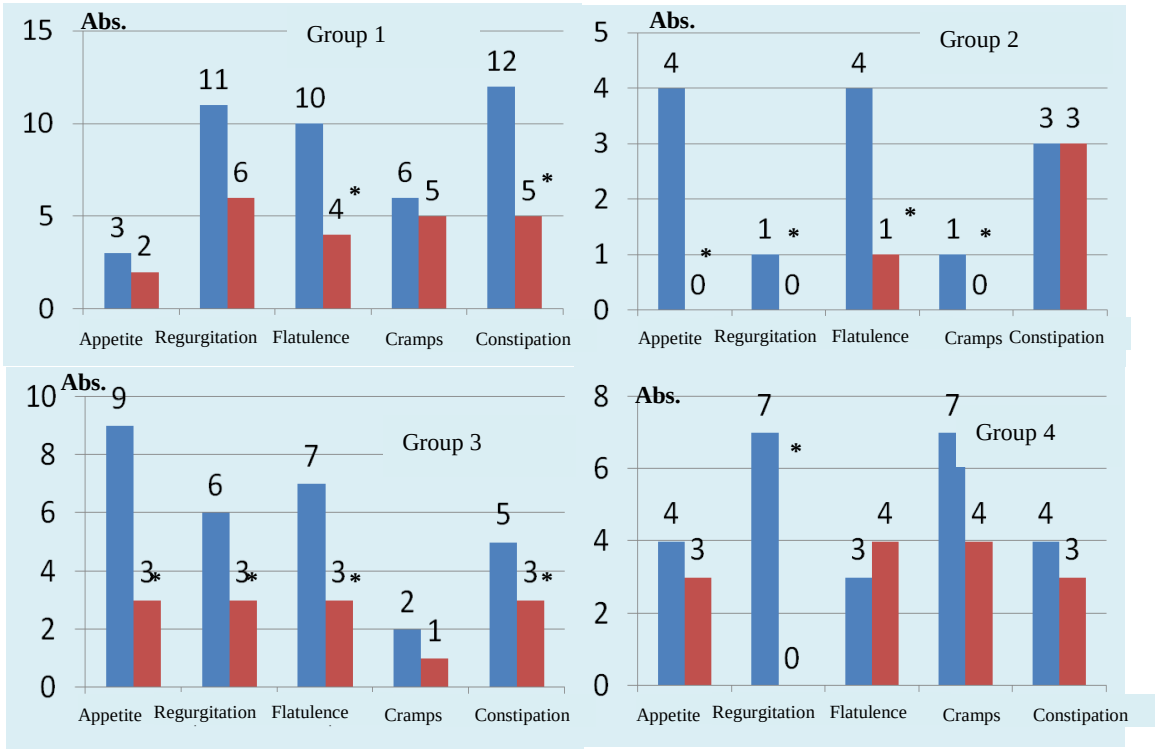

Fig. 2. Changes in the prevalence of functional disorders of the gastrointestinal tract against the background of the studied supplementary foods use.
Note. * p <0,05 — when compared to the baseline figure.

The results of the coprological study

Against the background of the supplementary foods use in the children's diet (vegetable and meat purees, juices), in most cases, a decrease in frequency of detection of neutral fat, mucus, vegetable cellular tissue (in groups 1, 2 and 3), and starch (in groups 1, 2 and 4) in the feces. In the group 4, a positive trend in frequency of detection of these coprogram's components was also recorded, but significant differences were not found (Table 4).

Table 4. Results of coprological research on the background of the studied supplementary foods introduction

Indexes	**Group 1, abs. (%)**		***p***	**Group 2, abs. (%)**		***p***	**Group 3, abs. (%)**		***p***	**Group 4, abs. (%)**		***p***
	Before, *n* =50	After, *n* =50		Before, *n* =50	After, *n* =46		Before, *n* =50	After, *n* =47		Before, *n* =50	After, *n* =47	
Neutral fat	14 (28)	2 (4)	0,001	25 (50)	15 (33)	0,046	17 (34)	7 (15)	0,048	21 (42)	13 (28)	0,105
Starch	9 (18)	3 (6)	0,001	12 (24)	9 (20)	0,028	5 (10)	4 (8,5)	0,301	14 (28)	5 (11)	0,001
Slime	6 (12)	2 (4)	0,001	19 (38)	6 (13)	0,001	14 (28)	8 (17)	0,001	30 (60)	17 (36)	0,897
Vegetable cellular tissue	14 (12)	9 (18)	0,001	17 (34)	13 (28)	0,033	15 (30)	7 (15)	0,001	22 (44)	15 (32)	0,220
White blood cells	0	0	–	2 (4)	1 (2)	0,001	10 (20)	1 (2)	0,001	14 (28)	6 (13)	0,001

DISCUSSION

Summary of the key research finding

The use of the supplementary foods with a low sensitizing potential in the diet of children of the allergy risk group can prevent the formation of atopic status.

Discussion of the key research finding

Currently, there is a consensus of experts of allergists and neonatologists leading scientific societies, that the optimal age of the supplementary foods introduction is between 4-6 months of life, which corresponds to the "tolerance window" [8, 10, 11]. These terms are also recommended for children of the allergy risk group [10]. It is also considered possible to appoint them "highly allergenic" products (milk, eggs, etc.). It was concluded that there is currently no convincing evidence of the need for specific recommendations for children of the allergy risk group in the period of the supplementary foods introduction (EAACI) [12, 13].

In the previous NCCH study, it was found that the Phadiatop Infant (ImmunoCAP, Sweden) qualitative test in children with clinical manifestations of allergy, (allergic skin reactions, food allergies, and atopic dermatitis) during the 1st year of life was positive in children with a burdened allergologic anamnesis – in 36%, and without a burdened anamnesis – in 30% of cases [9]. The increased content of sIgE to the protein of cow's milk and its protein fractions, to the protein of chicken eggs, and to the goat's milk is marked in the same children with both burdened and not burdened allergologic anamnesis. At the same time, higher concentrations of sIgE to antigens of wheat, white cabbage, and potatoes were registered in patients with allergoloic burdened heredity. The results indicate the formation of atopic status in these children [9].

Our and international experience show that knowledge of the kinds of products with high and low sensitizing potential allows us to develop effective full rations for children of the allergy risk group [10, 14, 15].

In our study, we obtained good effect when used the studied supplementary foods lines in the diet of children of the allergy risk group. The formation of specific IgE and atopic status formation in children were not revealed in any case. This indicates the low immunogenicity of the food antigens of pumpkin, rabbit and turkey meat, apples, pears, and plums.

CONCLUSION

The study of tolerability and safety of monocomponental supplementary foods has shown that low-allergenic products are well tolerated and assimilated, did not cause skin and gastrointestinal allergic reactions in healthy infants of the allergy risk group. Food antigens (mashed pumpkin, rabbit and turkey meet puree, mashed potatoes, apple, pear, plum), included in the meat and fruit-based supplementary foods, had low immunogenicity, and did not cause the formation of specific IgE in the blood serum. The studied supplementary foods can be used both in the diet of healthy children and in the diet of children of high allergy risk group, and also as a part of therapeutic diets of patients with allergic diseases.

Source of funding

This research was held with the support of the «PROGRESS» OJSC.

Conflict of interest

T.V. Turti, E.P. Zimina, E.A. Bakovich, Z.F. Zokirova, M.M. Snovskaya, O.L. Lukoyanova — received a research grant from the "PROGRESS" OJSC.

L.S. Namazova-Baranova, A.A. Gorbacheva declared they have no competing interests to disclose.

Acknowledgements

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We express our gratitude to the staff of the rehabilitation treatment for children with perinatal pathology department of the Scientific Center of Children's Health (Moscow).

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