Fecal zonulin as a prognostic marker of atopic march in children with food allergy

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Nelli G. Prihodchenko, Tatiana A. Shumatova, Daria V. Kovalenko

Pacific State Medical University, 2, Ostryakov Avenue, 690002, Vladivostok, Russia

Nelli Grigorievna Prikhodchenko — Dr. Sci., Associate Professor, Professor, Institute of Pediatrics, Pacific State Medical University, ORCID ID: 0000-0002-2106-2572, e-mail: prikhodchenko_n@mail.ru.

Tatyana Alexandrovna Shumatova — Dr. Sci., Professor, Director of the Institute of Pediatrics, Pacific State Medical University, ORCID ID: 0000-003-2668-8483, e-mail: shumatov@mail.ru.

Daria Vadimovna Kovalenko — assistant of Institute of Pediatrics, Pacific State Medical University, ORCID ID: 0000-0002-4852-6103, e-mail: sunny.dashu@mail.ru.

Abstract

Introduction. The onset of allergic diseases most often occurs in early childhood with the onset of food allergies, which can subsequently lead to the implementation of the atopic march. Increased intestinal permeability with high production of zonulin, the main moderator of intestinal tight junctions, can be an important link in the development of comorbid allergic diseases.

Material and methods. In order to study the significance of fecal zonulin as a marker for predicting the atopic march in children with food allergy, a cross-sectional retrospective study was conducted on 73 children aged 5 years who were diagnosed with food allergy (FA) to cow's milk proteins in the first year of life. In all children, when the diagnosis was made in the first year of life, the content of zonulin in feces was determined using the ELISA method.

Results. As a result of dynamic observation, all children with food allergy were divided into 2 groups: the first group consisted of children with food allergy who developed allergic rhinitis and/or bronchial asthma within 5 years (group I, n = 39), group 2 consisted of 34 children with food allergy who did not implement the atopic march within 5 years of observation (group II, n = 34). Our study showed statistically significant differences in the fecal zonulin level in the first year of life: group I Me = 2.39 ng/ml (Q1-Q3: 1.78–2.65 ng/ml), group II Me = 1.85 ng/ml (Q1-Q3: 0.49–0.91 ng/ml), p = 0.034. Strong direct correlations were found (Spearman correlation coefficient S = 0.681 ($p < 0.05$)) between the zonulin level in feces at the onset of the disease and the development of allergic rhinitis and/or bronchial asthma up to 5 years of age, the data were confirmed by comparing the areas under the curves during ROC analysis, AUC in the study of fecal zonulin as a prognostic marker of the risk of atopic march in children is 0.887, the optimal threshold (cutoff point) is 1.94 ng/ml.

Conclusions. Fecal zonulin level in children with food allergy can be an effective prognostic marker of atopic march development, its values in feces above 1.94 ng/ml allow us to predict with a high degree of probability the risk of atopic march development in children with food allergy to cow's milk proteins within 5 years.

Keywords: fecal zonulin level, atopic march, food allergy, children, intestinal barrier permeability

Conflict of interests:
The authors declare no conflict of interest.

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For correspondence:
Nelli Grigorievna Prikhodchenko, Doctor of Medical Sciences, Associate Professor, Professor of the Institute of Pediatrics, Pacific State Medical University.

Address: 2, Ostryakov Avenue, 690002, Vladivostok, Russia.

E-mail: prikhodchenko_n@mail.ru.

Для корреспонденции:
Приходченко Нелли Григорьевна, д. м. н., доцент, профессор Института педиатрии Тихоокеанского государственного медицинского университета.

Адрес: 690002, Владивосток, проспект Острякова, 2, Россия.

E-mail: prikhodchenko_n@mail.ru.

Фекальный уровень зонулина как прогностический маркер атопического марша у детей с пищевой аллергией

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Приходченко Н. Г., Шуматова Т. А., Коваленко Д. В.

Федеральное государственное бюджетное образовательное учреждение высшего образования «Тихоокеанский государственный медицинский университет» Министерства здравоохранения Российской Федерации, 690002, Владивосток, проспект Острякова, 2, Россия

Приходченко Нелли Григорьевна — д. м. н., доцент, профессор Института педиатрии Тихоокеанского государственного медицинского университета, ORCID ID: 0000-0002-2106-2572, e-mail: prikhodchenko_n@mail.ru.

Шуматова Татьяна Александровна — д. м. н., профессор, директор Института педиатрии Тихоокеанского государственного медицинского университета, ORCID ID: 0000-003-2668-8483, e-mail: shumatov@mail.ru.

Коваленко Дарья Вадимовна — ассистент Института педиатрии Тихоокеанского государственного медицинского университета, ORCID ID: 0000-0002-4852-6103, e-mail: sunny.dashu@mail.ru.

Аннотация

Актуальность. Дебют аллергических заболеваний чаще всего происходит в раннем детском возрасте с появления пищевой аллергии, что в последующем может привести к реализации атопического марша. Повышенная проницаемость кишечника при высокой продукции зонулина, основного модератора плотных контактов кишечника, может являться важным звеном развития коморбидных аллергических заболеваний.

Материалы и методы. С целью изучения значимости фекального зонулина как маркера прогнозирования атопического марша у детей с пищевой аллергией было проведено кросс-секционное ретроспективное исследование 73 детей в возрасте 5 лет, у которых на первом году жизни был выставлен диагноз пищевой аллергии (ПА) к белкам коровьего молока. У всех детей при постановке диагноза на первом году жизни в кале определяли содержание зонулина методом ELISA.

Результаты. В результате динамического наблюдения все дети с пищевой аллергией были разделены на 2 группы: первую группу составили дети с пищевой аллергией, у которых в течение 5 лет развился аллергический ринит и (или) бронхиальная астма (I группа, n = 39), вторую группу составили 34 ребенка с пищевой аллергией, которые не реализовали атопический марш в течение 5 лет наблюдения (II группа, n = 34). Наше исследование показало статистически значимые различия в фекальном уровне зонулина на первом году жизни: I группа Me = 2,39 нг/мл (Q1-Q3: 1,78–2,65 нг/мл), II группа Me = 1,85 нг/мл (Q1-Q3: 0,49–0,91 нг/мл), p = 0,034. Выявлены сильные прямые корреляционные связи (коэффициент корреляции Спирмена S = 0,681 (p < 0,05)) между уровнем зонулина в кале в дебюте заболевания и развитием аллергического ринита и (или) бронхиальной астмы до 5 лет, данные подтверждены при сравнении площадей под кривыми при проведении ROC-анализа, AUC при изучении фекального зонулина как прогностического маркера риска реализации атопического марша у детей составляет 0,887, оптимальный порог (точка отсечения) 1,94 нг/мл.

Выводы. Фекальный уровень зонулина у детей с пищевой аллергией может являться эффективным прогностическим маркером развития атопического марша, его значение в кале выше 1,94 нг/мл свидетельствовало о высоком риске развития у детей с пищевой аллергией к белкам коровьего молока аллергического ринита и (или) бронхиальной астмы в течение 5 лет.

Ключевые слова: фекальный уровень зонулина, атопический марш, пищевая аллергия, дети, проницаемость кишечного барьера

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A global burden on health care and the quality of life of patients in general is the widespread increase in the incidence, duration and severity of allergic diseases over the last few decades. Allergic diseases most commonly begin to manifest in young children, with food allergy (PA) being the starter disease, which is becoming more common each year. According to various authors, up to 10% of children in the first year of life are currently suffer from food allergies [1, 2]. It has also been observed that children with FA early in life have an increased risk of developing other allergic diseases later in life, including after the acquisition of immune tolerance to primary food allergens, which contributes to the realization of the atopic march (AM) [3, 4]. AM is characterized by significant costs to the health care

system and to families, and is practically the most expensive allergic condition [5, 6].

A number of authors have found that the development of clinical manifestations of FA in children is preceded by an increase in the permeability of the intestinal mucosa to macromolecules [7, 8]. Thus, the authors pointed out the relationship between increased permeability of the intestinal barrier and the development of allergic diseases of the respiratory system (allergic rhinitis and bronchial asthma); a direct correlation between the severity of diseases and intestinal permeability has been established [7]. This can be explained by the fact that the simultaneous presence of mucosal defects can be observed in many organs, and, in turn, antigenic load and the influence of environmental factors can cause the onset of clinical manifestations of this defect initially in one organ with subsequent accession of symptoms of damage to other organs and systems [9, 10]. For example, the same histologic changes were observed in the mucous membrane of duodenum and bronchi [11, 12].

Currently, only one physiologic mediator responsible for the regulation of intestinal permeability has been determined, and it is human zonulin [13, 14]. Zonulin has been shown to reversibly open tight junctions in protease-activated receptor 2 (PAR2) and epidermal growth factor receptor (EGFR), causing ZO-1 to be displaced from tight junctions. Under physiologic conditions, there is a tight control of mucosal antigen transport (antigen selection) that, in combination with specific immune cells and mediators of chemokines and cytokines, causes anergy and therefore mucosal tolerance [14]. Inadequate production of increased amounts of zonulin and subsequent loss of intestinal barrier function causes antigen transport from the lumen into the intestinal lamina, triggering innate and immunoregulatory reactions, forming a pro-inflammatory microenvironment. If this process continues, an adaptive immune response is determined, causing the production of proinflammatory cytokines, including interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), which cause further opening of the paracellular pathway and antigen passage, creating a vicious cycle [15]. Moreover, antigen presentation in human macrophages has been shown to be regulated by zonulin.

This changes the cytokine profile and causes the transition from immune tolerance to pathological reactions with the subsequent onset of allergic or chronic inflammatory disease, the nature of which depends on the genetic status of the individual, which determines which organ or tissue will be the target of the inflammatory process [16]. Increased intestinal permeability due to increased levels of zonulin is a key factor in hypersensitivity to exogenous allergens and the realization of atopic march [15–16].

OBJECTIVE of the present study was to investigate the significance of fecal zonulin levels as a marker for predicting atopic march in children with food allergy.

STUDY MATERIAL AND METHODS.

This work is a continuation and addition to the research work carried out by FGBOU VSMU of the Ministry of Health of Russia. Some results of this study were published earlier [17-18]. A cross-sectional retrospective study of 73 children aged 5 years who were diagnosed with food allergy (FA) to cow's milk proteins in the first year of life was conducted. The diagnosis was made in accordance with federal clinical guidelines, recommendations of the European Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists, the European Academy of Allergology and Clinical Immunology, and the European Academy of Allergology and Clinical Immunology. To confirm the diagnosis, sIgE to cow's milk was tested using a PHADIA 250 analyzer (Immuno CAP technology, the range of sIgE measurement to molecular components is from 0.10 to 100 kUA/l). The comparison group consisted of 20 healthy children of the

Table 1. **Mean values, median, interquartile range of fecal zonulin levels in children with food allergy and healthy children (author's table)**
Таблица 1. **Средние значения, медиана, интерквартильный размах фекального уровня зонулина у детей с пищевой аллергией и здоровых детей (таблица автора)**

Zonulin, ng/mL	FA (n = 73)	Control group (n = 20)
Mean	2,18	0,76
Minimum	0,84	0,26
Maximum	4,64	1,51
Mean deviation	0,35	0,19
Median	2,28	0,705
Quartile 1	1,75	0,49
Quartile 3	2,65	0,91

control group, with an unremarkable allergic history. All patients gave written consent to participate in the study.

In all children at diagnosis in the first year of life, the content of zonulin was determined in feces using reagents from Immundiagnostik (Germany) by enzyme-linked immunosorbent assay (ELISA). All children with food allergy were prescribed a strict elimination diet with the exclusion of cow's milk protein. Dynamic follow-up of the patients was carried out for 5 years

The study results were processed on a personal computer using the application program package STATISTICA 13.3 by StatSoft Inc. (USA). Methods of nonparametric statistics were used. Data are presented as median and quartiles (Me (Q1; Q3)). The nonparametric Mann-Whitney test was calculated for comparing quantitative indices, correction for multiple comparisons was performed using the Hill method. Correlation analysis with determination of Spearman correlation coefficient was used to identify the relationship, its degree and significance of differences between the signs. Sensitivity (Se), as well as specificity (Spe) of the identified predictors were assessed using ROC-curves, cutoff thresholds were determined.

RESLUTS. The mean age of the children at the time of diagnosis was 7.0 [4.0-10.0] months, 48 (65.7%) boys and 25 (34.3%) girls. The first symptoms of food allergy occurred in the first six months of life in 50 children (68.5%), with 27.4% (n = 20) in the first three months of life.

The most frequent manifestation of food allergy at the time of diagnosis in our study was gastrointestinal symptoms (regurgitation and vomiting, changes in the nature and consistency of stools, poor weight gain, malabsorption syndrome), which were observed in 78% of children (n = 57). Stools were unstable in 50 children (68.5%), intestinal colic and increased gas formation in 27 children (36.9%), diarrheal syndrome was characteristic of 18 patients (24.7%), constipation in 12 children (16.4%), regurgitation was noted in 49 patients (67.1%), and vomiting in 9 children (12.3%).

Skin symptoms were observed in 49 patients (67.1 %). In the majority of children (n = 42, 57.5 %) skin manifestations were mild, quickly regressed on the background of dietary therapeutic measures and external therapy. In 4 children (5.5 %), the skin syndrome manifested as urethral rashes after consumption of products containing cow's milk; the rashes disappeared independently or with the use of antihistamines.

There was a combination of symptoms of skin lesions and gastrointestinal tract in 45.2% (n = 33) of children, skin symptoms in these children were characterized by more pronounced rashes, torpid to the applied therapy.

Fecal zonulin levels were determined in all children with food allergy during acute clinical manifestations at diagnosis (Table 1). Our study showed a statistically significant (p = 0.014) increase in fecal zonulin in patients with FA (Me = 2.28 ng/mL, Q1-Q3: 1.75-2.65 ng/mL) compared with that of the control group (Me = 0.76 ng/mL, Q1-Q3: 0.49-0.91 ng/mL).

As a result of dynamic observation it was found that tolerance to cow's milk protein was formed by 15.1% of children (n = 11) aged, 41.1% of children (n = 30) aged 3 years, 36.9% of children (n = 27) aged 5 years. In 6.9% of children (n = 5), signs of FA to cow's milk protein persisted 5 years after diagnosis.

Allergic rhinitis developed in 17 children (23.3%), bronchial asthma in 12 (16.4%), and allergic rhinitis and bronchial asthma in 10 (13.7%) during the observation period. 34 children (46.6%) had no comorbid allergic conditions.

We analyzed the initial level of zonulin at the onset of the disease in all observed children depending on the realization of the atopic march. The first group consisted of children with food allergy who developed allergic rhinitis and/or bronchial asthma within 5 years (group I, n=39), the second group included 34 children with food allergy who did not realize the atopic march within 5 years of observation (group II, n=34).

Mean fecal zonulin concentrations in group I children were Me = 2.39 ng/mL (Q1-Q3: 1.78-2.65 ng/mL), in group II children — Me = 1.85 ng/mL (Q1-Q3: 0.49-0.91 ng/mL), in comparison group children were (Me = 0.76 ng/mL, Q1-Q3: 1.38-2.19 ng/mL), p = 0.034. Strong direct correlations (Spearman correlation coefficient S = 0.681 ($p < 0.05$)) were found between the level of zonulin in feces at the onset of the disease and the development of allergic rhinitis and/or bronchial asthma (realization of atopic march).

The following tests were used to evaluate the diagnostic values of the obtained results: diagnostic sensitivity (Se), diagnostic specificity (Sp), predictive value of positive result (PPV), predictive value of negative result (NPV), test accuracy (diagnostic efficiency of the test) (De). The distribution of groups was based on discriminant analysis.

The test result analysis of the analyzed groups revealed the sensitivity of the prediction model at the level of 90.9 %, and specificity — 76.4 %. At the same time, the predictive value of a positive result was 85.7 %, and that of a negative result — 74.6 %.

This suggests that the level of zonulin in feces at disease onset is non-invasive criterion of the risk of atopic march realization in children with food allergy and can be used as an objective prognostic marker indicating the risk of allergic rhinitis and/or bronchial asthma development.

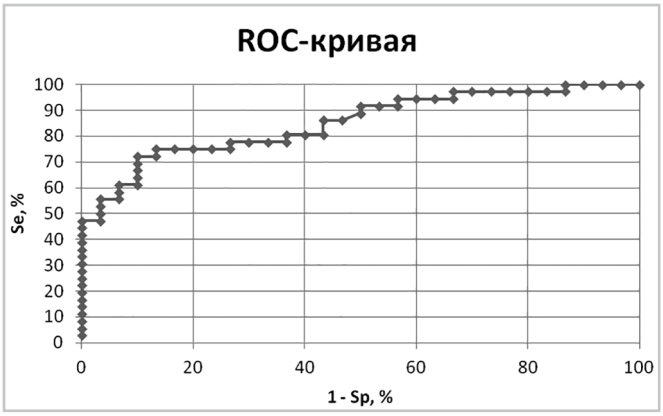

Fig. 1. **ROC analysis when comparing areas under the curves (illustration by the author)**
Рис. 1. **ROC-анализ при сравнении площадей под кривыми (иллюстрация автора)**

These observations were confirmed using ROC analysis when comparing the Area Under Curve (AUC) (Figure 1).

The AUC value in the study of fecal zonulin as a prognostic marker of the risk of atopic march in children is 0.887, the optimal threshold (cut-off point) is 1.94 ng/ml. According to the existing approaches to the evaluation of ROC-analysis results, the AUC value at the level of 0.8-0.9 corresponds to good quality of the model and can be used in clinical practice.

DISCUSSION OF FINDINGS.

The formation of the syndrome of increased epithelial permeability occupies a special place in the pathogenesis of allergic diseases. Disruption of barrier function, caused by defects in dense epithelial contacts, has a systemic effect and allows environmental triggers to penetrate more easily into the respiratory

tract and then interact with immune and inflammatory cells, in fact, being a factor in the realization of systemic allergic inflammation and the formation of atopy march [19, 20]. In continuation of our previous studies [18], we found that in patients with realized atopic march had significantly higher fecal zonulin levels at the debut of food allergy than children who had developed tolerance to cow's milk and had not realized other allergic diseases during 5 years. Zonulin is one of the few physiological mediators of paracellular intestinal permeability and is associated with the development of persistent inflammation. Inadequate activation of zonulin production causes functional loss of the epithelial barrier and causes a tolerance disorder with subsequent development of allergic intestinal diseases [21]. A number of studies have demonstrated that patients with bronchial asthma and allergic rhinitis have higher serum zonulin levels and concomitant increased intestinal permeability [22, 23], prolonged antigenic stimulation of the immune system subsequently causes inflammation of the airways [24].

These data are consistent with the results of a systematic review conducted by Alduray-wish S. A. et al [25], who showed that children with FA had a 2.1-5.3-fold and 1.6-5.1-fold higher risk of allergic rhinitis and bronchial asthma than children without FA, respectively. Moreover, sensitization to food allergens before 2 years of age increased the risk of asthma (pooled odds ratio OR 2.9, 95% confidence interval (CI) 2.0-4.0), atopic dermatitis (pooled OR 2.7, 95% CI 1.7-4.4) and allergic rhinitis (pooled OR 3.1, 95% CI 1.9-4.9) [25]. The authors have convincingly demonstrated that young children with food allergy have a high risk of additional allergic diseases with progression of atopic march. Therefore, preventing the development of atopic march and/or its progression at an early stage is important.

Our study showed that the threshold value of fecal zonulin level of 1.94 ng/mL is effective in predicting the risk of atopic march. This method allows to predict with high probability the risk of atopic march within 5 years in children with food allergy to cow's milk proteins with high sensitivity and specificity and provides an opportunity to carry out preventive measures for patients from the risk group.

The predictive value of the negative test is also high, which allows to predict reliably enough not only high but also low risk of atopic march realization.

Currently, various strategies have been proposed to moderate environmental factors, the microbiome, and to modify nutritional approaches in children at risk for allergy and atopy [25-30]. Given the multifactorial nature of allergic pathology, there are currently no evidence-based recommendations on the efficacy of any specific preventive approaches, but some measures currently proposed and used may indeed reduce the risk of atopic march. The nutrition of children in the first year of life is considered one of the most significant modifiable factors in early life and an important target for personalized interventions to prevent atopic marshes.

In most studies known to date, the protective effect of long-term (more than 6 months of life) breastfeeding has been proven, as it reduces not only the incidence of atopic dermatitis, but also other allergic diseases [25].

Analysis of data from the German Infant Nutritional Intervention (GINI) cohort at 20-year follow-up showed that, if breastfeeding is not possible, interventional use of a formula based on partially hydrolyzed whey proteins (NAN® Hypoallergenic 1, Nestle, Germany) in the first 4 months of life has a significant preventive effect on the risk of atopic dermatitis throughout the 20 years of follow-up, and reduces the prevalence of bronchial asthma and allergic rhinitis [26].

The data obtained in clinical studies by different authors on the possible preventive efficacy of different mixtures based on partially hydrolyzed proteins (pHF-W) served as a basis for rethinking the results of numerous studies on the effectiveness of pHF-W in preventing the development of allergic diseases.

The hydrolysis process of proteins is a key factor determining their biological function involving the formation of specific peptides. Peptide size alone is too simplistic to assess allergenic and tolerogenic potential. The amino acid sequence in peptides, which is directly affected by the method of hydrolysis, plays an important role in their ability to induce an allergic response and/or immune tolerance. The data presented in numerous sources show that not all pHF-Ws are equal with respect to their tolerogenic potential, as different pHF-Ws differ in their peptide composition, which depends on the production technology used for each particular mixture. In this context, the meta-analysis by H. Szajewska and A. Horvath [27], which included randomized trials evaluating the efficacy of a single formula based on partially hydrolyzed whey proteins (NAN® Hypoallergenic 1, Nestle, Germany) for allergy prevention in children, is of particular interest. The data presented in these studies provided further evidence that this pHF-W is tolerogenic and able to reduce the risk of atopic dermatitis in children at risk. Li X. et al. (2024) also found sufficient evidence that pHF-W reduces the risk of eczema in children younger or older than 2 years of age (OR: 0.71; 95% CI: 0.52, 0.96 and OR: 0.79; 95% CI: 0.67, 0.94, respectively). The authors also found moderate systematic evidence indicating that pHF-W reduces the risk of wheezing at age 0-2 years (OR: 0.50; 95% CI: 0.29, 0.85) [28].

A recent experiment evaluated the effect of NAN® Hypoallergenic infant formula (Nestle, Germany) on transepidermal water loss (TEWL) and allergic antibody production in mice dermally exposed to Aspergillus fumigatus [29]. Addition of the mixture to the diet of newborn mice caused a significant reduction in TEWL and total IgE, and aquaporin-3 gene expression, which is associated with skin hydration, was found to be modulated in mouse skin and human primary keratinocytes after exposure to pHF-W. Improvement of the skin barrier may be an additional mechanism by which pHF-W in NAN® Hypoallergenic formula may potentially reduce the risk of atopic march.

One of the key questions in developing preventive strategies for atopic march is to promote effective immunologic tolerance when introducing potentially allergenic foods into the infant's diet. As a result of several intervention studies, a scientific consensus is developing that earlier (but not earlier than 4 months of age) introduction of these foods may be recommended to improve prognosis and prevent the development of atopic marsch [31].

Thus, the global increase in allergic diseases significantly reduces the quality of life and necessitates the search for new approaches to their treatment and prevention. The atopic march theory facilitates our understanding of the pathophysiology of allergic disease comorbidity and further contributes to the early detection, prevention and treatment of children at risk of atopic march progression. Our study demonstrated the feasibility of investigating fecal zonulin levels to predict the risk of atopic marsch realization. Further studies are needed to validate and standardize the threshold value of zonulin as a biomarker of allergic inflammation. Currently, therapeutic and preventive strategies for food allergy are shifting from a "passive" elimination diet to an "active dietary therapy" that can shorten the duration of the disease and protect against the onset of an atopic march.

REFERENCES

1. Pampura A.N. Food allergies in young children. Pediatrics. Journal named after G.N. Speransky. 2016; 95(3):152–157. (In Russ.)
2. Renz H., Allen K.J., Sicherer S.H. et al. Food allergy. Nat Rev Dis Primers. 2018; 4: 17098. Published 2018 Jan 4. https://doi.org/10.1038/nrdp.2017.98.
3. Aw M., Penn J., Gauvreau G.M., Lima H., Sehmi R. Atopic march: collegium internationale allergologicum update. Int Arch Allergy Immunol. 2020; 181: 1–10. https://doi.org/10.1159/000502958.
4. Prikhodchenko N.G., Samal T.N., Ukraintsev S.E. et al. Stepped diet therapy for allergies to cow's milk proteins: a new strategy for safe change of stages. Questions of children's dietetics. 2021; 19 (2): 14–22. https://doi.org/10.20953/1727-5784-2021-2-14-22. (In Russ.)
5. Paparo L., Picariello G., Bruno C., et al. Tolerogenic effect elicited by protein fraction derived from different formulas for dietary treatment of cow's milk allergy in human cells. Front Immunol. 2021; 1: 3910. https://doi.org/10.3389/fimmu.2020.604075.

6. Revyakina V.A. The problem of food allergies at the present stage. Nutrition issues. 2020; 89 (4): 186–192. https://doi.org/10.24411/0042-8833-2020-10052. (In Russ.)
7. Ibragimova Z.Z., Gadzhieva S.M., Abdurashidova L.M. et al. Pathological physiology of food allergies in children. International Journal of Medicine and Psychology. 2023; 6 (1); 160–166. (In Russ.)
8. Yavuz S.T., Buyuktiryaki B., Sahiner U.M., et al. Factors that predict the clinical reactivity and tolerance in children with cow's milk allergy. Ann Allergy Asthma Immunol. 2013; 110 (4): 284–289.
9. Wang C.W., Preclaro I.A., Lin W.H., Chung W.H. An Updated Review of Genetic Associations With Severe Adverse Drug Reactions: Translation and Implementation of Pharmacogenomic Testing in Clinical Practice. Front Pharmacol. 2022; 13: 886377. https://doi.org/10.3389/fphar.2022.886377.
10. Sochaczewska D., Ziętek M., Dołęgowska B., Kordek A., Szczuko M. Implications of Indirect Biomarkers of Intestinal Permeability in the Stools of Newborns and Infants with Perinatal Risk Factors for Intestinal Colonization Disorders and Infant Feeding Patterns. Nutrients. 2022; 14 (11): 2224. https://doi.org/10.3390/nu14112224.
11. Levy M.L., Ward A., Nelson S. Management of children and young people (CYP) with asthma: a clinical audit report. NPJ Prim Care Respir Med. 2018; 28 (1): 16. https://doi.org/10.1038/s41533-018-0087-5.
12. West C.E., Renz H., Jenmalm M.C. [et al.]. The gut microbiota and inflammatory noncommunicable diseases: associations and potentials for gut microbiota therapies. J Allergy Clin Immunol. 2015; 135: 3–13; quiz 14. https://doi.org/10.1016/j.jaci.2014.11.012.
13. Ohlsson B., Orho-Melander M., Nilsson P.M. Higher levels of serum zonulin may rather be associated with increased risk of obesity and hyperlipidemia, than with gastrointestinal symptoms or disease manifestations. Int J Mol Sci. 2017; 18 (3): 582. doi: 10.3390/ijms18030582.
14. Kolyva S., Triga M., Kritikou D., Chrysis D. The effect of feeding patterns on serum zonulin levels in infants at 3–4 months of age. Eur J Pediatr. 2021; 180 (11): 3273–3278. https://doi.org/10.1007/s00431-021-04102-2.
15. Meyer R., Fox A.T., Chebar Lozinsky A., Michaelis L.J., Shah N. Non-IgE-mediated gastrointestinal allergies — Do they have a place in a new model of the Allergic March. Pediatr Allergy Immunol. 2019; 30 (2): 149–158. https://doi.org/10.1111/pai.13000.
16. Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Res. 2020; 9: 1000. https://doi.org/10.12688/f1000research.20510.1.
17. Prikhodchenko N.G., Shumatova T.A., Katenkova E.Yu., Kovalenko D.V. Clinical phenotypes of food allergy to cow's milk in children depending on the molecular profile of sensitization. Allergology and Immunology in Pediatrics. 2022; 2: 13–18. https://doi.org/10.53529/2500-1175-2022-2-13-18. (In Russ.)
18. Prikhodchenko N.G., Shumatova T.A., Kovalenko D.V. Assessment of the diagnostic significance of zonulin as a marker of the consistency of the intestinal barrier in children with food allergies. Modern problems of science and education. 2020; 5: 87. https://doi.org/10.17513/spno.30095. (In Russ.)
19. Yang L., Fu J., Zhou Y. Research Progress in Atopic March. Front Immunol. 2020; 11: 1907. https://doi.org/10.3389/fimmu.2020.01907. PMID: 32973790; PMCID: PMC7482645.
20. Prikhodchenko N.G., Shumatova T.A., Grigoryan L.A., Gordeets A.V. Tight intercellular junctions and zonulin in the formation of oral tolerance and food allergy. Pacific Medical Journal. 2019; 4 (78): 5–9. (In Russ.)
21. Yamaide F., Oniki N., Fikri B., Sato N., Nakano T., Shimojo N. Cord blood zonulin is associated with high-level sensitization to food allergen and food allergy development. Allergol Int. 2023: S1323–8930(23)00109-0. https://doi.org/10.1016/j.alit.2023.10.005.
22. Koksal B.T., Zengin H.Y., Ozbek O.Y. Assessment of Mucosa-Associated Epithelial Chemokine, Thymus-Expressed Chemokine, Periostin and Zonulin Levels in Infants With Atopic Dermatitis. Indian J Dermatol. 2022; 67 (3): 312. https://doi.org/10.4103/ijd.ijd_834_21.
23. Niewiem M., Grzybowska-Chlebowczyk U. Assessment of Selected Intestinal Permeability Markers in Children with Food Allergy Depending on the Type and Severity of Clinical Symptoms. Nutrients. 2022; 14 (20): 4385. https://doi.org/10.3390/nu14204385.
24. Baioumy S.A., Elgendy A., Ibrahim S.M. [et al.]. Association between serum zonulin level and severity of house dust mite allergic asthma. Allergy Asthma Clin Immunol. 2021; 17 (1): 86. Published 2021 Aug 31. https://doi.org/10.1186/s13223-021-00586-7.
25. Alduraywish S.A., Lodge C.J., Campbell B., Allen K.J., Erbas B., Lowe A.J., Dharmage S.C. The march from early life food sensitization to allergic disease: A systematic review and meta-analyses of birth cohort studies. Allergy. 2016; 71: 77–89. https://doi.org/10.1111/all.12784.
26. Gappa M., Filipiak-Pittroff B., Libuda L., von Berg A., Koletzko S., Bauer C.P., Heinrich J., Schikowski T., Berdel D., Standl M. Long-term effects of hydrolyzed formulae on atopic diseases in the GINI study. Allergy. 2021 Jun; 76 (6): 1903–1907. https://doi.org/10.1111/all.14709.

27. Szajewska H., Horvath A. A partially hydrolyzed 100 % whey formula and the risk of eczema and any allergy: an updated metaanalysis. World Allergy Organ J. 2017; 26; 10 (1): 27. https://doi.org/10.1186/ s40413-017-0158-z.
28. Li X., He T., Duan S., Liang J., Feng G., Li F., Shen Z., Ye W., Liu B., Jiang B., Chen Y., Liu N., Szeto I.M., Cai L. Infant Formulas With Partially or Extensively Hydrolyzed Milk Proteins for the Prevention of Allergic Diseases: A Systematic Review and Meta-Analysis of Clinical Trials. Adv Nutr. 2024; 15 (5): 100217. https://doi.org/10.1016/j.advnut.2024.100217.
29. Holvoet S., Nutten S., Dupuis L., Donnicola D., Bourdeau T., Hughes-Formella B., Simon D., Simon H.U., Carvalho R.S., Spergel J.M., Koletzko S., Blanchard C. Partially Hydrolysed Whey-Based Infant Formula Improves Skin Barrier Function. Nutrients. 2021; 13 (9): 3113. https://doi.org/10.3390/nu13093113.
30. Boggio Marzet C., Burgos F., Del Compare M., Gerold I., Tabacco O., Vinderola G. Approach to probiotics in pediatrics: the role of Lactobacillus rhamnosus GG. Arch Argent Pediatr. 2022; 120 (1): e1–e7. English, Spanish. https://doi.org/10.5546/aap.2022.eng.e1.
31. Vale S.L., Lobb M., Netting M.J., Murray K., Clifford R., Campbell D.E., Salter S.M. A systematic review of infant feeding food allergy prevention guidelines — can we AGREE? World Allergy Organ J. 2021; 14 (6): 100550. https://doi.org/10.1016/j.waojou.2021.100550.

ЛИТЕРАТУРА

32. Пампура А.Н. Пищевая аллергия у детей раннего возраста. Педиатрия. Журнал им. Г. Н. Сперанского. 2016; 95(3):152–157.
33. Renz H., Allen K.J., Sicherer S.H. et al. Food allergy. Nat Rev Dis Primers. 2018; 4: 17098. Published 2018 Jan 4. https://doi.org/10.1038/nrdp.2017.98.
34. Aw M., Penn J., Gauvreau G.M., Lima H., Sehmi R. Atopic march: collegium internationale allergologicum update. Int Arch Allergy Immunol. 2020; 181: 1–10. https://doi.org/10.1159/000502958.
35. Приходченко Н.Г., Самаль Т.Н., Украинцев С.Е., и др. Ступенчатая диетотерапия аллергии к белкам коровьего молока: новая стратегия безопасной смены этапов. Вопросы детской диетологии. 2021; 19 (2): 14–22.
36. Paparo L., Picariello G., Bruno C., et al. Tolerogenic effect elicited by protein fraction derived from different formulas for dietary treatment of cow's milk allergy in human cells. Front Immunol. 2021; 1: 3910. https://doi.org/10.3389/fimmu.2020.604075.
37. Ревякина В.А. Проблема пищевой аллергии на современном этапе. Вопросы питания. 2020; 89 (4): 186–192. https://doi.org/10.24411/0042-8833-2020-10052.
38. Ибрагимова З.З., Гаджиева С.М., Абдурашидова Л.М., и др. Патологическая физиология пищевой аллергии у детей. International Journal of Medicine and Psychology. 2023; 6 (1); 160–166.
39. Yavuz S.T., Buyuktiryaki B., Sahiner U.M. et al. Factors that predict the clinical reactivity and tolerance in children with cow's milk allergy. Ann Allergy Asthma Immunol. 2013; 110 (4): 284–289.
40. Wang C.W., Preclaro I.A., Lin W.H., Chung W.H. An Updated Review of Genetic Associations With Severe Adverse Drug Reactions: Translation and Implementation of Pharmacogenomic Testing in Clinical Practice. Front Pharmacol. 2022; 13: 886377. https://doi.org/10.3389/fphar.2022.886377.
41. Sochaczewska D., Ziętek M., Dołęgowska B., Kordek A., Szczuko M. Implications of Indirect Biomarkers of Intestinal Permeability in the Stools of Newborns and Infants with Perinatal Risk Factors for Intestinal Colonization Disorders and Infant Feeding Patterns. Nutrients. 2022; 14 (11): 2224. https://doi.org/10.3390/nu14112224.
42. Levy M.L., Ward A., Nelson S. Management of children and young people (CYP) with asthma: a clinical audit report. NPJ Prim Care Respir Med. 2018; 28 (1): 16. https://doi.org/10.1038/s41533-018-0087-5.
43. West C.E., Renz H., Jenmalm M.C., et al. The gut microbiota and inflammatory noncommunicable diseases: associations and potentials for gut microbiota therapies. J Allergy Clin Immunol. 2015; 135: 3–13; quiz 14. https://doi.org/10.1016/j.jaci.2014.11.012.
44. Ohlsson B., Orho-Melander M., Nilsson P.M. Higher levels of serum zonulin may rather be associated with increased risk of obesity and hyperlipidemia, than with gastrointestinal symptoms or disease manifestations. Int J Mol Sci. 2017; 18 (3): 582. https://doi.org/10.3390/ijms18030582.
45. Kolyva S., Triga M., Kritikou D., Chrysis D. The effect of feeding patterns on serum zonulin levels in infants at 3–4 months of age. Eur J Pediatr. 2021; 180 (11): 3273–3278. https://doi.org/10.1007/s00431-021-04102-2.
46. Meyer R., Fox A.T., Chebar Lozinsky A., Michaelis L.J., Shah N. Non-IgE-mediated gastrointestinal allergies. Do they have a place in a new model of the Allergic March. Pediatr Allergy Immunol. 2019; 30 (2): 149–158. https://doi.org/ 10.1111/pai.13000.
47. Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Res. 2020; 9: 1000. https://doi.org/10.12688/f1000research.20510.1.

48. Приходченко Н.Г., Шуматова Т.А., Катенкова Э.Ю., Коваленко Д.В. Клинические фенотипы пищевой аллергии к коровьему молоку у детей в зависимости от молекулярного профиля сенсибилизации. Аллергология и Иммунология в Педиатрии. 2022; 2: 13–18. https://doi.org/10.53529/2500-1175-2022-2-13-18.
49. Приходченко Н.Г., Шуматова Т.А., Коваленко Д.В. и др. Оценка диагностической значимости зонулина как маркера состоятельности кишечного барьера у детей с пищевой аллергией. Современные проблемы науки и образования. 2020; 5: 87. https://doi.org/10.17513/spno.30095.
50. Yang L., Fu J., Zhou Y. Research Progress in Atopic March. Front Immunol. 2020; 11: 1907. https://doi.org/10.3389/fimmu.2020.01907.
51. Приходченко Н.Г., Шуматова Т.А., Григорян Л.А., Гордеец А.В. Плотные межклеточные контакты и зонулин в формировании оральной толерантности и пищевой аллергии. Тихоокеанский медицинский журнал. 2019; 4 (78): 5–9.
52. Yamaide F., Oniki N., Fikri B., Sato N., Nakano T., Shimojo N. Cord blood zonulin is associated with high-level sensitization to food allergen and food allergy development. Allergol Int. 2023: S1323–8930 (23) 00109-0. https://doi.org/10.1016/j.alit.2023.10.005.
53. Koksal B.T., Zengin H.Y., Ozbek O.Y. Assessment of Mucosa-Associated Epithelial Chemokine, Thymus-Expressed Chemokine, Periostin and Zonulin Levels in Infants With Atopic Dermatitis. Indian J Dermatol. 2022; 67 (3): 312. https://doi.org/ 10.4103/ijd.ijd_834_21.
54. Niewiem M., Grzybowska-Chlebowczyk U. Assessment of Selected Intestinal Permeability Markers in Children with Food Allergy Depending on the Type and Severity of Clinical Symptoms. Nutrients. 2022; 14 (20): 4385. https://doi.org/10.3390/nu14204385.
55. Baioumy S.A., Elgendy A., Ibrahim S.M. [et al.]. Association between serum zonulin level and severity of house dust mite allergic asthma. Allergy Asthma Clin Immunol. 2021; 17 (1): 86. Published 2021 Aug 31. https://doi.org/10.1186/s13223-021-00586-7.
56. Alduraywish S.A., Lodge C.J., Campbell B., Allen K.J., Erbas B., Lowe A.J., Dharmage S.C. The march from early life food sensitization to allergic disease: A systematic review and meta-analyses of birth cohort studies. Allergy. 2016; 71: 77–89. https://doi.org/10.1111/all.12784.
57. Gappa M., Filipiak-Pittroff B., Libuda L., von Berg A., Koletzko S., Bauer C.P., Heinrich J., Schikowski T., Berdel D., Standl M. Long-term effects of hydrolyzed formulae on atopic diseases in the GINI study. Allergy. 2021 Jun; 76 (6): 1903–1907. https://doi.org/10.1111/all.14709.
58. Szajewska H., Horvath A. A partially hydrolyzed 100 % whey formula and the risk of eczema and any allergy: an updated metaanalysis. World Allergy Organ J. 2017; 26; 10 (1): 27. https://doi.org/10.1186/ s40413-017-0158-z.
59. Li X., He T., Duan S., Liang J., Feng G., Li F., Shen Z., Ye W., Liu B., Jiang B., Chen Y., Liu N., Szeto I.M., Cai L. Infant Formulas With Partially or Extensively Hydrolyzed Milk Proteins for the Prevention of Allergic Diseases: A Systematic Review and Meta-Analysis of Clinical Trials. Adv Nutr. 2024; 15 (5): 100217. https://doi.org/ 10.1016/j.advnut.2024.100217.
60. Holvoet S., Nutten S., Dupuis L., Donnicola D., Bourdeau T., Hughes-Formella B., Simon D., Simon H.U., Carvalho R.S., Spergel J.M., Koletzko S., Blanchard C. Partially Hydrolysed Whey-Based Infant Formula Improves Skin Barrier Function. Nutrients. 2021; 13 (9): 3113. https://doi.org/10.3390/nu13093113.
61. Boggio Marzet C., Burgos F., Del Compare M., Gerold I., Tabacco O., Vinderola G. Approach to probiotics in pediatrics: the role of Lactobacillus rhamnosus GG. Arch Argent Pediatr. 2022; 120 (1): e1–e7. https://doi.org/10.5546/aap.2022.eng.e1.
62. Vale S.L., Lobb M., Netting M.J., Murray K., Clifford R., Campbell D.E., Salter S.M. A systematic review of infant feeding food allergy prevention guidelines — can we AGREE? World Allergy Organ J. 2021; 14 (6): 100550. https://doi.org/10.1016/j.waojou.2021.100550.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted taking into account the requirements of the Helsinki Declaration of the World Association "Ethical Principles of Conducting Scientific Medical Research with human Participation" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of the Russian Federation dated 06/19/2003, No. 266. This study was approved by the Interdisciplinary Local Ethics Committee of the Pacific State Medical University of the Ministry of Health of the Russian Federation.

ЭТИЧЕСКОЕ ОДОБРЕНИЕ И СОГЛАСИЕ НА УЧАСТИЕ

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THE AUTHORS' CONTRIBUTION TO THE WORK

Nelly G. Prikhodchenko — conceptualization, formal analysis, investigation, visualization, writing — original draft.

Tatyana A. Shumatova — conceptualization, formal analysis, investigation, visualization, writing — review & editing.

Darya V. Kovalenko — investigation, conducting a research and investigation process, specifically performing the experiments, and data/evidence collection. Specifically writing the initial draft (including substantive translation). Provision of study materials, and patients.

ВКЛАД АВТОРОВ В РАБОТУ

Приходченко Н. Г. — разработка концепции, формирование идеи; формулировка и развитие ключевых целей и задач, анализ и интерпретация полученных данных, применение статистических и математических методов для анализа и синтеза данных исследования, подготовка и создание, оценка и редактирование текста, принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

Шуматова Т. А. — развитие ключевых целей и задач, проведение исследований, в частности сбор данных, ресурсное обеспечение исследования, утверждение окончательного варианта статьи, контроль и ответственность руководства за планирование и проведение научной деятельности.

Коваленко Д. В. — проведение исследований, в частности сбор данных, участие в научном дизайне, ресурсное обеспечение исследования, предоставление пациентов, лабораторных образцов для анализа, утверждение окончательного варианта статьи.