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Agreement between standard methods of Food hypersensitivity diagnostics

Introduction

Hypersensitivity to food products in children remains actual medical problem. Among the existing difficulties in the management of such patients lack of a single protocol for oral challenge test (OCT) is often mentioned [6]. In practice, especially for preschool children, traditional methods of diagnostics are still often used: skin tests, determination of antibody levels. A number of multicenter studies have shown that due to limitations of OCT, it is possible to use results of skin test and the definition of sIgE to predict results of the OCT. Such approach can reduce risk of anaphylaxis, simplify diagnostic search [3, 5, 9]. Other studies have shown that results of the prick test are informative to determine the need for OCT. It was proved that 50% of children with negative skin tests had positive OCT [4]. Moreover, experts recently recommended performing OCT when the results of the skin test and determination of specific IgE antibodies have insufficient clinical significance (recommendation level IV, D) [6]. Differential diagnosis of primary specific hypersensitivity and cross-reactivity to protein with common epitopes will help to avoid unnecessary elimination diet and improve the quality of life of patients. In this regard traditional methods of allergic examination often have irrelevant results [6]. That is why the actual search for the simple and effective approaches to correct use of traditional methods for diagnostics of food hypersensitivity (FH), which minimizes possibility of a misdiagnosis, remains actual. The key to this is the correct association of anamnestic, clinical and additional methods. Also it is important to take to consideration possibility of the processes of natural formation of oral tolerance, which may affect the age-specific features of diagnostic approaches [1]. Taking into account scientific and practical interest to the study of agreement between standard methods for diagnostics of food hypersensitivity in children of all ages there is a need to clarify the possibility of their replacement use.

The aim of the research was to study agreement between standard methods of diagnostics of Food hypersensitivity (FH) in children.

Materials and methods of research

From 2011 to 2016, the study included 424 children aged 1 month to 18 years with symptoms of food hypersensitivity (FH) on the skin (age was 26.3 [12.1; 54,25] months). Children were randomly recruited from patients of the allergic department of the communal institution «Zaporizhzhya city many profile hospital № 5», the outpatient department of the University Clinic of the Zaporizhzhya State Medical University.

Statistically significant gender differences were absent ($\chi 2 = 0.08$, $p = 0.7$), boys (n = 210 (49%)) and girls (n = 214 (51%)) did not differ by age (Mann –Whitney U Test, U = 21496.00, p = 0.44). The majority of patients were under the age of 4 years – 59.4% (n = 252). FH was diagnosed and evaluated in accordance with EAACI (European Academy of Allergy and Clinical Immunology) and the recommendations of the WAO (World Allergy Organization) (Johansson S.G. et al. 2001; Johannson S.G.O. et al., 2004). Presence of skin allergy-related symptoms associated with the intake of food products, which appear or intensify during repeated use, was a criterion for inclusion in the study. 100% of children had a reported FH according to the questionnaire. The average age of the debut was 7 [3; 15.5] months, the average duration of the disease was 13.65 [2.05; 32.28] months.

Examination included skin allergy testing with standardized allergy test (Immunolog Ltd, Ukraine), determination of specific antibodies to food allergens (sIgE) in blood serum by immunoassay (ELISA). Skin allergy testing was conducted in accordance with the generally accepted methodology. Blood samples were taken from the elbow vein in a sitting position using vacutiters in special refrigerated transport tubes. Transportation of samples to the laboratory was carried out with the storage of in cold chain + 2 – + 8°C. The provocative tests were performed according to the recommendations of DBPCFCPractall–JACI-2012 after evaluating of the anamnestic and clinical data, obtaining results of skin testing and determining of the level of antibodies [1, 11]. In the presence of clinical signs of an immediate type of allergic reaction, as well as in the age of one year and from one to three years, only an open oral provocative test was used. The evaluation of the results was carried out only in the presence of objective symptoms.

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Statistical analyzis of the results was carried out with statistical software package «Statistica 6.0» (StatSoftInc package, USA, license number AXXR712D833214FAN5). All data was given in the form of the median (Me), interquartile interval [Q25; Q75]. The hypothesis about the normality of the distribution of the studied parameters was checked using the criterion Shapiro–Wilk. To analyze the conjugation tables 2X2, when comparing categorized variables, the Chi2 test was used. Mann–Whitney U Test was used to compare unbound groups. The effect of factors on the sign was studied using one–factor dispersion analysis (Kruskal–Wallis test ANOVA). The differences were considered to be valid at values $p < 0.05$. The assessment of consistency between diagnostic methods was performed with Kappa Cohen coefficient (κ). Agreement was considered as high when Kappa coefficient (κ) was higher than 0.75, good – from 0.4 to 0.75, poor – less than 0.4. The calculation was done using Microsoft Excel.

The work was carried out within the framework of the research work of the Department of Faculty of Pediatrics of the ZSMU of the Ministry of Health of Ukraine and is a fragment of the planned scientific topic: «Development of methods for early diagnosis of the most common allergic diseases in children of different age groups, prevention and treatment of major functional disorders and concomitant pathology in this group of patients», state registration number 0112U005648.

Results. According to the standard diagnostic algorithm, skin allergy tests were performed in 290 children, the rest (31%, n = 134) of the patients had contraindications due to the severity of clinical manifestations. Increased levels of specific IgE to food products were detected in 21.2% of children. More often, specific IgE antibodies were detected to cow milk and hen egg allergens. Oral challenge test with food allergens was positive in 36% (n = 125) patients (Table 2).

Statistically significant difference between age groups was found only by assessing of anamnestic data (Kruskal–Wallistest: H (4, N = 424) = 16.4 p = 0.003) and the oral provocative test results (H (4, N = 196) = 29.5 p = 0.001), as well as their combination (H (4, N = 196) = 29.50 p = 0.001). Analysis of the combination of tests presented in Fig. 1

As it can be seen from the Fig. 1, self–reporting and detection of sIgE can detect immune FH in children under 1 year of age significantly more often than after 1 year. Combination of anamnesis and skin tests is roughly informative in different age groups. At the same time, the highest number of FH can be confirmed by a combination of anamnesis and OCT: from 60% to 1 year, to 15% in children from 4 to 6 years. It should be noted that the majority of such children were at an early age (average age 35 [14; 50] months, mean age of the debut of symptoms was 11.5 [5; 18] months).

Agreement level (Kappa Cohen) between methods was calculated depending on the age of the patient (Table 3).

As it can be seen from the Table. 3, the range of values of Kappa coefficient did not exceed 0.4, which corresponded to low coherence between the methods. It has been found that children over the age of 1 may have the reproducibility of the skin prick–test and evaluation of sIgE (κ 0.5 (95% CI 0.4–0.59), sIgE and OCT (κ 0.5 (95% CI 0.47–0.53).

Table 1. Demographic data of patients

Age	Total, n (%)	Males, n (%)	Females, n (%)
Total	424 (100%)	210 (49%)	214 (51%)
Up to 1 year	118 (27,8%)	56 (26,6%)	62 (28,9%)
1–3 years (early pre-school period)	134 (31,6%)	74 (35%)	60 (28%)
4–6 years (pre-school period)	114 (26%)	60 (28,5%)	54 (25,2%)
7–11 years (junior school period)	48 (11,3%)	16 (7,6%)	32 (14,9%)
12–18 years old (senior school period)	10 (2,3%)	4 (1,9%)	6 (2,8%)

Table 2. Prevalence of immune food hypersensitivity in children of different age groups, detected by different methods

	Self-reporting (n = 424)	sIgE (n = 254)	Skin prick-test (n = 370)	Oral provocation test (n = 340)
Up to 1 year	80/118 (67%)*	18/62 (29%)*	14/9 (15%)*	51/84 (60%)*
1–3 years	62/134 (46%)	22/90 (24%)$	23/118 (19%)	48/116 (41%)#,$
4–6 years	54/114 (47%)	12/66 (18%)	12/113 (10%)	14/90 (15%)
7–11 years old	30/48 (62%)	2/30 (6%)	2/45 (4%)	10/42 (23%)
12–18 years old	4/10 (40%)	4/10 (40%)	2/9 (22%)	2/8 (25%)
Total	230/424 (54,2%)	54/254 (21,2%)	53/378 (14%)	125/340 (36%)

Note: statistically significant difference ($\chi 2$) ($p < 0,05$), namely: * – compared to children of all other age groups, # – children aged 1–3 years, $ – children aged 4–6, | – Children aged 7–11 years.

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The range of the confidence interval indicates the possibility of false results, since the values correspond to a range of average or good coherence. None of the methods was highly consistent.

Discussion of the results

A literature review has shown that anamnesis analysis remains a valuable first step in verifying the diagnosis. Metaanalyzes of recent studies by other authors have shown that the evaluation of anamnestic data, or so–called «self–report» (self–reporting), remains relevant. However, as it was shown by the Jorge A. et al., 2017, its prevalence varies from 3 to 35% depending on age, region, and methodology, which may cause problems with verifying the diagnosis of FH [10]. Some references contain conclusions that patients in most cases overestimate the association of allergy symptoms on the skin with foods [6].

The results of our work have shown that the combination of data from anamnesis and skin tests is approximately equally informative in different age groups. At the same time, the highest number of FH can be confirmed by combination of anamnesis and OCT: from 60% to 1 year, to 15% in children from 4 to 6 years. This was confirmed by the data of the Kruskal–Wallis test: H (4, N = 424) = 16.4 p = 0.003 and H (4, N = 196) = 29.5 p = 0.001, respectively).

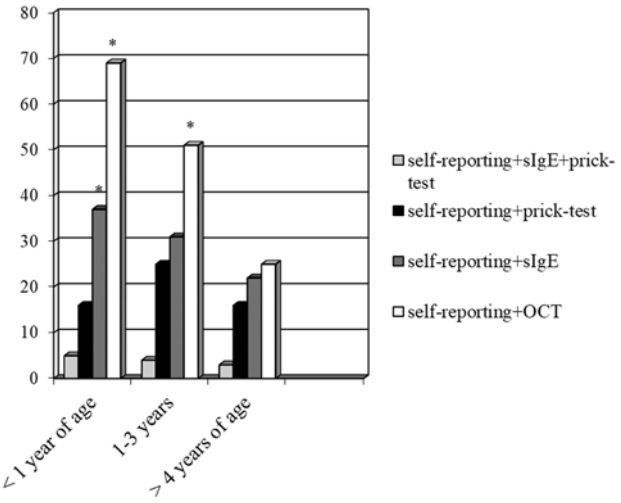

Fig. 1. **Prevalence of FH, which was confirmed by a combination of traditional methods of allergic diagnosis, at different age periods.** ***Note: difference between groups calculated with tables of the expected frequencies χ2 (p > 0,05), * – a statistically significant difference compared with the group of children over the age of 4 years.***

It was found that the highest prevalence of FH, which can be detected by traditional allergic tests, was obtained among the young patients (from 15% to 60% depending on the method), while after 4 years the number of positive results in all diagnostic methods decreased sharply (10% –18% depending on the method). However, the results of one–factor dispersion analysis (Kruskal–Wallis test ANOVA) showed that the statistically significant difference between age groups was found only in the analysis of anamnestic data (Kruskal–Wallistest: H (4, N = 424) = 16.4 p = 0.003) and the oral provocation test (H (4, N = 196) = 29.5 p = 0.001), as well as their combination.

Assessment of the diagnostic significance of the categorical diagnostic approach for verifying of FH, which is the most widespread and relevant for general practitioners was done in this research. Literature review showed different informative value of such approach, even depending on the size of the reaction on the skin when tested and the levels of specific antibodies [7]. However, despite the large number of these works, they all provide different data depending on the type of food product, underline age–specific features of the skin and the immune system [2]. Results of the performed work showed that the evaluation of classical methods of allergic examination, when the absolute levels of specific antibodies and the absolute size of the skin reaction, as well as the type of allergen are not taken into account, but only the fact of the positive result of the test, has had the greatest effectiveness in children, who had debut symptoms of FH on the skin occurred at the age of more than 1 year. This conclusion coincides with the work of Ling L. et al. (2016) who proved that in the case of allergies to seafood, nuts and eggs in adults interchangeability of these methods is possible, which was confirmed by the consistency between them (Kappa from 0.4 to 0.87, p < 0.05) [8]. At the same time, Chauveau A. and co–authors (2017) who studied the consistency of these survey methods in school–age children, noted that despite the same AUC for skin testing and specific antibodies, their compliance for the detection of asthma and allergic rhinitis was estimated for kappa coefficient, the mean, prick test is still more specific than sIgE, although their sensitivity is not different [11]. The range of values of the Kappa coefficient based on the results of our work did not exceed 0.4, which corresponded to a low consistency

Table 3. Agreement (κ) between traditional methods for diagnostics of the immune food hypersensitivity in children of different age groups

	Agreement (κ), κ (95% CI)				
	Between self-reporting and sIgE	Between self-reporting and prick-test	Between prick-test and sIgE	Between prick-test and OCT	Between sIgE and OCT
Age of patients < 1 year >1 year	 0,21 (–0,20–0,62) 0,14 (–0,07–0,37)	 0,02 (–0,35–0,29) 0,12 (–0,07–0,32)	 0,16 (–0,1–0,42) 0,5 (0,4–0,59)	 0,29 (–0,09–0,68) 0,56 (0,49–0,62)	 0,19 (–0,1–0,40) 0,50 (0,47–0,53)
In general	0,18 (–0,01–0,37)	0,09 (–0,07–0,49)	0,41 (0,34–0,49)	0,49 (0,35–0,51)	0,42 (0,30–0,55)

Note. κ – Cohen's Kappa coefficient, 95% CI – confidence interval.

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between the methods. The age–specific features, namely, the possibility of reproduction in children over the age of 1 year in the prick–test and sIgE (κ 0.5 (95% CI 0.4–0.59), sIgE and OCT (κ 0.5 (95% CI 0, 47–0.53) were the highest. However, the range of the confidence interval indicates the possibility of erroneous results, since the values correspond to a range of average coherence. In children under the age of 1 year, the level of consistency was unsatisfactory (less than 0.4) These results indicate the need for the entire algorithm standard diagnosis of food hypersensitivity and the impossibility of replacing one method with others, as in children older than 12 months and in children aged less thanr 1 year even with positive results of prick tests and determination of specific Ig E.

Conclusions. It was found that FH more frequently can be confirmed by a combination of anamnesis and OCT: from 60% to 1 year, to 15% in children from 4 to 6 years. The results of statistical analysis showed that the statistically significant difference between age groups was found only on the basis of an analysis of anamnestic data (Kruskal–Wallistest: H (4, N = 424) = 16.4 p = 0.003) and the oral challenge test (H (4, N = 196) = 29.5 p = 0.001), as well as their combination (H (4, N = 196) = 29.50 p = 0.001).

The agreement between the standard methods of allergic diagnostics of food hypersensitivity in children younger than 1 year of age is low. It was found that in children older than 1 year the coherence of average strength was detected between the skin prick–test and sIgE (κ 0.5 (95% CI 0.4–0.59), sIgE and OCT (κ 0.5 (95% CI 0, 47–0.53).

Conflict of interest. The authors do not have any conflict of interest.

Список літератури

1. Begin P., Nadeau K.C. Diagnosis of Food Allergy. Pediatric annals. 2013. Vol 42 (6). P. 102–109. URL: doi:10.3928/00904481–20130522–10.
2. Schoos A.M., Chawes B.L., Isgaard N.V. et al. Disagreement between skin prick test and specific IgE in young children. Allergy. 2015. Vol. 70 (1). P. 41–48. URL: doi: 10.1111/all.12523.
3. O'Keefe A.W., De Schryver S., Mill J. et al. Diagnosis and management of food allergies: new and emerging options: a systematic review. J. Asthma Allergy. 2014. Vol. 7. P. 141–164.
4. Asero R., Fernandez–Rivas M., Knulst A.C., Bruijnzeel–Koomen C.A. Double-blind, placebo-controlled food challenge in adults ineveryday clinical practice: a reappraisal of their limitations and real indications. Curr. Opin. Allergy Clin. Immunol. 2009. Vol. 9 (4). P. 379–385.
5. Muraro A., Werfel T., Hoffmann–Sommergruber K. et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014. Vol. 69 (8). P. 1008–1025.
6. Kido J., Hirata M., Ueno H. et al. Evaluation of the skin–prick test for predicting the outgrowth of cow's milk allergy. Allergy Rhinol (Providence). 2016. Vol. 7 (3). P. 139–143. URL: doi: 10.2500/ar.2016.7.0175.
7. Nedelska S.N., Pakholchuk O.P. An 8–month old with Erythema nodosum – clinical case report, literature review. Pathology. 2015. Vol. 2. P. 114–116.
8. van Kampen V., Rabstein S., Sander I. et al. Prediction of challengetestresults by flour–specific IgE and skin prick test in symptomatic bakers. Allergy. 2008. Vol. 63 (7). P. 897–902. URL: doi: 10.1111/j.1398–9995.2008.01646.x.
9. Jorge A., Soares E., Sarinho E. et al. Prevalence and clinical features of adverse food reactions in Portuguese children. Allergy, Asthma, and Clinical Immunology: Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2017. Vol. 13. P. 40. URL: doi:10.1186/s13223–017–0212–y.
10. Chauveau A., Dalphin M.L., Mauny F. et al. Skin prick tests and specific IgE in 10–year–old children: Agreement and association with allergic diseases. Allergy. 2017. Vol. 72 (9). P. 1365–1373. URL: doi: 10.1111/all.13148
11. Пахольчук О.П., Недельська С.М. Вікові особливості IgE-залежної гіперчутливості до харчових продуктів у дітей різного віку, підтвердженої методом прик та патч-тестування. Здоровье ребенка. 2017. № 7 (12). С. 749–753.

References

1. Begin P, Nadeau KC. Diagnosis of Food Allergy. Pediatric annals. 2013;42(6):102–109. URL: doi:10.3928/00904481–20130522–10.
2. Schoos AM, Chawes BL, Isgaard NV, et al. Disagreement between skin prick test and specific IgE in young children. Allergy. 2015;70(1):41–48. URL: doi: 10.1111/all.12523.
3. O'Keefe AW, De Schryver S, Mill J, et al. Diagnosis and management of food allergies: new and emerging options: a systematic review. J. Asthma Allergy. 2014;7:141–164.
4. Asero R, Fernandez–Rivas M, Knulst AC, Bruijnzeel–Koomen CA. Double–blind, placebo–controlled food challenge in adults ineveryday clinical practice: a reappraisal of their limitations and real indications. Curr. Opin. Allergy Clin. Immunol. 2009;9(4):379–385.
5. Muraro A, Werfel T, Hoffmann–Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008–1025.
6. Kido J, Hirata M, Ueno H, et al. Evaluation of the skin–prick test for predicting the outgrowth of cow's milk allergy. Allergy Rhinol (Providence). 2016;7(3):139–143. URL: doi: 10.2500/ar.2016.7.0175.
7. Nedelska SN, Pakholchuk OP. An 8–month old with Erythema nodosum – clinical case report, literature review. Pathology. 2015;2:114–116.
8. van Kampen V, Rabstein S, Sander I, et al. Prediction of challengetestresults by flour–specific IgE and skin prick test in symptomatic bakers. Allergy. 2008;63(7):897–902. URL: doi: 10.1111/j.1398–9995.2008.01646.x.
9. Jorge A, Soares E, Sarinho E, et al. Prevalence and clinical features of adverse food reactions in Portuguese children. Allergy, Asthma, and Clinical Immunology: Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2017;13:40. URL: doi:10.1186/s13223–017–0212–y
10. Chauveau A, Dalphin ML, Mauny F, et al. Skin prick tests and specific IgE in 10–year–old children: Agreement and association with allergic diseases. Allergy. 2017;72(9):1365–1373. URL: doi: 10.1111/all.13148
11. Pakhol'chuk OP, Nedel's'ka SM. Vikovi osoblivosti IgE-zalezhnoï giperchutlivosti do kharchovikh produktiv u ditey riznogo viku, pidtverdzhenoï metodom prik ta patch-testuvannya (Age features of IgE-dependent hypersensitivity to food products in children of all ages, confirmed by the method of prick and patch testing). Zdorov'e rebenka. 2017;7(12):749–753.

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