Embase (Elsevier)

ORIGINAL ARTICLE

Immune Correlations in Chronic Child Urticaria

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Article Information

Received: 03 Jan 2016
Accepted: 21 Mar 2016
Plagiarism software: Turnitin

Keywords:
Immune correlations,
IgG4 antibodies,
Chronic urticaria

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ABSTRACT

Introduction: The growing prevalence of urticaria in children over the last decade and the importance of determining the involved pathogenic mechanisms as well as of detecting the etiologic factors are some of the aspects that led to the choice of research topic.

Materials and Methods: The early diagnosis and the establishment of the therapeutic and prophylactic conduct in the urticaria are a necessity. There have been evaluated through a retrospective questionnaire, anamnesis and biochemical evaluation a number of 246 children diagnosed with chronic IgE and non IgE mediated urticaria, and prick tested for a wide range of food allergens. The assessment of the intensity of the eruption was done by calculating the urticaria activity score (UAS), both at diagnosis and at subsequent evaluations to assess the response to the treatment. The immunological investigations which were carried out included the determination of the IgA, IgG, IgM, total IgE and specific IgE to food allergens and airborne allergens, as well as the determination of the IgG4-type antibodies to 20 food allergens by means of enzyme immunoassay. The ELISA method was used for dosing the total IgE, while the CLA System Quanti Scan method (Innogenetics, Heiden, Germany) was used for determining the serum-specific IgE for 20 of the most common food allergens and airborne allergens (Innogenetics, Heiden, Germany).

Results: Positive statistical correlations have been made with IgE and non IgE mediated reactions, also with IgG4 antibodies. The result of the multivariate analysis shows that the existence of the atopy represents a risk factor which significantly influences the allergic sensitisation (HR = 3.186 → 95% CI: 2.57-5.96), followed in the order of importance by food diversification before the age of 6 months (HR = 2.157 → 95% CI: 1.86-5.35), natural feeding before 3 months of age (HR = 1.78 → 95% CI: 1003-4581) and artificial or mixed feeding (HR = 1.56 → 95% CI: 1056-3861).

Conclusion: There have been reported different correlations between specific IgE and IgG4 with different food allergens and the period of time between the onset and the duration of chronic urticaria. The regression of specific IgE has a predictive value upon the remission of urticaria (AUC=0.557, p=0.447, 95%CI: AUC→0.398–0.717). The logistic regression for analysis of the predictives factors for the regresson of urticaria showed several factors involved: Speciphic IgE values, compliance for the eliminating diet and treatment, allergic antecedents and the eventual polisensitivisation.

INTRODUCTION

Urticaria represents a multifactorial disease, with dermic or hypodermic localisation, frequently assesed on teenagers and children, with discretly increased incidence among female young population.[1]

The diagnosis and treatment of different child urticaria types constitutes a continuous challenge, because of its onsite particularities, also due to the polymorfism of clinical signs and therapeutical alternatives. The severity of the clinical manifestations în urticaria and angioedema imposes a sharp therapeutical action, for most of the situations can evolve to exitus. Urticaria and angioedema may occur individually or associated.[2]

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530/ami.2016.2.14	

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In order to establish a suitable, appropriate therapeutic plan, it is required an accurate etiological diagnosis, therefore this study evaluates the diagnostic intervention that could lead to health state improvement, making a point and clinical correlations, that reveals the intervention of the etiological factors for the urticaria's debut.

Milk cow allergy for infants comes out to 2-3% of the babies who are exclusively milk cow feeded, due to allergenic proteic fractions present in the cow's milk only, and not also in the natural maternal milk.[1] Thus, it is essential to promote the natural maternal breast feeding, in order to evict the infant from a potențial cow milk hypersensitivity. After 6 months, once solid food, there will be new occasions food sensitivisations, therefore the parents should avoid potentially immunoallergenic food stuff, especially for children with family history.[1,3]

Purpose of Study

The present study is an attempt to address the multiple aspects of urticaria and it is also motivated by the impact that this pathology (particularly when it has an allergic origin) has on paediatric patients.

Based on the findings of studies on food allergies (Sicherer, 2014), the present study aims to assess the allergenic factors involved in food urticaria and to identify the IgE-mediated and the non- IgE-mediated mechanisms.[1,3,4]

METHODS

The study was conducted on a sample of 246 patients diagnosed with urticaria and hospitalised in the 2nd Paediatrics Clinic of the Emergency Hospital for Children "Saint Mary" of Iaşi.

Patients' assessment was done by means of epidemiological data, anamnesis, general clinical examination, laboratory tests (haematological, biochemical, immunological) and allergy skin tests.

The study protocol followed the evolutionary clinical, biological and immunological aspects as well as the recommended specific therapeutic conduct. The patients were evaluated when they were first admitted to hospital, and then periodically, at different intervals depending on the evolution of their condition.[5,6] Criteria for inclusion in the study:

- Patients had to meet the criteria for the clinical and biological diagnostic, suggestive history, family atopy;
- Next-of-kins had to sign the informed consent form.

The exclusion criteria were: the existence of cutaneous pathologies similar to urticaria, yet without meeting the diagnostic criteria set out in the guide issued by the European Academy of Allergy and Clinical Immunology.

The risk factors for allergic sensitization were percentage expressed aș the followings: mixt or artificial feeding (68,29%), family atopy (53,66%), eary solid feeding onset (52,44%), breast feeding less than 3 months (37,80%), prolonged antibiotherapy (23,58%).

The patients were evaluated when they were first admitted to hospital, and then periodically, at different intervals depending on the evolution of their condition.

The assessment of the intensity of the eruption was done by calculating the urticaria activity score (UAS), both at diagnosis and at subsequent evaluations to assess the response to the treatment.[7,8]

The immunological investigations which were carried out included the determination of the IgA, IgG, IgM, total IgE and specific IgE to food allergens and airborne allergens, as well as the determination of the IgG4-type antibodies to 20 food allergens by means of enzyme immunoassay.[9-11]

The ELISA method was used for dosing the total IgE, while the CLA System Quanti Scan method (Innogenetics, Heiden, Germany) was used for determining the serum-specific IgE for 20 of the most common food allergens and airborne allergens (Innogenetics, Heiden, Germany) (Table 1).[3,12]

The threshold for a positive specific IgE for food allergens and for "allergic sensitizations" is class 2, or values > 0,7 UI/ml. This is a valuable sustainable point (Table 2), for weakly positive IgE cannot be considered to be sufficient to incriminate a particular food as the cause of an allergic reaction (Sampson H.A., JACI 2001).

Table 1: Quantification of specific IgE levels

Class	Reference unit (UI/ml)	Interpretation
0	0-0.34	Absent/slightly present
1	0.35-0.69	Slightly detectable
2	0.7-3.49	Slightly increased
3	3.5-17.49	Increased
4	17.5-49.9	Significantly increased
5	50.0-100.0	Very increased
6	>100.0	Extremely increased

Table 2: Interpretation of results for specific IgG4 antibodies

Class	Reference unit	Assessment
0	<0.35 U/mL	Negative- no IgG4 antibodies
1	0.35-0.7 U/mL	Borderline- low titre of IgG4 antibodies
2	0.7-3.5 U/mL	Positive- moderate titre of IgG4 antibodies
3	3.5-17.5 U/mL	Distinctively positive- high titre of IgG4 antibodies
4	>17.5 U/mL	Highly positive- very high titre of IgG4 antibodies

The characteristics of the TM IgG4 Screen 20 ELISA test are shown in Table 3.

Urticaria Activity Score (UAS)

The assessment of the intensity of the eruption was done by calculating the urticaria activity score (UAS), both at diagnosis and at subsequent evaluations to assess the response to the treatment (Table 4).[8,13-15]

RESULTS

Urticaria Activity Score (UAS) at Onset and in Dynamics

The analysis of the UAS at onset and in dynamics demonstrates the positive evolution of the cases under treatment, clearly highlighting the decreased frequency of cases with increased score (UAS → 4, 5, 6) and showing a very low frequency of cases with increased scores at the moment of the final evaluation.

Statistical indicators of UAS on admission (UAS 0), after a week (UAS 1) and after 6 weeks (UAS 2) are shown in the following analysis (Figure 1 and 2).

These are the data for the total Ig E on UAS patients, specific for the T0 moment of recruitment (Table 5.)

Previous results were also confirmed by the nonparametric analysis of the activity score which demonstrates significant decrease in the activity score 6 weeks after the treatment ($H_{Kruskal-Wallis}$=513.9, p<<0.05, 95%CI). The nonparametric analysis, which was used when the urticaria activity score was an ordinal and heterogeneous variable, showed significantly lower values of UAS after treatment (Figures 3 and 4).[16-18]

ANOVA analysis of variance revealed the presence of statistically significant differences between the UAS initial values, which had an average of 4.11 ± 1.12SD, and those recorded one week after treatment (mean value → 1.49 ± 1.2DS); in addition, it showed significant differences between the UAS values after 6 weeks of treatment and those recorded after one week of treatment (F = 889.089, p << 0.01, 95% CI) (Table 5').

Table 3: The characteristics of the test for the determination of IgG4 antibodies

IgG4 ELISA	Egg white	Cow's milk	Tomato
Intra-assay precision	7.7%	8.0%	8.7%
Inter-assay precision	6.6-10.9%	8.4-13.0%	4.6-7.4%
Inter-lot precision	2.5-11.4%	5.6-11.8%	0.5-9.6%
Analytical sensitivity	0.22 U/ml	0.17 U/ml	0.16 U/ml
Coverage	90-107%	89-103% 87-97%	
Linearity	82-114%	73-100%	102-120%
Cross-reactivity	No cross-reactivity to IgE		
Interference	No interference with bilirubin >0,3 mg/ml or Hb >8 mg/ml		
Clinical specificity	88%	86%	90%
Clinical sensitivity	86%	94%	80%

Table 4: Urticaria activity score

Score	Papules	Pruritus
0	Absent	Absent
1	<20 papules/24 h (mild eruption)	Mild (present, yet without being annoying)
2	20-50 papules/24 h (moderate eruption)	Moderate (present, yet without interfering with ADLs or sleep)
3	>50 papules/24 h or confluent papules in plaques (intense eruption)	Intense (severe, interfering with ADLs or sleep)

Sum of scores: 0-6

ANALYSIS OF RISK FACTORS FOR ALLERGIC SENSITISATION

The frequency rate of risk factors for allergic sensitisation (Table 8) was as follows: artificial or mixed feeding (68.29%), family atopy (53.66%), food diversification before 6 months of age (52, 44%), natural feeding for less than 3 months (37.80%) and prolonged antibiotic therapy (23.58%).

Multivariate Analysis of Risk Factors for Allergic Sensitisation

Logistic regression for the assessment of risk factor prediction on allergic sensitisation

Table 5': Total Ige/ T0

	IgE average	Average		STD	SE	Min	Max	Q25	Median	Q75
		-95%	+95%							
IgE total T0	256.98	132.36	381.60	677.62	62.91	5.29	6244.10	30.26	85.34	242.89

Table 5: Statistical indicators of UAS in dynamics

	UAS average	Average		STD	SE	Min	Max	Q25	Median	Q75
		–95%	+95%							
UAS T0	4.11	3.97	4.25	1.12	0.07	2.00	6.00	3.00	4.00	5.00
UAS T1	1.49	1.34	1.64	1.20	0.08	0.00	4.00	0.00	2.00	2.00
UAS T2	0.31	0.22	0.40	0.71	0.05	0.00	3.00	0.00	0.00	0.00

In the next study, the parameters which can be considered to be risk factors for the allergic sensitisation of patients suffering from urticaria were analysed by means of multivariate analysis; potential parameters, which were shown to have a significant influence in the literature, were included (Figure 5).[14]

The multivariate analysis has allowed the design of a model that defines the predictive factors for the allergic sensitisation.

The logistic regression provides a useful means of modelling the dependence of the occurrence of the condition on one or more explanatory variables called "predictors", which can be categorical or continuous.[19,20] The risk is mathematically modelled as an equation which is a collection of predictor variables. Modelling can be done in a single phase in which all covariates are included simultaneously, or it can be performed stepwise, either by gradually including a number of predictors or by gradually excluding some predictors (Table 7).[14,19,21,22]

In the analysis, the independent variables (covariates) included the factors known from the literature as being significant risk factors for the allergic sensitisation, and which showed significant differences in the univariate analysis. In the analysis, the condition of co linearity of the independent variables had to be satisfied, which involved verifying the inter-correlations between them.[21,23-26] Thus, the variables selected and introduced as risk factors did not show interdependencies (r <0.2, p> 0.05, 95% CI).

Table 6: Test for checking the validity of the model (the "enter"method)

Hosmer and lemeshow test			
Step	**Chi-square (test χ^2)**	**Df (DOF)**	**Sig.p (SIGLVL)**
1	2.0571	4	0.624

Table 7: The result of the assessment of the predictive power of the model

Model summary			
Step	**–2 Log likelihood**	**Cox & snell R square**	**Nagelkerke R square**
1	0.0032[a]	0.697	0.751

The "enter" method was applied, in which all predictors were included in a single step; the Hosmer-Lemeshow test results ($\chi 2 = 2.0571$, df = 4, p = 0.5349, 95% CI) indicate that the model is appropriate (Table 6). The R^2 Nagelkerke

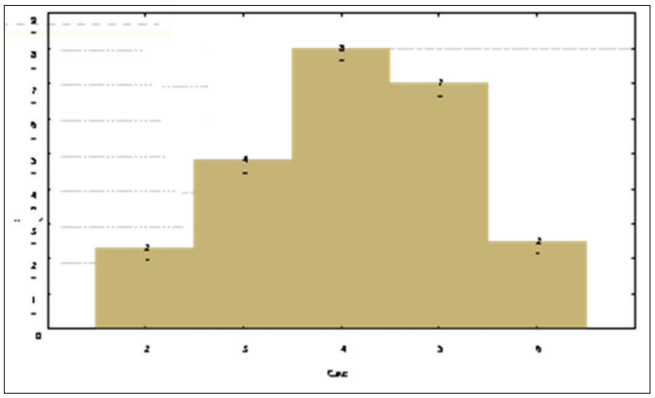

Figure 1: Case distribution relative to the UAS score at onset

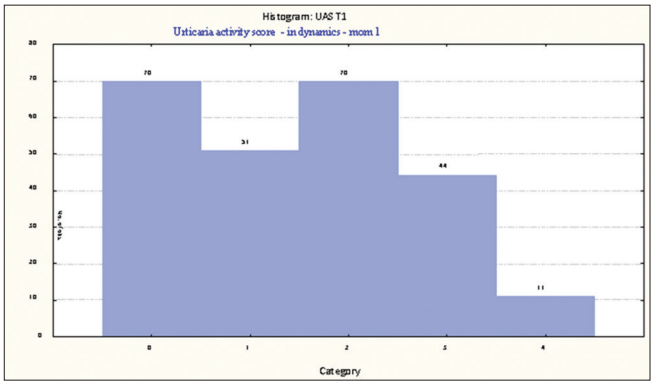

Figure 2: Case distribution relative to the UAS score after a week

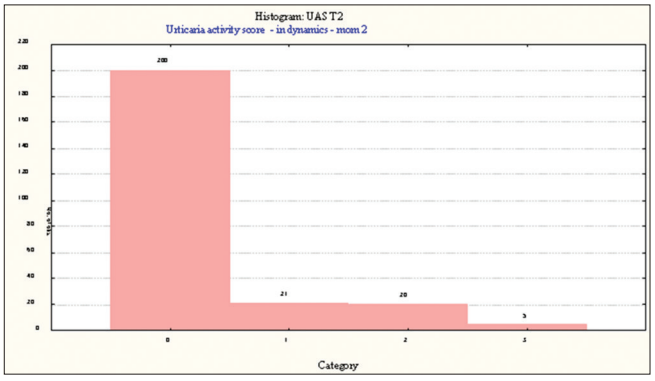

Figure 3: Case distribution relative to the UAS score after 6 weeks

Table 8: Coefficients and the Wald test in the logistic regression regarding the allergic sensitisation vs. risk factors

Multivariate analysis	Beta	SE	Wald	Sig. p	Hazard ratio exp (β)	95% CI for exp (B)	
						Lower	Upper
Artificial or mixed feeding	1.564	0.002	9.614	0.0309	1.564	1.056	3.861
Atopy	3.186	0.091	11.061	0.0015	3.186	2.571	5.967
Food diversification <6 months	2.157	0.425	6.524	0.0024	2.157	1.861	5.352
Natural feeding <3 months	1.786	0.681	3.687	0.0341	1.786	1.003	4.581
Prolonged antibiotic therapy	1.392	0.677	1.885	0.0357	1.392	1.211	3.657

χ^2 statistic test=1.577 (the suitability of the model); df=7; P=0.0628; 95%CI. CI: Confidence interval, df: Degrees of freedom, HR: Hazard ratio, SE: Standard error

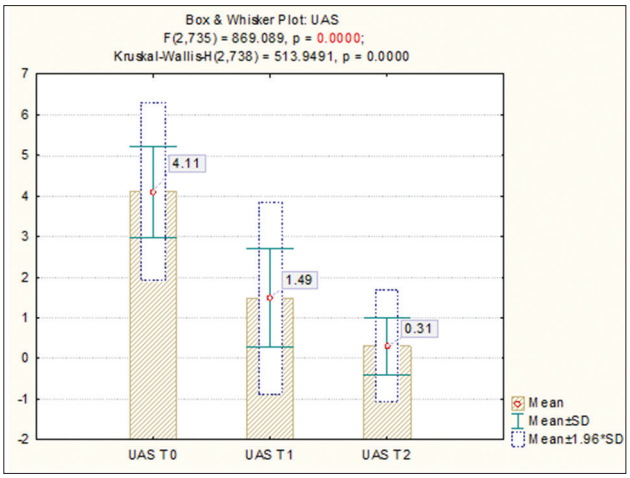

Figure 4: UAS dynamic values

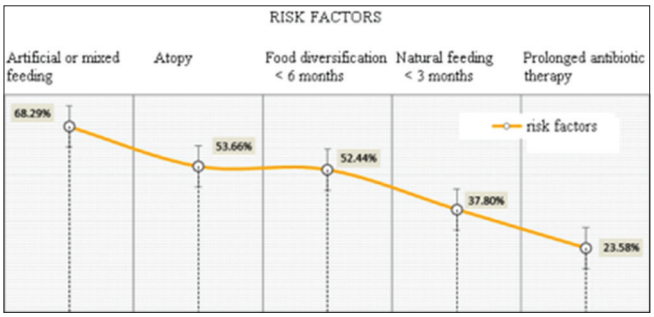

Figure 5: Risk factors for allergic sensitisation

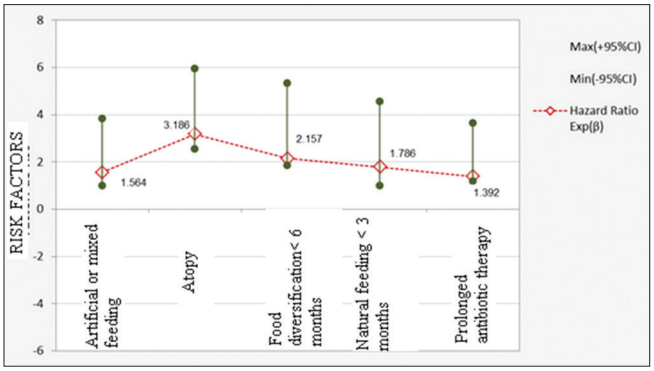

Figure 6: Multivariate assessment of risk factors - Hazard Ratio (HR)

value was 0.624, suggesting that the model is very useful in making predictions, although the contribution of two explanatory variables to the prediction is statistically significant, the effect size is significant.

The result of the multivariate analysis shows that the existence of the atopy represents a risk factor which significantly influences the allergic sensitisation (HR = 3.186 → 95% CI: 2.57-5.96), followed in the order of importance by food diversification before the age of 6 months (HR = 2.157 → 95% CI: 1.86-5.35), natural feeding before 3 months of age (HR = 1.78 → 95% CI: 1003-4581) and artificial or mixed feeding (HR = 1.56 → 95% CI: 1056-3861) (Figure 6). These

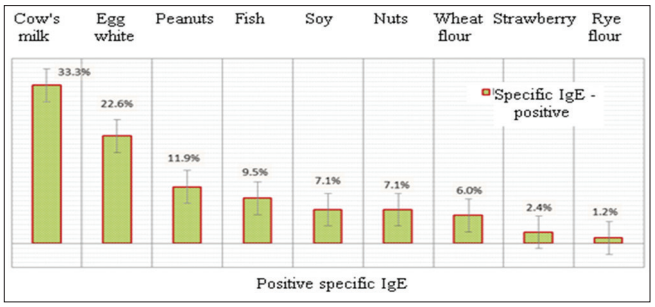

Figure 7: Positive specifc IgE - food allergens

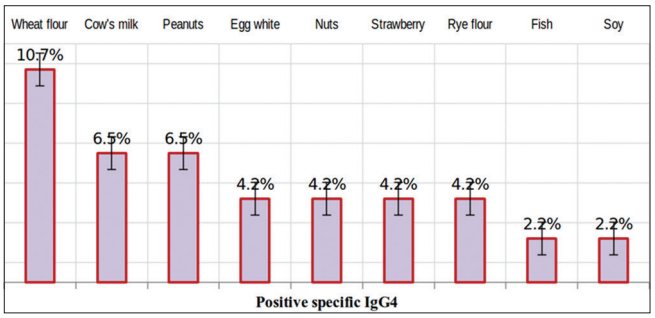

Figure 8: Positive specifc IgG4 – food allergens

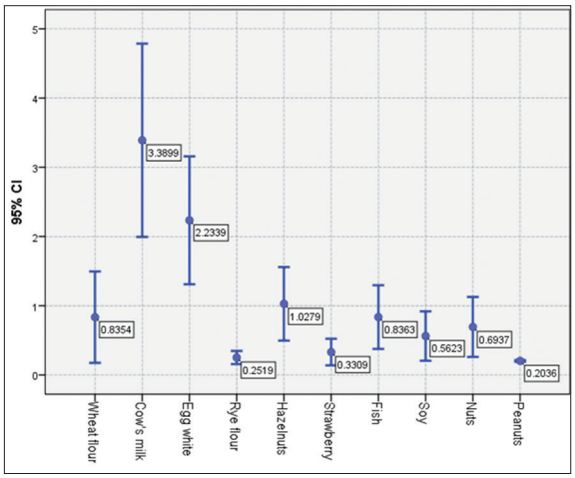

Figure 9: IgG4 values in the study group

parameters can be considered highly predictive factors for the allergic sensitisation, with HR values greater than 1.5.[21,23,25,26]

The determination of specific IgE to food allergens was performed on a total of 132 cases. The values of specific IgE were positive for one or more food allergens in 84 cases (63.64%).

For the 47 cases where the specific IgE had low values but the clinical manifestations and the history were suggestive of allergy (47 cases/of n = 132c) - 35.6%), IgG4 antibodies were determined for 20 food allergens. Of these, 20 cases (15.2% - of n = 132c) showed positive values of IgG4.

The analysis of specific IgE and IgG4 reveals that 63.649% of the cases show food allergy mediated by IgE mechanisms, while 15.2% of cases show food allergy mediated by IgG4 antibody mechanisms (Figures 7 and 8).

IgG4 value analysis shows elevated values for wheat flour, peanuts, cow's milk, strawberries, egg white, nuts and soy. For the other analysed foods, the values were below 0.3 (Figure 9).

DISCUSSIONS

Urticaria affects mostly the 1-5 years old group of age; On the studied population, more than 50% of the allergic urticarias are due to alimentary allergens; Drug allergy has been diagnosed to aprox.11% of the cases, mostly involved are beta-lactam antibiotics; Percentage frequence of the involved allergens showed breast or artficial feeding (68,18%), atopic familial. Factor (53,17%), breast feeding less than 3 months (37,1%), prolonged antibiotherapy (23,48%), early onset of diversification (62,5%).

The most frequently involved alimentary allergens are Beta lactoglobulin from cow milk, white egg, peanuts, wheat and fish.

Dynamic surveillnace of the speciphic IgE shows that the lowerance of their level comparing to the allergenic proteins preceds the immune tolerance occurrence, and for an IgE level constantly high, associates the persistance of the allergic phenomenon, showing thus a positive predictive value în developping a IgE mediated hypersensitivity reaction. Avoiding the incriminated allergen induces a dynamic decrease of speciphic IgE levels.

For the cases with food urticaria that have had low levels of speciphic IgE, we have determined speciphic IgG 4 antibodies for 20 alimentary allergens, for pointing out the nonIg E mediated allergies. From that, 21 cases have presented positives values for IgG4, for the following allergens: wheat, cow milk, white egg, peanuts, rye wheat, strawberry, nuts, fish and soya. For the patients with positive values of IgG4, 89% have presented digestive manifestations associated to cutaneous manifestations, which leads to the conclusion that IgG4 speciphic antiboidies have high values to the pacients with gastro intestinal allergy, but have no predictive value.

IgE speciphic values can be considered positive predictive for the remission of allergic urticaria ((AUC=0.557, p=0.447, 95%CI: AUC→0.398–0.717).

Speciphic IgE values have a moderate correlation at the debut of the urticaria, considering UAS values of 5 or 6; after 1 week, there is an significant increase of the positive correlation between Ig E and UAS(χ^2=14.75, p=0.031, 95%CI). Quantitative evaluation of UAS, 1 week post therapy points a highly increased positive correlation, especially when positive values of speciphic IgE ($H_{Kruskal-Walis}$=4.27, p=0.04).

The result of logistic regression demonstrates the fact that IgE speciphic level (HR=3.95 →1.12–4.57) diet's compliance (HR=3.48→1.71–4.09) and treatment's comppliance (HR=2.27→1.10–3.70), directly influences the occurrence of new urticaria episodes.

There have been reported different correlations between specific IgE and IgG4 with different food allergens and the period of time between the onset and the duration of chronic urticaria. The regression of specific IgE has a predictive value upon the remission of urticaria (AUC=0.557, p=0.447, 95% CI: AUC→0.398–0.717). The logistic regression for analysis of the predictives factors for the regresson of urticaria showed several factors involved: Speciphic IgE values, compliance for the eliminating diet and treatment, allergic antecedents and the eventual polisensitivisation.

CONCLUSIONS

Due to the fact that the prevalence of food allergy has increased during the last ten years, this study is oriented to a higher education, awareness and empowerment of the family and parents for their children's nourishment, especially for those with atopic background, an action completely justified by the major impact of allergy (with an emphasis on food allergy) on the quality of life of pediatric population.

Declaration of Interest

None of the authors have no competing interests, financial or non financial on the case report. The study was entirely supported by the authors, as a personal contribution to the research in this field.

Author's Contribution

All authors have equal contribution, Celina Stafie and Monica Ungureanu are main authors, clinical involved în the research, Cristina Dascalu and Mihaela Moscalu have been involved in the statistical work. All the authors have read and approved the final manuscript.

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How to cite this article: Stafie C, Dascalu C, Moscalu M, Ungureanu M. Immune correlations in chronic child urticaria. Acta Medica International. 2016;3(2):61-67.

Source of Support: Nil, **Conflict of Interest:** None declared.