ORIGINAL ARTICLE

Cytokine Profile in Children With Asthma Undergoing Food Challenges

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Abstract

Background: The influence of food allergens on the profile of inflammatory markers in children with asthma has not been investigated. To ascertain the influence of food allergens on the intensity of the inflammatory process, a cytokine profile was determined before and after a food challenge test in the peripheral blood of children with asthma and coexistent food allergy.
Material and methods: We studied 22 children with asthma and immunoglobulin (Ig) E-dependent food allergy. Oral challenge tests were carried out using double-blind placebo-controlled food challenge (DBPCFC). Blood was sampled before, and 4 and 24 hours after the oral challenge test. The inflammatory markers interleukin (IL) 4, IL-5, IL-10, tumor necrosis factor (TNF) α, intereron (IFN)-γ, sIL-2R, and sCD23 were evaluated. The level of cytokines in serum was determined using a commercial enzyme-linked immunoassay Bender Med Systems (Vienna, Austria).
Results: The median IL-4 level before the challenge test was 23.5 pg/mL, after 4 hours it was 38.8 pg/mL, and after 24 hours it was 35.4 pg/mL. The median IL-5 levels measured at the same time points were 4.6 pg/mL, 5.7 pg/mL, and 7.5 pg/mL. A significant increase in IL-4 and IL-5 levels 4 hours ($P = .0006$; $P = .006$) and 24 hours ($P = .014$; $P = .015$) after food challenge was observed. No statistically significant differences in the levels of the other cytokines during allergen or placebo challenge tests were recorded.
Conclusions: Determination of plasma IL-4 and IL-5 levels can be a useful tool for evaluation of the effects of food challenge tests on children with asthma and coexisting IgE-dependent food allergy. The results of determining serum IL-10, TNF-α, interleukin (IL) IFN-γ, sIL-2R, and sCD23 levels during the challenge test are not significant.

Resumen

Antecedentes: la influencia de los alérgenos alimentarios en el perfil de marcadores inflamatorios en niños con asma no ha sido investigada. Para investigar la influencia de los alérgenos en la intensidad del proceso inflamatorio, se ha determinado el perfil de citocinas en sangre periférica de niños asmáticos y alergia alimentaria concomitante antes y después de una prueba de provocación alimentaria.
Material y métodos: Hemos realizado el estudio en 22 niños con asma y alergia alimentaria dependiente de inmunoglobulina (Ig) E. Se realizaron pruebas de provocación orales usando provocación alimentaria doble ciego controlada con placebo (PADCCP). Se tomaron muestras sanguíneas antes, y 4 y 24 horas después de la prueba de provocación oral. Se evaluaron los marcadores inflamatorios IL-4, IL-5, IL-10, TNF-α, IFN-γ, sIL-2R, y sCD23. El nivel de citoquinas en el suero de los pacientes se determinó mediante un enzimo-inmunoanálisis comercial Bender Med Systems (Viena, Austria).
Resultados: La mediana de los niveles de IL-4 antes de la prueba de provocación fue de 23,5 pg/mL, después de 4 horas fue 38,8 pg/mL, y tras 24 horas fue 35,4 pg/mL. La mediana de los niveles IL-5 medidos en los mismos tiempos fueron 4,6 pg/mL, 5,7 pg/mL, y 7,5 pg/mL. Se observó un aumento significativo de los niveles de IL-4 e IL-5 a las 4 ($P = .0006$; $P = .006$) y 24 horas ($P = .014$; $P = .015$) después de la prueba de provocación alimentaria. No se observaron diferencias significativos en los niveles de las otras citocinas durante las pruebas de provocación con alimentos o placebo.
Conclusiones: La determinación de los niveles de IL-4 e IL-5 puede ser una herramineta útil para evaluar los efectos de la prueba de provocación alimentaria en niños asmáticos con alergia alimentaria dependiente de IgE. Los resultados de la determinación de los niveles séricos de IL-10, TNF-α, IFN-γ, sIL-2R, y sCD23 durante la prueba de provocación no se modifican de forma significativa.

Palabras clave: Citoquinas. Asma. Alergia alimentaria. Niños.

Introduction

Food-induced respiratory symptoms are not frequent, although their role in asthma patients has recently been emphasized [1,2]. Warner [3] reported asthma exacerbation associated with food consumption in 21% of patients. Data from studies involving challenge tests have shown that food allergens were responsible for the induction of respiratory tract symptoms in 2% to 29% of children [4]. Between 2% and 9% of patients with asthma are thought to have a coexisting food allergy that is responsible for exacerbation of respiratory tract symptoms [5]. We used a double-blind placebo-controlled oral food challenge (DBPCFC) to evaluate the effects of food allergens on disease course in children with asthma and coexisting food allergy. Although DBPCFC is considered the gold standard approach to the diagnosis of allergy, it does have some limitations. Therefore, we need new methods of assessing the effects of food allergens on the inflammatory process and of predicting the results of the challenge tests (eg, determination of plasma markers such as cytokines). To date, authors have focused on the relationship between cytokine type and concentrations, disease intensity, influence of additional agents, and the effects of challenge tests [6-9]. The influence of food allergens on inflammatory marker profile in children with asthma has not yet been investigated. Our approach to this problem is original, because the allergic inflammatory process develops systemically in children, thus improving the probability of appreciating changes in plasma samples. We evaluated the peripheral blood cytokine profile in children with asthma and food allergy before and after the challenge test. We also analyzed the usefulness of the cytokine profile in the assessment of the food challenge test results.

Table 1. Characteristics of the Study Group

	Children With Asthma and FA	
Number	22	
Age, y (range) Mean (SD)	5.5 - 18 9.5 (4.69)	
Clinical symptoms (history): Atopic dermatitis (history), n (%) Atopic dermatitis (recently), n (%) Urticaria, n (%) Vasomotor edema, n (%) Digestive symptoms n (%) FA (history), n (%)	 14 (62.5) 18 (75) 10 (41.7) 2 (8.3) 14 (58.3) 23 (95.8)	
tIgE (IU/mL) mean (SD)	612.33 (304.2)	
	Before provocation	After provocation
FEV_1 mean SDS (SD) Challenge with allergen Challenge with placebo	 −0.25 (2.19) −0.4 (1.83)	 −0.55 (1.62) −0.8 (1.55)
	Before provocation	After provocation
PC_{20} mg/mL mean (SD) Challenge with allergen Challenge with placebo	 1.41 (1.12) 1.37 (1.08)	 0.86 (0.71) 1.42 (1.1)

Abbreviations: FA, food allergy; FEV_1 forced expiratory volume in 1 second; PC_{20}, provocative concentration of a substance producing a 20% decline in FEV_1; SDS, standard deviation score.

Material and Methods

The initial study group consisted of 304 subjects who were admitted to the Department of Pediatric Allergology, Gastroenterology and Nutrition of the Medical University of Lodz, Lodz, Poland for the evaluation of food hypersensitivity. A final group of 24 children with atopic asthma and concomitant immunoglobulin (Ig) E-mediated food allergy participated in the study. Food allergy was confirmed by questionnaires, skin prick tests (SPT), specific IgE determination, and DBPCFC, which was completed at the same time as blood sample collection. Two children were excluded from the study due to lack of cooperation. Thus, the study group consisted of 22 patients (Table 1). The allergens responsible for positive results in the challenge were egg in 13 children, milk in 5, wheat flour in 1, celery in 1, and nuts in 2. Nine of the children had early reactions, 11 late reactions, and 2 mixed reactions. In the group of children with early reactions, 3 had airway symptoms, 4 had cutaneous symptoms, and 4 had gastrointestinal symptoms. In the group of children with late reactions, 4 had respiratory symptoms, 6 had cutaneous symptoms, and 4 had gastrointestinal symptoms. In the 2 children with mixed reactions, the symptoms were cutaneous, respiratory, and gastrointestinal.

The study was conducted in stable patients with no exacerbations for at least the last 6 weeks. SPT was standard according to the position papers of the European Academy of Allergy and Clinical Immunology (EAACI) [10]. Standard allergen extracts were provided by Allergopharma (Reinbek, Germany). The positive control was histamine 10 mg/mL (Allergopharma), and the negative control was a 50% glycerosaline solution. Reactions to each allergen were measured 15 min after the pricks. Positivity was defined as a wheal of at least 3 mm and greater than the negative control. The specific serum IgE levels were measured using the UniCAP 100 Pharmacia Upjohn (Pharmacia Diagnostics AB, Uppsala, Sweden). Results greater than 0.71 kU_A/L (> class 2) were considered positive. The oral challenge was performed using the DBPCFC method. The trials were carried out in hospitalized patients according to EAACI

recommendations, after a minimum 2-week eliminating diet [10]. Maintenance medication was checked for possible masking of clinical symptoms and influence on cytokine production. Systemic corticosteroids were contraindicated, and systemic antihistamines were withdrawn according to their half-life. The use of topical corticosteroids for the airways was no reason to discontinue testing; topical corticosteroids for skin complaints were tapered to the minimum dose and kept constant throughout the challenge procedure. When necessary during challenge tests, topical corticosteroids for the airways ($ß_2$-adrenergic agonists), topical corticosteroids in skin topical preparations, and topical antihistamines were used. Native forms of samples were applied. The type of food was determined by history, results of the skin prick test, and plasma-specific IgE concentration. The allergens used in the challenge tests were eggs, milk, wheat flour, celery, and nuts. Prior to each test, antihistamines were discontinued for 2 weeks, and there was a 48-hour break in taking inhalants. Patients were under observation for at least 48 hours. Blood samples were collected before, and 4 and 24 hours after completion of the oral challenge test. Plasma levels of the inflammatory markers interleukin (IL) 4, IL-5, IL-10, tumor necrosis factor (TNF) α, interferon (IFN) γ, sIL-2R, and sCD23 were determined by enzyme-linked immunoassay (Bender Med Systems, Vienna, Austria). The children and/or parents gave their informed consent. The study protocol was approved by our ethics committee.

Statistical Analysis

Data are expressed as the median (interquartile range) and as the mean (SD). Comparisons between groups were made with the Mann-Whitney U test or the Wilcoxon test. A P value of $< .05$ was considered statistically significant. All calculations were made using the program STATGRAPHICS Plus 5.1 (Statpoint Technologies Inc, Warrenton, Virginia, USA).

Results

Before the food challenge, the median IL-4 level was 23.5 pg/mL (16.26-39.84); before the placebo challenge it was 29.2 pg/mL (17.23-49.68). There were no statistically significant differences before the challenge test between the placebo and allergen ($P > .05$). The IL-4 level increased 4 hours after the food challenge (median 38.8 pg/mL [26.26-58.08]; $P = .0006$) and after the placebo challenge (median 37.5 pg/mL [25.18-48.75]; $P > .05$). The IL-4 level continued to increase 24 hours after the food challenge (median 35.4 pg/mL [21.74-58.19] compared with baseline; $P = .014$), and after the placebo challenge (median 31.3 pg/mL [23.17-53.9]; $P > .05$). Therefore, a marked increase in IL-4 levels was observed both 4 and 24 hours after the challenge test with allergen (Figure).

Before the food challenge, the median IL-5 level was 4.6 pg/mL (2.33-10.88); before the challenge test with placebo it was 7.2 pg/mL (3.03-11.19). There were no statistically significant differences before the challenge test between placebo and allergen intake ($P > .05$). Four hours after the food challenge, the median IL-5 level was 5.7 pg/mL (3.36-15.04) ($P = .006$), and after the challenge test with placebo it was 6.1 pg/mL (4.09-13.23). Twenty-four hours after the food challenge, the median IL-5 level was 7.5 pg/mL (3.54-16.25) and after administration of the placebo it was 6.5 pg/mL (4.01-14.02) ($P = .015$). Thus, 4 and 24 hours after the food challenge, a marked increase in IL-5 level was observed. The same increase in IL-5 was not seen after the challenge test with placebo (Figure).

The levels of IL-10, TNF-α, IFN-γ, sIL-2R, sCD23 in plasma, before and 4 and 24 hours after food and placebo challenge are presented in Table 2. There were no statistically significant differences in these parameters with respect to the time point or agent used in the challenge test (placebo or allergen).

Discussion

Determination of serum cytokine levels in patients with asthma or food allergy has been the subject of many studies

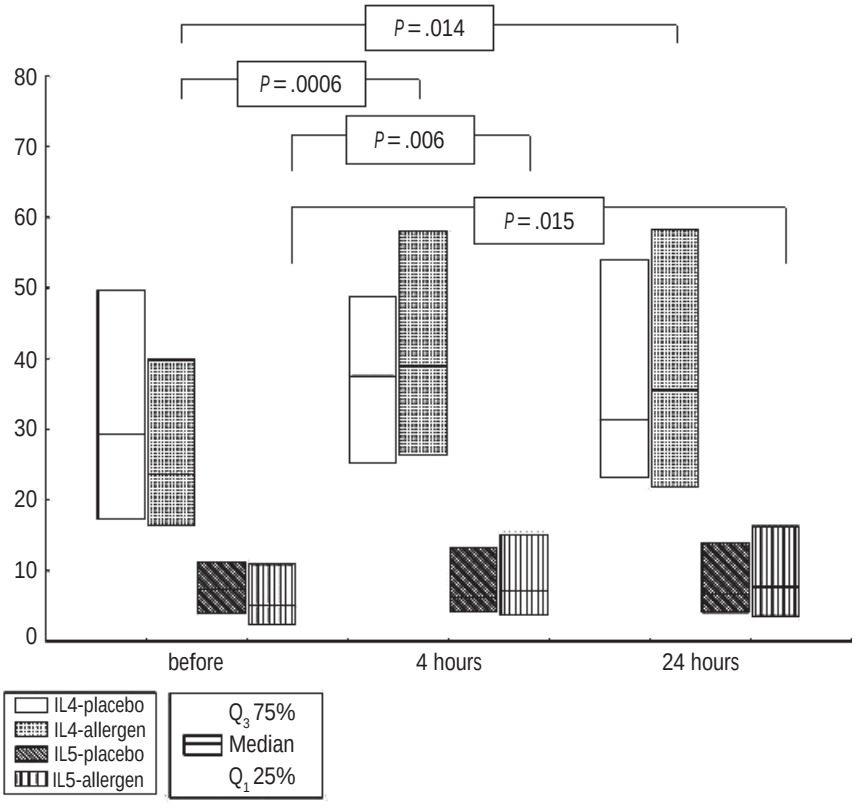

Figure. IL-4 and IL-5 level before, 4 hours and 24 hours after the oral challenge test with allergen or placebo.

Table 2. IL4, IL5, IL10, TNF-α, sIL-2R, sCD23 Levels Before, and 4 and 24 Hours After Allergen or Placebo Challenge

Values before and after allergen or placebo challenge (pg/mL)	IL4	IL5	IL10	TNF-α	IFN-γ	sIL-2R	sCD23
Values before allergen challenge							
Median (interquartile range)	23.5 (16.26-39.84)	4.6 (2.33-10.88)	4.8 (1.59-14.68)	31.5 (20.06-39.08)	0.9 (0.47-2.02)	2.3 (1.39-3.61)	98.4 (62.69-112.7)
Values 4 hours after allergen challenge							
Median (interquartile range)	38.8 (26.26-58.08)	5.7 5.7 (3.36-15.04)	7.3 (1.52-19.35)	36 (25.49-50.81)	0.9 (0.44-1.28)	2.5 (1.28-4.6)	92.5 (74.63-110.7)
Values 24 hours after allergen challenge							
Median (interquartile range)	35.4 (21.74-58.19)	7.5 3.54-16.25)	3.4 (3.1-11.47)	33.6 (22.58-59.04)	0.9 (0.69-1.55)	2.7 (1.45-3.93)	87.1 (75.12-125.3)
Values before placebo challenge							
Median (interquartile range)	29.2 (17.23-49.68)	7.2 (3.03-11.19)	5.4 (2.45-12.07)	37 (20.67-48.84)	1.1 (0.58-1.55)	2.9 (1.64-3.95)	96 (76.09-127.6)
Values 4 hours after placebo challenge							
Median (interquartile range	37.5 (25.18-48.75)	6.1 (4.09-13.23)	7.6 (2.85-18.48)	32.7 (19.73-58.23)	0.9 (0.58-1.49)	2.8 (1.57-4.68)	88.5 (76.35-124.7)
Values 24 hours after placebo challenge							
Median (interquartile range)	31.3 (23.17-53.9)	6.5 (4.01-14.02)	10.7 (3.76-16.67)	39.7 (26.15-48.82)	0.9 (0.63-1.2)	2.9 (1.54-4.53)	90.4 (73.05-124.3)

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

[6-9]. Animal studies have made it possible to conclude that elevated levels of IL-4 and IL-5, a less significant increase in levels of TNF-α, and undetectable levels of INF-γ and IL-10 are characteristic of allergic inflammation [11].

Studies also suggest that IL-4 production increases in patients with asthma and food allergy in comparison with healthy people [12,13]. Rautava and Isolauri [14] showed a significant systematic increase in IL-4 level in neonates with atopic dermatitis and cow's milk allergy after an oral challenge test. Similar results were described by Andre et al [13], who revealed increased levels of IL-4 after a challenge test in patients with food allergy. Bohle [15] detected synthesis of large amounts of IL-4 and IL-13 by allergen-specific T lymphocytes isolated from children with food allergy. Moreover, adult patients with food allergy have been shown to have a higher level of IL-4 in culture supernatant than healthy individuals. Maximum IL-4 secretion was observed 24 hours after the stimulation [16].

The results of our research are consistent with those of the aforementioned studies. After an oral challenge test with allergen in our patients, we observed a statistically significant increase in serum IL-4 level that was not observed after the challenge with placebo. As with Andre et al, who demonstrated a maximum increase in IL-4 level 24 hours after the challenge test [16], we showed a significant increase in IL-4 levels after the same period. However, we observed a very significant increase as early as 4 hours after the challenge test—this may be due to methodological differences: Andre et al studied adults with food allergy, while we studied children with asthma and food allergy; we determined serum IL-4 levels, whereas Andre et al evaluated IL-4 level in the culture supernatant. Cytokine determination in culture supernatant is believed to be a useful method for diagnosing food allergy [17], although it is more difficult, time-consuming, and expensive than serum cytokine determination.

When they determined the IL-5 level in patients with asthma or food allergy, Matsumoto et al [18] revealed a significant decrease in IL-5 level and clinical improvement after a 2-week elimination diet in an infant with cow's milk allergy. The results of our study show a significant increase in

the plasma IL-5 level of children with asthma and food allergy 4 and 24 hours after the challenge test with food allergen, but not with placebo.

IL-2 also plays an important role in allergic inflammation [19,20]. The results of our study did not show any changes in the concentration of sIL-2R, which could be due to a generally low serum level of this cytokine.

We found no statistically significant differences between sCD23 serum levels, although our observation period may have been too short. However, Matsumoto et al [18] did show a significant decrease in sCD23 level in an infant with allergy to cow's milk after a 2-week elimination diet.

TNF-α has been shown to affect the capacity to induce an inflammatory reaction to food allergens in patients with food allergy [9]. In children with cow's milk allergy, peripheral blood mononuclear cells (PBMC) secrete more TNF-α after a challenge test with milk, and this leads to increased intestinal permeability [17]. Bordignon et al [21] showed a higher TNF-α level in the culture supernatants of PBMC from children with cow's milk allergy compared with healthy individuals. However, other studies [18,22] observed no changes in the TNF-α level of children with atopy, in comparison with children without atopy whose disease was stable. We did not observe significant changes in the serum TNF-α level of children with asthma and food allergy after the challenge test both with an allergen and with placebo.

We obtained similar results for IL-10. It is known that food allergy in early childhood predisposes patients to allergy to inhaled allergens in the future. Dustan et al [23] demonstrated a correlation between this phenomenon and lower IL-10 production in children with atopic dermatitis than in healthy individuals. Moreover, these authors proved that an oral challenge test with food allergens induced an increase in serum IL-10 level in patients with food allergy. It has recently been emphasized that the development of food tolerance is connected with modulating IL-10 action [24]. According to other studies [21], children with atopic dermatitis and cow's milk allergy have a larger number of IL-10–producing cells in culture than children with atopic dermatitis but no cow's milk allergy. The lack of any significant changes in IL-10 level in the patients in our group may be a consequence of our methodology. More precise methods, such as culture determination, would probably increase the sensitivity of the study.

There were no essential changes in the plasma levels of IFN-γ or IL-10. Some authors [25] have found that IFN-α is usually undetectable in patients with asthma, regardless of the disease severity. The results of other studies indicate a correlation between IFN-γ level and asthma severity [26]. Sütas et al [27] and Pohjavuori et al [28] found that, after an oral challenge test in children with atopic dermatitis and food allergy, there was a decrease in the production of IFN-α by PBMC, whereas a higher IFN-γ level was observed before the challenge test. Andre et al [13], however, did not find any changes in the IFN-γ level before or after the challenge test with food allergens in patients with food allergy and children with a negative oral challenge result. This is consistent with the results of our studies.

Some authors [29] suggest that the objective determination of inflammatory markers may be a useful tool in the diagnosis of food allergy. However, difficulty in the interpretation of the DBPCFC results made it impossible to determine a characteristic inflammatory marker profile.

We observed no changes in the levels of the markers studied, except for IL-4 and IL-5. This may be due to the study methodology. It is known that no activated circulating lymphocytes are detected in the course of allergic reaction, although an increase in local lymphocyte activity may be observed [30]. Thus, the results of the study would have shown more statistically significant differences if the parameters had not been determined in blood but in other biological materials.

Considering how much easier it is to obtain serum than biological material from BAL or intestinal cells, especially in children, determination of selected cytokines in serum appears to have a valid role in the assessment of food challenge test results.

Conclusions

The determination of IL-4 and IL-5 levels in plasma can help evaluate the effects of a food challenge test in children with asthma and coexisting IgE-dependent food allergy. Determination of serum IL-10, TNF-α, INF-γ, sIL-2R, and sCD23 during the challenge test does not provide significant results.

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