

Serum Levels of the CC Chemokines CCL2, CCL5, and CCL11 in Food Allergic Children with Different Clinical Manifestations

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Abstract—Food allergies (FA) are frequent in 8 % of children under 3 years old and approximately 2 % of adults. Chemokine are involved in various allergies such as FA. The present study was aimed to determine CCL2, CCL5, and CCL11 levels in FA. The study population of this cross-sectional study contained 63 patients suffering from FA and 100 healthy controls. Concentrations of CCL2, CCL5, CCL11, and IgE were measured by enzyme-linked immunosorbent assay (ELISA). Eosinophils were counted using Casy I cell counter + analyzer system model SCAREF system GmbH. Differences were considered significant at $P < 0.05$. Current results showed that FA patients had significantly elevated numbers of circulating periphery eosinophils than the disease-free controls. Serum IgE levels in FA patients were also higher than controls. We also showed that serum levels of CCL2 and CCL11 were significantly enhanced in FA patients compared to control but CCL5 was not detectable. Results of present study revealed that both CCL2 and CCL11 were more elevated in FA children suffering from anaphylaxis and urticaria than bronchial asthma and atopic dermatitis. These results also indicated that more increased levels of CCL2 and CCL11 were observed following consumption of cow's milk and pistachio nuts. Overall, findings of the present study proposed that serum levels of CCL2 and CCL11 are elevated in FA and these may be considered as useful parameters in diagnosis of disorder. It is also possible to design treatments on the basis of blocking of chemokines expression by application of antibodies against them to overcome allergic complications in patients suffering from FA.

KEY WORDS: food allergy; CC chemokine; CCL2; CCL5; CCL11.

INTRODUCTION

Food allergies are frequent in approximately 8 % of children under 3 years old and around 2 % of adults [1]. The incidences of FA have increased over the past decade [2]. However, the central mechanisms involved in FA reactions are only partially known, but molecular events to alleviate food allergen-induced allergic manifestations are yet to be clearly understood. The inner surface of mucuses of the gut epithelial cells serves as a strong barrier against potential foreign antigens. In the absence of this intestinal epithelial cells barrier, the specific food allergens are able to easily activate the mast cells. Mast cells comprise approximately 2–3 % of the cell population within the lamina propria in healthy

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individuals [3]. Following allergic reactions, mast cells undergo proliferation up to tenfolds [4]. Mast cells respond to immunoglobulin E (IgE)/allergen and release bioactive mediators such as IL-4, TNF- α , and histamine into the adjacent tissues within a few minutes that induce relative responses [5]. Compounds which down-regulate the level of these mediators have been considered as anti-allergic agents in clinical settings.

Although, IgE is frequently applied as a clinical biomarker for the diagnosis of allergy, this immunoglobulin does not always reflect the allergic status accurately. This is because allergic symptoms involve the activation of both IgE- and non-IgE-mediated pathways [6], [7]. Several cell types, including eosinophils, CD4⁺ T cells, and mast cells contribute to the allergic responses [8]. In particular, eosinophils accumulate in the foci of allergic reactions and their granules contain a wide spectrum of proinflammatory mediators which contribute in the allergic reactions [9]. Normally, eosinophils comprise only a small proportion of circulating or tissue-dwelling cells, and eosinophils number is markedly increased in allergic diseases. Several mediators have been demonstrated to exhibit eosinophil chemoattraction, including non-classic chemotactic factors such as lipid mediators (platelet-activating factor and leukotrienes), bacterial products (formyl-methionyl-leucyl-phenylalanine), and classic chemokines (e.g., CCL2, CCL11, and CCL4). Classic chemokines are classified in to four distinct groups as CXC, CC, CX3C, and C, on the basis of the presence, absence, or position of the cystein motifs in their N-terminus. The CXC subfamily is further subdivided based on presence or absence of a motif called ELR (Arg-Leu-Glu) before the first cysteine residue in to ELR⁺ and ELR⁻ subdivision [10], [11]. However, none of these mediators are considered as specific eosinophil recruiter and they are unlikely to be the primary mediators of the tissue eosinophilia which is present in a wide variety of hypereosinophilic disorders [12].

The eotaxin sub group of CC chemokines subset consists of eotaxin-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26). It is well evidenced that eotaxins promote the recruitment of eosinophils [11], [13]. These three eotaxins share CCR3, are predominantly expressed on both eosinophils and basophils surface membrane [14], [15]. Investigations showed elevated serum CCL2 and CCL5 levels in allergic patients with bronchial asthma and atopic dermatitis [16]. It is well accepted that predisposition to FA involves a complex interaction between several genes and environmental factors, including chemokines.

Almost little is known regarding relationship between these chemokines serum levels, eosinophils and basophils count, and the levels of IgE in patients suffering from FA. In the present study, we asked whether if the levels of CCL2, CCL5, and CCL11, were changed in FA. We also sought to examine the differential pattern of chemokine expression with regard to clinical manifestations as well as the type of allergen (food) consumed by FA patients.

MATERIAL AND METHODS

Study Subjects

The study population of this cross-sectional study contained 63 patients suffering from FA and 100 healthy controls (Table 1). The FA subjects showed food-mediated acute allergic reactions above grade 2 [17] including anaphylaxis and/or urticaria. The anaphylaxis was diagnosed by a physician based on the anaphylaxis criteria [18]. Patients were diagnosed as FA by an expert specialist according to medical history, laboratory findings (e.g., serum IgE level), dietary elimination examinations, and specific skin prick tests. All of the approved food allergic patients were also screened regarding asthma using spirometry test. The respiratory symptoms were increased after food allergic symptoms in the asthmatic patients. Sampling was performed during active symptoms (anaphylactic reaction or an asthma attack) and diagnostic tests were performed to include or exclude participants. The control subjects were 100 disease-free children, especially free of allergy. All of the

Table 1. Some of the Clinical Characteristics of FA and Healthy Children

Variable	Allergic patient	Control
Subject	63	100
Age (years)		
Gender (male–female)	6.5±2	6.3±1.9
Related complications		
Anaphylaxis	40	0
Bronchial asthma	10	0
Atopic dermatitis	7	0
Urticaria	6	0
Source of allergen		
Bird egg	20	0
Cow's milk	22	0
Cacao	4	0
Pistachio nuts	15	0
Eosinophils (10 ⁶ /l)	612±837	117±96
IgE (IU/ml)	1,112±1,082	24±9

children having fever, diarrhea, infectious diseases, or other chronic diseases were excluded from the study. An informed consent was obtained from caregivers and/or parents of the patients and controls prior to enrollment in the study. The study protocol was approved by local Ethical Committee of Rafsanjan University of Medical Sciences.

Measurements

Peripheral blood specimens were harvested *via* venous puncture. Serum specimens were isolated and stored at -20°C for further use. Hemolyzed samples were avoided. Concentrations of IgE, CCL2, CCL5, and CCL11 were measured by ELISA (R&D Systems, Minneapolis, MN). The limits of detection for kits were 2 pg/ml for each chemokine. Eosinophils were counted using Casy I cell counter + analyzer system model SCAREF system GmbH.

Statistical Analysis

Data are presented as means $\pm$ SEM. The results were analyzed by *t* test using SPSS software package version 18. However, we had a small sample size, but due to normal distribution of the analyzed parameters, we preferred to use the *T* student test as a parametric statistical method.

RESULTS

Samples were collected from 63 FA patients including 33 male and 30 female children, along with 100 control children. As depicted in Table 1, FA patients had significantly elevated numbers of circulating eosinophils than the disease-free controls ($6.12 \pm 8.37 \times 10^9/\text{l}$ vs. $1.17 \pm 9.6 \times 10^9/\text{l}$, $P < 0.001$). The mean age of FA children and healthy children was 6.5 ± 2 and 6.3 ± 1.9 years, respectively. The serum level of IgE in FA patients was higher than controls ($1,112 \pm 1,082$ vs. 24 ± 9 UI/ml, $P < 0.001$). As illustrated in Fig. 1, serum CCL11 level in children suffering from FA (143.7 ± 28.2 pg/ml, $n = 63$) was approximately 2.5-folds more than controls (55.32 ± 13.41 pg/ml, $P < 0.001$). However, these findings showed elevated levels of both CCL2 and CCL11 but CCL5 was undetectable in our patients. The average serum CCL2 level in FA patients and the controls was 337.1 ± 28.8 and 144.8 ± 16.7 pg/ml, respectively ($P = 0.01$), and almost all of FA patients had higher CCL2 in compare to control (Fig. 2).

The number of children who were suffering from anaphylaxis, bronchial asthma, atopic dermatitis, and urticaria was 40, 10, 7, and 6, respectively (Table 1).

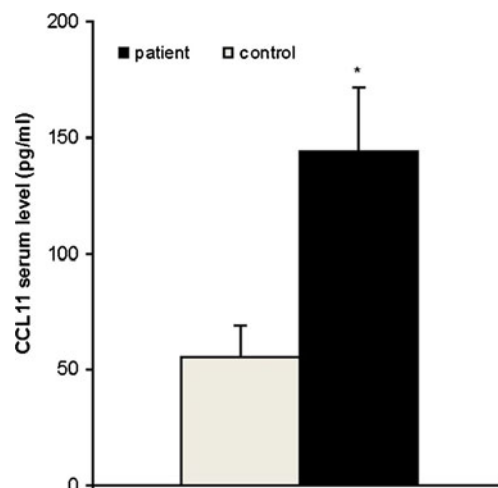


Fig. 1. Circulating levels of CCL11 in food allergic children and controls. Asterisk Significant difference between food allergic children and control.

Also, the number of children who were suffering from allergy to bird egg, cow's milk, cacao, and pistachio nuts was 20, 22, 4, and 15, respectively (Table 1).

The serum levels of CCL2 in children suffering from anaphylaxis, bronchial asthma, atopic dermatitis, and urticaria were 352.3 ± 21.2 , 251.2 ± 27.8 , 174.3 ± 19.6 , and 273.7 ± 28.2 pg/ml, respectively (Table 2). The serum levels of CCL11 in children with anaphylaxis, bronchial asthma, atopic dermatitis, and urticaria were 154.2 ± 22.9 , 98.3 ± 13.23 , 87.1 ± 12.4 , and 113.9 ± 11.4 pg/ml, respectively (Table 2). The serum levels of CCL2 in children suffering from allergy to bird egg, cow's milk, cacao, and pistachio nuts were 243.6 ± 18.5 , 327.41 ± 31.3 , $186.4 \pm$

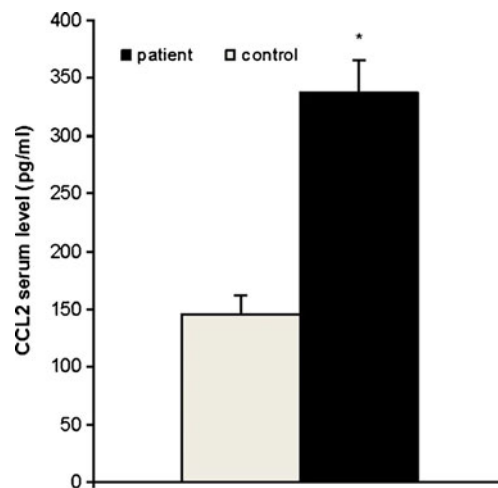


Fig. 2. Circulating levels of CCL2 in food allergic patients and controls. Asterisk Significant difference between food allergic children and control.

Table 2. Serum Levels of Studied Chemokines According to the FA Complications and Type of Allergens Used

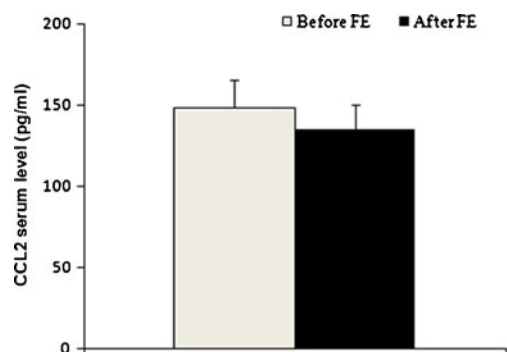
Variable	CCL2	CCL5	CCL11
Type of complication			
Anaphylaxis	352.3±21.2 ^a	ND	154.2±22.9 ^b
Bronchial asthma	251.2±27.8	ND	98.3±13.23
Atopic dermatitis	174.3±19.6	ND	87.1±12.4
Urticaria	273.7±28.2 ^c	ND	113.9±11.4 ^d
Source of allergen			
Bird egg	243.6±18.5	ND	111.1±14.3
Cow's milk	327.41±31.3 ^e	ND	148.7±23.2 ^f
Cacao	186.4±23.4	ND	95.4±17.1
Pistachio nuts	348.7±25.4 ^g	ND	152.1±31.3 ^h

ND not detectable

^a Significant difference with bronchial asthma, atopic dermatitis, and urticaria^b Significant difference with bronchial asthma, atopic dermatitis, and urticaria^c Significant difference with bronchial asthma and atopic dermatitis^d Significant difference with bronchial asthma and atopic dermatitis^e Significant difference with cacao and bird egg^f Significant difference with cacao and bird egg^g Significant difference with cacao and bird egg^h Significant difference with cacao and bird egg

23.4, and 348.7±25.4 pg/ml, respectively (Table 2). The serum levels of CCL11 in children exhibiting allergy to bird egg, cow's milk, cacao, and pistachio nuts were 111.1±14.3, 148.7±23.2, 95.4±17.1, and 152.1±31.3 pg/ml, respectively (Table 2).

Treatment of patients with food elimination (FE) therapy protocol revealed that the serum level of CCL11 was resistant to change; however, we observed an approximately twofolds decrease in CCL2 level in FE group in compare to non-treated. Our findings indicated that the mean serum level of CCL11 in FE group before and after treatment was 148.3±17.2 and 134.7±15.4 pg/ml, respectively (Fig. 3). Our findings also demonstrated that the mean serum level of CCL2 in FE group before

**Fig. 3.** Circulating levels of CCL11 before and after food elimination. FE = food elimination.

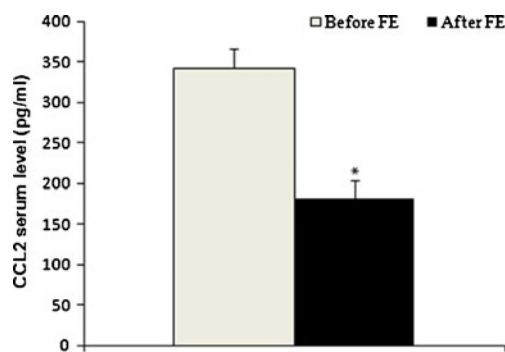
and after treatment was 342.3±24.2 and 181.4±21.2 pg/ml, respectively (Fig. 4).

DISCUSSION

Compelling evidences displayed critical roles for T lymphocytes in pathogenesis of IgE-mediated food allergic disorders. T cells are concerned as central actors in the pathogenesis of non-IgE-mediated gastrointestinal allergic disorders including, eosinophilic gastrointestinal disorders [19].

The present study was carried out to measure three of more relevant CC chemokines such as CCL2, CCL5, and CCL11, at serum level in children who suffering from FA in compare to control. Consistent with this report, the increased CCL11 level has been shown in several clinical circumstances including bronchoalveolar lavage fluid [20] and sputums [21, 22] of asthma patients, human milk of allergic mothers [23], and skin biopsies obtained from patients suffering from atopic dermatitis [24]. In an investigation, Fulkerson *et al.* demonstrated that response to chronic allergic airways inflammation was impaired in eosinophil, animals as well as CCL11-deficient and CCR3 knockout mice. Their results in a way may confirm: (a) the core role played by eosinophils and (b) this duty of eosinophils is related to CCL11/CCR3 interaction because CCR3 which is the specific receptor for CCL11 and is expressed on eosinophils surface membrane.

In agreement with our study, previous investigations revealed that CCL11 is elevated in AD and asthma patients [25], [26]. Our FA group showed increased levels of CCL11. To determine whether our observations were due to the AD, the FA subjects were divided into

**Fig. 4.** Circulating levels of CCL2 before and after food elimination. Asterisk Significant difference between before and after food elimination therapy.

four distinct groups as anaphylaxis, bronchial asthma (BA), AD, and urticaria. The CCL11 levels were significantly higher not only in whole FA patients but it was also at high level in all of subgroups in comparison to control. However, CCL5 is not detectable in FA patients' serum but there was a significant difference in CCL2 and CCL11 levels between the patients showing anaphylaxis complication and other complications groups of FA patients. As there were only few studies regarding chemokine expression in FA, Berkman *et al.* reported that baseline eotaxin 3 (CCL26) expression did not differ in asthmatic patients in comparison with control; however, it was remarkably enhanced 24 h following allergen challenge [27]. In another closely related study, Kagami *et al.* reported that the serum levels of this chemokine were correlated to the disease activity in AD [28]. In contrast to our findings, Poltzer *et al.* reported that both CCL11 and CCL24 remained unchanged in patients with active Churg while CCL26 was elevated [29]. Recruitment of eosinophils in an allergen-induced fashion to the airways indicated to be abolished in CCL11-, CCL24-, and CCR3-deficient mice [30].

Taking into account the ability of CCL11 to recruit eosinophils and CCL2 to attract lymphoid subtypes toward tissues as well as activate the drastic proinflammatory effectors functions of the cells [30], thus, both CCL2 and CCL11 could be considered as candidate pathogenic molecules in FA.

However, FE resulted in significant decreased serum levels of CCL2 but the CCL11 was not affected. Although, to the best of our knowledge there is not a similar study to compare with, regarding CCL2 but in agreement with our study, Matsuura *et al.* reported unchanged CCL11 level following FE therapy in FA patients [31]. CCL2 is known as an inflammatory chemokine and its decreased level after FE diet could possibly be due to the following facts: (a) Decreased stimulatory activities of food allergens on gastrointestinal tract epithelial cells and other cell types are involved in CCL2 production. Because CCL2 showed to be produced by several cell types including lymphocytes, monocyte, and epithelium of gastrointestinal tract and colon, and CCL11 is produced by limited cell systems such as eosinophils, basophils, and lymphocytes, this may explain the decreased CCL2 but unchanged CCL11 [32]. (b) Some of the allergens present in foods probably affect CCL2 production in gastrointestinal epithelium and other sources at mRNA level; and in the absence of these allergens, probably CCL2 may decrease at mRNA

level or even its mRNA half-life reduces. This could be examined probably by addition of these allergens to the cell cultures and further analyzing the mRNA and protein levels of CCL2 in response to food allergens. Due to the lack of information regarding the role of these proinflammatory chemokines in food elimination diet patients, further studies are required to elucidate the exact role of these chemokines in FA patients treated with FE.

On the other side of this scenario, the CD23 is expressed on human intestinal epithelial cells surface which can trigger the up-regulation of epithelial chemokines [25]. Following cleavage of the epithelial barrier triggered by IgE-Ag complex and CD23, the release of chemokines such as CCL20 and CXCL8 from the epithelium could be induced. The paramount role played by the chemokines in the development of allergic inflammation is important and this is well documented by studies indicating that experimental allergic disease cannot be induced in animals with specific chemokine deficiencies [33], [34]. These chemokines can recruit both inflammatory and adaptive immune cells including dendritic cells (DCs), T cells, and B cells. CCL2 and CCL5 are chemoattractant for immature DCS, memory T cells, and B cells, whereas CCL11 is a chemoattractant for eosinophils and reported to be increased in late-phase allergic inflammation. Overall, findings of the present study proposed that serum levels of CCL2 and CCL11 are elevated in FA and these may be considered as useful parameters for diagnosis of this disorder. However, it seems far to achieve this, but it is also possible to design therapy protocols based on the blocking of chemokines expression by application of their antagonists or antibodies against them to overcome allergic complications in patients suffering from FA.

Furthermore, it is also possible that clinicians speculate either the severity of disease or the event of entering of patients to the acute or chronic phase, according to the serum CCL2 and/or CCL11 levels. Therefore, the increased level of these chemokines may aid both adaptive and inflammatory immune cells as well as eosinophils to the allergic regions and may worsen the clinical symptoms of the disorder.

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