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Assessment of Serum CCL2 and Inflammatory Biomarkers in Pediatric Chronic Spontaneous Urticaria

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ABSTRACT

Objective: Chronic Spontaneous Urticaria (CSU) has a complex and multifactorial pathogenesis, and a substantial proportion of pediatric patients achieve adequate disease control with second-generation antihistamines. Whereas several biomarkers, including C-C ligand 2 (CCL2), have been associated with CSU in various adult populations, their role in pediatric patients is less clear. The current study aims at investigating serum levels of CCL2 in relationship with disease severity in a population of children affected by CSU, along with other inflammatory and autoimmune markers, in order to improve understanding and management strategies of pediatric CSU.

Materials and Methods: In the pediatric immunology and allergy clinic, a prospective study was conducted on 39 pediatric CSU patients and 38 healthy controls. Disease activity was monitored by the UAS-7, and ASSTs were also performed. Serum levels of CCL2 and other biomarkers, including eosinophils, D-dimer, fibrinogen, and CRP, were measured.

Results: There were no significant differences between the serum levels of CCL2 in CSU patients and healthy controls ($p = 0.601$) or between mild and moderate-to-severe CSU ($p = 0.83$). Similarly, no significant association was observed between the levels of CCL2 and positivity to ASST ($p = 0.238$). On the other hand, the relationship between CCL2 and fibrinogen levels presented an inverse correlation: $p = 0.012$. Eosinophil counts had a significant relation to UAS-7 scores, at $p = 0.044$. IgE, CRP, D-dimer, and ANA did not relate to the severity of disease.

Conclusion: In this pediatric CSU cohort, CCL2 did not show a clear association with clinical or laboratory measures. As the study was exploratory and based on a limited sample, these observations should be interpreted with caution. The primary contribution of this work is the generation of preliminary pediatric data in a field where evidence is limited. Larger, well-designed studies are needed to more accurately determine the roles of CCL2 and other potential biomarkers in the assessment and management of pediatric CSU.

Keywords: Chronic spontaneous urticaria, pediatric urticaria biomarkers, CCL2 chemokine, eosinophils and urticaria severity, autologous serum skin test

INTRODUCTION

Chronic Spontaneous Urticaria (CSU) is characterized by a complex and multifactorial pathogenesis. While a substantial proportion of pediatric patients achieve adequate disease control with second-generation antihistamines, a subset remains refractory to conventional therapy and may require treatment with biological agents. Several mechanisms are involved in the pathophysiology of CSU, including mast cell activation and degranulation, activation of the coagulation cascade, and acute phase responses, in addition to autoimmune and hematopoietic system dysfunctions. Kolkhir et al. reported correlations between CSU and the biomarkers D-dimer, C-reactive protein, and fibrinogen (1). Similarly, a recently performed retrospective study reported a high prevalence of autoimmune disease positivity among CSU patients, which similarly supports the multifactorial etiology of the disease (2). Puxeddu et al. also demonstrated that serum levels of CRP and D-dimer were elevated in adult CSU patients

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(3). These findings imply that inflammation is important in the pathophysiology of CSU, and several pro-inflammatory biomarkers have been investigated regarding their involvement in this process. Among these biomarkers, C-C motif ligand 2 (CCL2), a chemokine of the C-C type, has been shown to be associated with inflammatory and autoimmune-related diseases like CSU (4,5). CCL2 exerts strong signaling to draw memory T cells, monocytes, and natural killer cells to the site (4). It is crucial during the development of adaptive Th2 responses and contributes to mast cell and basophil degranulation. Along with other mediators, CCL2 is believed to promote the release of histamine and serotonin from mast cells. Although earlier studies have described increased CCL2 mRNA expression in CSU patients, data on the serum level of CCL2 in CSU have been rather limited (5,6).

Although some clinical investigations among pediatric populations exist in support of pathophysiological theories of inflammation and autoimmunity, there are no data in children exploring the relationship between CCL2 and severity of CSU (5). In general, the limited pathophysiological and clinical research restricts knowledge and competence in healthcare given to this pediatric population. This, therefore, is an exploration of the effects that the pro-inflammatory and autoimmune biomarkers will have on the treatment and management of children with CSU so as to improve the global understanding and awareness of the disease.

MATERIAL and METHODS

Study Population

The study was done prospectively at the outpatient department of the pediatric immunology and allergy clinic. Written informed consent was obtained from parents or legal guardians, and age-appropriate assent was obtained from children when applicable.

The study was approved by the Institutional Ethics Committee (2018/1049) and conducted in conformity with the principles of the Declaration of Helsinki.

The study included 39 children diagnosed with CSU and 38 healthy controls. All patients met the EAACI/GA(2)LEN/EDF/WAO criteria for the diagnosis of CIU (7).

Individuals younger than 6 years and older than 18 years, as well as those with inducible urticaria, urticaria vasculitis, allergic rhinitis, asthma, or food allergies, were excluded from the study.

Patient's Data

The age, sex, duration of symptoms, and family history of atopy for each patient were recorded. Disease activity was assessed according to the Urticaria Activity Score 7 (UAS-7), calculated as recommended by the EAACI/GA-2LEN/EDF/WAO (7).

All the patients also underwent an ASST; a 10 cc sample of venous blood was drawn and then placed in sterile plain tubes, where it clotted for 30 minutes at room temperature. Then, the blood sample was centrifuged at 500 g for 15 minutes in order to obtain serum. Fifty µl of serum was intradermally injected into the volar aspect of the forearm with an insulin syringe. Controls included 10 µl of histamine (Allergopharma, Germany) injected intradermally as a positive control and 50 µl of physiological saline solution as a negative control, 5 cm away from the ASST injection site. After 30 minutes, the diameter of erythema and induration was measured; a positive result was defined as an induration greater than 1.5 mm compared to the saline control. All the ASST procedures were performed by the same researcher (8).

For the measurement of CCL2, blood samples were drawn into biochemical tubes and centrifuged at 4000 rpm for 10 minutes. The sera were stored at -80°C until analysis. CCL2 levels were measured using commercially available ELISA kits (Human CCL2, lot number: 173441-039; Invitrogen®, USA) having an analytical detection range of 15.6-1,000 pg/mL, with a minimum detectable limit of 7 pg/mL. Intra- and inter-assay CVs were cited as 5.5% and 6.6%, respectively.

Some laboratory tests could not be performed in all patients because a proportion of patients were receiving ongoing antihistaminic treatment, which precluded the reliable assessment of certain parameters. Additionally, two children were excluded from the final analysis due to unexpectedly high UAS-7 scores that did not meet the predefined eligibility criteria for the study.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics v. 22 Armonk, NY: IBM Corp. The Shapiro-Wilk test was conducted to evaluate the normality of data distribution.

Data with a normal distribution is presented as mean, standard deviation, and frequency. Comparisons between two groups were performed by Student's t-test in normally distributed data and by the Mann-Whitney U test in non-normally distributed variables.

Comparison of categorical variables was performed using Fisher's exact test. Correlations were assessed by Pearson's test for normally distributed variables and by Spearman's rho for non-normally distributed variables. A p-value of less than 0.05 was considered significant.

RESULTS

Patient's Characteristics

The study population consisted of 77 children, including 39 patients with CSU and 38 healthy controls. The patient and control groups did not differ significantly in terms of age or sex. In the patient group, the mean age was determined as 12.53±2.95 years, and 53.8% (n=21) of the patients were male. While the duration of symptoms varied between 2 and 42 months, the mean was determined to be 13.51±13.11 months, with a median of 6 months. Most of the cases had mild to moderate disease severity, and other clinical and laboratory findings are outlined in Table I.

CCL2 With Laboratory Findings

There was no significant difference in the serum levels of CCL-2 between patients with CSU and healthy controls [mean±SD: 621.41±154.27 vs. 601.16±183.35 pg/ml, p=0.601]. Serum levels of CCL-2 in patients with mild CSU were also not significantly different from those of patients with moderate-to-severe CSU [640.12±133.7 vs. 629.64±160.89 pg/ml, p=0.83]. Moreover, no significant association was seen in terms of CCL-2 levels between patients with positive and negative ASST results {683.78±175.5 vs. 595.06±176.07 pg/ml} [p=0.238].

There was no statistically significant correlation between serum CCL-2 levels and other variables such as age, sex, duration of symptoms, UAS-7 scores, serum IgE levels, eosinophil counts, D-dimer levels, basophil counts, or CRP levels (p>0.05). The only statistically significant relationship was an inverse correlation between CCL-2 levels and fibrinogen (p=0.012; p<0.05) (Table II). Moreover, a statistically significant relationship was found between UAS-7 scores and eosinophil counts, with lower eosinophil values observed in patients with milder UAS-7 scores (p=0.044; p<0.05). However, no significant relationship was found between UAS-7 scores and other variables such as age, sex, duration of symptoms, serum IgE levels, D-dimer, fibrinogen, basophil counts, CRP, ANA, or ASST results (p>0.05) (Table III).

A post-hoc power calculation was carried out to assess if the sample size in this study had sufficient power to detect differences in serum CCL2 levels in pediatric CSU patients compared to healthy controls. By calculating the effect size through the mean and standard deviations of the two groups, the effect size was Cohen's d = 0.12, reflecting a very small effect: CSU, 621.4±154.3 pg/mL; controls, 601.2±183.4 pg/mL. The post-hoc power for detecting this effect, with two-tailed $\alpha = 0.05$ and using the actual sample sizes, $n_1 = 39$ and $n_2 = 38$, was estimated to be approximately 7.5%. This indicates that the study was underpowered to identify small between-group differences in CCL2 levels.

Table I: Clinical and laboratory findings of the patients

	Mean ±SS / Median
Age (years)	12.53±2.95
Duration of symptoms (months)	13.51±13.11
Total IgE (n=38)(median) (U/ml)	73
Eosinophil counts % (n=39)	2.58±2.08
D dimer (n=38)(median) (microgram/mL)	357
Fibrinogen (n=37) (mg/dl)	274.70±56.24
CRP (mg/dl) (n=36)(median)	0.82
Basophil count % (n=24)	0.40±0.27
	%
Family history of atopy	12.8
Angioedema (n=39)	28.2
Allergen sensitivity	
Aeroallergens	23.5
Food allergens*	5.9
ASST positivity (n=25)	36
ANA positivity (n=32)	25
UAS-7 (n=39)	
Mild	66.7
Moderate	28.2
Severe	5.1

UAS-7: Urticaria Activity Score-7, **ANA:** Antinuclear antibody -positive **ASST:** Autologous serum skin test -positive
*Oral provocation test with sensitive food result negative

Table II: Correlation of serum CCL2 levels with clinical and laboratory parameters

		CCL2
Age	r	-0.188
	p	0.102
Duration of symptoms	r	0.204
	p	0.214
Serum IgE level	r	0.055
	p	0.744
Eosinophil %	r	-0.007
	p	0.967
D dimer	r	-0.13
	p	0.435
Fibrinogen	r	-0.408
	p	0.012*
CRP	r	-0.016
	p	0.927
Basophil%	r	-0.016
	p	0.942
UAS score	r	-0.214
	p	0.191

Pearson correlation analysis. *p<0.05

Table III: Evaluation of study parameters according to UAS score

	UAS score		p
	Mild	Moderate	
	Mean±SD	Mean±SD	
Age (years)	12.46±2.89	11.91±2.63	0.589[1]
Duration of symptoms (month) (median)	6	4	0.255[2]
Serum IgE level (median)	77.4	131	0.525[2]
Eosinophil % (median)	1.8	3.1	**0.044**[2*]
D dimer(median)	328	417	0.223[2]
Fibrinogen	266.48±48.59	285.6±71.75	0.367[1]
CRP (median)	0.8	1.1	0.637[2]
Basophil % (median)	0.4	0.3	0.436[2]
	n (%)	n (%)	p
Sex			
Female	12 (46.2)	4 (36.4)	0.723[3]
Male	14 (53.8)	7 (63.6)	
ASST			
Negative	10 (62.5)	5 (62.5)	1.000[3]
Positive	6 (37.5)	3 (37.5)	
ANA			
Negative	17 (73.9)	7 (87.5)	0.642[3]
Positive	6 (26.1)	1 (12.5)	

[1]Student t test, [2]Mann-Whitney U test, [3]Fisher's exact test. *p<0.05
PS: Two children were excluded from the analysis because the UAS-7 score was high

DISCUSSION

In the present study, we investigated whether C-C motif ligand 2 (CCL2) could serve as a biomarker in pediatric patients with chronic spontaneous urticaria (CSU). Serum CCL2 levels were higher in patients than in healthy controls; however, no significant association with disease activity was observed. These findings suggest that although CCL2 may be involved in inflammatory pathways relevant to CSU, its value as a marker of disease activity in pediatric populations appears limited. Importantly, this distinction between biological involvement and clinical usefulness is critical when evaluating candidate biomarkers.

C-C motif ligand 2 is a chemokine that plays a key role in the recruitment of monocytes, memory T lymphocytes, and dendritic cells to sites of inflammation and contributes to mediator release from monocytes and basophils (9). Chemokines, including CCL2, are essential regulators of leukocyte trafficking and the maintenance of inflammatory responses, and increased levels have been reported in various inflammatory and immune-mediated conditions (10-16). Therefore, the elevated CCL2 levels observed in our cohort likely reflect underlying inflammatory activation rather than disease severity per se. This interpretation is consistent with the concept that systemic biomarkers may reflect the presence of inflammation but not necessarily its clinical intensity.

Inflammation in CSU is also closely linked to activation of the coagulation and fibrinolytic systems. Endothelial activation, cytokine signaling, and leukocyte recruitment provide mechanistic links between inflammatory and coagulation pathways, and acute-phase reactants such as fibrinogen may serve as indirect indicators of this interaction (17). Previous studies have reported increased fibrinogen and coagulation marker levels in CSU and other inflammatory conditions; however, results have been heterogeneous, particularly in pediatric populations (18-20). These inconsistencies suggest that age-related immunological and physiological differences may influence bio-

marker behavior. Although we observed a statistically significant inverse correlation between CCL2 and fibrinogen levels, this finding should be interpreted cautiously. Given that multiple biomarkers were evaluated simultaneously, the risk of a type I error cannot be excluded. Accordingly, this result should be regarded as hypothesis-generating rather than definitive, and confirmation in larger, adequately powered studies is necessary.

Differences between adult and pediatric CSU populations may be particularly relevant in this context. Children generally have fewer comorbidities, lower baseline inflammatory burden, and distinct patterns of immune maturation, all of which may affect systemic biomarker profiles. Several studies focusing on pediatric CSU have emphasized weaker or more variable associations between inflammatory markers and disease activity compared with adult cohorts (3,20,21). Our findings support this observation and reinforce the need for age-specific validation of candidate biomarkers rather than direct extrapolation from adult data.

In our cohort, CCL2 levels did not correlate with disease activity. This finding does not exclude a pathogenic role for CCL2 but suggests that circulating levels alone may not adequately reflect the complexity of disease activity. It is plausible that local tissue-level inflammatory processes, mast cell activation, and microvascular changes play a more decisive role in determining clinical severity than systemic chemokine concentrations. Such compartmentalization of inflammatory responses has been described in other chronic inflammatory diseases and may partly explain the limited performance of circulating biomarkers.

In addition to CCL2, we evaluated several laboratory parameters to obtain a broader perspective on biomarker utility in pediatric CSU. Eosinophil counts showed modest clinical relevance, consistent with studies demonstrating eosinophil infiltration and inflammatory cell accumulation in urticarial lesions (22-24). However, the relatively small differences observed and the lack of a clear association with disease activity categories suggest that peripheral blood eosinophil counts may have limited sensitivity as markers of clinical severity.

Basophil counts have been reported to correlate inversely with disease activity in adult CSU cohorts, yet this association was not observed in our pediatric population (25). This discrepancy may reflect developmental differences in immune regulation, differences in disease phenotype, or the predominance of mild-to-moderate disease in our cohort. It is also possible that basophil functional changes, rather than absolute counts, are more relevant indicators of disease activity.

D-dimer has been widely described as a biomarker associated with disease severity in adult CSU, and elevated levels have been reported particularly in patients with severe disease (26-29). Elevated D-dimer levels have also been documented in pediatric urticaria, especially in prolonged or severe cases (30). In contrast, we did not observe significant variation between mild and moderate disease activity groups, and fibrinogen levels were not clearly associated with disease activity. These findings may indicate that systemic coagulation-inflammation interactions are less pronounced in pediatric CSU or that larger cohorts are required to detect subtle differences (17-20,29).

Total IgE levels were higher in patients with moderate disease activity, which may be consistent with the contribution of IgE-mediated mechanisms in a subset of pediatric CSU cases. At the same time, the established role of autoantibodies in CSU indicates that multiple immunological pathways, including both type I and type II hypersensitivity mechanisms, may coexist. This immunological heterogeneity may further limit the diagnostic and prognostic performance of single biomarkers (7).

Although inflammation is central to CSU pathophysiology, classical systemic inflammatory markers such as CRP were not significantly associated with disease activity in our cohort, despite reports of such associations in adult populations (31-33). This discrepancy may reflect differences in disease phenotype, lower systemic inflammatory burden in children, or variability in disease duration and activity patterns.

Autoimmune markers, including ANA and ASST, have been proposed as tools to identify autoimmune subtypes of CSU; however, their clinical significance in pediatric populations remains uncertain (8). In our study, ANA and ASST positivity were not associated with disease activity, in line with previous reports suggesting limited predictive value of these markers in children (20,34,35).

Several limitations should be considered when interpreting these findings. First, the predominance of patients with mild disease and the relatively small number of individuals with moderate-to-severe CSU limited the ability to analyze associations across the full spectrum of disease

severity. Second, the cross-sectional design did not allow assessment of temporal changes in biomarker levels, which may be relevant for evaluating their role in disease monitoring. Third, the single-center nature of the study may limit generalizability.

Despite these limitations, this study provides additional evidence that systemic inflammatory and coagulation-related biomarkers may have limited value in reflecting disease activity in pediatric CSU. From a clinical perspective, these findings suggest that routine measurement of such markers may not provide substantial additional information for disease activity assessment in children, and clinical evaluation remains the cornerstone of disease monitoring.

In conclusion, while inflammatory mediators, chemokines, and coagulation-related markers are involved in the complex pathophysiology of CSU, their value as reliable biomarkers of disease activity in pediatric patients remains uncertain. Future prospective studies with larger cohorts, longitudinal designs, and integration of cellular, molecular, and functional biomarkers may help identify more sensitive indicators of disease activity and improve the clinical management of pediatric CSU.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Statement

This study received approval from the local Ethical Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital, University of Health Sciences (2018/1049).

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Author Contributions

Concept: **EY, DO,** Design: **DO,** Data collection or processing: **EY, OD,** Analysis or Interpretation: **OD,** Literature search: **HG,** Writing: **HG, DO,** Approval: **DO.**

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