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Original Research Article

Serum interleukin-6 as a biomarker of disease activity and severity in chronic spontaneous urticaria: a case control study in urban south Indian population

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ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a challenging dermatological condition marked by recurrent wheals lasting over six weeks without identifiable triggers. While its pathogenesis is not fully understood, emerging evidence suggests a role for pro-inflammatory cytokines, particularly interleukin-6 (IL-6), in disease activity. However, its relevance as a biomarker for disease severity remains to be clarified. To evaluate serum IL-6 levels in CSU patients and determine their correlation with disease severity, compared to healthy controls.

Methods: A case-control study was conducted in the Department of Dermatology at Raja Rajeswari Medical College and Hospital from April 2023 to September 2024. Fifty CSU patients and fifty age- and sex-matched healthy controls were enrolled. Disease severity was assessed using the Urticaria Activity Score over 7 days (UAS7). Serum IL-6 levels were measured using ELISA. All calculations were performed using Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago).

Results: Most CSU patients (66%) were young adults (20–40 years), with equal gender distribution. Severe disease (UAS7: 16–42) was observed in 72% of patients. Mean IL-6 levels were significantly higher in CSU patients than in controls (9.1±5.1 vs. 3.12±2.8 pg/ml, p=0.004). IL-6 levels showed a significant positive correlation with disease severity.

Conclusions: Serum IL-6 is significantly elevated in CSU patients and correlates with disease severity. It may serve as a promising biomarker for monitoring disease activity and tailoring treatment in CSU, warranting further investigation into its therapeutic potential.

Keywords: CSU, Cytokines, IL-6, UAS7

INTRODUCTION

Chronic spontaneous urticaria (CSU) represents a complex and challenging dermatological disorder characterized by recurrent, transient and pruritic wheals that persist for more than six weeks without an identifiable external trigger. This condition significantly impacts patients' quality of life, causing substantial physical discomfort and psychological distress. The pathogenesis of CSU is multifaceted, involving intricate immunological mechanisms that remain only partially understood, highlighting the critical need for comprehensive research into its clinical and immunological characteristics.[1] The immunopathological landscape of CSU is predominantly governed by autoimmune processes, with emerging evidence suggesting the involvement of multiple immunological pathways. Various interleukins have been increasingly

recognized as potential key mediators in disease progression, particularly interleukin-6 showing clinical significance.[2] These autoimmune phenomena trigger mast cell and basophil activation, leading to excessive histamine release and subsequent inflammatory cascades that manifest as urticarial lesions.[3]

Immunological biomarkers have emerged as promising diagnostic and prognostic tools in comprehending CSU's complex pathogenesis. Specific immunological biomarkers such as Interleukin–6 (IL-6) and various cytokine profiles have demonstrated potential role in elucidating disease mechanisms and predicting treatment responses.[4] This research aims to systematically investigate the relationships between clinical manifestations and IL-6 in CSU patients by conducting a comprehensive analysis of the same to identify potential correlation and prognostic indicators.

METHODS

The study was conducted Department of Dermatology at Raja Rajeswari Medical College and Hospital from April 2023 to September 2024 following approval from the Institutional Ethics Committee (IEC/XXX/2023).

The sample size was calculated based on the average outpatient attendance in the dermatology department, which was approximately 3 to 4 patients per week. Using the Yamane formula for sample size estimation (where N represents the population size and e denotes the margin of error, set at 0.05 for a 95% confidence level), a total of 100 participants were recruited. This included 50 clinically diagnosed cases of chronic spontaneous urticaria and 50 age and gender-matched healthy controls. Prior to enrolment, written informed consent was obtained from all participants, with consent forms provided in bilingual format to ensure comprehensive understanding and voluntary participation.

Detailed demographic profiles, medical histories and physical examination were documented. The disease severity was assessed using the Urticaria Activity Score (UAS7) from the Australasian Society of Clinical Immunology and Allergy CSU Guidelines. Patients on immunomodulatory drugs within the past 4 weeks, those with other types of chronic inducible urticaria, pregnant and lactating women and those with chronic inflammatory or connective tissue disorders were excluded.

Venous blood samples were collected in clot activator tubes and sera were separated and stored at 80°C until the time of estimation and analysed for Interleukin-6 (IL-6). The biomarker was quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Invitrogen by Thermo Fisher Scientific, Life Technologies, Frederick, U.S.A) following the manufacturer's instructions at the central research laboratory. Calibration curves were plotted on semi-logarithmic graph paper and the optical density (OD) values of the samples were determined from the standard curve generated using the ELISA kit.

Principle of sandwich enzyme linked immunosorbent assay

Analyte capture

The microplate provided in the ELISA kit is pre-coated with a specific capture antibody. When standards or samples are added to the wells, the target analyte binds to the immobilized antibody. Any unbound substances are then removed through washing steps.

Binding of horseradish peroxidase-conjugated detection antibody

A horseradish peroxidase (HRP)–labelled detection antibody is subsequently introduced, which specifically binds to the captured analyte. Excess unbound detection antibody is eliminated by additional washing.

Color development and detection

Tetramethylbenzidine (TMB), the substrate for HRP, is added to each well. A blue color forms in proportion to the amount of bound analyte. The enzymatic reaction is halted by adding a stop solution, resulting in a yellow color. The optical density (OD) is then measured at 450 nm. These readings are used to generate a standard curve from which the concentration of the analyte in the samples is calculated.

Statistical analysis

Data was analysed using SPSS version 21. Qualitative data were expressed as frequencies and percentages, while quantitative data were presented as mean, median, standard deviation and ranges. The results were analysed statistically using Chi square test, Mann–Whitney U tests and Spearman's correlation method. A paired student's t-test was used to assess statistical significance with $p<0.05$ considering as significant.

RESULTS

This case-control study included 50 patients with confirmed CSU and 50 healthy controls. Table 1 presents the fundamental demographic profile of the study population, including age distribution, gender ratio and disease characteristics. The majority of participants in both groups were young adults (20-40 years), with a notably equal gender distribution in the CSU group. Disease severity assessment revealed that 72% of CSU patients presented with severe disease (UAS 16-42), while 28% had moderate symptoms (UAS 7-15). Disease duration analysis showed that most patients (62%) had experienced symptoms for less than 5 years, with smaller proportions having longer-standing disease. No

significant differences were observed in age and gender distribution between cases and controls, ensuring demographic comparability between groups. Table 2 highlights the significant alterations in IL-6 levels in CSU patients and controls. Mean IL-6 levels were significantly higher in CSU patients (9.1±5.1 pg/ml) when compared to controls (3.12±2.8 pg/ml, p=0.004). Table 3 demonstrates the correlation between disease severity (UAS score) and interleukin-6 providing insight into potential disease activity indicators. IL-6 demonstrated pronounced correlation, increasing more than threefold from 3.12±2.8 pg/ml in controls to 10.3±4.9 pg/ml in severe cases (p<0.001). These findings collectively identify IL-6 as a potential biomarker for monitoring disease activity in CSU indicating that patients with more severe disease had higher IL-6 concentrations.

Table 1: Demographic and clinical characteristics.

Characteristic	Case (n=50) (%)	Control (n=50) (%)
Age (in years)		
20-40	33 (66)	36 (72)
41-60	16 (32)	14 (28)
>60	1 (2)	0 (0)
Gender		
Female	25 (50)	26 (52)
Male	25 (50)	24 (48)
Disease duration (in years)		
<5	31 (62)	-
5-10	14 (28)	-
>10	5 (10)	-
UAS score		
0	0 (0)	50 (100)
7-15 (moderate)	14 (28)	0 (0)
16-42 (severe)	36 (72)	0 (0)

Table 2: Immunological biomarker.

Marker (mean±SD)	Case	Control	P value
IL-6 (pg/ml)	9.1±5.1	3.12±2.8	0.004

Table 3: Association of UAS with IL-6.

Marker	UAS Score (mean±SD)			P value
	0 (control)	7-15 (moderate)	16-42 (severe)	
IL-6 (pg/ml)	3.12±2.8	6.1±4.3	10.3±4.9	<0.001

DISCUSSION

Our study demonstrated significant alterations in serum interleukin-6 levels in CSU patients compared to healthy controls. The disease duration analysis revealed that most patients (62%) had experienced symptoms for less than 5 years, consistent with findings by Maurer et al who reported approximately 70% of CSU patients experiencing symptoms for 1-5 years.[2] The gender distribution was balanced (50% each), which differs slightly from previous studies such as that by Kolkhir et al, which reported a female predominance.[4] The demographic profile of our study population showed a predominance of young adults (20-40 years), constituting 66% of cases, which aligns with findings by Zajac et al.[5] CSU is a cutaneous disorder primarily driven by mast cell activity and characterized by intricate disturbances in immune regulation. While H1-antihistamines and biologics like omalizumab (anti-IgE) are mainstays of treatment, a subset of patients remains refractory. This has prompted investigation into alternative cytokine targets, mainly interleukin-6 (IL-6). IL-6 levels were significantly higher in CSU patients compared to controls (9.1±5.1 vs 3.12±2.8 pg/ml, p=0.004), correlating strongly with the disease severity in our study.

This finding aligns with research by Fujii et al and Atwa et al who proposed IL-6 as a potential biomarker for CSU severity.[7,8] IL-6 is a multifunctional cytokine produced by T cells, B cells, mast cells, endothelial cells and fibroblasts. It promotes the acute phase response and inflammation, both of which are pathognomonic in CSU. IL-6 supports the data showing its involvement in CSU pathogenesis. Multiple studies have demonstrated a strong association between increased serum IL-6 concentrations and the severity of urticaria as determined by the urticaria activity score (UAS7), as well as a clear link between IL-6 levels and diminished quality of life,

assessed using the dermatology life quality index (DLQI). IL-6, primarily secreted by mast cells and T lymphocytes functions as a B-cell differentiation factor and is linked to the Th2 immune response. It plays a key role in inflammation, hematopoiesis and immune regulation. Given that a subset of CSU patients exhibits autoimmune features such as the presence of anti-IgE or anti-FcεRI antibodies, IL-6 is thought to contribute to the autoimmune mechanisms underlying CSU as well.[9] IL-6 inhibitors represent a promising therapeutic option for refractory CSU, especially in autoimmune or highly inflammatory phenotypes. However, their use remains experimental requiring a pending validation in larger, controlled studies on similar lines to our research.

Though the study provides valuable insights, some limitations must be considered. Firstly, the relatively small sample size may limit the statistical power of the results. Second, this study design captures IL-6 levels at a single time point before initiation of treatment, limiting the assessment of their response. Additionally, quality-of-life metrics such as the dermatology life quality index (DLQI) were not assessed, which might have further strengthened the clinical relevance of IL-6 elevation.

CONCLUSION

This comprehensive study provides significant insights into the immunological profile of CSU and its relationship with disease severity. CSU patients exhibit significantly elevated levels of IL-6 showing a particularly strong correlation with disease severity. These findings collectively enhance our understanding of CSU pathophysiology and suggest potential therapeutic targets, supporting the utility of monitoring immunological markers, particularly IL-6 as objective measures of disease activity and pave the way for discovery of novel treatment modalities. Based on the existing literature and our findings, we believe that our work and that others of in the domain lay the groundwork for future research on this aspect.

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