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Assessment of C Reactive Protein in Chronic Urticaria as a Marker of Disease Activity and Underlying Systemic Inflammation: A Case Control Study

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Original Research Article

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Abstract: Chronic urticaria (CU) defined by presence of urticaria (hives), on most days of the week, for 6 weeks or more. No external allergic cause can be identified in 80-90 % of these patients. CRP (C reactive protein) an acute phase response protein has been studied recently as a consequence or as a possibility of non-specific systemic inflammation in CU patients. CRP is a sensitive marker of an underlying systemic inflammation and is triggered mainly as a response to IL-6. We aimed to determine the CRP levels in CU patients and investigate any possible correlation between CRP levels and the severity of chronic urticaria (CU), assessed clinically by urticaria activity scores (UAS). After obtaining the institutional ethics committee approval, we enrolled 40 patients with CU of varying severity as well as 40 sex and age matched healthy participants, following written informed consent. This was a case- control study, carried over a period of 6 months. Each participant was evaluated with detailed history, clinical examination, urticaria activity score (UAS), CRP levels, ASST, haematological and biochemical investigations. The CRP levels were measured by latex agglutination assay. All the data was later tabulated and analysed. Of the 40 patients, 22 (55%) were females & 18 (45%) were males. The male to female ratio was 0.9: 1.1. Among the CU patients, ASST was found positive in 12 patients and negative in the remaining 28 patients. Serum CRP levels were significantly higher in CU patients when compared with healthy participants (0.312 mg/dl vs. 0.156 mg/dl respectively, $p = 0.022$). Patients with higher CRP levels had higher urticaria activity scores. A significant correlation was observed in patients who had moderate and severe disease activity scores than in those who had mild disease activity score ($p < 0.001$, $p < 0.001$, respectively). CRP levels appeared to correlate with the disease activity in 75% of our CU patients who had higher urticaria activity scores. These findings support the relationship of the inflammatory process in CU patients and therefore, CRP may be considered as a marker of the ongoing systemic inflammation in these patients. Further studies with a larger sample size are required to validate the same.

Keywords: Chronic urticaria, acute phase response, C-reactive protein, urticaria activity score, interleukin-6.

INTRODUCTION

Chronic urticaria (CU) is defined by the presence of urticaria (hives), on most days of the week, for a period of six weeks or longer. No external allergic cause or contributing disease process can be identified in 80 to 90 percent of these patients. Therefore, for adequate treatment of patients, evaluation of disease severity and activity of chronic urticaria (CU) is essential. However, there is no reliable biomarker for such evaluations. Lately, CRP (C reactive protein) levels have been studied along with the role of fibrin, fibrin degradation products (FDP), d-dimer and thromboxane in chronic uricaria. CRP which is an acute phase response protein has been studied recently to raise the possibility of systemic inflammation being causative or a consequence in CU patients. Although CRP synthesis and secretion is carried out locally and in other regions as well, plasma CRP production is only performed by hepatocytes and this largely occurs under the transcriptional control of IL-6 [1]. CRP, a sensitive marker of an underlying systemic inflammation is thought to be triggered mainly as a response to IL-6.

So far, there is very limited data available regarding the correlation of CRP levels in CU patients. Considering the importance of inflammatory response

into the pathophysiology and activity of the disease, CRP levels may provide an essential insight into the severity of the disease. Therefore, we conducted this study to investigate the correlation of CRP levels with the disease severity and to evaluate the role of CRP as a marker of systemic inflammation in CU patients.

AIM AND OBJECTIVES

The aim of our study was to determine the CRP levels in CU patients and investigate any possible correlation between CRP levels and the severity of chronic urticaria (CU), assessed clinically by urticaria activity scores (UAS).

MATERIALS AND METHODS

This was a case control study which included equal number of patients presenting with chronic urticaria and healthy participants over a period of 6 months i.e August 2013 to Jan 2014. All patients with recurrent urticaria with or without angioedema for a period of 6 weeks or greater were included. Patient's ≤ 18 years, those having recent infection or overt comorbid inflammatory systemic disease and those on oral corticosteroids within the past 2 months were excluded. The study group consisted of 40 participants with chronic urticaria and they were diagnosed clinically by two senior dermatologists of the department. The control group consisted of 40 sex and age matched healthy participants. After obtaining the written informed consent; a detailed history, systemic & cutaneous examination, CRP levels, haematological, biochemical, thyroid autoantibodies, urine and stool investigations were carried out. Autologous serum skin test (ASST) and other investigations had been performed to exclude any known causes of the diseases or the concomitant diseases.

Evaluation of urticaria activity scores

All CU patients had active disease at the time of evaluation and were divided into subgroups according to their urticarial activity. Urticaria activity score (UAS) was calculated according to EAACI/GA2LEN/EDF guidelines [2]. The UAS was estimated according to the number of wheals and pruritus intensity, on the day of blood sampling, applying the following criteria: no wheals = 0, 1-10 wheals = 1, 11-50 wheals = 2, 50 wheals = 3 and pruritus intensity: no = 0, mild = 1, moderate = 2, severe = 3. UAS scores: daily (minimum = 0; maximum = 6). The UAS was classified as follows: 0-2 (mild), 3-4 (moderate) and 5-6 (severe). In our study, 10 patients had mild, 16 patients had moderate and 14 patients had severe chronic urticaria symptoms.

Blood collection and assay of CRP

All blood samples were obtained by antecubital puncture and serum CRP concentration was measured between 7 and 9 a.m. by latex agglutination assay. Raised serum CRP level was defined as higher than 5.0 mg/l.

STATISTICAL ANALYSIS

Data were delivered as medians and interquartile ranges. Kruskal–Wallis variance analysis was used for screening differences between the groups. Mann–Whitney U test was used to compare data between the patient groups and the healthy controls. Correlation coefficient was obtained by Spearman test. Values of p lower than 0.05 were considered significant.

RESULTS

Forty patients with CU of duration ranging from 2 months to 11 years, without any concomitant physical urticaria were enrolled in the study group. A total of 22 (55%) females and 18 (45%) males were studied. The male to female ratio was 0.9: 1.1. The control group consisted of 40 sex and age matched healthy participants. At least 14 days before the study, none of the controls took any treatment. The mean age observed was 37.6 years and majority of the patients belonged to the 4th decade (45%). In the study group, family history of diabetes mellitus was present in 20 patients and hypertension in 12 while in the control group, 10 had family history of diabetes mellitus and 9 had hypertension.

Negative ASST was found in 28 patients and 12 patients had a positive reaction. All the controls responded negatively to ASST. Twenty-eight patients gave no history of angioedema; however, 12 gave history of angioedema. Seasonal variation of the disease was seen in 2 patients and 5 patients related the symptoms of CU to the history of food intake. All of them were being treated with antihistamines; however antihistamines were stopped 4 days before the study. Two patients gave history of complete improvement of the symptoms, 5 had no improvement and the remaining 33 patients gave history of partial improvement with the antihistamine therapy.

Median serum CRP concentrations in patients with mild, moderate and severe symptoms were 0.210, 0.336 and 0.648 pg/ml, respectively; $p > 0.05$, $p < 0.05$ and $p < 0.05$ respectively. Raised CRP was observed in thirty (75%) CU patients and only four (10%) participants from the control group. [*Figure 1*] The patients with higher CRP levels had higher urticaria activity scores (UAS). CRP levels appeared to correlate with the disease activity in 75% of our patients who had higher urticaria activity scores. The median CRP levels were significantly higher in CU patients when compared with healthy controls (0.312 mg/dl vs. 0.156 mg/dl respectively, $p = 0.022$). There was a statistically significant association between UAS and serum CRP concentrations ($p = 0.039$).

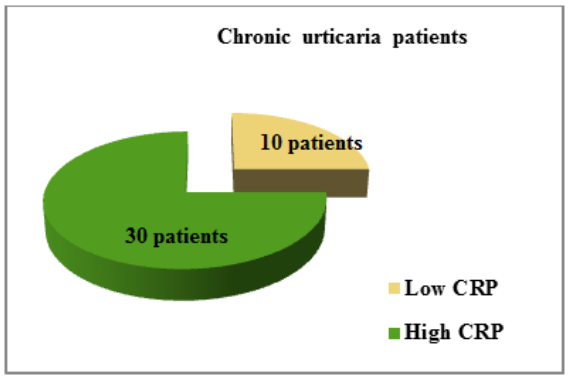

Fig-1: Showing CRP levels in chronic urticaria patients

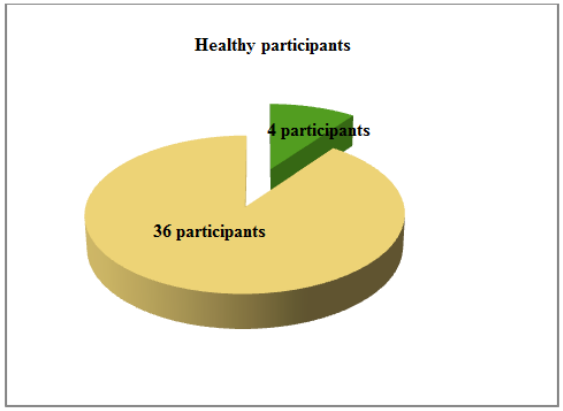

Fig-2: Showing CRP levels in healthy participants

DISCUSSION

Urticaria is a widespread, debilitating condition characterized by itchy lesions or wheals [3]. There is little accurate information on the prevalence of the disease, but it is thought to affect 15– 23% of the US population and internationally, the numbers are likely to be similar. Urticaria is characterized by transient pruritic and erythematous or pale plaques and papules which fade without a trace [4]. Urticaria induces a systemic inflammatory process, termed the acute phase response (APR). Acute-phase response (APR) is a local and systemic coordinated reaction following infections, inflammatory processes or tissue injury elicited usually for the maintenance or restoration of homeostasis [5].

The prominent biochemical features of APR are numerous changes in concentration of several circulating proteins, including C-reactive protein (CRP), serum amyloid A, haptoglobin or fibrinogen regulated predominantly by cytokines.

Different cytokines, interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α) seem to be the main stimulators of APR. IL-6 is the key stimulator, serving as an inducer of acute-phase response proteins, including CRP, controlling the extent of the local and systemic inflammatory responses as well. CRP is a very sensitive marker of the underlying systemic inflammation, but may also participate actively in APR. CRP is a potent activator of the classical cascade of complement and in this way, under certain circumstances, may initiate or exacerbate the inflammatory lesions.

Chronic urticaria is a persisting inflammatory disorder of the skin ,characterized by mast cell degranulation and perivascular, non-necrotizing infiltrate of CD4(+) lymphocytes, consisting of a mixture of Th1 and Th2 subtypes as well as monocytes ,neutrophils, eosinophils and basophils [6].

CU is characterized by systemic inflammatory process indicated by the increased circulating CRP, accompanied by parallel changes in IL-6 concentration, elevated IL- 6 concentration characterizes the active phase of CU as much as IL-6 behaves dynamically during the clinical course of the disease [7].

Some studies showed increased concentrations of circulating inflammatory cytokines, for example TNF-α, IL-1β, IL-4, IL-13, IL-18, while in contrast, other studies did not show elevations of IL-4 or TNF-α in CU patients. Interestingly, IL-31, a cytokine belonging to the IL-6 family was increased in CU patients, without significant correlation with the disease activity score.

It can be speculated that a defective endogenous anti-inflammatory mechanism could

contribute to the maintenance of urticarial inflammation, the association observed between the circulating IL-6 concentration and CRP indicates that elevated IL-6 is reflected by the increased CRP concentration.

Elevations of serum interleukin 6 (IL6), a cytokine thought to be key in promoting CRP elevations [8], in patients with acute allergic reactions have been described [9].

CRP concentration parallels both, the disease activity as well as IL-6 concentration, which is the case in most, though not all diseases. In our study we found that mean CRP was raised in chronic urticaria patients compared to that in controls. However, Kasperska-Zajac *et al*. found significant association between concentrations of CRP and IL-6 and reported significantly higher serum CRP concentrations in CU patients as compared with the healthy participants which correlated with the disease activity and severity, but the same was not referred to in the study by Dos Santos [7, 10]

Kasperska-Zajac *et al*. have shown the increased plasma IL-6 levels to be a reversible phenomenon, which increased during the active disease and decreased in remission [11].

Increased levels of CRP were found in CU patients [11-14]. However, very few studies investigated its relationship with the disease activity score [11-13]. Pattern of CRP appeared to correlate with disease activity in most of our patients as in other previous studies. Unfortunately, we did not study a correlation between IL-6 and CRP in CU patients, which certainly limits our conclusions. In our study, serum CRP concentration was significantly higher in CU patients as compared with the healthy controls. The relationship between the disease activity score and CRP was significant in the study.

Few studies have also shown that circulating levels of CRP are significantly elevated in CU patients and they corresponded to the severity and activity of the disease. [11, 15, 16] A study described elevations in CRP levels in urticaria patients and attributed these to infection, which caused the urticaria [17]. Some patients with infectious urticaria have also been described, but those patients all had febrile illnesses [18].

CONCLUSION

The concentration of CRP may reflect IL-6 levels, which are not routinely measured but are easy to determine in clinical practice. The concentrations of IL-6 and CRP in circulation may be beneficial in detecting patients with more severe diseases and may lead clinicians to further select advanced treatment, such as immunosuppressants. [11] This may ensure better life quality with less delay in controlling the disease symptoms. One of the most important aspects of this study is the potential utility of CRP as a useful marker for the detection of systemic inflammation with increased CRP resulting from the active non-specific urticarial inflammation. Further studies on such patients will be required on a larger scale to explore this hypothesis and to determine the prevalence of CRP elevations in this clinical setting.

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Conflict of Interest: None declared.

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