

SHORT REPORT

Acute phase inflammatory markers in patients with non-steroidal anti-inflammatory drugs (NSAIDs)-induced acute urticaria/angioedema and after aspirin challenge

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Abstract

Background Active chronic urticaria, identified as a mast cell- and basophil-dependent inflammatory disorder of the skin is able to elicit acute phase response (APR). However, systemic inflammatory response in different types of urticaria is poorly characterized.

Aim To determine APR pattern in a clearly defined group of patients with acute urticaria and/or angioedema – induced by NSAIDs.

Methods Plasma IL-6 and serum C-reactive protein (CRP) concentrations were studied in 17 patients with NSAIDs-induced acute urticaria/angioedema (NSAIDsAU) and in 20 healthy controls. Eleven patients who used NSAIDs were presented at the emergency room with acute urticaria/angioedema while the remaining six manifested the symptoms during the aspirin challenge test. Patients were examined in a dynamic manner: during the acute phase, and next, after subsidence of the symptoms.

Results CRP and IL-6 concentrations increased significantly in patients with NSAIDsAU as compared with their asymptomatic period and the healthy subjects. In addition, NSAIDsAU patients showed elevated concentration of the biomarkers following aspirin provocation with the baseline values recovered in the asymptomatic period.

Conclusion These results indicate that an acute systemic inflammatory response is activated in patients with NSAIDs-induced urticaria and/or angioedema. The study supports the evidence proving that up-regulation of CRP and IL-6 in urticaria/angioedema does not necessarily reflect any concomitant infection or other inflammatory processes, but may be due to the disease itself.

Received: 15 September 2011; Accepted: 31 January 2012

Conflict of interest

None declared.

Funding sources

None declared.

Introduction

Urticaria/angioedema are the most common non-allergic hypersensitivity reactions caused and/or aggravated by aspirin and other NSAIDs drugs.¹

Interestingly, it has been indicated that active chronic spontaneous urticaria may cause a low-grade of acute phase response (APR).^{2,3} There are two key players of APR: interleukin-6 (IL-6) performs as a major determinant of the reaction, required for induction

acute phase proteins, while the included C-reactive protein (CRP) is a sensitive clinical marker of a systemic inflammatory response.^{4,5}

Yet, the data available regarding activation of systemic inflammatory response in the course of acute urticaria as well as physical urticarias appear scarce and inconclusive.³

Therefore, the study was performed to determine plasma IL-6 and serum CRP concentrations in a clearly defined group of patients with acute urticaria/angioedema induced by NSAIDs

(NSAIDsAU) as well as to assess the APR pattern changes following the aspirin provocation test.

Materials and methods

Patients

Seventeen patients with NSAIDsAU (Table 1). The drugs above were administered to treat acute pain. Eleven of the patients had confirmed history of at least two episodes of reactions to more than one NSAID. The remaining six had a clinical history of only one episode of acute urticaria/angioedema induced by the drugs; therefore the aspirin challenge test was performed to confirm the diagnosis.

All the patients developed a moderate-severe reaction, according to a daily urticarial activity score.⁶ The patients received steroids and/or antihistamines with resolution of the symptoms during several hours.

The exclusion criteria included: (i) acute urticaria/angioedema episodes other than those induced by NSAIDs; (ii) other phenotypes of NSAIDs hypersensitivity; (iii) history of infection during the preceding 1 month; (iv) chronic diseases; (v) treatment with any medication in the preceding 2 months.

The control group consisted of 20 sex- and age-matched healthy subjects.

This study was approved by the Ethics Committee of the Medical University of Silesia.

Blood sampling

Peripheral venous blood for CRP and IL-6 assay was obtained according two different protocols.

Protocol I – patients who underwent the aspirin challenge test following the EAACI/GA2LEN guidelines⁷ Briefly, the challenges were performed 1 day after the administration of placebo, at hourly intervals by progressive, oral administration of aspirin 71, 117 and 312, reaching the cumulative dose of 500 mg or appearance of a positive reaction. Skin/mucosa changes, vital signs, and forced expiratory value 1 s (FEV₁) were recorded. The unequivocal development of urticaria and/or angioedema was regarded as a positive reaction for diagnosis of NSAIDs hypersensitivity manifested by urticaria/angioedema.

Blood samples were obtained three times: (i) before aspirin provocation; (ii) 24 h following the onset of a positive reaction – the acute phase; and (iii) again 1 month after resolution of the symptoms.

In addition samples were taken during the placebo administration: (i) in the morning before the provocation; and (ii) 24 h after (directly before the aspirin challenge).

Protocol II – patients without the aspirin challenge test. (who reported NSAIDsAU at emergency rooms of Allergy, Dermatology and Laryngology).

Blood samples were taken twice from all the patients: (i) first, during the acute phase of the disease before the treatment was administered (several hours after the onset of symptoms); (ii) secondly, 1 month following the subsidence of symptoms.

In vitro assays

Plasma IL-6 concentration was determined by ELISA (R&D Systems Inc., Minneapolis, MN, USA). Sensitivity of the assay was 0.70 pg/mL.

Table 1 Characteristics of patients with NSAIDs-induced urticaria and/or angioedema

Case	Age/Sex	Clinical manifestation – angioedema (A) and/or urticaria (U)	Angioedema location	Cause*
1	25/F	A + U	Periorbital + perioral	Aspirin
2	36/F	A + U	Periorbital + perioral	Ibuprofen
3	18/F	A + U	Periorbital	Ibuprofen
4	45/F	A + U	Massive face	Diclofenac
5	50/F	A + U	Massive face	Diclofenac
6	39/F	A + U	Massive face, tongue	Aspirin
7	29/F	U	–	Ibuprofen
8	37/F	A	Periorbital + perioral	Ibuprofen
9	48/M	A	Periorbital	Ketoprofen
10	41/F	A	Massive face	Aspirin
11	52/M	A	Massive face + tongue, floor of the mouth	Ketoprofen
12	43/F	A + U	Periorbital + perioral	Aspirin challenge (188 mg)
13	40/F	A + U	Periorbital + perioral	Aspirin challenge (188 mg)
14	40/F	A + U	Periorbital + perioral	Aspirin challenge (188 mg)
15	32/F	A + U	Massive face swelling	Aspirin challenge (188 mg)
16	52/M	A	Massive facial swelling	Aspirin challenge (500 mg)
17	39/F	A	Massive facial swelling	Aspirin challenge (500 mg)

*Drugs responsible for urticaria/angioedema symptoms during blood sampling.

NSAIDs, non-steroidal anti-inflammatory drugs induced acute urticaria/angioedema.

Serum CRP concentration was measured by an automated turbidimetric latex agglutination method (CRP-Latex, BioSystems SA, Barcelona, Spain) with a detection limit of 1.0 mg/L. Elevated serum CRP was defined as higher than 5.0 mg/L.

Statistical analysis

The analysis was made using Kruskal-Wallis test as well as Mann-Whitney *U* test. Correlation coefficient was obtained by Spearman test. *P* values lower than 0.05 were considered significant.

Results

Plasma concentration of IL-6 was significantly higher in patients with NSAIDsAU (as a whole group, $n = 17$) as compared with the values at the asymptomatic period (one month after subsidence of the lesions) and with the healthy subjects (median and range: 1.9 (1.7–2.4) vs. 0.9 (0.8–1.2) vs. 1.05 (0.7–1.25) pg/mL, respectively; $P < 0.001$) (Fig. 1).

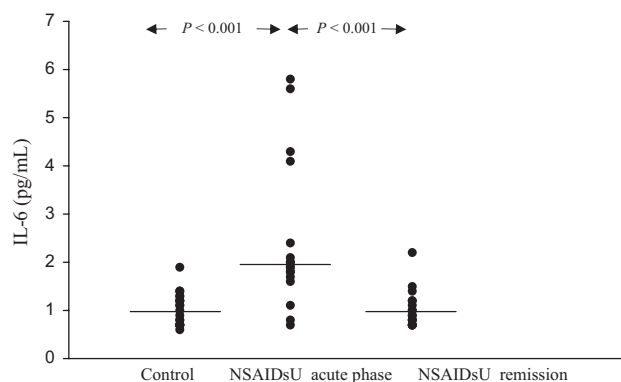


Figure 1 Individual plasma IL-6 concentration in healthy subjects and non-steroidal anti-inflammatory drugs-induced acute urticaria/angioedema (NSAIDsAU) patients during the acute phase and remission of the symptoms. Horizontal lines represent the median value.

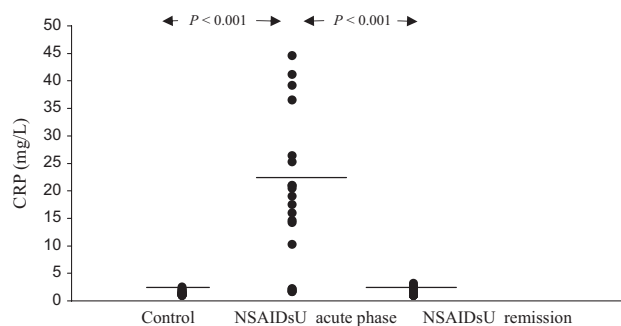


Figure 2 Individual serum C-reactive protein (CRP) concentration in healthy subjects and non-steroidal anti-inflammatory drugs-induced acute urticaria/angioedema (NSAIDsAU) patients during the acute phase and remission of the symptoms. Horizontal lines represent median value.

Serum concentration of CRP was significantly higher in patients with NSAIDsAU (as a whole group, $n = 17$) as compared with their the values at the asymptomatic period (one month after cleaning of the lesions) and with the healthy subjects (median and range: 20.5 (14.6–26.4) vs. 1.2 (1.0–2.1) vs. 1.4 (1.15–1.75) mg/L, respectively; $P < 0.001$) (Fig. 2).

A total of 15 patients out of 17 showed CRP concentrations above the normal range upper limit at the time the active period, to recover the normal values upon the second examination. In the other two patients with angioedema symptoms only serum CRP concentration was within the normal lab range.

Significant correlation was found between concentrations of IL-6 and CRP ($r = 0.91$, $P < 0.001$) in urticaria/angioedema patients.

Changes in plasma IL-6 and serum CRP concentration following the aspirin challenge test

The median plasma IL-6 concentrations increased from 1.0 pg/mL (range: 0.9–1.2) to 2.2 pg/mL (range: 1.9–4.1, $P < 0.01$) during 24 h to recover then the baseline value of 0.95 pg/mL (range: 0.8–1.0).

The median serum CRP concentrations increased significantly from 1.2 mg/L (range: 1.0–1.3) to 23.7 mg/L (range: 20.5–36.5; $P < 0.01$) 1 day after the provocation and then returned to the baseline values 1.15 mg/L (range: 1.0–1.3). One day after the provocation all the patients showed markedly increased CRP concentration (3–8 fold) above the upper limit of the normal range (Fig. 3).

The APR markers were not affected by placebo (1.15 vs. 1.0 pg/mL and 1.1 vs. 1.2 mg/L; for IL-6 and CRP, respectively).

Discussion

Our results indicate that patients with NSAIDsAU had significantly elevated concentrations of plasma IL-6 and serum CRP.

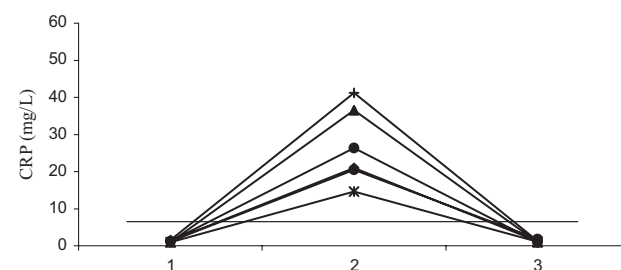


Figure 3 Changes in serum C-reactive protein (CRP) concentrations in six patients with non-steroidal anti-inflammatory drugs-induced acute urticaria/angioedema (NSAIDsAU) after aspirin provocation: 1 – baseline, 2 – 24 h after aspirin challenge, 3 – 1 month later. The horizontal line represents the upper limit of the normal range (5 mg/L). 24 h after the aspirin challenge all the patients had strongly increased CRP concentration (3–8 fold) above the lab norm.

So far, increased concentrations of the APR biomarkers have been observed in patients with spontaneous chronic urticaria,^{2,8–11} acute severe urticaria¹² or delayed pressure urticaria (DPU).¹³ It is worth noting that CRP values in some urticaria/angioedema patients, such as those recorded upon infection, e.g. some viral infections, are associated with modest CRP elevation (20–40 mg/L). This interesting observation calls however for very careful interpretation of CRP value in such cases. Increased CRP in acute urticaria appears then not only as a concomitant infection but first of all points to high activity of the urticarial inflammation itself.

The current study describes increased plasma concentration of IL-6 in patients with NSAIDsAU. So far, only one study described the activity of APR markers in the course of acute urticaria induced by various drugs (NSAIDs, antibiotics, analgetics).¹⁴ In the study, the majority of patients confirmed the use of more than one drug from different groups, before urticaria onset,¹⁴ which is an obstacle to direct comparison with our results.

A significant correlation was found between concentrations of IL-6 and CRP in NSAIDsAU, indicating the importance of IL-6 in determination of the circulating CRP concentration in the disease.

Available data regarding the behaviour of APR markers in angioedema are scarce and the results appear inconclusive. Bas *et al.* reported that patients treated with angiotensin-converting enzyme inhibitors (ACEIs) exhibited increased plasma levels of CRP in contrast to patients with angioedema of unknown causes.¹⁵ In another study, none of the patients with ACEIs-induced angioedema exhibited elevation of serum CRP concentration.¹⁶ Yet, Takahagi *et al.* observed increased concentration of CRP in some patients with idiopathic angioedema.⁹ We observed that patients with NSAIDs-induced angioedema without urticaria symptoms showed remarkable increase of the values (2–4 fold above the upper limit). However, two of six patients did not exceed the normal value. The patients did not demonstrate any massive angioedema.

Taken together, we speculate that the degree of APR activation in angioedema alone depends first of all, on the extent of angioedema symptoms as well as an individual predisposition to CRP response. Different genetic and non-genetic factors may determine the basal and stimulated concentrations of CRP during the infectious or inflammatory processes.¹⁷

Indeed, the putative mechanism of this disorder is believed to link with inhibition of cyclooxygenase-1 (COX-1) and formation of leukotrienes. We speculate, however that increased APR is associated with non-specific urticarial inflammation resulting from activation of mast cells and other inflammatory cells involved in the process. Similarly to chronic spontaneous urticaria or DPU. Leukotrienes might however act as additional proinflammatory factors intensifying this response. In addition, APR markers, especially IL-6, maybe involved in amplification of urticarial inflammation (for review 3).

There have been several limitations of our study. The first was the small size of our study group during the aspirin provocation test. It should be noted however that an evident growth of the APR biomarkers concentration was observed following the challenge, despite medication, including the anti-inflammatory drugs, received upon appearance of the symptoms. No other procedure was available in such case, as no treatment applied would have been unethical. Secondly, no serial marking was performed; therefore we are not able to define the peak of the inflammatory response or the exact time when the markers recovered their baseline levels. Such markings seem unjustified in our schemes as the patients had received medication before which might have affected the results. Next, lacking observations during the early postprovocation hours (up to first 6–8 h), further studies focused on the early inflammatory response are needed. In addition, it was not possible to obtain blood samples from all the subjects at the same time after the symptoms onset. This however should not deny the objective of our study which is consistent with the dynamic pattern of CRP behaviour following an acute stimulus. A growth above the normal limits is reached within 6 h, peaking after 48–50 h, and recovering the normal value during 3–7 days following the stimulus withdrawal (plasma half-life about 19 h).^{4,18}

The results indicate that an acute systemic inflammatory response is activated in NSAIDs-induced acute urticaria/angioedema, manifested by raised circulating concentrations of APR markers. The study supports the evidence proving that up-regulation of CRP and IL-6 in urticaria/angioedema does not necessarily reflect the concomitant infection or any other inflammatory process, but may occur due to the disease itself.

Acknowledgements

This study was supported by a research grant from the Committee for Scientific Research.

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