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Increased Plasma Levels of S100A8, S100A9, and S100A12 in Chronic Spontaneous Urticaria

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Abstract

Background:

Chronic spontaneous urticaria (CSU) is a skin disorder with an important immunologic profile. S100A8, S100A9, and S100A12 are the members of S100 family that have been reported to play important role in autoimmune diseases, but the characteristics of these three S100 members have not been defined in CSU.

Aims:

This study was performed to investigate the levels of these three S100s in patients with CSU and to study whether they were associated with the severity and clinical characteristics of CSU.

Materials and Methods:

The levels of plasma S100A8, S100A9, and S100A12 were measured in 51 CSU patients and 20 healthy controls using enzyme linked immunosorbent assay kits. The values in the patient group and that of the healthy controls were statistically compared. The relationships between the different markers were evaluated by correlation analysis.

Results:

The plasma levels of S100A8, S100A9, and S100A12 were significantly higher in CSU patients than those in controls. Interestingly, the level of S100A12 was significantly correlated with S100A8 and S100A9 in CSU patients ($P < 0.05$ and $P < 0.001$, respectively). In addition, S100A8, S100A9, and S100A12 were all significantly inversely correlated with blood basophil percentage.

Conclusions:

Plasma S100A8, S100A9, and S100A12 levels were elevated in CSU patients. They might be useful biomarkers of CSU, with the potential role in the pathogenesis of CSU.

KEY WORDS: *Chronic spontaneous urticaria, S100A8, S100A9, S100A12*

Introduction

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous appearance of transient itchy wheals, angioedema or both, for at least 6 weeks.[1] While it affects 0.5%–1% of the population, it not only has negative visual impact on patients, but also decreases the quality of life. CSU is an inflammatory disease, probably caused by an interactive combination of immune, genetic, and environmental factors, including infections.[2,3] Various changes in levels of immune-inflammatory, coagulation/fibrinolytic, hormonal, and metabolic markers have been reported in CSU patients.[4,5,6,7,8]

S100 family consists of a series of EF-hand calcium (Ca^{2+})-binding proteins, with more than 20 distinguished proteins.[9,10] It is reported that S100A8, S100A9, and S100A12 play important roles in the pathogenesis of immunological disorders in the human body.[11] They are involved in the development of autoimmune-associated diseases, such as psoriasis, rheumatoid arthritis, and systemic lupus erythematosus.[12,13,14] They all play positive feedback roles on the active inflammatory responses.[15,16,17] Moreover, several studies suggest a role for S100A8 and S100A9 in regulating the epidermal response to tissue injury[18] and inflammation.[19] Similarly, in affected psoriatic epidermis, S100A12 is expressed in the suprabasal epidermal layers.[20]

Since CSU is also related to autoimmune response, we hypothesize that S100A8, S100A9, and S100A12 may be involved in the development of CSU. So far, there are no available data regarding behavior of S100A8, S100A9, and S100A12 in patients with CSU. Therefore, this study was undertaken to investigate plasma levels of S100A8, S100A9, and S100A12 in CSU patients and compare with that of healthy controls.

Materials and Methods

Study subjects A total of 51 CSU patients referred from the dermatology outpatient clinic in a tertiary hospital of China between February 2015 and October 2016 were enrolled for this study. CSU was diagnosed according to the EAACI/GA²LEN/EDF/WAO guidelines.[1] Patients with chronic cholinergic and/or chronic inducible urticaria as well as patients with other concomitant diseases were excluded from the study. Patients had not taken any antihistamine within 1 week, or any corticosteroids or immunosuppressive drugs within 8 weeks. Urticaria Activity Score (UAS) was used to assess the activity of urticaria, including the wheal numbers and pruritus.[21,22] UAS7 was the sum of daily UASs for 7 days in a single CSU patient. The control group comprised of 20 sex- and age-matched healthy subjects. The controls did not have any history of allergic diseases, such as urticaria, asthma, rhinitis, or systemic diseases, or of taking medicine. The study protocol was approved by the Institutional Review Board for Human Studies (The Affiliated Hospital of Medical School, Ningbo University, Ningbo, China). All subjects provided written informed consent before participation and methods in this study were performed in accordance with the relevant guidelines and regulations.

Assay of plasma S100A8, S100A9, and S100A12 The plasma separated from blood samples had been stored in -80°C freezer, until further analysis of S100A8, S100A9, and S100A12 levels. Plasma levels of S100A8, S100A9, and S100A12 were assessed using human S100A8, S100A9, S100A12 enzyme linked immunosorbent assay (ELISA) kit (Shanghai Future Industry Co., Ltd., Shanghai). ELISA was performed by following the manufacturer's instructions. Thermo MK3 microplate reader 490 nm was used to measure the optical density values. The actual concentrations of samples were calculated based on the established standard curve.

Statistical analysis Data were presented as means $\pm$ standard deviation. Mann–Whitney U test was applied for comparing data between the patient group and the healthy controls. The relationships between the different markers were determined using Pearson correlation analysis. All analyses for significance

were run by two-sided tests and $P < 0.05$ was considered as significant. Analysis of data was performed by using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) and Statistical Product and Service Solution version 20.0 (SPSS, Chicago, IL, USA).

Results

General characteristics for patients are summarized in [Table 1](#). There were 51 CSU patients (16 males and 35 females; age: 28.18 ± 13.34 years) and 20 healthy controls (6 males and 14 females; age: 32.25 ± 14.37 years). No significant difference was observed between the two groups in terms of gender or age. The mean duration of CSU patients was 12.32 ± 20.24 months. In addition, the median UAS7 for the patients was 28.33 ± 0.93 .

Compared to the healthy controls, the levels of S100A8 (2105.97 ± 21.40 pg/ml vs. 1379.59 ± 27.96 pg/ml, $P < 0.001$; [Figure 1a](#)), S100A9 (862.76 ± 18.26 pg/ml vs. 389.97 ± 13.97 pg/ml, $P < 0.001$; [Figure 1b](#)), and S100A12 (3224.59 ± 38.94 pg/ml vs. 1827.34 ± 42.06 pg/ml, $P < 0.001$; [Figure 1c](#)) were significantly higher in CSU patients. However, plasma S100A8, S100A9, and S100A12 levels were not significantly correlated with UAS7 [[Figure 2a-c](#)].

We evaluated the correlation of S100A8, S100A9, and S100A12 in plasma by the Pearson correlation analysis. Interestingly, the level of S100A12 was significantly correlated with those of S100A8 ($r = 0.3092$, $P = 0.0273$; [Figure 3b](#)) and S100A9 ($r = 0.6171$, $P < 0.001$; [Figure 3c](#)) in CSU patients. However, the levels of S100A8 in plasma were not correlated with that of S100A9 [[Figure 3a](#)].

There was significant inverse correlation between plasma S100A8, S100A9, S100A12 levels and blood basophil percentage when analyzed in the combination data of CSU patients and healthy controls ($r = -0.4691$, $P < 0.0001$, [Figure 4a](#); $r = -0.3649$, $P < 0.0018$, [Figure 4b](#); $r = -0.4366$, $P < 0.0001$, [Figure 4c](#); respectively). No significant correlation was observed between levels of S100A8, S100A9, and S100A12 with eosinophil percentage.

Discussion

S100A8, S100A9, and S100A12 are predominant cytoplasmic proteins of neutrophils and are produced by various cells, playing important role in innate immunity and the inflammatory process. There is evidence that they were involved in many autoimmune-associated diseases including psoriasis, rheumatoid arthritis, atopic dermatitis, and so on.[\[11,12,13,14,23,24,25,26\]](#) However, there are no available data regarding behavior of S100A8, S100A9, and S100A12 in patients with CSU. This study was performed to investigate S100A8, S100A9, and S100A12 levels in plasma of CSU patients and to compare with that of healthy controls. The results from our study demonstrated that plasma S100A8, S100A9, and S100A12 levels were elevated in CSU patients. These findings indicated that S100A8, S100A9, and S100A12 might be useful biomarkers of CSU.

A total of 51 CSU patients and 20 sex- and age-matched healthy subjects were enrolled in this study. Compared with healthy controls, the levels of S100A8, S100A9, and S100A12 were significantly higher in CSU patients. In addition, the level of S100A12 was significantly correlated with S100A8 and S100A9, but no statistical association was found between S100A8 and S100A9. In this study, we further investigated whether the levels of S100A8, S100A9, and S100A12 were associated with the severity of disease using the 7-day UAS. However, we failed to find a correlation between three S100 proteins levels and the urticaria activity.

To the best of our knowledge, this is the first study to date to evaluate whether the levels of S100A8, S100A9, and S100A12 were associated with the development of CSU. S100 family plays an important role in many diseases, such as immune-mediated diseases, inflammatory problems, and procancer activities, contributing positive feedback on procedures of these diseases. S100A8, S100A9, and S100A12 are also associated with some dermatology diseases, such as psoriasis, systemic lupus erythematosus, and so on.[\[11,27,28\]](#) During inflammatory process, the expression of S100 may be raised in epithelial cells. It is reported that about 50% of CSU are attributed to autoimmune diseases. The results from our study demonstrated that plasma S100A8, S100A9, and S100A12 levels were elevated in CSU patients. These findings indicated that S100A8, S100A9, and S100A12 might be involved in the inflammatory process inducing CSU.

The exact pathogenic role of S100A8, S100A9, and S100A12 in the development of CSU is still unknown. We propose that these three S100 proteins are involved in the pathogenesis of CSU in several ways. Firstly, these three S100 proteins bind to and activate responses by two widely expressed but divergent receptors, namely, toll-like receptor 4 (TLR4) and the receptor for advanced glycation end-products (RAGE). [29,30,31] The engagement of these two receptors by S100 proteins is linked to an array of signaling pathways, notably NF- κ B and mitogen-activated protein kinases; the induction of p38 signaling was known to trigger the release of proinflammatory cytokines including interleukin (IL)-6, tumor necrosis factor (TNF)- α , and IL-1 β through the action of NF- κ B.[32,33,34,35] On the other hand, it is increasingly clear that chronic urticaria is characterized by a systemic proinflammatory state. Chronic urticaria patients were found to show increased levels of a series of cytokines including TNF- α , IL-1, IL-6, and IL-10. [36,37] Recent evidence suggests that these three S100 proteins were associated with IL-1. A recent report indicated that the epithelial cells could produce IL-1 and IL-1 was involved in the expression of S100A8/A9 in a human epidermal keratinocyte cell line (HaCaT).[38] In another study, the investigators observed that S100A12 was closely linked to IL-1 expression.[39] IL-1 is an important key cytokine related to inflammatory diseases. IL-1 evokes immune responses and induces skin lesions in urticaria and other allergy-related diseases including asthma, atopic dermatitis, and contact dermatitis.[40,41] Anti-IL-1 therapy has been a useful strategy in different types of urticaria.[37] So, S100A8, S100A9, and S100A12 might be involved in the inflammatory process inducing CSU. Secondly, S100A12 is a mild activator of granulocyte functions and a potent inducer of mast cell functions.[42,43,44] S100A12 has been shown to activate mast cells by releasing histamine and other cytokines including IL-6 and monocyte chemotactic protein-1, even in the absence of RAGE expression on mast cells.[44] Furthermore, S100A12 has chemotactic activity for mast cells, which appears to be mediated by a G-protein coupled receptor and independent of RAGE.[45] As we all know, mast cells are the major effector cells in chronic urticaria;[46] S100A12 may be implicated in the pathogenesis of chronic urticaria through activated mast cells.

It should be noted that the levels of S100A8, S100A9, and S100A12 were significantly correlated with percentages of basophils in peripheral blood. Published data have demonstrated elevated levels of inflammatory cells, including eosinophils and basophils, in the skin lesions of CSU patients.[47] One report indicated that the histamine, mast cells, basophils, and some unknown mediators played important roles in the pathology of CSU.[37] The symptoms of CSU patients would be expressed on release of histamine and other mediators from basophils and mast cells.[1,48,49,50] Current evidences indicate the abnormalities of absolute number, function, and structure of basophil in CSU. In our study, the percentage of basophil was much lower in CSU patients than in healthy controls, implying that basophils were consumed for releasing histamine. Although, the concept of a central role of immunoglobulin E (IgE) and high-affinity IgE receptor (Fc ϵ RI) in priming basophils for degranulation was widely reported, the causative factors leading to degranulation of basophils were still not fully understood. Human basophils are found to express high levels of TLR4.[51] Komiya *et al.*[52] reported that a TLR4 ligand lipopolysaccharide plays a functionally significant role in basophil activation. High levels of S100A8, S100A9, and S100A12 might also contribute to the basophil activation mediated by TLR4 in CSU.

Conclusion

The results from our study demonstrated that plasma S100A8, S100A9, and S100A12 levels were elevated in CSU patients than those of healthy controls. These findings indicated that S100A8, S100A9, and S100A12 might be useful biomarkers of CSU. In addition, the levels of S100A8, S100A9, and S100A12 were significantly associated with percentages of basophil cells in peripheral blood. Further well-design larger studies are needed to confirm these findings.

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Conflicts of interest There are no conflicts of interest.

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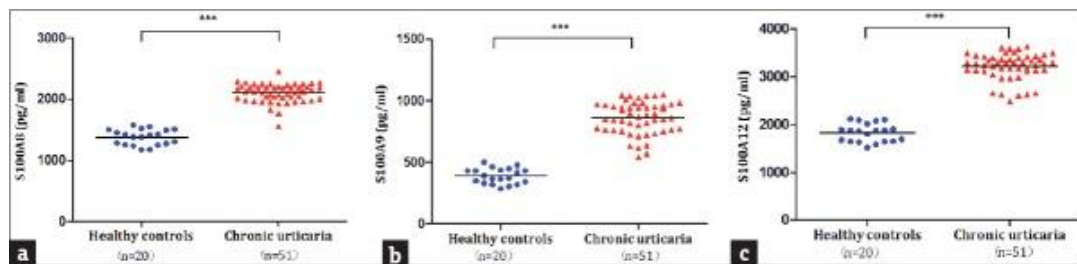
Figures and Tables

Table 1

Features of patients with CSU and healthy controls

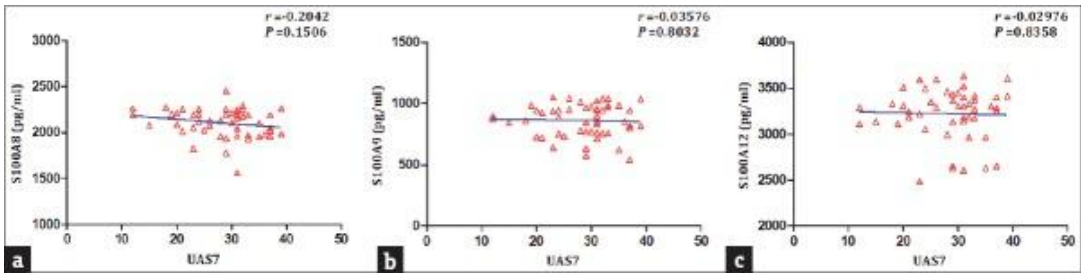
Variable	CSU (n=51)	HCS (n=20)	P
Age in years (Mean±SD)	28.18±13.34	32.25±14.37	0.285
Male/Female	16/35	6/14	0.91
Basophil % (Mean±SD)	0.23±0.02	0.40±0.03	<0.0001
Eosinophil % (Mean±SD)	1.66±0.18	2.21±0.35	0.133
Disease duration (months)	12.32±20.24		
Presence of angioedema	17/51 (33.3%)		
UAS7	28.33±0.93		
IgE-positive	29/51 (56.86%)		
CRP mg/L	3.79±13.04		

CSU: Chronic spontaneous urticaria, HCs: Healthy controls, UAS7: Weekly urticaria activity score, IgE: Immunoglobulin E, CRP: C-reactive protein

Figure 1

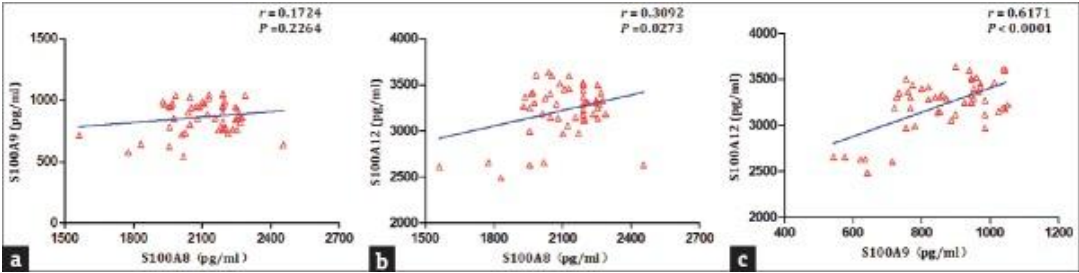
Comparison of plasma S100A8, S100A9, and S100A12 levels in CSU patients and healthy controls. The levels of plasma S100A8 ($P < 0.001$) (a), S100A9 ($P < 0.001$) (b), and S100A12 ($P < 0.001$) (c) were significantly higher in CSU patients than in healthy controls

Figure 2

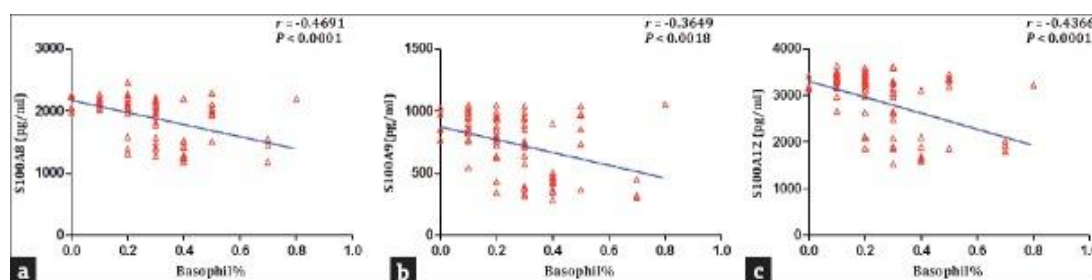


Correlation of S100A8, S100A9, and S100A12 levels with UAS7. Plasma S100A8, S100A9, and S100A12 levels were not significantly correlated with UAS7

Figure 3



Correlation of S100A8, S100A9, and S100A12 levels in CSU patients. Both S100A8 and S100A9 were significantly correlated with S100A12 ($P < 0.05$). However, S100A8 was not significantly correlated with S100A9

Figure 4

Correlation of S100 with basophil percentage. S100A8, S100A9, and S100A12 plasma levels were all significantly correlated with blood basophil percentage in the combination data of CSU patients and healthy controls ($P < 0.05$)

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