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ORIGINAL PAPER

The expression of serotonin transporter protein in the skin of patients with chronic spontaneous urticaria and its relation with depression and anxiety

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Abstract

Studies have indicated a possible role for serotonin transporter protein (SERT) in the pathophysiology of inflammatory skin disorders. This study was aimed to determine the expression of SERT in the skin of patients with chronic spontaneous urticaria (CSU) and its relation to depression and anxiety. In this case–control study, 30 CSU patients and 30 healthy controls were evaluated with skin biopsies to evaluate the expression of the SERT protein based on histopathologic findings. Beck depression and anxiety inventories were used to investigate depression and anxiety in the case group. Data were analyzed by SPSS software. P values < 0.05 were considered significant. The case group showed significantly higher percentage of stained cells ($P < 0.0001$) and intensity of SERT expression ($P < 0.0001$) compared with the control group. The patients with uncontrolled CSU showed significantly higher percentage ($P < 0.002$) and intensity ($P < 0.006$) of SERT expression, compared with those with controlled CSU. The intensity of SERT expression in CSU patients had no significant correlation with the severity of depression, but was significantly correlated with the severity of anxiety ($r = 0.555$; $P = 0.001$). The percentage of stained cells was significantly correlated with the severities of depression ($r = -0.433$; $P = 0.017$) and anxiety ($r = 0.528$; $P = 0.003$). The SERT expression in patients with CSU was higher compared with controls, which can demonstrate the role of serotonin in the pathogenesis of this disease. This higher SERT expression is correlated with the severity of the disease.

Keywords Chronic spontaneous urticaria · Serotonin transporter protein · Anxiety · Depression

Introduction

Chronic spontaneous urticaria (CSU), defined as recurrent spontaneous wheals of unknown etiology associated with pruritus and persisting for at least 6 weeks, is a relatively common disabling disorder that has remained a challenging problem for both patients and physicians. CSU has been estimated to cost 244 million USD in the United States alone. The lifetime costs are even more significant, as about half of the patients reported a duration of over 4 years [4, 5, 12, 21].

It has been well established that CSU greatly impairs the quality of life (QOL) of patients. CSU not only is a dermatological disorder, but also it has been linked to several psychiatric comorbidities, of which the most common are anxiety, depression, and somatoform disorders. CSU patients have been reported to suffer from sleep disturbance, marked energy loss, alexithymia, emotional and physical dysfunction, and social life limitations [7, 14, 15, 24, 29, 31, 40, 45].

The close interaction between the neuroendocrine and immune systems is mainly involved in inflammatory disorders of the skin, including CSU. Many recent studies have indicated serotonin, also known as 5-hydroxytryptamine (5-HT), as the major mediator of this important interaction.

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Serotonin has been reported to be involved in the activation of immune cells through manifold mechanisms [27, 37-39].

The pathophysiology of CSU remains unknown. However, many studies have indicated that activation of cutaneous mast cells is the cornerstone of its pathogenesis [3, 18]. Human serotonin transporter protein (SERT), which mediates the duration and magnitude of the responses to serotonin by controlling its re-uptake, is expressed on several cells in the skin, including mast cells, keratinocytes, melanocytes, Langerhans cells, dermal fibroblasts, T cells, natural killer cells, and sensory nerve endings [17, 20]. It has an important role in pathophysiology of inflammatory dermatoses through modifying serotonin functions, including production of chemotactic biomarkers, delayed-type hypersensitivity responses, and macrophage-mediated natural immunity [1, 26]. Alterations in the serotonergic system, especially serotonin transporters, have been associated with a variety of psychological conditions [2, 19, 30, 32]. Besides, selective serotonin reuptake inhibitors (SSRIs) that inhibit SERT have been shown to have beneficial effects in treatment of inflammatory disorders of the skin [8, 36, 43, 44].

Given all the abovementioned reasons, SERT can potentially be a factor involved in the pathophysiology of CSU. Moreover, several studies have recently suggested SERT to be involved in the pathogenesis of different skin disorders [11, 33, 41, 42]. Therefore, we conducted the present study to compare the expression of SERT in the skin of CSU patients with that of healthy controls. We also investigated the relation of SERT expression to depression and anxiety in patients with CSU.

Methods

Design and subjects

In this case–control study, 30 patients with CSU who were referred to our Allergy Outpatient Clinic were included. An expert clinical immunologist confirmed the sole diagnosis of CSU (non-inducible wheals, with or without angioedema, that last for at least 6 weeks) in all patients via complete medical history, physical examination, and laboratory findings.

A sample of 30 age- and sex-matched controls were selected from individuals with no history of inflammatory dermatoses or allergic disorders who referred to the same clinic in the same period as patients' companions. In both groups, participants were excluded if they had a documented psychiatric diagnosis or a history of taking any serotonin-relevant drugs, such as SSRIs.

The subjects were selected using random available sampling method and were consented before they enter the study. This study was approved by the ethics committee of Mashhad University of Medical Sciences (Registered No.: MUMS.fm.REC.1396.531).

Specimen collection

The patients were asked to avoid all treatments of the disease for a 1-week period and refer to the clinic as soon as they developed new wheals and no later than 12 h from the first appearance of the lesion. Punch biopsies of 3-mm diameter were taken from one skin lesion (wheals) in all patients as soon as possible within a maximum time of 12 h form the onset of new wheals. Biopsies were also taken from the control group in the same standard settings, from the lower back skin, by the same dermatologist.

Processing and assessment of the specimens

The specimens were sent to the pathology department for fixation, paraffin embedding, and further immunohistochemical assessment of SERT protein expression to quantitate the percentage of stained cells and the intensity of SERT expression. SERT expression has been estimated through histopathology in several previous studies [41, 42].

The immunohistochemical staining was performed using anti-serotonin transporter antibodies (ab174770; dilution 1:400; Abcam, Cambridgeshire, UK) according to the manufacturer protocol. Positive control was the human cerebral cortex and negative control was assessed by omitting the primary antibody. All immunostained slides were scanned by Nikon light microscope (Nikon, Japan). An expert pathologist, who was blind to group assignments of each sample, scored the intensity of staining semi-quantitatively on a scale of 0–3, according to which the scores were given as follows: 0 (absent), 1 (weak), 2 (moderate), or 3 (strong). The same pathologist also blindly scored the rate of stained cells in each slide recorded in percentage.

Urticaria control test

The clinical severity of urticaria in the case group was evaluated by using Urticaria Control Test (UCT) questionnaire [46]. We have previously validated the Persian version of UCT questionnaire. With an internal consistency reliability (Cronbach's alpha) of 0.68, we have also confirmed its reliability.

Beck depression inventory

A validated Persian version of Beck Depression Inventory (BDI) was used to investigate the existence and severity of depression in patients with chronic urticaria. The BDI is a 21-item scale that measures physical, behavioral, and cognitive symptoms of depression. In each item, the severity of

depression symptoms can be scored between 0 and 3. A total score of 0–9 defines normal status (no depression), 10–18 shows mild depression, 19–29 specifies moderate depression, and 30–63 marks severe depression [10].

Beck anxiety inventory

The validated Persian version of the Beck Anxiety Inventory [10] was used to assess the anxiety of patients with CSU. BAI is a self-report 21-item questionnaire designed to measure the severity of anxiety. Each item reflects a symptom of anxiety and the patient can score its severity from 0 to 3, reflecting absent to severe symptoms. The total score ranges from 0 to 63 and is interpreted as follows: 0–7 shows no anxiety, 8–15 indicates a mild anxiety, 16–25 specifies a moderate anxiety, and 26–63 reflects a severe anxiety [16].

Statistical analysis

Data were analyzed using SPSS statistics software (version 22 for Windows, IBM Corporation, Chicago, USA). Data were presented by descriptive statistics. Normal distribution of data was assessed using the Kolmogorov–Smirnov test. We used Chi-square test, independent samples *T* test, Mann–Whitney test, and Spearman correlation test to analyze the data. In all analyses, a P value < 0.05 was considered statistically significant.

Results

Demographic findings

Overall, 60 patients were studied in 2 groups of CSU cases ($N = 30$) and controls ($N = 30$). Twenty-two patients (73.3%) in the case group and 21 patients (70%) in the control group were women ($P = 0.774$). The mean age was 35.2 ± 11.2 years in the case group and 35.6 ± 10.9 years in the control group ($P = 0.836$).

Comparison of SERT expression between case and control groups

Twenty-eight patients in the case group (93.3%) and 16 participants in the control group (53.3%) had positive SERT expression in their epidermal cells. Table 1 shows the distribution of different expression intensities in both groups. As shown in Fig. 1, only epidermal cells, which apparently were keratinocytes, were positive in skin samples of the subjects and none of them had positive cells in the dermis. It is also evident that the sample from control subjects showed no stained cells.

Table 1 Comparison of percentage and intensity of SERT between case and control groups

Variables	Case ($N = 30$)	Control ($N = 30$)	P value
Percentage (%)[a]	66.3 ± 24.1 70 (0–90)	31.0 ± 33.9 15 (0–90)	< 0.0001[†]
Intensity[b]			< 0.0001[‡]
Negative	2 (6.7)	14 (46.7)	
Weak	8 (26.7)	11 (36.7)	
Moderate	17 (56.7)	4 (13.3)	
Strong	3 (10)	1 (3.3)	

[†]Mann–Whitney test was used

[‡]Chi-square test was used

[a]Data presented as mean ± SD, median (range)

[b]Data presented as frequency (percent)

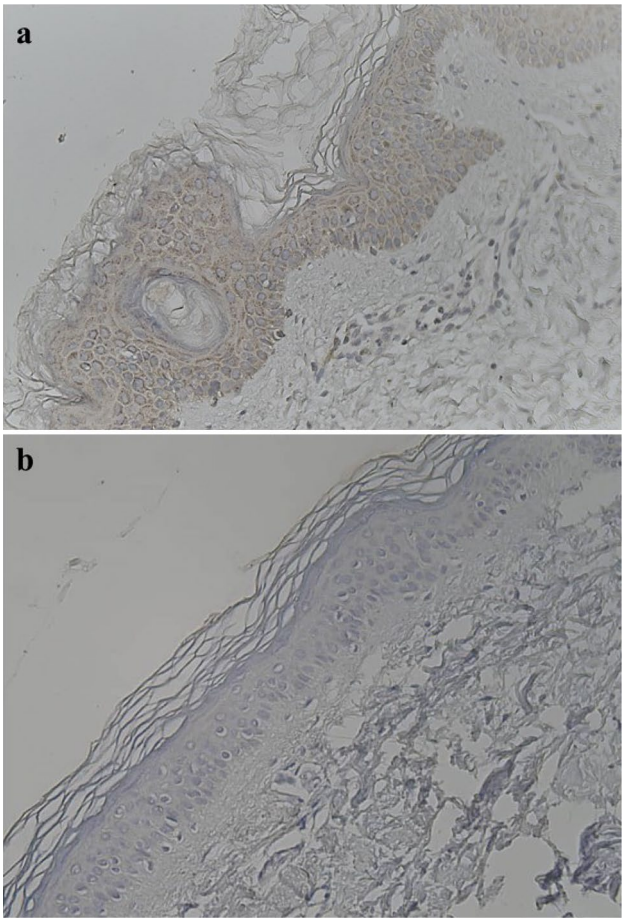

Fig. 1 **a** Strong expression of SERT in a skin sample of patients with CSU; **b** absence of SERT expression in a skin sample of controls

The case group showed a significantly higher percentage of stained cells (rate of SERT expression), compared with the control group ($P < 0.0001$). The intensity of SERT expression was also significantly higher in the case group,

compared with the controls ($P < 0.0001$). Table 1 compares the rate and intensity of SERT expression in the case and the control group.

Comparison of depression and anxiety between case and control groups

Twenty-three participants (76.7%) in the case group and 24 (80%) in the control group had different degrees of depression (Table 2). The severity of depression was not significantly different between the two groups ($P = 0.694$).

Table 2 also shows the different degrees of anxiety among the case and control groups. As the table implies, 26 participants (86.7%) in the case group and 25 (83.3%) in the control group had different degrees of anxiety. Moreover, the severity of anxiety had no significant difference between the two groups (0.938).

Correlations between SERT expression and depression and anxiety in the case group

The percentage of stained cells in the case group was significantly and negatively correlated with the severity of depression ($r = -0.433$; $P = 0.017$). However, it had a positive correlation with the severity of anxiety ($r = 0.528$; $P = 0.003$).

The intensity of SERT expression in the case group had no significant correlation with the severity of depression ($r = -0.037$; $P = 0.847$). However, it was significantly and positively correlated with the severity of anxiety ($r = 0.555$, $P = 0.001$).

Table 2 Relationship between intensity of SERT, depression, and anxiety

Variables[a]	Case ($N = 30$)	Control ($N = 30$)	P value[†]
Depression			
Negative	7 (23.3)	6 (20)	0.694
Weak	18 (60)	21 (70)	
Moderate	4 (13.3)	3 (10)	
Strong	1 (3.3)	0 (0)	
Anxiety			
Negative	4 (13.3)	5 (16.7)	0.938
Weak	10 (33.3)	11 (36.7)	
Moderate	9 (30)	7 (23.3)	
Strong	7 (23.3)	7 (23.3)	

[†]Chi-square test was used

[a]Data presented as frequency (percent)

SERT expression in patients with different clinical severities of CSU

We divided the case group based on clinical severity of urticaria and compared the rate and intensity of SERT expression between 8 patients (26.7%) with controlled CSU and 22 (73.3%) with uncontrolled CSU. The patients with uncontrolled CSU showed significantly higher rate ($P < 0.002$) and intensity ($P < 0.006$) of SERT expression, compared to those with controlled CSU (Table 3).

Depression and anxiety in patients with different clinical severities of CSU

Those with uncontrolled CSU had a significantly lower BDI score, compared to the controlled patients (12.59 ± 4.83 vs. 19.63 ± 7.55; $P = 0.005$). The mean BAI score was significantly higher in the uncontrolled patients, compared to the ones with controlled CSU (20 ± 10.47 vs. 10.5 ± 3.46; $P = 0.001$). The severities of depression ($P = 0.029$) and anxiety ($P = 0.006$) were also significantly different between the patients with controlled CSU and those with uncontrolled CSU (Table 4).

Discussion

SERT polymorphism has been associated with multitudinous human diseases, especially neuropsychological disorders [25, 28, 35, 47]. The role of SERT as a mediator of the bidirectional contact between the immune and neuroendocrine systems in the pathophysiology of inflammatory skin disorders has gained growing research interest in recent years. There are several studies on the role of SERT in the pathogenesis of skin diseases such as psoriasis [33,

Table 3 Comparison of percentage and intensity of SERT in terms of clinical severity

Variables	Clinical severity		P value
	Controlled ($N = 8$)	Uncontrolled ($N = 22$)	
Percentage (%)[a]	36.2 ± 24.4 45 (0–60)	77.3 ± 11.6 80 (50–90)	0.002[†]
Intensity[b]			0.013[‡]
Negative	2 (25)	0 (0)	
Weak	4 (50)	4 (18.2)	
Moderate	2 (25)	15 (68.2)	
Strong	0 (0)	3 (13.6)	

[†]Independent samples T test was used

[‡]Chi-square test was used

[a]Data presented as mean ± SD, median (range)

[b]Data presented as frequency (percent)

Table 4 Comparison of depression and anxiety in terms of clinical severity

Variables[a]	Clinical severity		*P* values[†]
	Controlled (*N* = 8)	Uncontrolled (*N* = 22)	
Depression			
Normal	1 (12.5)	6 (27.3)	0.029
Mild	3 (37.5)	15 (68.2)	
Moderate	3 (37.5)	1 (4.5)	
Severe	1 (12.5)	0 (0)	
Anxiety			
Normal	2 (25)	2 (9.1)	0.006
Mild	6 (75)	4 (18.2)	
Moderate	0 (0)	9 (40.9)	
Severe	0 (0)	7 (31.8)	

[†]Chi-square test was used

[a]Data presented as frequency (percent)

41, 42] and eczema [6, 23]. For instance, Lonne-Rahm et al. found a changed innervation and modulation of the serotonergic system in patients with chronic atopic eczema, especially during chronic stress [23]. However, there is no comprehensive study available on the role of SERT in chronic urticaria so far.

Knowing the main role of dermis and mast cells in the pathophysiology of urticaria, we expected to observe dermal stained cells in the CSU patients [3, 18]. However, surprisingly, we found positive stained cells only in the epidermis. Although we could not exactly determine the type of these cells, we hypothesize that they might probably be keratinocytes. Physiological activity of keratinocytes through expression of SERT has been reported to be involved in several inflammatory skin conditions [17, 42]. Therefore, it might be possible that the epidermal cells in skin samples of our patients, which apparently were keratinocytes, also play pro-inflammatory roles in CSU via SERT expression. Altered protein expression in the epidermis has been reported to be involved in CSU and associated with its clinical severity [49].

We observed the rate and intensity of SERT expression to be significantly higher in the CSU group in comparison with the control subjects. Our results, therefore, somehow support the theory that serotonergic neuroendocrine system, in communication with the immune system, may be involved in the pathogenesis of CSU through alterations in the expression of SERT. Thus, there is a possibility that modulating the level of SERT expression, for instance, via SSRIs that have been reported to be efficacious in treating inflammatory disorders of the skin as well as rheumatic disorders, can be effective in treatment of CSU patients [34, 36, 43, 44].

Consistently, a study reported that a 40-year-old woman with a 14-year history of CSU was successfully treated with escitalopram (an SSRI), which significantly improved her behavior, anxiety, and depression [9]. Moreover, Yasharpour and Randhawa in their comprehensive review on the effect of currently available antidepressants on CSU indicated that Serotonin–norepinephrine reuptake inhibitors (SNRIs), doxepin, and alprazolam have been reported to have better efficacy in treatment of CSU because they have a clear effect on H1 receptors [48]. In addition, Gupta et al. presented two patients with chronic spontaneous urticaria along with panic disorder, in whom both of the disorders showed a favorable response to SSRIs fluoxetine, and sertraline. This suggests a common pathogenic factor in panic disorder and chronic urticaria that possibly involves serotoninergic mechanisms [13].

Moreover, among CSU patients, the rate and intensity of SERT expression were significantly associated with the clinical severity of urticaria. Thorslund et al. showed that there was a significant relationship between the severity of psoriasis and the expression of SERT [41]. These results, to some extent, can justify the possibility of a regulating role for SERT in the pathophysiology of inflammatory dermatoses.

We found no significant difference in terms of anxiety and depression between CSU patients and controls. Therefore, it can be stated that CSU might be independently associated with the expression of SERT, regardless of psychological conditions such as anxiety and depression.

Among our CSU patients, depression was correlated inversely and significantly with percentage of SERT expression. However, the severity of anxiety had a direct significant correlation with the percentage and intensity of SERT expression in CSU patients. We also found a significantly higher severity of depression and a significantly lower severity of anxiety in patients with controlled CSU, compared with the uncontrolled patients. The difference between the correlation of SERT expression in the epidermis of CSU patients with depression and anxiety can possibly be ascribed to the different serotonergic changes in these two psychiatric entities. However, this issue requires further research.

Psychiatric comorbidities in CSU patients, including chronic stress, depression, and anxiety have been linked to prolonged inflammatory processes. Prolonged anxiety and stress are associated with reduced serotonin turnover [22]. These facts can justify the findings of our study regarding the significant correlation of SERT expression and anxiety. However, it is yet to be determined that whether the intensity of SERT expression or its rate is more important in this regard.

One limitation of this study was that we could not perform double staining method to identify the stained cells in the epidermis. Moreover, our control subjects showed

relatively higher rates of anxiety and depression compared with the general population, which might have had an effect on the outcomes, particularly regarding SERT expression. Lastly, investigating the expression of different types of serotonin receptors in the skin of CSU patients would have been helpful in providing a better understanding of the possible role of serotonergic system in the pathophysiology of CSU.

In conclusion, higher epidermal SERT expression in CSU patients compared with controls can possibly demonstrate the role of serotonergic system of the epidermis in the pathogenesis of this disease. This higher SERT expression is correlated with the severity of the disease. Our findings can provide new insights in the pathophysiology of CSU and the possible role of serotonergic system of skin in this regard. Further studies, especially controlled prospective trials are needed to clarify the effect of serotonergic medications on CSU.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures involving human participants were in accordance with the ethical standards of the national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of Mashhad University of Medical Sciences (Registered no.: MUMS.fm.REC.1396.531).

Informed consent Informed consent was obtained from all individuals who participated in the study.

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