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RESEARCH LETTER

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Exaggerated neurophysiological responses to stressor in patients with chronic spontaneous urticaria

To the Editor,

Chronic spontaneous urticaria (CSU) has detrimental effects on patients' quality of life (QoL) and emotional well-being.[1] Patients with CSU have increased levels of emotional distress, anxiety, depression and somatoform disorders, and their elevated stress correlates with CSU activity.[2,3] Mechanisms of stress-induced CSU exacerbation suggest that patients with CSU may be vulnerable to stressors and have altered and exaggerated stress responses. This may trigger the secretion of neuropeptides from sensory skin nerves[4] that, in turn, interact with mast cells and prime them for degranulation and the release of histamine, and result in CSU attacks.[5] Furthermore, stress levels assessed with the Perceived Stress Scale (PSS) were shown to significantly correlate with urticaria activity and control.[6] Stress has become an integral part of the Western lifestyle, emphasizing the need to illuminate its role in CSU.

Here, we compared stress responses with acoustic startle and stress levels between CSU patients and healthy controls (HC). We used objective measures of stressor-induced electrophysiological and vascular skin responses and assessed stress levels with the PSS. The study included 47 CSU patients and 56 HC, matched by age, gender and socio-economic status recruited at the Bnai Zion Medical Center, Haifa, Israel, and the Charité - Universitätsmedizin Berlin, Germany (Table S1). Exclusion criteria were any severe health condition that may affect the results of the study (such as psychiatric or neurologic disorders, cancer). The study was approved by the Local Ethics Committee (No. 2917-BNZ), and all participants provided informed consent. Study participants were asked to sit comfortably in a chair, while looking at a computer screen with changing kaleidoscope pictures. After one minute of acclimatization, the stressor exposure session began and continued for 3 minutes. A 57 dB background broadband (white) noise was delivered continuously binaurally throughout the session via headphones. During these 3 minutes, participants were exposed to 40 randomly spaced auditory startle stimuli as follows: 20 startles were given at 72 dB. The duration of each of these startles was 20 msec. The other 20 startles were given at 108 dB, each lasted 30 msec. Ten times the 72 dB startle appeared 100 msec before the 108 dB startle. The use of the latter paired stimuli enabled the assessment of the startle response inhibition by a less intense pre-stimulus.[7] This test is named pre-pulse inhibition (PPI), which in our study was based on the Auditory Sustained and Attention Test.[8] Acoustic stimuli were provoked and measured by SR-HLAB STARTLE REFLEX; San Diego Instruments, San Diego, CA. The stimulus appearances were pre-programmed and performed by the Mindtension software (Mindtension, Israel). Responses to the startle stimuli were measured by: (a) electromyography (EMG)-based assessment of the contraction amplitude of the orbicularis oculi muscle (mV) for each startle stimulus and the number of eye blinks. Both were measured via the same apparatus that generated and delivered the startle stimuli (SR-HLAB STARTLE REFLEX); PPI was calculated based on the ratio between the EMG mean values in response to single 108 dB startles and 108 dB startles preceded by 72 dB startles. Data were recorded with a 1 KHz sampling rate and a band-pass filter of 10–300 Hz. Analysis of the data was performed at the first 300-msec time window, and EMG maximal peak (Max Value) was recorded. (b) Electrodermal activity (EDA)—a measure of skin conductance that reflects the reactivity of the sympathetic nervous system—was assessed after the first startle and monitored for the remainder of the stress exposure session. Two 5-mm-diameter electrodes (Mindlife) were applied to the fingertips of the second and fourth digit of the non-dominant hand and connected to a sensor and to an amplified receiver. The outcome measures of EDA were as follows: (i) the amplitude rise time (seconds) following the first startle (a single startle at 108 db), that is the time it takes for baseline skin conductance, at the beginning of the acoustic startle, to reach the maximum skin conductance level; (ii) the amplitude height (microsiemens), that is the maximum skin conductance level; and (iii) the relax latency, that is the time it takes for skin conductance to get to the minimal amplitude value. (c) Changes in skin blood flow in the volar forearm in response to the stress exposure protocol were assessed by use of laser speckle contrast-based imaging (moorFLPI-2; Moor Instruments). Skin blood flow was assessed at three time points: baseline, after the first auditory startle and at the end of the stress exposure session. Values are expressed as perfusion units (PUs). Stress-level assessment in daily life was done by the PSS.[9]

Chronic spontaneous urticaria patients exhibited stronger responses to acoustic startles with high mean EMG values of the

TABLE 1 Comparing the startle reflex parameter and the mean flux in the laser speckle measurements of cutaneous perfusion between both groups

	Healthy controls (n = 29)		CSU patients (n = 7)			
	Mean	SD	Mean	SD	Mann-Whitney	*p*
EMG values (in mV)[a]	1410.88	1464.65	3052.84	2095.09	86.5	.003
Probability of eye blinks (%)	47.31	24.86	68.66	17.26	92.5	.005
PPI values (in mV) (higher mV represents reduced inhibition)[b]	1028.86	1010.92	2623.22	1735.62	70.5	<.0001
% of EMG value reduction in PPI	28%		14%			
Flux after 1st startle stimulus (PUs)	46.35	14.05	58.62	13.49	−2.31	0.021
Flux at the end of the stress exposure (PUs)	42.92	20.45	59.46	37.98	−2.72	0.007

Abbreviation: CSU, chronic spontaneous urticarial; EMG, electromyography; PUs, perfusion units; SD, standard deviation.

[a]To conduct the EMG and eye blink measures, two electrodes (4-mm recording area, EL254, Biopac Systems Inc.) were attached to adhesive disc (ADD 204, Biopac Systems Inc.) filled with SIGNAGEL® (Parker Labs) and were placed below the pupil on the orbicularis oculi muscle, and a third reference electrode was placed on the mastoid bone. Mean EMG values and number of eye blinks were calculated over the entire 3 minutes of the stress exposure session

[b]PPI calculation; 100 − (max response to 'pre-pulse' trial / max response to 'pulse alone' trial × 100), which is the per cent of the inhibited response.

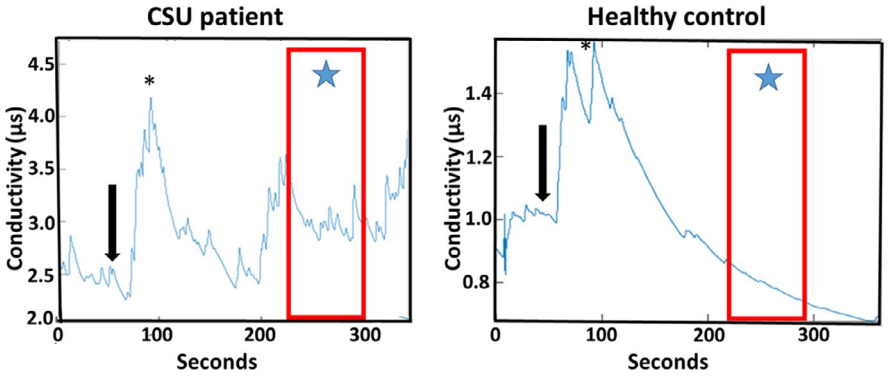

FIGURE 1 Example of EDA recordings from a CSU patient and a healthy participant. The black arrow shows the time point of the first startle (given after 60 seconds). * The maximum skin conductance level following the first startle. In CSU patient, it is 4.4 microsiemens versus 1.6 microsiemens in healthy control. The rectangle represents the relaxation time after first startle session. CSU, chronic spontaneous urticarial; EDA, electrodermal activity

orbicularis oculi muscle and less PPI in EMG values as compared to HC. CSU patients also had a higher number of startle-induced eye blinks than HC and faster EDA responses (shorter amplitude rise time) than HC (Table 1). Patients with CSU also had longer stress responses, that is a longer time for skin conductance to get to the minimal amplitude value, compared with HC (236.1 ± 8.5 sec vs. 226.7 ± 20.3 sec, p = .018). Figure 1 shows an example of EDA recording. CSU patients had stronger skin vasculature responses as assessed by laser speckle measurements of cutaneous perfusion, both after the first startle (58.6 ± 13.5 vs. 46.4 ± 14.1, p = .021) and at the end of the stress exposure session (59.5 ± 38.0 vs. 42.9 ± 20.5, p = .007). Finally, stress levels in CSU patients were higher than in HC, as assessed by PSS (mean ± SD: 19.2 ± 4.8 vs. 16.1 ± 4.8, p = .002). PSS scores were higher than 14 (the cut-off for moderate stress) in 75% of the CSU patients as compared to 25% of HC (chi^2 = 4.24, p = .03). Across all participants, greater reactivity to acoustic startles as assessed by EDA (higher amplitude of response) correlated with higher stress levels measured with PSS (r = .24, p = .02). Longer time for skin conductance to get to the minimal amplitude value also correlated with higher PSS scores (r = .30, p = .005). As for EMG responses, higher PSS scores correlated with more frequent stressor-induced eye blinks (r = .34, p = .03) and with less efficient PPI (r = .39, p = .01). Also, skin blood flow after stressor provocation correlated with stronger stress responses to the first acoustic startle in EDA (r = .51, p = .02).

Based on these results, we conclude that CSU patients have enhanced stress responses as compared to HC using objective and subjective measures. The increased reactivity of CSU patients to startle stimuli and impaired PPI in CSU patients suggests a disrupted activity of their nervous system. EDA is considered to be one of the most sensitive and valid markers of sympathetic arousal in response to changes in emotional state. Our findings demonstrate the distinctive stress responses of CSU patients in EDA, as reflected by higher and prolonged changes in skin conductance compared with HC. This may be seen as physical evidence for the enhanced and unmodulated sympathetic activity to stress, in

CSU patients, and supports previous reports about their higher tendency to experience stress and anxiety in their daily life.[10] Moreover, this is the first study to use the laser speckle measurements of cutaneous perfusion to measure stress response in patients with CSU. Skin blood flow was significantly higher in CSU patients as compared to HC after the first startle and at the end of the stress exposure session. This reflects their less efficient adaptation to stress, demonstrated also with other objective measures, that is EMG and EDA. Interestingly, blood flow after provocation correlated with stronger stress responses to the acoustic startle in EDA. These findings imply that acute stress may facilitate the appearance of CSU signs and symptoms by increasing blood flow to the skin, providing a possible link between CSU disease activity and stress, which was reported previously.[2,3]

Taking it all together, underlying neuroimmune mechanisms that explain stress reactivity in patients with CSU should be explored further, using objective laboratory measures. This information may assist in focusing intervention on patients' real life context. As of now, it is not clear whether the pattern of exaggerated neurophysiological responses demonstrated in CSU is unique for this disease. Nevertheless, our results suggest that patients with CSU are more vulnerable to stressor exposure. They may perceive stress in an enhanced manner and have difficulty to inhibit it. It is possible that stress predisposes to CSU and that CSU increases stress to form a disease amplification loop. The limitations of this study include its small sample size, the possibility of selection bias and the lack of a disease control group, and that clinical parameters such as disease activity and duration or current medication that might influence the results were not included in our analysis. Further studies on larger samples, with the application of objective measures of stress, should be performed.

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

AUTHOR CONTRIBUTIONS

EYB, KA and J-I S designed the study; EYB, HT and ZS performed experiments and analysed the data; EYB, KA, MM and AA provided methodological expertise, resources and experimental assistance; EYB, KA and AA supervised the experiments; and EYB, KA and MM wrote the paper.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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