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Disease activity and stress are linked in a subpopulation of chronic spontaneous urticaria patients

To the Editor,

Chronic spontaneous urticaria (CSU) is a condition characterized by the development of itchy wheals (hives), angioedema, or both, with reoccurring symptoms for more than 6 weeks. CSU is often fluctuating and unpredictable in its course,[1] which is a great burden to the patients, especially when no underlying causes are found. Psychosomatic and psychiatric comorbidities are often reported and an association between CSU and stress was proposed, in which psychosocial strain may initiate a vicious cycle of stress-induced worsening of the disease causing a higher psychosocial burden, which in turn amplifies the stress influence on the disease.[2-5]

At present, systematic studies in support of a stress- and disease-relationship in CSU are largely missing, rendering the stress-contribution to CSU unclear. Comprehensive studies of the association between stress and urticaria are needed to answers to the following questions: Do CSU patients report relevant stress levels? Are stress levels higher when no underlying cause can be identified (CSU– CSU+ patients)? Do CSU– patients suffer from higher disease activity compared to CSU+ patients? And finally, are stress levels in CSU– and CSU+ patients linked to disease activity? To address these knowledge gaps, we studied stress perception and resilience and their association with disease severity, assessed by use of the urticaria activity score (UAS7) in an explorative manner. In addition, selected routinely assessed immune outcomes that have been discussed to play a role in stress effects in urticaria (IgE, basophils, eosinophils) were studied.

The exploratory study was approved by the ethics committee of the Charité - Universitätsmedizin Berlin, Germany. A total of 303 CSU patients that provided informed written consent were assessed for mental distress, resilience, and immune outcomes (ELISA, complete blood count), and then, for potentially relevant underlying conditions, the results of which were disclosed to the patient after completion of the comprehensive workup of the etiologic tests by a team of experienced dermatologists (EMP, MM, MM). The scales "worries," "tension," "and "demands" of the Perceived Stress Questionnaire (PSQ) were used to assess stress perception, "joy" and the Self-efficacy, Optimism and Pessimism (SWOP) questionnaire to assess resilience to stress.[6,7] PSQ "summary score" values above 50 are one SD (=17) higher, values below 16 are one SD lower than the mean (=33) in a German reference population,[6] and were set as cut-offs for severe, medium and low stress, respectively. Additional data obtained included age, sex, body mass index, previous steroid- and anti-histamine intake. Investigated potentially relevant underlying clinical and laboratory conditions included autoreactivity, chronic viral, bacterial, fungal, and parasitic infections, intolerance to food

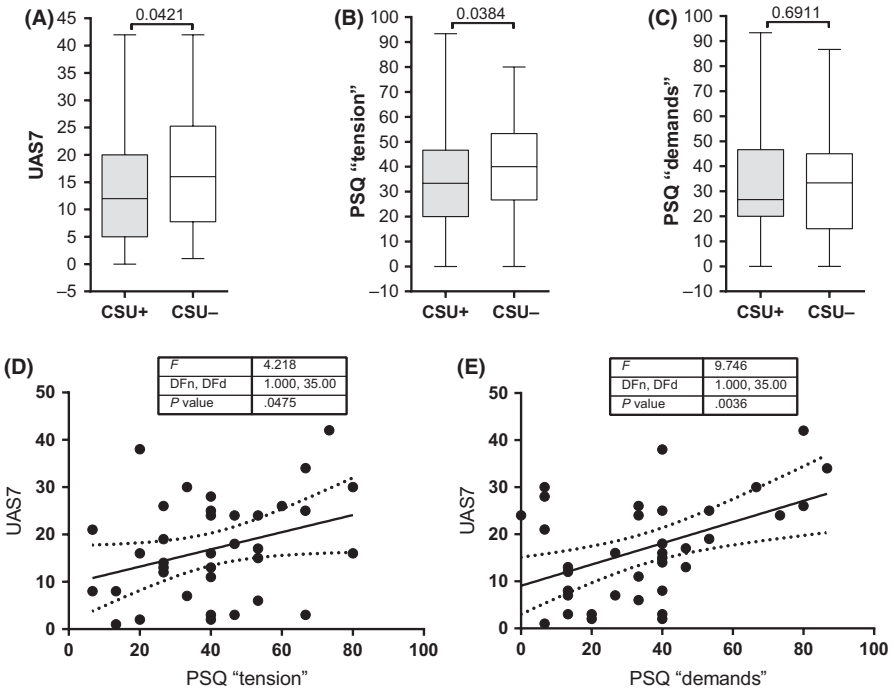

FIGURE 1 A, B, C, CSU+ and CSU– differ significantly in UAS7 and PSQ "tension". Median and minimum to maximum are shown. D,E, Linear regression analyses showed that the urticaria activity during the 7 d prior to enrollment in the diagnostic workup (UAS7) could be predicted by "tension" and "demands" (adjusted R^2 = .082 and .195, respectively) in patients with CSU–

TABLE 1 Spearman Rank correlations between urticaria disease activity and immunological measures with self-rated psychological stress and resilience

		PSQ "worries"		PSQ "demands"		PSQ "tension"	
		ϱ	*P*	ϱ	*P*	ϱ	*P*
UAS7	Total group	0.043	.494	0.102	.106	0.065	.309
	CSU+	0.022	.744	0.050	.468	0.021	.762
	CSU−	0.188	.265	**0.362**	**.028**	*0.292*	*.079*
Total IgE	Total group	0.070	.250	0.074	.223	0.055	.362
	CSU+	0.052	.437	0.059	.378	0.056	.226
	CSU−	0.162	.261	0.184	.200	0.067	.645
Basophils	Total group	0.026	.673	−0.065	.285	−0.009	.883
	CSU+	0.066	.320	−0.065	.333	0.023	.734
	CSU−	−0.196	.178	−0.064	.661	−0.196	.177
Eosinophils	Total group	0.072	.229	0.019	.752	0.020	.742
	CSU+	0.084	.209	0.024	.715	0.034	.608
	CSU−	0.044	.762	−0.025	.863	−0.034	.814

The UAS7 is the gold standard and guideline-recommended instrument to assess CSU activity.[9] UAS7 values are calculated based on the daily recordings of wheal numbers (none; <20; 20-50; >50) and itch intensity (none, mild, moderate, severe). Spearman rank correlations were calculated and given as rho = ϱ. Associations were considered as weak if $-0.3 < \varrho < 0.3$, medium if $0.3 < \varrho < 0.49$ or $-0.3 > \varrho < -0.49$ and strong if $\varrho > 0.5$ or <-0.5.[10] *P*-values are indicated as *P*. Bold are significances below 0.05, italic trends below 0.1.

components, intolerance to physical provocation and chronic inflammatory diseases including autoimmune disorders and allergies.

In 249 CSU patients, potentially relevant underlying conditions were identified (CSU+) as opposed to 54 patients without potentially relevant underlying conditions (CSU−). Only a minority received oral medication prior to the assessment (antihistamines 20%, steroids 6%) and no medication or demographic differences were found between CSU+ and CSU− patients (Table S1). Levels of self-reported stress perception and resilience in CSU patients showed a wide range of mental distress levels, with low, moderate, and high PSQ scores in 21%, 64%, and 15% of patients, respectively. The mean PSQ "summary score" in women (32.05 ± 17.04, 72% of all patients) was slightly but not significantly higher than in men (29.82 ± 15.06). Patients younger than 45 years (55% of all patients) had slightly but not significantly higher PSQ "summary score" levels (33.12 ± 16.20) than older patients (29.55 ± 16.73).

Chronic spontaneous urticaria− patients had significantly higher disease activity than CSU+ patients (Figure 1A). In CSU− patients, 52.6%, 31.6%, and 15.8% had UAS7 levels indicative of mild, moderate, and severe CSU, respectively, as compared to 64.2%, 25.8%, and 10% in CSU+ patients. CSU− patients reported higher PSQ "worries," "tension," and "demands," with statistically increased values for the scale "tension" (Figure 1B,C, Table S2). In contrast, stress resilience in CSU− and CSU+ patients was similar. No group differences with respect to selected immunological measures such as total serum IgE, blood basophil and eosinophil counts were found (Table S3).

Correlation analyses revealed that in CSU− patients, UAS7 scores showed a moderate positive correlation with the results of the PSQ-scales "demands" ($r = .362$; $P = .028$) and a trend for "tension" ($r = .292$; $P = .0791$) (Table 1). A regression analysis (including the confounders age, gender, and body mass index) confirmed these links in CSU− patients (adjusted R^2 "demands" = 0.195; F(1/35) = 9.746; $P = .004$, Figure 1D; adjusted R^2 "tension" = 0.082; F(1/35) = 4.218; $P = .048$, Figure 1E). The explained variance of 19.5% expresses a medium effect of $f^2 = 0.24$ and of 8.2% a low effect of $f^2 = 0.09$, respectively. By contrast, the common confounders age, gender, and body mass index were not significant predictors of the UAS7 in this group.

Our comprehensive analyses of stress in patients with CSU are the first to demonstrate that most CSU patients report stress, but also that mean levels of mental distress are comparable to the general population.[8] More importantly, our findings confirm that in CSU− perceived stress and disease activity are linked in the absence of demographic group differences and even before CSU− patients know that no underlying cause for their urticaria will be found. These observations are relevant and may help to destigmatize CSU patients, who often feel that their doctors and peers do not take their disease-burden seriously and attribute their suffering to the seemingly minor mental problem of having too much stress.

In conclusion, our findings suggest a possible causal link between CSU and mental distress and encourage further research to confirm whether the increased levels of stress in the CSU− subpopulation are the reason or the result of their high disease levels. Clearly, in some CSU patients, the signs and symptoms of urticaria and stress are linked, which confirms the need to assess both the clinical symptoms and stress, ideally by daily diary-assessments and during patient visits, and also to address both by therapy and research, for example by the implementation of psychological interventions.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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IgE reactivity against herpes simplex virus 1 in patients with atopic dermatitis complicated by eczema herpeticum

To the Editor,

Eczema herpeticum (EH) is a severe and widespread viral skin infection caused by herpes simplex virus 1 (HSV-1), which particularly affects patients with atopic dermatitis (AD) who have a more severe course of the disease, higher allergen sensitization, and greater Th2 polarization.[1,2] The condition has been named ADEH (AD complicated by EH). The pronounced shift to a Th2 immune response in ADEH has been proposed as a cause of an ineffective immune response against microorganisms.[3] Th2 cell predominance goes along with overproduction of cytokines such as IL-4 and IL-13 which are key for IgE induction and may prevent the development of cellular immunity against microorganisms. Specific IgE can be produced against microorganisms such as bacteria and yeasts in a subgroup of patients with AD with a potential contribution to AD severity.[4,5] Evidence also exists that IgE can be produced against viruses.[6,7,S1-S3] Although the role of specific IgE in viral infections is still unknown, this might be associated with exacerbation of atopic diseases.[8,9,S4-S5] In humans, specific IgE against different viruses has be linked with poorer prognosis.[S2,S3,S6] In that respect, it has been suggested that virus-specific IgE should be analyzed due to its possible association with atopic diseases.[S4] Currently, there is only sparse information about IgE-mediated mechanisms against viruses