Acta Derm Venereol 2011; 91: 557–561

CLINICAL REPORT

High Prevalence of Mental Disorders and Emotional Distress in Patients with Chronic Spontaneous Urticaria

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Quality of life, which is impaired in patients with chronic spontaneous urticaria (CSU), is influenced by comorbid mental disorders. The aim of this study was to assess the prevalence and spectrum of mental disorders and to determine levels of emotional distress in patients with CSU. One hundred patients with CSU were investigated for mental disorders (by specialized diagnostic interviews and psychometric instruments), levels of emotional distress (by the Global Severity Index of the Symptom Check List; SCL-90R GSI) and underlying causes of their urticaria (by dermatological assessment). Forty-eight percent of patients with CSU were diagnosed with one or more psychosomatic disorders; most common were anxiety disorders (especially phobias), followed by depressive and somatoform disorders. The use of psychometric instruments confirmed these findings. Levels of emotional distress were significantly higher and more commonly increased in patients with CSU with mental disorders. In conclusion, patients with CSU frequently experience anxiety, depression, and somatoform disorders, and these disorders are linked to increased emotional distress. These findings call for screening of patients with CSU for mental disorders in routine clinical practice as well as for controlled clinical trials. ***Key words: anxiety; comorbidity; depression; itching; somatoform disorders; urticaria.***

(Accepted January 3, 2011.)

Acta Derm Venereol 2011; 91: 557–561.

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Urticaria is a group of skin diseases characterized by pruritic wheals and/or angioedema. Chronic spontaneous urticaria (CSU), the most common type of non-acute urticaria, frequently results in severely impaired quality of life (QoL) (1). Recently, we have shown that QoL is significantly more impaired in patients with CSU who also exhibit mental disorders (2).

As yet, there is limited information on which comorbidities are common in patients with CSU and on how prevalent they are. Also, there is currently no information other than QoL data on the impact of comorbidities including psychosomatic conditions in CSU on patient-reported outcomes (PROs), such as compliance, emotional distress, willingness to pay, satisfaction and trust. The last two have recently shown to be low in patients with CSU (3). Importantly, PROs have been recommended to be used for assessing the benefits of interventions in routine CSU patient management. In addition, PROs have been recommended to be used as primary outcome of controlled trials in CSU (4). For the implementation of these recommendations better knowledge of the characteristics and of modulators of PROs in patients with CSU is required.

We present here data on the prevalence and distribution of mental disorders in patients with CSU as well as their impact on the PRO emotional distress.

MATERIALS AND METHODS

Subjects

The study subjects were unscreened patients consecutively referred to our dermatological inpatient clinic (Johannes Gutenberg University Hospital Mainz, Germany) over a period of 20 months for the diagnostic evaluation of CSU. All subjects gave written informed consent, and approval of the Ethics Committee Ärztekammer Rheinland-Pfalz was obtained prior to the start of the study. The study was performed in accordance with the Declaration of Helsinki and German law and European Good Clinical Practice Guidelines.

Mental assessment

All patients were evaluated by one to three extensive diagnostic interviews, and by Mini-DIPS. The diagnostic interviews systematically checked for the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (5). They were conducted by a senior specialist in psychosomatic medicine who was blinded to the patients' dermatological status and psychometric results. The Mini-DIPS is a shortened German version of the common international diagnostic interview for mental disorders (DIPS). The Mini-DIPS is based on the diagnostic criteria of the DSM-IV and International Classification of Diseases (ICD-10) (6, 7). It allows for a sufficiently precise diagnosis of all mental disorders, with the exception of organic cerebral psycho-syndromes and personality disorders.

Psychometric instruments

The psychometric instruments used were the Hospital Anxiety and Depression Scale – German version (HADS) for anxiety and depression and the Symptom Check List (SCL-90R) for somatization. The HADS is a self-rating questionnaire used to measure anxiety and depression on two separate scales with 14 items. It is a reliable and validated psychometric instrument (8, 9). There are four possible answers for each item (score 0–3) that express an increasing level of severity. HADS was found to perform well in assessing the presence and severity of anxiety disorders and depression in somatic, psychiatric and primary care patients and in the general population. The SCL-90R is a 90-item, self-reported inventory widely used to measure current psychopathological symptoms. Nine separate syndrome scales, including somatization, can be calculated. Evidence supporting the reliability and validity of the German version of the SCL-90R is similar to evidence supporting the original version. The reliability (inner consistency) of the nine scales lies between 0.80 and 0.90. Various studies have proven the validity of the scales (10, 11).

Assessment of emotional distress

To characterize the levels of emotional distress and to identify patients with increased emotional distress, we used the Global Severity Index of psychological distress (GSI) as assessed by the SCL-90R. The GSI captures overall levels of emotional distress by calculating an aggregate score across clinical scales (10, 11).

Dermatological investigations

All patients were subjected to a dermatological diagnostic programme to identify underlying causes of CSU, such as food/histamine intolerance, chronic infections, autoreactivity (circulating histamine-releasing factors), autoimmune diseases and other underlying disorders including sensitization to type I allergens. Patients who did not meet the diagnostic criteria of one of these CSU subgroups were considered to experience chronic idiopathic urticaria (CIU) (1).

Identification of CSU due to intolerance. Patients were subjected to a 21-day diet largely devoid of food additives such as preservatives, colorants, natural pseudo-allergens and histamine. During this time, disease activity was assessed daily using the urticaria activity score (12). Patients who showed drops in score values (number of wheals + intensity of pruritus) by more than 50% after 21 days of elimination diet, indicating improvement of disease activity, were subjected to oral provocation tests for 2 days with pseudoallergen- and histamine-containing meals. Patients who showed increased CSU activity after provocation (i.e. increases in wheal + pruritus scores by > 50%) and/or reported disease remission after more than 3 months on a diet low in pseudo-allergens and histamine were considered to have CSU due to food/histamine intolerance (1).

Identification of CSU due to infectious processes. Diagnostic procedures included: (*i*) blood testing for markers of infectious inflammation (C-reactive protein, erythrocyte sedimentation rate, fibrinogen, complement, immune complexes, hepatitis serology), urease testing for *Helicobacter pylori*; (*ii*) clinical investigations to exclude infections of the intestinal or upper respiratory tract and nasopharynx, including maxillary sinusitis, streptococcal tonsillitis, and tooth infections; (*iii*) stool analysis for worm eggs, pathological germs, parasites, and *Candida albicans*. CSU was held to be caused by an infection: (*i*) if at least one potentially relevant infectious process was identified; and (*ii*) if eradication therapy was effective, i.e. improvement of CSU activity by > 50% following successful treatment of the infection (1).

Identification of CSU due to autoreactivity. All patients were subjected to autologous serum skin testing (ASST) as previously described. Briefly, venous blood was taken and serum was obtained by centrifugation (3,000 U/min for 10 min at room temperature). Samples (50 µl) of autologous serum, histamine (1 mg/ml, ALK-Scherax, Hamburg, Germany) and sterile saline 0.9% were separately injected intracutaneously (lower arm). Gaps of at least 5 cm were left between injection sites, and areas that showed spontaneous wheals during the last 24 h were avoided. Antihistamines were withdrawn at least 3 days prior to the skin tests (1). Wheal and flare responses were measured at 30 min and the ASST response was taken to be positive when the serum-induced wheal had a diameter that was at least 2 mm greater than the saline-induced response. ASST-positive patients were diagnosed with CSU due to autoreactivity and subjected to screening for other autoimmune diseases (antinuclear and other autoantibodies, thyroid hormones) (1).

Identification of CSU due to other underlying causes. Diagnostic procedures to identify other causes included prick testing for common type-I-allergens, intracutaneous testing for sensitization to moulds or *C. albicans*, stool and blood analyses (eosinophil cationic protein, total IgE, vitamin B6, differential blood count, C1-esterase inhibitor, serum IgA and IgG, and rheumatoid factor), abdominal sonography and X-ray of thorax (1).

Statistics

All statistical calculations were unifactorial multivariate variance analyses with *post-hoc* tests for individual differences after Scheffé unless specified otherwise.

RESULTS

A total of 111 patients with CSU were screened for enrolment in this study. Seven patients exhibit chronic physical or cholinergic urticaria, but not CSU. Four patients ultimately had dermatological diseases other than urticaria. These 11 patients were excluded from the analyses, resulting in a total sample size of 100 patients (69 females, mean age 43.8 years).

Forty-eight of the 100 patients with CSU were found to have one or more mental disorder as assessed by diagnostic interviews and mini-DIPS (Fig. 1). Mental disorders were of similar prevalence in male and female patients with CSU (Fig. 1). The most common mental disorders were anxiety disorders (30%), followed by depressive and somatoform disorders (17% each), adjustment disorder (4%), post-traumatic stress disorder, harmful use of alcohol (3% each), hypochondria, obsessive compulsive disorder (2% each) and alcohol dependency, multiple substance abuse (1% each). Agoraphobia was found to be the most frequent anxiety disorder in patients with CSU (15%; Fig. 2). Patients with CSU with depression commonly presented recurrent depressive disorder or dysthymia, whereas somatization disorders, somatoform autonomic dysfunction and undifferentiated somatofom disorders were the most frequent somatoform disorders in patients with CSU (Fig. 2).

Assessment for coexisting anxiety, depression and somatoform disorders by standardized psychometric

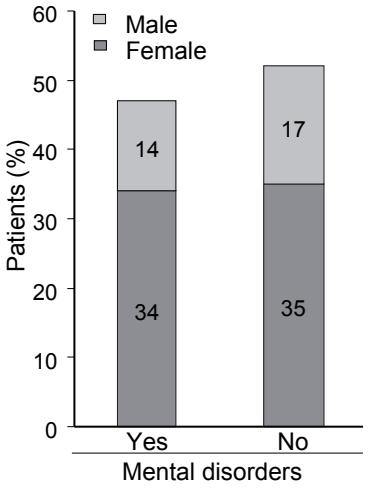

Fig. 1. Prevalence and sex distribution of mental disorders in patients with chronic spontaneous urticaria (CSU). Forty-eight of 100 patients with CSU experience at least one mental disorder (34 women and 14 men) as assessed by diagnostic interviews and mini-DIPS.

instruments showed that a significant percentage of patients with CSU exhibit elevated scores indicative of these disorders. Increased scores for anxiety (by HADS), depression (by HADS), and somatization (by SCL-90R) were found in 30%, 21%, and 23% of patients, respectively (Table I). Interestingly, all three scores were found to be significantly higher and to be elevated more often in CSU patients diagnosed with a mental disorder by diagnostic interview(s) and mini-DIPS (Table I).

Patients with CSU diagnosed with one or more mental disorder by diagnostic interview(s) and mini-DIPS showed significantly higher levels of emotional distress as assessed by use of the SCL-90R GSI (Fig. 3). Also, their levels of emotional distress were significantly more often increased above cut-off levels than those in patients with CSU without a mental disorder (Fig. 3).

Extensive dermatological examinations resulted in the identification of underlying causes of CSU in 88 of 100 patients and showed that CSU due to food intolerance (30%), CSU due to chronic infection (31%), and CSU due to autoreactivity (19%) were the most common subforms of CSU. Eight percent of patients had other underlying causes, and in 12% of the patients with CSU no underlying causes could be found (CIU). Patients who were found to exhibit more than one underlying cause of CSU were assigned to the CSU subgroup that was considered to be most relevant in clinical terms (13 of 100 CSU patients). The prevalence of mental disorders was highest in patients with idiopathic CSU (71%), 64% in autoreactive CSU, 58% in intolerance CSU, 44% in CSU due to other causes and 40% (lowest) in patients due to CSU with infections.

DISCUSSION

We confirm here that mental disorders are frequent in patients with CSU. Also, we show, to our knowledge, for the first time, that levels of emotional distress are higher and more commonly increased in patients with CSU with mental disorders.

In line with our findings, patients with CSU have repeatedly been reported to show high rates of mental disorders, i.e. earlier studies examining patients with CSU have identified comorbidity rates ranging from 35% to 60% (12–14). In addition, anxiety, depression and somatoform disorders have previously been reported to be the most prevalent mental disorders in patients with CSU (15–18). In contrast to our findings, some studies have found higher prevalence rates of depression as compared with anxiety in CSU patients, which is most likely explained by differences in the patient populations studied (14, 19).

In our study, the rates for mental disorders identified by means of a diagnostic interview by a senior psychiatrist and by self-rated questionnaires were very similar. This suggests that questionnaires such as HADS and

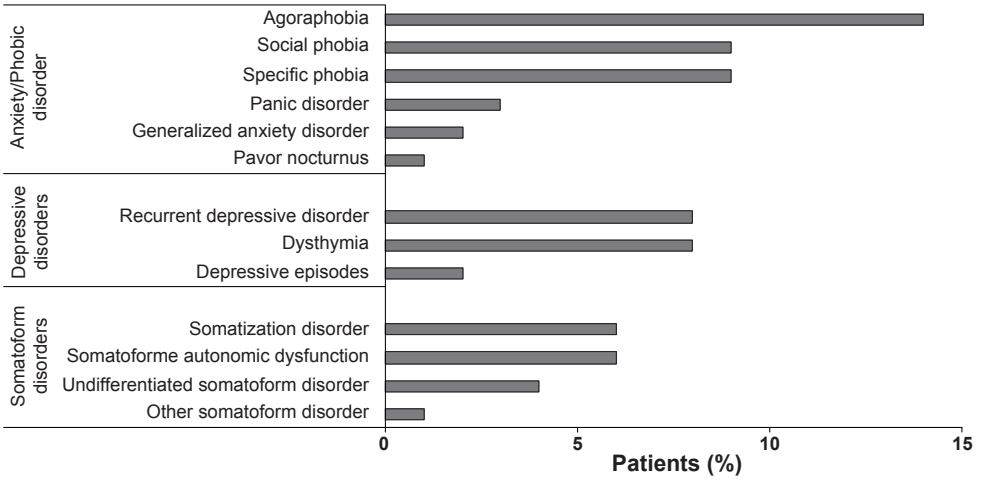

Fig. 2. Prevalence of anxiety disorders, depressive conditions, and somatoform disorders in patients with chronic spontaneous urticaria as assessed by diagnostic interviews and mini-DIPS.

Table I. *Results of psychometric investigations of patients with chronic spontaneous urticaria*

	Score values		Patients with above cut-off score values	
	Without psychosomatic comorbidity Mean ± SD	With psychosomatic comorbidity Mean ± SD	Without psychosomatic comorbidity Mean ± SD	With psychosomatic comorbidity Mean ± SD
Anxiety (HADS)	4.4 ± 3.2	9.5 ± 4.0*	7 of 52 (14%)	30 of 48 (63%)*
Depression (HADS)	2.7 ± 2.4	7.1 ± 4.2*	1 of 52 (2%)	21 of 48 (44%)*
Somatization (SCL90R)	48.9 ± 10.4	59.8 ± 13.8*	8 of 51 (16%)	23 of 47 (49%)*

*p < 0.05.Population means ± SD for anxiety (HADS): 6.7 ± 4.5, depression (HADS):4.8 ± 4.0 (8) and somatization (SCL90R): 54.1 ± 13.2 (10). Mean ± SD for all patients with CSU for anxiety (HADS): 6.8 ± 4.1, depression (HADS): 5.1 ± 3.8, and somatization (SCL90R): 50.0 ± 10.0. SD: standard deviation.

SCL90R can be valuable tools to screen patients with CSU for psychosomatic conditions. Given the high rates of mental disorders in CSU patients, our findings recommend to test HADS and SCL90R for their use as screening tools for depression, anxiety and somatoform disorders in the routine management of CSU patients. Interestingly, a study in patients with coronary heart disease has confirmed that HADS is a reliable and valid screening instrument for anxiety and depression (20).

We and others have previously shown that psychiatric comorbidity is a relevant driver of QoL impairment in patients with CSU (2). Specifically, our study and a subsequent confirmatory report by Engin and co-workers show that the severity of depression and anxiety as assessed by psychometric instruments is positively correlated with the extent of QoL decrease in patients with CSU (15). These results suggest that psychiatric comorbidity could influence PROs outcomes other than QoL, such as emotional distress. Indeed, our findings from the present study clearly demonstrate that emotional distress is more pronounced and more commonly increased in patients with CSU with mental disorders than in those without. This observation has several implications. (*i*) Patients with CSU should be investigated and treated for mental disease, which is likely to improve QoL and reduce emotional distress. (*ii*) Mental disorders must be expected to influence, in addition to QoL and emotional distress, other PROs, such as illness perception, behaviour, preferences, satisfaction with medical procedures, adherence to treatment and willingness to pay. These influences should be investigated. (*iii*) Increased emotional distress levels may influence other PROs, some of which are commonly used to assess disease activity (e.g. symptoms scores). This should be taken into account in routine clinical practice as well as when designing clinical trials.

In conclusion, our data show that patients with CSU experience high rates of anxiety, depression, and somatoform disorders, with one in two patients with CSU affected by at least one of these conditions. Patients with CSU with a mental disorder exhibit significantly increased emotional distress levels, as shown by our present study, and impairment of their QoL. Therefore, our findings call for mental health evaluations of patients with CSU in routine clinical practice, and questionnaires such as the ones used in this study should be evaluated for their use as tools to do so. Also, patients with CSU should be investigated for improvement of emotional distress levels as well as QoL after psychosomatic therapy when indicated by means of controlled clinical trials.

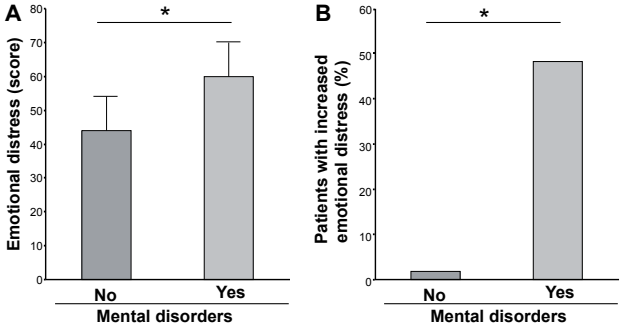

Fig. 3. Emotional distress is increased in patients with chronic spontaneous urticaria (CSU). (A) Levels of emotional distress and (B) percentage of patients with emotional distress levels increased above cut off assessed by the Global Severity Index of the Symptom Check List (SCL-90R GSI) in patients with CSU with and without mental disorders. *$p < 0.001$.

ACKNOWLEDGEMENTS

This work was supported in part by the urticaria network e.V. (UNEV, www.urtikaria.net) and by the European Allergy Research Centre Foundation (ECARF). We thank Karoline Krause for helpful discussions and Jodie Urcioli for proof-reading the manuscript.

The authors declare no conflicts of interest.

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