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REVIEW ARTICLE

Psychosocial factors and chronic spontaneous urticaria: a systematic review

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Abstract

Background: Chronic spontaneous urticaria (CSU) is one of the most costly allergic conditions challenging physicians as well as patients and their families. Despite evident lacunae in the understanding of the pathogenesis, at least some findings suggest that psychosocial factors likely contribute to the development and exacerbation of CSU. We aim to assess the contribution of psychological factors to CSU.

Methods: Systematic search of PubMed and OVID/Medline databases was conducted from 1 January 1935 to 1 January 2012. Studies selected include original research in English, Spanish and French exploring the association between CSU and psychosocial factors. Two investigators independently reviewed all titles and abstracts to identify potentially relevant articles and resolved discrepancies by repeated review and discussion and arbitration of a third reviewer. Quality of systematic reviews and meta-analyses was assessed using a measure based on the Newcastle-Ottawa Scale and psychological conditions of CSU patients.

Results: We identified 114 eligible studies spanning 77 years and featuring 17 reviews, 67 studies related to neither CSU nor psychosocial factors, and eight studies that provided either no prevalence estimates or insufficient sample size. Pooling effect sizes using random effects, analyses revealed that, despite large heterogeneity (I^2 of 97.60%), psychosocial factors had a prevalence of 46.09% (95% confidence interval, 44.01%, 48.08%).

Conclusion: Future research needs to better establish the contribution of psychosocial factors to the pathogenesis and exacerbation of CSU, and explore the possible benefit of behavioural interventions to the development of new management strategies.

Chronic spontaneous urticaria (CSU) is a common and debilitating allergic condition. CSU affects 0.5%–1% of the population typically presenting with transient wheals, which last for at least 6 weeks, sometimes with concomitant angioedema. The pathogenesis of, and effective treatment for, CSU are at best unclear and tenuous, respectively (1, 2). Furthermore, because IgE-mediated allergy rarely emerges as an aggravating factor, the conceptualization of CSU should probably weigh less on its notion as an allergic condition and more on the idea of a chronic inflammatory disease (3). Whereas many physicians may consider the non-life-threatening symptoms of CSU as relatively mild, most specialists concur that the disfigurement and discomfort associated with this disorder can often pose a serious challenge to the treating clinician and a long-term hardship for patients and their families (4). With spontaneous remission occurring in only 30–55% of cases within five years, individuals with CSU often seek multiple consultations with different allergists, dermatologists and other practitioners in a desperate attempt to relieve their challenging symptoms (1, 5). This trend introduces a prolonged burden to the healthcare system while decreasing the quality of life for individuals with CSU. Compared to the general population, furthermore, individuals with CSU frequently rank in the lowest quartile on

physical functioning and below the 20th percentile for items indexing psychological health (4). Adults with CSU are absent from work more days than any other group of individuals suffering from allergic conditions; children with CSU perform worse than those without CSU at school (6). In this regard, CSU is one of the most costly and poorly controlled inflammatory conditions. A recent survey examining the controversial influence of psychological factors in CSU showed that the majority of Canadian allergists reported that psychosocial parameters played a notable role in the pathogenesis of CSU (5). In line with previous efforts (7), the present paper examines how tenable these clinical impressions are by providing a systematic review documenting the involvement of psychological components in CSU and discussing implications for potential therapeutic approaches.

Methods

We first conducted a search of the PubMed and OVID/Medline databases using the keywords 'urticaria', 'chronic urticaria', 'chronic spontaneous urticaria' – given that the definition of CSU was not clearly established in early studies, we also included more general terminology such as urticaria and chronic urticaria, but excluded articles clearly assessing physical or acute urticaria – 'psychopathology', 'stress', 'depression', 'anxiety' 'life events' and 'axis I' and 'axis II', including full-text accessible articles in English, French and Spanish. We then performed a meta-analysis that included all these studies (see Fig. 1) from 1 January 1935 to 1 January 2012. After two reviewers (M.B.S. and I.B.) independently evaluated all potentially relevant studies, we conducted statistical analyses using STATA® version 12 (StataCorp LP, College Station, TX, USA).

Methodological quality of included studies

In order to assess the quality of the aforementioned studies, we employed a standardized measure specifically tailored to this systematic review, based on the Newcastle-Ottawa Scale (NOS) (8). This approach included the appraisal of external and internal validity, as well as biases common to observational studies specific to CSU and psychosocial factors. The independent reviewers mentioned above evaluated the study quality separately and resolved the differences in opinion by consulting a third reviewer (A.R.) (Table 1).

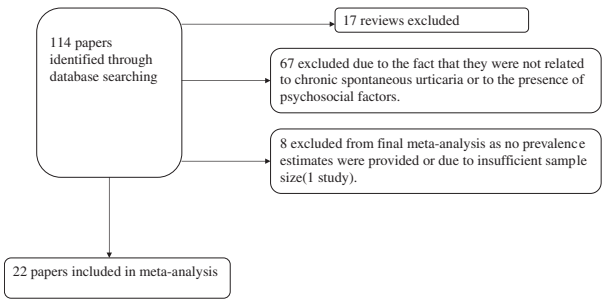

Figure 1 Results of search strategy of systematic review and meta-analysis.

Pathogenesis

Whereas mast cells play a role in chronic urticaria, experts rarely consider allergens to be the triggers. Examining IgE sensitization and allergy in 128 adults with chronic urticaria, researchers found that of 105 patients with interpretable skin prick tests, only 46.7% were IgE-sensitized (3). Two patients had clinically relevant positive skin prick tests, but their chronic urticaria had many other triggering factors, and neither completely remitted after the withdrawal of the implicated allergens. Thus, the authors concluded that although IgE sensitization is higher in chronic urticaria patients than in the global adult population, it does not constitute an expression of an IgE-mediated allergy. Instead, the authors suggest the possibility of a chronic inflammatory disease, more frequent in IgE-sensitized individuals and favoured by multiple factors, among which the IgE-mediated allergy is exceptional.

Patients with CSU comprise at least two subgroups: those truly idiopathic and those who had been previously diagnosed with idiopathic disease but who later turned out to have autoimmune CSU – approximately 40–50% of adults and children (9). Allergists often characterize the latter, autoimmune CSU, by a positive autologous intradermal injection test (10) wherein functional mast cells are stimulated by IgG antibodies towards the alpha chain of the high-affinity IgE receptor and, rarely, towards IgE itself (11); the former group is a diagnosis by exclusion.

In line with an unclear pathogenesis, conundrums persist regarding potential triggers of CSU. For example, some clinicians maintain that infections are triggers despite the evidence showing little, if any, association between CSU and infections (e.g. bacterial, viral, parasitic) in both children and adults (9). Similar confusion lingers concerning psychological components. Although many practitioners concur that psychosocial factors are likely contributors to the exacerbation of symptoms in existing CSU, some experts largely dismiss the involvement of psychological parameters in the onset, and even manifestation, of CSU; yet the overwhelming tenor from many allergists intimates that psychological factors play a role in the pathogenesis of this condition (5).

Results of meta-analysis related to potential psychopathology in CSU

Clinicians have long speculated the presence of an association between psychological factors and CSU (12, 13); however, reports elucidating this relationship are both scantily available and methodologically weak. Tables 1 and 2 list 30 such studies – 15 employing a case–control design and 15 using cross-sectional methods – and provide a brief description of their gist. The majority of these studies examined the effect of psychosocial factors through prevalence estimates (13–34), with a single study providing the odds ratio for this effect (35). Five studies assessed the effect

Table 1 Methodological quality of included studies

	External validity		Internal validity										
			Performance (of exposure = CSU)		Detection (of outcome)		Attrition	Selection bias/control for confounding					
Study	Representative*	Participation rate†	Clear definition of CSU	Exclusion of cases with identifiable trigger	Use of validated measure to define psychopathology	Blinded assessors	Completeness‡	Age	Sex	Presence of autoimmune diseases	Presence of atopy	Baseline psychiatric problem	% (95% CI)
Stokes (CS)	NS	NS	_	_	_	_	NS	_	_	_	_	_	83 (75.64, 90.36)
Graham (CS)	NS	NS	_	_	_	_	✓	_	_	_	_	_	96 (90.24, 103.09)
Wittkower (CS)	NS	NS	_	_	_	_	NS	_	_	_	_	_	76 (61.85, 90.15)
Shoemaker (CS)	NS	NS	_	_	NS	_	NS	_	_	_	_	_	67.5 (52.98, 82.015)
Fava (CS)	NS	NS	✓	✓	✓	_	NS	_	_	_	✓	_	90 (76.85, 103.14)
Miller (CS)	NS	NS	_	_	_	NS	NS	_	_	_	_	_	46 (32.18, 59.81)
Juhlin (CS)	NS	NS	✓	✓	_	NS	NS	_	_	_	_	_	16 (12.04, 19.95)
Sperber (CC)	NS	NS	✓	NS	✓	_	NS	_	_	_	_	_	§ (§)
Sengupta (CS)	✓	NS	✓	NS	✓	NS	NS	_	_	_	_	_	§ (§)
Anasagasti (CS)	NS	NS	_	NS	✓	NS	NS	✓	✓	_	_	_	66 (44.11, 87.88)
Sheehan-Dare (CC)	NS	NS	✓	✓	✓	NS	NS	✓	✓	_	_	_	14.7 (2.79, 26.60)
Badoux_1 (CS)	NS	NS	_	_	✓	NS	NS	_	✓	_	_	_	11 (0.00, 22.80)
Badoux_2 (CS)	NS	NS	_	_	✓	NS	NS	_	✓	_	_	_	53 (38.73, 67.27)
Hashiro (CC)	NS	NS	✓	NS	✓	_	NS	_	_	_	✓	_	70 (53.60, 86.39)
Pulimood (CS)	NS	✓	_	NS	✓	NS	NS	_	_	_	_	_	75 (56.02, 93.98)
Yang (CC)	NS	NS	✓	✓	✓	✓	NS	✓	✓	✓	✓	✓	4.9¶ (1.65, 14.45)
Berrino (CS)	NS	✓	✓	✓	✓	NS	NS	_	_	_	_	_	63.33 (46.09, 80.57)
Maniaci (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	_	_	_	50 (34.50, 65.49)

Table 1 (continued)

	External validity		Internal validity: Performance (of exposure = CSU)		Detection (of outcome)		Attrition	Selection bias/control for confounding					
Study	Representative*	Participation rate†	Clear definition of CSU	Exclusion of cases with identifiable trigger	Use of validated measure to define psychopathology	Blinded assessors	Completeness‡	Age	Sex	Presence of autoimmune diseases	Presence of atopy	Baseline psychiatric problem	% (95% CI)
Pasaoglu (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	_	✓	_	§
Vargas	NS	NS	_	NS	✓	NS	NS	_	_	_	_	_	§
Ozkan (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	✓	✓	_	60 (49.52, 70.47)
Uguz (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	✓	✓	_	49.40 (39.05, 59.83)
Silvares (CS)	NS	NS	NS	NS	_	NS	NS	_	_	_	_	_	15 (8.74, 21.25)
Malhotra (CS)	NS	NS	NS	NS	✓	NS	NS	_	_	_	_	_	16 (5.84, 26.16)
Engin (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	✓	✓	_	§ (§)
Dyke (CC)	NS	NS	✓	✓	_	_	✓	_	_	_	_	_	** (**)
Bashir (CS)	NS	NS	_	✓	✓	NS	NS	_	_	_	_	_	†† (††)
Chung (CS)	NS	✓	✓	✓	✓	NS	✓	_	_	✓	NS	✓	68 (58.86, 77.14)
Hergüner (CC)	NS	NS	✓	✓	✓	NS	NS	✓	✓	_	_	✓	70 (52.71, 87.29)
Staubach (CS)	NS	✓	_	✓	✓	NS	✓	_	_	✓	_	_	48 (38.20, 57.49)
Barbosa (CC)	NS	✓	✓	✓	✓	NS	✓	_	_	_	_	✓	76.64 (66.63, 88.65)‡‡

CS, cross-sectional study; CC, case–control study; OR, odds ratio; ✓indicates the measure was adequately addressed in the study; NS, not specified.

*Studies received a ✓ if the sample included all eligible CU patients over a defined period of time, or in a defined catchment area, or a random or systematic sample of these.

†Studies received a ✓ if the percentage participation was 80% or more.

‡Studies received a ✓ if the percentage of participants in the final analysis was 80% or more of the original sample, or if a full description of those lost to follow up was not suggestive of bias. For selection bias/control of confounding, a ✓ indicates that the group variable was either balanced between groups (10% or less difference) or adjusted for during the analysis.

§Reported significantly higher scores for psychiatry disorders but no OR nor prevalence estimates provided.

¶OR for this study were used to assess the effect of psychopathology.

**This study explored the effect of stress on basophil function in CSU patients and did not assess the prevalence of psychosocial factors in these patients.

††Only three patients with chronic urticaria were recruited.

‡‡For severe/moderate anxiety.

Table 2 Chronic spontaneous urticaria (CSU) and psychosocial factors

Study	Publication year	Country	Study design	Sample size	Effect	Reference number
Stokes	1935	USA	Cross-sectional	100 individuals with CSU	Abnormal psychoneurogenous elements appeared in the background of 83% urticaria cases, as compared with 24% in a control series of cases of psoriasis, acne and impetigo	(15)
Graham and Wolf	1950	USA	Cross-sectional	30 individuals with urticaria	In 29 of 30 patients studied, there was an almost invariable relationship between a particular attitude and attacks of urticaria. The majority of urticaria attacks occurred at times of helpless resentment	(16)
Wittkower	1953	Canada	Cross-sectional	35 individuals with urticaria/angioneurotic oedema	Two-thirds of the patients in this series spontaneously stated that they missed parental, and especially maternal affection, as children. Events such as desertion or impending desertion by husband, wife or sweetheart; abroad were among the incidents preceding the onset of urticaria in 19 of 25 urticaria patients	(17)
Shoemaker	1962	USA	Cross-sectional	40 individuals with urticaria	13 of 40 patients were defined as socially normal	(18)
Miller	1968	USA	Cross-sectional	50 individuals with urticaria lesions for more than 8 weeks. Included were those for whom food, inhalants, infections and physical factors were associated with chronic urticaria, as well as those with vasculitis, mastocytosis and malignancies	23 of 50 patients had emotional factors associated with urticaria	(19)
Fava	1980	Italy	Cross-sectional	20 individuals with urticaria present more than 3 months	18 patients with chronic urticaria reported at least one stressful life event before illness onset	(20)
Juhlin	1981	Sweden	Cross-sectional	330 consecutive patients with recurrent urticaria of 3 months to 40 years duration	Severe psychiatric problems were mentioned by 16%	(21)
Sperber	1989	USA	Cross-sectional	19 outpatients with CSU	Urticaria patients, when compared to healthy controls, revealed substantially higher scores (based on SCL-90) on scales of somatization, obsessive–compulsive disorder, interpersonal sensitivity, depression and anxiety	(36)

Table 2 (continued)

Study	Publication year	Country	Study design	Sample size	Effect	Reference number
Sengupta	1982	India	Cross-sectional	40 patients with CU	Emotional liability and sense of insecurity but no estimates or score provided	(38)
Anasagasti	1985	Spain	Cross-sectional	18 patients with CU	Existence of abnormal personality factors – submission and dependence – in 61% and 66% of patients, respectively	(22)
Sheehan_Dare	1990	UK	Cross-sectional	34 patients with CSU	14.7% of patients with CSU had depressive symptoms *vs* 4.4% of controls, although difference did not reach significance.	(23)
Badoux group 1	1994	France	Cross-sectional	27 men	11% had increased scores of psychological symptoms	(24)
Badoux group 2	1994	France	Cross-sectional	47 women	53% had increased scores of psychological symptoms	(24)
Hashiro	1994	Japan	Case–control	30 outpatients with CSU and 39 normal controls	Psychologically positive responses to any one of three psychological tests were seen in 70% of the chronic urticaria patients, but in only 25.6% of the controls. These differences were statistically significant ($P < 0.01$)	(25)
Pulimood	1996	India	Cross-sectional	20	The highest rates of psychiatric morbidity were found in patients with CU (75%)	(26)
Yang	2005	Taiwan	Case–control	75 patients with CSU and 133 controls with tinea pedis	Patients with CSU had significantly more stressful life events and more severe insomnia	(35)
Berrino	2006	Italy	Cross-sectional	30 subjects with CSU	Most of the patients experienced a 'stressor' event within the six months before the onset of CSU	(27)
Maniaci	2006	Turkey	Cross-sectional	40	CSU patients had higher alexithymia levels ($P < 0.05$) in comparison with the normal population	(28)
Pasaoglu	2006	Turkey	Cross-sectional	59 CSU patients and 59 controls	Scores for hypochondriasis, depression, hysteria, psychopathic deviance, paranoia, psychasthenia, schizophrenia and social introversion were higher in patients with CIU compared to the control group ($P < 0.05$)	(39)
Vargas	2006	Spain	Cross-sectional	29 CSU patients	Chronic urticaria had a significantly higher anxiety state when compared to control.	(40)
Ozkan	2007	Turkey	Case–control	84 CSU patients and 75 controls	A psychiatric diagnosis was given to 60% of the patients, with depressive disorders being the most prevalent (40%). Most patients (81%) believed that their illnesses were due to stress	(29)
Uguz	2007	Turkey	Case–control	89 CSU patients and 60 controls	Of patients with CSU, 44 (49.43%) had at least one axis I diagnosis, and 40 (44.9%) had at least one personality disorder. The most common axis I disorder was obsessive–compulsive disorder (25.84%), and the most common axis II disorder was obsessive–compulsive (30.33%) personality disorder	(30)
Silvares	2007	Brazil	Cross-sectional	125 CSU patients	15% reported stress as the main trigger.	(31)

Table 2 (continued)

Study	Publication year	Country	Study design	Sample size	Effect	Reference number
Malhotra	2008	India	Case–control	50 CU and 50 psoriasis patients	16% of CU patients had stressful life events (mainly death of a close family member) occur within a year prior to onset of symptoms	(32)
Engin	2008	Turkey	Case–control	73 patients with CSU and 34 healthy subjects	Beck Depression Inventory and the Beck Anxiety Inventory were significantly higher in CSU patients	(37)
Dyke	2008	UK	Case–control	30 patients with CSU and 30 normal controls	Both corticotrophin-releasing factor (CRF) and adrenocorticotrophic hormone (ACTH) were shown to activate basophils. The mean increase in the percentage of basophils expressing CD63 was 24.5% (95% CI, 21.8, 27.2%) for the CSU patients and 10.8% (95% CI = 8.9–12.7%) for the volunteer controls	(42)
Bashir	2010	Pakistan	Cross-sectional	3 patients with CU	2 of 3 with chronic urticaria had depression	(41)
Chung	2010	UK	Case–control	100 CSU and 60 allergy patients	Compared to allergy patients, CSU patients had worse comorbidity and higher levels of life event stress and perceived stress. Emotion-focussed coping was associated with the severity of CSU	(13)
Hergüner	2011	Turkey	Case–control	27 children with CSU and 27 age- and sex-matched controls	The study group had more frequent psychiatric diagnoses than the control group (70% *vs* 26%, $P = 0.002$) and the most common psychiatric disorders were social anxiety disorders	(14)
Staubach	2011	Germany	Cross-sectional	100 individuals referred to a dermatological inpatient clinic over a period of 20 months for the diagnostic evaluation of CSU	48% patients with CSU were found to have one or more mental disorders as assessed by diagnostic interviews and mini-DIPS	(33)
Barbosa	2011	Portugal	Case–control	55 CSU patients and 31 controls	76.64% of CSU patients reported moderate/severe anxiety symptoms *vs* 29% of controls. There was a significant statistical difference between CSU patients and the control group for anxiety symptoms scores ($\chi^2 = 4.966$; $P < 0.026$ and $t = 5.574$; $P < 0.0001$)	(34)

OR, odds ratio; RR, relative risk; CI, confidence interval.

through the differences in quantitative measures of psychosocial factors (36–40), one study involved only three patients with CSU (41), and one explored the function of the hypothalamic–pituitary–adrenal axis hormones as well as basophil activation, in the link between psychological stress and CSU (42). Altogether, we included 22 studies in our meta-analysis, assessing the prevalence of psychosocial factors in CSU patients. The majority of these studies failed to control for potential confounds, and a substantial percentage neglected to measure psychosocial factors by the way of a validated test (prevalence estimates summarized in Table 2 and Fig. 2). The studies that did use standardized methods largely relied on interviews, such as the Structured Clinical Interview for DSM-III/IV Axis I & II (SCID-I/SCID-II) (29) and the mini International Diagnostic Interview for Mental Disorders (mini-DIPS) (33), in combination with questionnaires such as the Hospital Anxiety and Depression Scale (HADS) (34), the Beck Depression Inventory (BDI) (37) and the Symptom Checklist-90 Revisited (SCL-90R) (36). Such measures permit researchers to rigorously examine a broad range of psychological parameters. The pooled prevalence of psychosocial factors was 46.09% (95% CI, 44.01%, 48.08%) with an $I(2)$ of 97.60%, reflecting the high heterogeneity among studies.

Several of the aforementioned studies report on the involvement of socio-cognitive factors in the exacerbation of urticaria. Historically, early studies reported that psychological factors were important in urticaria cases (12, 43). Later, a study examining 40 individuals who experienced bouts of urticaria for at least three months found that the majority of patients suffered from psychopathology – largely anxiety and depression – and responded favourably to psychotherapy (18). [Intimating that a generic emotional theme was too simplistic an explanation for CSU, the study concludes that 'chronic urticaria can be best understood as a physical reaction to a condensation of biological and psychological elements arising out of the personal history of an individual under the stress of a particular set of life circumstances' (p. 365).] More recent studies reveal that, when compared to controls with no medical history of chronic hives, individuals suffering from CSU had worse comorbidity, higher levels of stress related to either perceived events or actual life experiences (16, 17, 21, 42, 44). Table 2 provides a comprehensive list of studies reporting that, compared to a healthy control group, individuals with urticaria had significantly higher scores on measures of somatization, obsessive–compulsive disorder, interpersonal sensitivity and depression, anxiety (29, 34, 36, 37); insomnia (35); and stressful life events (e.g. death of a close family member) (32).

Caveats and limitations

Over the span of 77 years, methodologies and diagnostic approaches have changed substantially. Given that this systematic analysis assesses different types of psychopathologies, pooled estimates may reflect disparate prevalence estimates of specific psychosocial process in patients with CSU. Given the wide range of estimates [16% (32) to 96% (16)] and sparse data documenting psychopathology in CSU, we provide a rough index for the involvement of psychopathological component in these patients. These factors may be a consequence of, rather than a cause for, CSU (e.g. anxiety and depression often coexist with chronic pain (45) and other disease groups, including chronic skin conditions (46)). This chicken-or-egg conundrum, wherein clinicians struggle to unravel whether psychosocial factors precede or follow CSU, remains a conceptual obstacle to understanding the mental and behavioural components in the symptomatology. The putative role of psychosocial factors may or may not cause

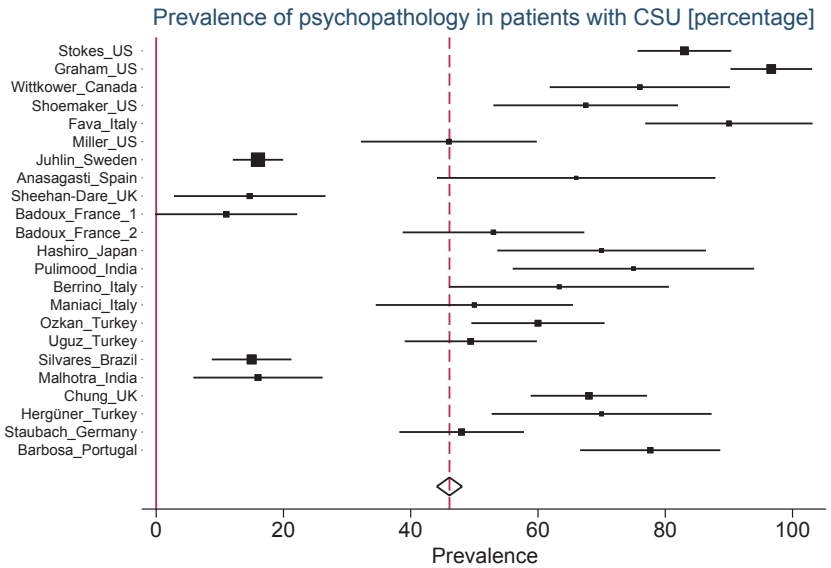

Figure 2 Prevalence (in percentage) of psychosocial factors in patients with chronic spontaneous urticaria. *Only studies reporting prevalence estimates were included. †Pooled estimate = 46.09% (95% CI, 44.01%, 48.08%); ($I(2)$ = 97.60%).

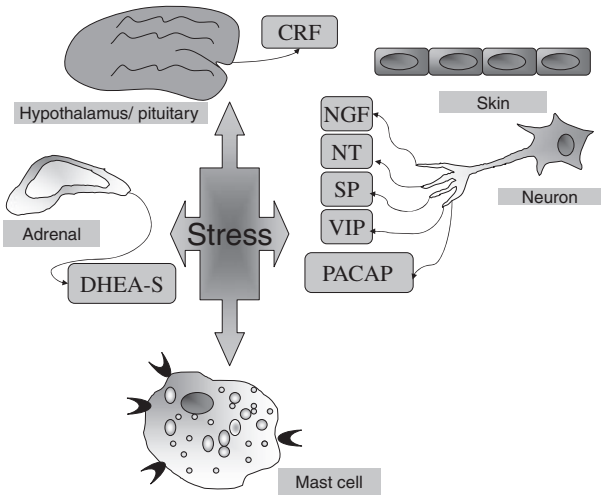

Figure 3 Neuropeptides and hormones capable of activating mast cells. CRF, corticotrophin-releasing factor; DHEA-S, dehydroepiandrosterone sulphate; SP, substance P; NGF, nerve growth factor; NT, neurotensin; PACAP, pituitary adenylate cyclase–activating polypeptide; VIP, vasoactive intestinal peptide.

CSU; however, given their presence in nearly 50% of patients, management approaches – especially those aiming to control psychosocial components – may constitute a substantial boon to individuals with CSU. Finally, publication bias remains a possibility (i.e. while we report a high prevalence, findings showing low prevalence may remain unpublished due to a file drawer effect).

Physiological mechanisms: bridging psychological factors with CSU

Several reports suggest that CSU may emerge through interactions between the nervous and immune systems (47). Symptoms result from mast cell activation, elicited through channels such as the hypothalamic–pituitary–adrenocortical axis (47), the sympathetic and adrenomedullary system (48) and local skin nerve fibres (49).

Other studies propose that stress-related mechanisms provide links to CSU. Animal models have shown that acute psychological stress results in cutaneous mast cell activation and links to the expression of corticotrophin-releasing factor (CRF) receptors (49). Although these receptors selectively release cytokines and other pro-inflammatory mediators, the findings suggest that administering anti-CRF prior to stress may inhibit mast cell activation (47). Human *in vitro* studies, examining basophil activation and serum cortisol concentrations as indications of stress, also reveal that basophils in CSU patients have heightened responses to CRF as well as adrenocorticotrophic hormone, and that CSU patients manifest higher levels of serum cortisol (42). Moreover, both the main CRF-R subtype in the human skin, CRF-R1, and histidine decarboxylase – the mast cell–related gene regulating the production of histamine – manifest more frequently in CSU than in normal foreskin, breast skin and cultured human keratinocytes (50).

Neuroendocrine mechanisms may also link psychological parameters to CSU exacerbation. Persons with CSU exhibit substantial decrease in dehydroepiandrosterone as well as in its sulphate derivative (DHEA-S). Whereas we know that the nervous system regulates the homoeostasis of the immune system wherein DHEA-S plays a role, it remains unclear whether lower circulating concentration of DHEA-S represents a primary phenomenon on its own or a secondary process associated with the illness response of different systems (i.e. bearing no direct contribution to the pathogenesis of urticaria) (48).

Direct interactions between mast cells and local skin nerve fibres pose another potential conduit for the emergence of CSU. Animal models reveal that neural stimulation, resembling stress, leads to the secretion of many neuropeptides capable of triggering mast cells, including substance P (SP), nerve growth factor (NGF), neurotensin (NT), pituitary adenylate cyclase–activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) (Fig. 3) (49).

Conclusion and future directions

Chronic spontaneous urticaria is a frequently occurring skin condition, associated with a severe societal burden and sorely lacking in effective treatment. In addition to our recent survey, indicating that almost 80% of Canadian allergists are of the opinion that psychological factors play a role in the pathogenesis of CSU (5), here we show that meta-analytic findings support the high prevalence of comorbidity between psychosocial factors and CSU. Although the high heterogeneity of the studies surveyed herein precludes a definitive conclusion ($I(2) = 97.60\%$), our pooled prevalence estimate of psychosocial factors in symptomatic patients suggests that such factors comprise close to 50% of CSU cases [46.21% (95% CI, 44.21%, 48.20%)]. Given that most studies exploring the role of psychological factors are either cross-sectional (15–24, 26–28, 31, 33, 36, 38–41) or traditional case–control studies (13, 14, 25, 29, 30, 32, 34, 35, 37, 42), future research should include randomized controlled trials, which would allow researchers to establish the effectiveness of behavioural interventions to treat psychosocial parameters. Even if psychological symptoms develop subsequent to CSU and play little or no part in its pathogenesis, the positive correlation between the disease and markers of poor psychological wellness (e.g. anxiety, alexithymia and low quality of life) indicates that psychotherapeutic treatments and behavioural interventions aimed at alleviating these problems may prove beneficial (34).

The findings show that suggestion and expectation can have beneficial effects in a number of clinical conditions (51), including in common dermatological conditions such as warts (52, 53) and chronic musculoskeletal pain syndromes (54). Such therapeutic suggestions can help control harmful habits, improve symptoms and provide both immediate and long-term relief (43). Only two studies, however, have explored the role of suggestion in CSU. In the early 1960s,

researchers used hypnosis with relaxation therapy in 15 adults with chronic urticaria, reporting that lesions cleared in six patients within 14 months, and improved in eight patients; 80% of subjects, moreover, reduced their intake of medication (55). In line with these results, a case study found that specific self-talk and relaxation techniques had significantly eased symptoms of urticaria in a young woman (56). Incorporating behavioural intervention techniques in the management of CSU therefore holds great potential to assuage symptoms and reduce the use of drugs with potential side-effects. Given the clinical impressions of allergists (5), the high value of heterogeneity, indexed by $I(2)$ and suggesting that the studies included in the present meta-analysis are difficult to compare, and the lack of effective pharmacological treatment options (4), randomized controlled trials exploring the benefits of psychological interventions in CSU are overdue. Establishing the efficacy of such potential interventions would be an enormous boon to patients, free up considerable medical resources and offer substantial financial savings as a function of reducing both direct and indirect expenses.

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Conflict of interest

All authors of this manuscript declare that they do not have a conflict of interest including relevant financial interests, activities, relationships and affiliation.

References

1. Zuberbier T, Asero R, Bindslev-Jensen C, Walter CG, Church MK, Gimenez-Arnau A et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009;**64**:1417–1426.
2. Zuberbier T, Asero R, Bindslev-Jensen C, Walter CG, Church MK, Gimenez-Arnau AM et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009;**64**:1427–1443.
3. Augey F, Gunera-Saad N, Bensaid B, Nosbaum A, Berard F, Nicolas JF. Chronic spontaneous urticaria is not an allergic disease. *Eur J Dermatol* 2011;**21**:349–353.
4. Ferrer M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. Alergologica 2005. *J Investig Allergol Clin Immunol* 2009;**19**(Suppl 2):21–26.
5. Ben-Shoshan M, Clarke A, Raz A. Psychosocial factors and the pathogenesis of chronic hives: a survey of Canadian physicians. *J Allergy Therapy* 2012;**3**:00–00.
6. Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol* 2008;**144**:35–39.
7. Buffet M. Management of psychologic factors in chronic urticaria. When and how? *Ann Dermatol Venereol* 2003;**130** Spec No 1:1S145–1S159.
8. Siegfried N, Muller M, Deeks J, Volmink J, Egger M, Low N et al. HIV and male circumcision–a systematic review with assessment of the quality of studies. *Lancet Infect Dis* 2005;**5**:165–173.
9. Sahiner UM, Civelek E, Tuncer A, Yavuz ST, Karabulut E, Sackesen C et al. Chronic urticaria: etiology and natural course in children. *Int Arch Allergy Immunol* 2011;**156**:224–230.
10. Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza BA, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999;**140**:446–452.
11. Wedi B. Urticaria. *J Dtsch Dermatol Ges* 2008;**6**:306–317.
12. Stokes JHT. The personality factor in psychoneurogenous reactions of the skin. *Arch Derm Syphilol* 1940;**42**:780–801.
13. Chung MC, Symons C, Gilliam J, Kaminski ER. The relationship between posttraumatic stress disorder, psychiatric comorbidity, and personality traits among patients with chronic idiopathic urticaria. *Compr Psychiatry* 2010;**51**:55–63.
14. Herguner S, Kilic G, Karakoc S, Tamay Z, Tuzun U, Guler N. Levels of depression, anxiety and behavioural problems and frequency of psychiatric disorders in children with chronic idiopathic urticaria. *Br J Dermatol* 2011;**164**:1342–1347.
15. Stokes JHT, Kulchar GV, Pillsbury D. Effect on the skin of emotional and nervous states. *Arch Dermat & Syph* 1935;**31**:470.
16. Graham DT, Wolf S. Pathogenesis of urticaria; experimental study of life situations, emotions and cutaneous vascular reaction. *J Am Med Assoc* 1950;**143**:1396–1402.
17. Wittkower ED. Studies of the personality of patients suffering from Urticaria. *Psychosom Med* 1953;**15**:116–126.
18. Shoemaker RJ. A search for the affective determinants of chronic urticaria. *Psychosomatics* 1963;**4**:125–132.
19. Miller DA, Freeman GL, Akers WA. Chronic urticaria. A clinical study of fifty patients. *Am J Med* 1968;**44**:68–86.
20. Fava GA, Perini GI, Santonastaso P, Fornasa CV. Life events and psychological distress in dermatologic disorders: psoriasis, chronic urticaria and fungal infections. *Br J Med Psychol* 1980;**53**:277–282.
21. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981;**104**:369–381.
22. Anasagasti JI, Peralta V, Harto A, Chinchilla A, Ledo A. Study of personality in patients with chronic urticaria using the 16-PF questionnaire. *Rev Clin Esp* 1986;**178**:177–180.
23. Sheehan-Dare RA, Henderson MJ, Cotterill JA. Anxiety and depression in patients with chronic urticaria and generalized pruritus. *Br J Dermatol* 1990;**123**:769–774.
24. Badoux A, Levy DA. Psychologic symptoms in asthma and chronic urticaria. *Ann Allergy* 1994;**72**:229–234.
25. Hashiro M, Okumura M. Anxiety, depression, psychosomatic symptoms and autonomic nervous function in patients with chronic urticaria. *J Dermatol Sci* 1994;**8**:129–135.
26. Pulimood S, Rajagopalan B, Rajagopalan M, Jacob M, John JK. Psychiatric morbidity among dermatology inpatients. *Natl Med J India* 1996;**9**:208–210.
27. Berrino AM, Voltolini S, Fiaschi D, Pellegrini S, Bignardi D, Minale P et al. Chronic urticaria: importance of a medical-psychological approach. *Eur Ann Allergy Clin Immunol* 2006;**38**:149–152.
28. Maniaci G, Epifanio MS, Marino MA, Amoroso S. The presence of alexithymia investigated by the TAS-20 in chronic urticaria patients: a preliminary report. *Eur Ann Allergy Clin Immunol* 2006;**38**:15–19.
29. Ozkan M, Oflaz SB, Kocaman N, Ozseker F, Gelincik A, Buyukozturk S et al. Psychiatric morbidity and quality of life in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2007;**99**:29–33.

30. Uguz F, Engin B, Yilmaz E. Axis I and Axis II diagnoses in patients with chronic idiopathic urticaria. *J Psychosom Res* 2008;**64**:225–229.
31. Silvares MR, Coelho KI, Dalben I, Lastoria JC, Abbade LP. Sociodemographic and clinical characteristics, causal factors and evolution of a group of patients with chronic urticaria-angioedema. *Sao Paulo Med J* 2007;**125**:281–285.
32. Malhotra SK, Mehta V. Role of stressful life events in induction or exacerbation of psoriasis and chronic urticaria. *Indian J Dermatol Venereol Leprol* 2008;**74**:594–599.
33. Staubach P, Dechene M, Metz M, Magerl M, Siebenhaar F, Weller K et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011;**91**:557–561.
34. Barbosa F, Freitas J, Barbosa A. Chronic idiopathic urticaria and anxiety symptoms. *J Health Psychol* 2011;**16**:1038–1047.
35. Yang HY, Sun CC, Wu YC, Wang JD. Stress, insomnia, and chronic idiopathic urticaria–a case-control study. *J Formos Med Assoc* 2005;**104**:254–263.
36. Sperber J, Shaw J, Bruce S. Psychological components and the role of adjunct interventions in chronic idiopathic urticaria. *Psychother Psychosom* 1989;**51**:135–141.
37. Engin B, Uguz F, Yilmaz E, Ozdemir M, Mevlitoglu I. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2008;**22**:36–40.
38. Sengupta B. A study of psychological and dermatophysiological aspects of chronic urticaria cases. *Indian J Dermatol* 1982;**27**:143–147.
39. Pasaoglu G, Bavbek S, Tugcu H, Abadoglu O, Misirligil Z. Psychological status of patients with chronic urticaria. *J Dermatol* 2006;**33**:765–771.
40. Vargas LE, Pena Payero ML, Vargas MA. Influence of anxiety in diverse cutaneous diseases. *Actas Dermosifiliogr* 2006;**97**:637–643.
41. Bashir K, Dar NR, Rao SU. Depression in adult dermatology outpatients. *J Coll Physicians Surg Pak* 2010;**20**:811–813.
42. Dyke SM, Carey BS, Kaminski ER. Effect of stress on basophil function in chronic idiopathic urticaria. *Clin Exp Allergy* 2008;**38**:86–92.
43. Broom BC. A reappraisal of the role of 'mindbody' factors in chronic urticaria. *Postgrad Med J* 2010;**86**:365–370.
44. Chung MC, Symons C, Gilliam J, Kaminski ER. Stress, psychiatric co-morbidity and coping in patients with chronic idiopathic urticaria. *Psychol Health* 2010;**25**:477–490.
45. Greenberg EN. The consequences of chronic pain. *J Pain Palliat Care Pharmacother* 2012;**26**:64–67.
46. Zirke N, Seydel C, Szczepek AJ, Olze H, Haupt H, Mazurek B. Psychological comorbidity in patients with chronic tinnitus: analysis and comparison with chronic pain, asthma or atopic dermatitis patients. *Qual Life Res* 2012; [Epub ahead of print].
47. Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E et al. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. *Endocrinology* 1998;**139**:403–413.
48. Kasperska-Zajac A. Does dehydroepiandrosterone influence the expression of urticaria?-A mini review. *Inflammation* 2010;**34**:362–366.
49. Theoharides TC, Donelan JM, Papadopoulou N, Cao J, Kempuraj D, Conti P. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol Sci* 2004;**25**:563–568.
50. Papadopoulou N, Kalogeromitros D, Staurianeas NG, Tiblalexi D, Theoharides TC. Corticotropin-releasing hormone receptor-1 and histidine decarboxylase expression in chronic urticaria. *J Invest Dermatol* 2005;**125**:952–955.
51. Raz A, Zephrani ZR, Schweizer HR, Marinoff GP. Critique of claims of improved visual acuity after hypnotic suggestion. *Optom Vis Sci* 2004;**81**:872–879.
52. Spanos NP, Williams V, Gwynn MI. Effects of hypnotic, placebo, and salicylic acid treatments on wart regression. *Psychosom Med* 1990;**52**:109–114.
53. Surman OS, Gottlieb SK, Hackett TP, Silverberg EL. Hypnosis in the treatment of warts. *Arch Gen Psychiatry* 1973;**28**:439–441.
54. Castel A, Cascon R, Padrol A, Sala J, Rull M. Multicomponent cognitive-behavioral group therapy with hypnosis for the treatment of fibromyalgia: long-term outcome. *J Pain* 2012;**13**:255–265.
55. Shertzer CL, Lookingbill DP. Effects of relaxation therapy and hypnotizability in chronic urticaria. *Arch Dermatol* 1987;**123**:913–916.
56. Fried RG. Nonpharmacologic treatments in psychodermatology. *Dermatol Clin* 2002;**20**:177–185.