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INVESTIGATIVE REPORT

Urticarial Dermographism: Clinical Features and Response to Psychosocial Stress

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Studies report that urticarial dermographism is exacerbated by "life events" and emotions. The aim of this study was to determine what aspects of life quality are affected by symptomatic dermographism and whether acute stress is a potential triggering factor. A total of 21 adult patients with urticarial dermographism completed a questionnaire on symptoms and quality of life. Twelve patients agreed to enrol in the study, which involved provocation by prick test and dermographism before and after a standardized psychosocial stress test (Trier Social Stress Test). Seventeen age-matched controls underwent corresponding tests. Of the patients answering the questionnaire, 43% reported that their disease had an impact on their quality of life and 33% that psychosocial stress precipitated the symptoms. However, the dermographic reaction in patients with urticaria factitia was not significantly intensified after the stress test. We conclude that the acute psychosocial stress test does not alter the magnitude of the dermographic reactions. ***Key words: urticaria factitia; dermographism; psychosocial stress; psoriasis; Trier Social Stress Test.***

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Urticaria is a group of disorders that share a distinct skin reaction pattern, i.e. the development of urticarial skin lesions (1). Apart from causing burning or itching it may limit activity and thus reduce quality of life. According to a survey on quality of life in 704 patients with the 10 most frequent skin diseases, chronic urticaria scored highest in the dimensions "social, leisure and work" (2). It has also been shown that psychological factors may contribute to flare-ups of urticaria at times of emotional stress (3).

A common approach to studying urticaria as a psychosomatic disease has been to evaluate the effect of stressful life events on its onset and exacerbation. Ninety percent (18 of 20) of patients with chronic urticaria reported a stressful life event immediately before the onset of illness (4). Stress, nervousness and exhaustion have been reported as factors exacerbating chronic urticaria in up to 77% of patients with chronic urticaria in different study series (5, 6). Occurrence of psychological distress, such as anxiety, depression or inadequacy, has been shown to be significantly more common in patients with chronic urticaria compared with those with a transient and short-lived skin disease, such as fungal infection (4). Studies have reported the successful use of relaxation, hypnosis and a combination therapy of psychotropic drugs and antihistamines in patients with chronic urticaria (7, 8). Hein et al. (9) reported that 29% of their 100 patients with chronic urticaria had depression. A British urticaria study group showed that patients with delayed pressure urticaria and cholinergic urticaria endure the greatest impairment of quality of life (10).

Dermographic urticaria or urticaria factitia is a chronic form of physical urticaria, with skin whealing occurring at sites of trauma, friction with clothing, or scratching (1). It has been reported to be the most common form of physical urticaria that is exacerbated by "life events" and emotions (11). Difficult life events coincided with exacerbation of urticaria factitia in 78% of 18 patients with this disorder, while emotions did so in 83% of patients (11).

The aim of the present study was to determine whether acute stress can aggravate urticarial dermographism, rather than simply elicit a subjective complaint of increased symptoms. While almost all research in this area is based on recall of past events, the present study aimed to determine whether a standardized psychosocial stress test influences the dermographic reaction and prick test reaction to histamine in patients with urticaria factitia. We compared these patients with healthy controls, and with psoriatic patients, known to respond to stress with flare up (12). The experimental part of this study is the first prospective investigation in urticarial dermographism dealing with the influence of stress on the cutaneous reactions.

MATERIALS AND METHODS

Subjects

Subjects were recruited through the register at the Department of Dermatology, which included 27 patients diagnosed with urticarial dermographism in the previous 14 months. A letter, together with a questionnaire containing 11 questions about the dermographism, was sent to all patients. Twenty-one responded (14 women and 7 men, age range 22–71 years,

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mean age 49 years). The patients were asked to answer the questionnaire and participate in a study with a psychosocial stress test, Trier Social Stress Test (TSST) (13) (for details see below). Twenty-one patients completed the questionnaire and 12 (mean age 50 years) who were interested in enrolling in the study also completed a written informed consent. Two of the patients participating in the experimental part of the study suffered from additional chronic urticaria. The patients were asked to stop their antihistamine therapy for one week before the experiments. Seventeen age-matched controls underwent corresponding tests except provocation of dermographism. Eight controls (mean age 38 years) were recruited from our sexually transmitted diseases (STD) clinic and 9 psoriatic patients (mean age 43 years) from our phototherapy unit. The psoriatic patients were on maintenance phototherapy, using only emollients and no corticosteroids.

The study was approved by the ethics committee of Lund University Medical Faculty.

Questionnaire

The questionnaire included information about the age of onset, duration of disease, precipitating factors and location of the eruption. Questions concerning the frequency, duration, and severity of attacks, and the extent to which dermographism affected lifestyle were also included. Patients were asked about personal and family history, including eczema, hay fever, asthma, and other forms of urticaria.

Experimental design

On arrival, the patients relaxed for 10 min and a basal sample of salivary free cortisol was taken. Prick tests were then conducted using physiological saline and histamine, dermographism was induced in urticaria factitia patients, and the results were documented. After having performed the TSST, the subjects were taken back to the laboratory, where prick tests again were conducted, dermographism was induced and the results documented. A sample of salivary free cortisol was taken when reported to be maximal, 20 min after the TSST (13). After the TSST, the participants were asked to evaluate how stressful the task was for them. A grading of the stress was performed by the examiner and was based on the report of the subjects and on an evaluation of their physiological symptoms, such as flushing or sweating. The scoring of the stress was: none at all (0), slight (1), moderate (2) or severe (3).

Salivary cortisol

Saliva from the subjects was collected using Salivette (Sarstedt, Rommersdorf, Germany) collection devices, and stored at room temperature until completion of the session. After centrifugation saliva was stored at –20°C until analysis. Cortisol in saliva was determined by radio-immunoassay (RIA) (Spectria, Orion Diagnostica, Espoo, Finland). The total coefficients of variation for this method were 7.9% and 5.9% at 7.0 and 32 nmol/l, respectively.

Prick test reaction

In order to be able to include control material we induced wheal and flare using a histamine prick test in both patients and controls before and after provocation with TSST. Histamine dihydrochloride, 10 mg/ml, and physiological saline (Soluprick, ALK, Denmark), were "pricked" into the volar aspect of the lower arm of each patient. Erythema was delineated after 5 min and infiltration was assessed after 20 min, when maximal. The flare was measured using planimetry. The volume of the wheal was calculated as the product of wheal area and depth (skin-fold thickness minus baseline/divided by 2) (14). When measuring the depth of the histamine reactions, saline-induced skin-fold thickness was used as baseline. The skin-fold thickness was measured using a low-tension spring-loaded calliper (Mitutoyo®, Neuss, Germany).

Dermographism

Testing for immediate dermographism consisted of stroking the skin of the upper part of the back with a calibrated dermographometer at a pressure of 3 kg/cm^2 (Fig. 1) (15). Two perpendicular 1.5 cm lines were drawn on the upper back, 3 times each, just at the upper border of the scapula. The stroked skin was observed for linear infiltration and surrounding flare, and assessed after 10 min (Fig. 2). The volume of the central part of the reaction was estimated by the product of the wheal area and depth; skin-fold thickness of the whealing where the 2 perpendicular lines crossed each other minus baseline (skin-fold thickness from the corresponding skin of the contralateral side of the back) divided by 2.

Psychosocial stress test

The TSST has repeatedly been found to induce profound endocrine and cardiovascular responses in 70–80% of the subjects tested (13). The patients were given an introduction to the TSST (2 min) and had about 10 min to prepare a speech on the subject "Application for a higher position within the same working place", to include leadership and greater responsibility for budget and results. Subjects were then taken to a conference room where they delivered the speech for 5 min in front of an audience of 2 people. A timer was placed on the table. The subjects were then subjected to a mental arithmetic task that involved subtracting 13 from 2322 and to continue subtracting 13 from each subsequent number. If they gave an incorrect answer they were asked to recount from the start of the task.

Statistical analysis and presentation of results

Reaction areas were given in mean values in mm^2 ±standard error of the mean (SEM), reaction volumes were given in mean values in mm^3 ±SEM, cortisol levels were given in mean values in nmol/l ±SEM. Wilcoxon matched pairs test and Wilcoxon rank-sum test were used for statistical analysis of intra- and inter-individual differences in response.

RESULTS

Questionnaire: clinical features and history of dermographism

Twenty-one patients (14 women and 7 men, age range 22–71 years, mean age 49 years) completed the ques-

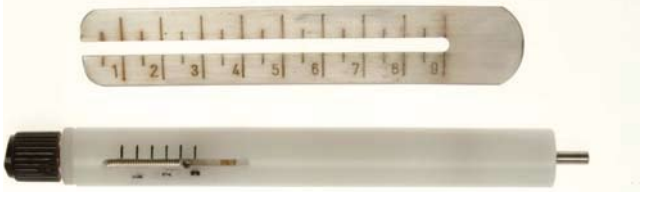

Fig. 1. Testing for immediate dermographism consisted of stroking the skin of the upper part of the back with a calibrated dermographometer at a pressure of 3 kg/cm^2.

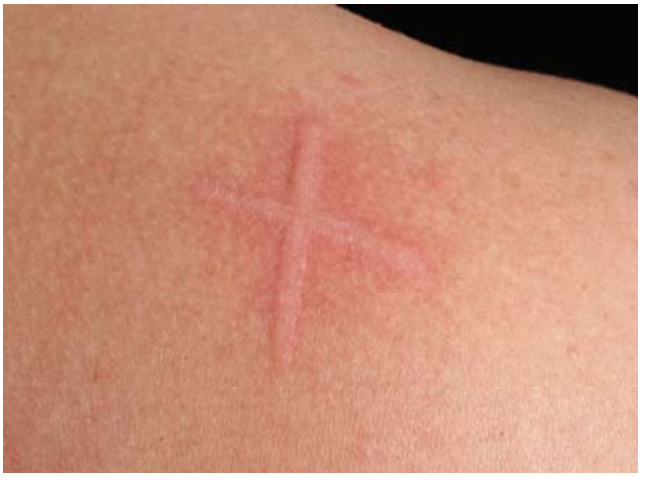

Fig. 2. Dermographic reaction 10 min after drawing 2 perpendicular 1.5-cm long lines on the upper back.

tionnaire. The age at onset ranged from 8 to 62 years, mean age 38 years. The duration of the disease was 1–61 years, mean duration being 11 years. Fifteen patients reported symptom-free periods, while others had continuous problems. Areas most commonly affected were extremities (19 patients), trunk (16), buttocks (10) and face (9). The precipitating factors were scratching (9), pressure (7), stress (7), tight clothes (6), shower (5), heat (5) and cold (3). The frequency was daily in 9 patients, weekly in 4 patients, monthly in 4 patients, and periodically in 4 patients. The severity of attacks was due to itching in 9 patients, burning in 8 patients and swelling in 4 patients. The associated symptoms mentioned were: frustration (2 patients), exhaustion (1 patient), swelling of fingers and face (1 patient) and itching and excessive body heat (2 patients). In response to the question concerning the extent to which dermographism affected lifestyle, 2 patients mentioned a restricted choice of clothing (not showing too much skin and not being tight), 3 reported restrictions with regard to showers or baths, 3 with regard to engaging in sport, and one mentioned deficient concentration. Eleven patients reported having chronic urticaria, 2 were atopic and 9 had a family history of atopy.

TSST and salivary cortisol levels (Table I)

Twelve patients (7 women, 5 men, aged 22–71 years, mean age 50 years) participated in the study on dermographism and stress provocation. Only one of them reported that her urticarial reactions were exacerbated by stress. In their TSST speech, the subjects had to explain why they were right for the job and request a higher salary. Some patients who were no longer working did not seem to get excited by a subject concerning an application for a job. Instead they were asked to think about and relate life events that made them feel anxious and angry. One patient talked about how she became burnt-out in her work and another explained how she had been cheated of her inheritance. Another patient talked about her hyperactive 5-year-old son, one patient talked about cutting off contact with her mother and yet another how he had been degraded at work. All subjects but one showed stress reactions during the speech test. Even after the arithmetic task most subjects reported stress or anger. Some flushed during the test, some reported sweating hands**.** Six patients with urticaria factitia expressed severe stress following TSST, 5 moderate and one slight stress reactions, resulting in an average score of 2.4±0.6. Salivary cortisol levels were not significantly increased (11.0±1.9 nmol/l vs. 9.4±1.7 nmol/l). The individual stress scores and concentrations of salivary cortisol are shown in Table I (subjects 1–12).

Two healthy controls showed severe stress following TSST, 4 moderate, one slight and one no stress at all, resulting in an average score of 1.9±1.0. Salivary cortisol

Table I. *Stress reactions (score 1–3) and salivary cortisol levels (nmol/l) in response to Trier Social Stress Test (TSST) in patients with urticaria factitia (no. 1–12), healthy controls (no. 13–20) and psoriasis patients (no. 21–29)*

			Cortisol		
Subjects	Sex	Age years	before TSST nmol/l	after TSST nmol/l	Stress score
Urticaria					
1	F	27	23.1	11.6	2
2	M	67	15.5	10.9	2
3	M	53	8.7	6.3	3
4	F	52	7.3	4.6	2
5	M	51	4.2	5.9	3
6	M	46	18.8	25.3	3
7	F	61	7.0	13.7	1
8	F	71	2.2	6.3	3
9	M	36	9.6	8.7	2
10	F	45	7.9	5.0	2
11	F	22	20.1	9.0	3
12	F	63	8.6	5.4	3
Mean		49.5±15.3	11.0±6.6	9.4±5.8	2.4±0.7
Controls					
13	F	50	1.5	3.8	3
14	M	72	4.3	5.6	2
15	M	24	13.2	5.6	2
16	F	22	13.4	6.6	1
17	F	23	3.3	3.3	2
18	M	22	14.6	10.6	2
19	F	30	12.9	12.7	0
20	F	25	20.0	16.7	3
Mean		33.5±18.1	10.4±6.5	8.1±4.7	1.9±0.9
Psoriasis					
21	F	21	12.7	5.2	3
22	M	54	4.9	2.5	3
23	F	30	16.8	5.5	3
24	F	77	19.1	7.6	3
25	F	48	NM	NM	3
26	F	54	3.8	3.7	3
27	F	28	3.6	2.6	2
28	F	32	1.3	3.7	2
29	M	46	5.8	2.3	3
Mean		43.3±17.6	8.5±6.7	4.1±1.8	2.8±0.4

NM: not measurable. This patient smoked and chewed gum. According to instructions she should not have smoked or chewed gum for 1 h before the TSST.

levels were not significantly changed (10.4±2.3 nmol/l vs. 8.1±1.7 nmol/l). The individual concentrations of salivary cortisol and stress scores are shown in Table I (subjects 13–20).

Five of 9 psoriasis patients participating in this study reported that their psoriasis was triggered by stress. Seven patients with psoriasis presented strong stress reactions following TSST and 2 moderate, resulting in an average score of 2.8±0.4. Salivary cortisol levels were significantly reduced following TSST (8.5±2.4 nmol/l vs. 4.1±1.8 nmol/l) (p=0.0001). The individual stress scores and concentrations of salivary cortisol are shown in Table I (subjects 21–29).

Dermographism and prick-test reactions

The dermographic reaction in urticaria factitia patients was not significantly intensified after the stress test (flare 564±83 mm^2 vs. 649±125 mm^2, p=0.6, and wheal 66±16 mm^3 vs. 94±23 mm,^{3} p=0.2), respectively) (not shown). Patients with urticaria factitia responded with significantly larger flare to the histamine prick test compared with healthy controls and psoriasis patients (1377±136 mm^2 vs. 794±98 mm^2 and 743±132 mm^2, respectively) (p=0.0014 and p=0.0056, respectively) (Fig. 3A). In comparison with healthy controls, the wheal induced by histamine prick test in urticaria factitia patients was significantly larger both before and after TSST (241±28 mm^3 vs. 126±25 mm^3, p=0.01 and 249±30 mm^3 vs. 121±30, p=0.03) (Fig. 3B). After TSST the flare and wheal of prick test reaction was unchanged compared with values before the test.

In healthy controls the flare and wheal reactions to the histamine prick test following stress provocation were not significantly increased (flare 794±98 mm^2 vs. 1034±181 mm^2 and wheal 126±25 mm^3 vs. 121±30 mm^3, respectively) (Figs. 3A and B).

Psoriatic patients showed unchanged flare in response to the histamine prick test, (flare 743±132 mm^2 vs. 687±149 mm^2) (Fig. 3A) while the wheal was reduced after the stress test (196±28 mm^3 vs. 78±13 mm^3) (p=0.004) (Fig. 3B).

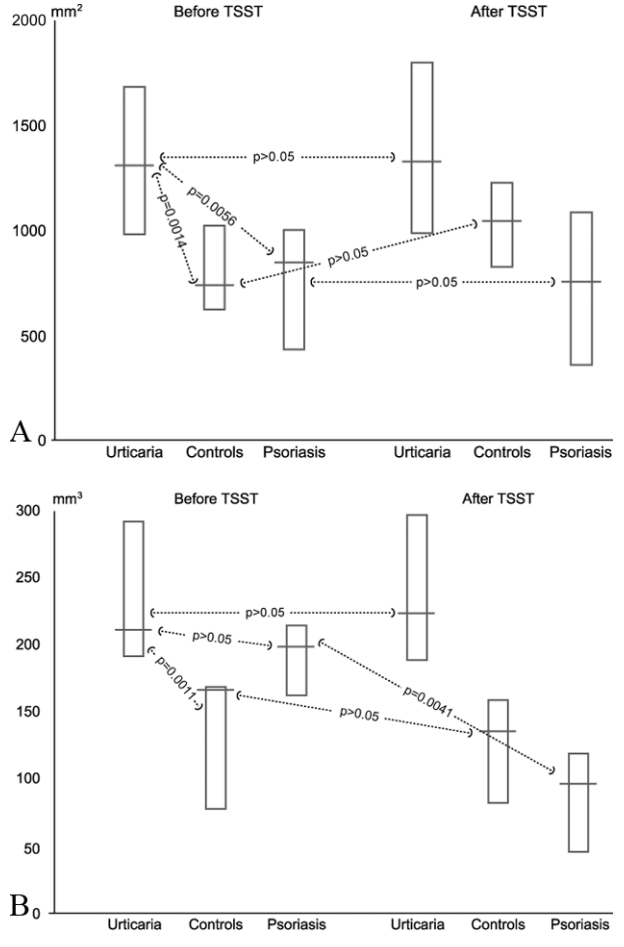

Fig. 3. (A) Area of the histamine flare and (B) volume of histamine wheal before and after Trier Social Stress Test (TSST) in urticaria factitia patients (n=12), controls (n=8) and psoriasis patients (n=9). The upper limit of the boxes corresponds to the 75th percentile and the lower limit to the 25th percentile. The horizontal lines denote the median values. p-values >0.05 were regarded as non-significant.

DISCUSSION

The results of the questionnaire suggest that urticaria factitia has an impact on everyday life, as 9 out of 21 patients reported that dermographism affected their choice of clothing, exercise, bathing or mental behaviour. Seven patients reported sensitivity to psychosocial stress, while 3 noticed frustration and exhaustion following the symptoms.

The urticaria factitia patients displayed stronger flare and wheal to histamine prick tests compared with controls and psoriatic patients. In urticaria factitia, trauma alone induces a wheal. In order to exclude the contribution of the shearing forces of the injections to the volume of the histamine wheal, saline-induced skinfold thickness was used as baseline when measuring the depth of the histamine reactions.

Stress provocation using the original TSST includes a speech on the subject "application for a higher position within the same workplace" (13). This topic caused stress in the younger participants, while it did not induce any deep concern in the already retired subjects. In such cases we interrupted the speech and asked the subjects to instead relate life events that made them feel anxious or angry. It was frequently difficult to stop the speeches because the participants became upset and wanted to finish their stories. TSST induced severe stress symptoms in 50% of the patients with urticaria factitia and the majority of those with psoriasis, while healthy controls stayed calmer. In this last group, salivary cortisol levels did not increase following psychosocial stress, in contrast to what has been found in other studies (13, 16, 17). The reason why normal controls did not respond

with a rise in salivary cortisol may be because the stressor was not severe enough in this group, which had the lowest stress score (1.9±1.0). Most of the patients with urticarial dermographism and those with psoriasis responded with higher stress scores (2.4±0.6 and 2.8±0.4, respectively). A lack of adjustment of cortisol response to stress has been reported in patients with psoriasis (18, 19) and may explain why these patients respond to psychosocial stress with flare up of the disease (12, 20). An attenuated cortisol response has also been described in children with atopic dermatitis (21). A common mechanism of blunted stimulation of hypothalamic-pituitary-adrenal axis in autoimmune diseases (22) may explain unchanged cortisol levels following TSST in our patients with urticarial dermographism.

Our data suggest that saliva cortisol levels alone can not be used to quantify the impact of TSST. Hypothetically, one would expect that transmitters of mood, such as serotonin, neuropeptide Y or substance P operating in the central nervous system, also act in the peripheral nervous system (23). Unmyelinated sensory nerve fibres localized mainly at the dermo-epidermal junction are the most peripheral free nerve fibres and constitute a functional unit with the mast cells, contributing to the neurogenic inflammation through neuropeptidergic transmitters (23). In a previous investigation, we studied wheal and flare responses to substance P injected intradermally before and just after a competitive endurance test (a handball match between top Swedish teams) lasting 45 min (24). The athletes displayed reduced flare responses but unchanged wheal following physical stress. However, in the present study, no subjects showed any alteration in the histamine prick test following social stress provocation. The difference in results compared with the study in athletes may be due to physical activity as a stressor and longer duration of the handball match compared with TSST.

In conclusion, although 33% of the patients answering the questionnaire reported that psychosocial stress amplified the symptoms of urticarial dermographism, the acute social stress test did not alter the magnitude of the dermographic reactions in the subgroup of factitia patients who volunteered for the experimental study. In addition, we found that saliva cortisol levels alone can not be used to quantify the impact of TSST.

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