

ORIGINAL ARTICLE

Psychosomatic or allergic symptoms? High levels for somatization in patients with drug intolerance

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ABSTRACT

Patients with dermatological diseases often have associated psychological problems. For patients with allergic diseases, only a few publications have focused on psychological aspects. The objective of this study was to assess the psychometric profile, including somatization, depression, anxiety and health-related quality of life (HRQoL), of patients suffering from drug intolerance or hymenoptera venom allergies. In a prospective cohort study design, patients who were admitted to hospital for a challenge test for an alternative drug ($n = 49$, 24.5% men) or for induction of desensitization therapy with hymenoptera venom ($n = 58$, 37.9% men) were included. Psychometric screening questionnaires focusing on somatization (Symptom Check List), depression and anxiety (Hospital Anxiety Depression Scale), and also on HRQoL (Short Form questionnaire) were assessed. The scores were compared with population scores and between the two groups. Both groups had significantly higher somatization scores ($P \leq 0.003$) than the normal population, and the challenge-test group had lower HRQoL than the normal population. Between-group analysis revealed significantly higher somatization scores in the challenge-test group ($P = 0.011$) and more impaired HRQoL (physical health domain $P < 0.001$). Anxiety/depression scores were not significantly different from those of the normal population, or between groups, although abnormally high scores for anxiety were frequent (18% and 12% for the challenge-test and allergy groups, respectively). Somatization, reduced HRQoL and anxiety seem to be part of the symptoms of patients with allergic diseases, especially for patients with drug intolerance. Standardized questionnaires could help to discover patients who may need psychological support. This may help to improve the patients' symptoms and quality of life.

Key words: allergy, anxiety, depression, psychometric profile, somatization.

INTRODUCTION

Patients with dermatological diseases often have associated psychological problems. One reason is the effect of the visibility of skin diseases in society. Moreover, dermatoses (e.g. atopic dermatitis) are known to be aggravated by psychological stress.¹ The role of psychological comorbidity in dermatological diseases has been demonstrated in several studies reporting that the diseases place them at greater risk of depression and suicide (e.g. for acne

vulgaris and psoriasis patients).^{2,3} For dermatology inpatients, it has been shown that 38% had a recommendation for psychotherapy after examination by a psychosomatician.⁴ Although awareness of the problem of psychological comorbidity in dermatology has increased in clinical routines in the last 10 years, psychological help is not often offered to patients.⁵

Most publications on the psychometric profiles of patients with allergies focus on those with allergic rhinitis. An association with anxiety is frequently described, and prevalence is between 19% and

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24%.^{6,7} There is also a negative association with the physical, psychological and social dimensions of health-related quality of life (HRQoL), both for generic and disease-specific measures.^{8–10} It has been shown that patients suffering from allergic rhinitis tend to somatize and have higher levels of depression.^{8,11} The latter has been revealed for urticaria patients also.¹² Other diseases are often thought to be allergic by the patients but are possibly psychogenic in origin; examples include so-called “environmental illness” or “multiple chemical sensitivity” and many of the amalgam “allergies”. In these groups, there are high levels of somatization and depression.^{5,13,14}

Few investigations have focused on patients with drug intolerance or with type 1 allergies with more severe clinical symptoms. Retamales¹⁵ found that patients allergic to drugs had more psychological disorders than allergic rhinitis and asthma patients. For patients reporting having experienced an allergic reaction to local anesthetics especially, investigations have shown that the reactions are often anxiety-induced events, for example consulting a dentist or surgeon, and not caused by allergy.^{16–18} The opposite is true for patients who have an anaphylactic reaction after an insect sting. In most of these cases, a hymenoptera venom allergy can be proved by laboratory and skin tests. Knowledge of the psychometric profile of different patients, for example their level of anxiety or tendency to somatization, enables treatment to be adapted to their specific needs.

The objective of this study was, therefore, to assess the tendency to somatization, depression and anxiety, and, in addition, the HRQoL, of patients with either intolerance of analgesics and/or local anesthetic drugs or with a hymenoptera venom allergy and were admitted to hospital for a challenge test for an alternative drug or induction of desensitization therapy with hymenoptera venom, respectively. These two groups were chosen because they differ in the respect that – in contrast with patients with a hymenoptera venom allergy – the allergic or pseudoallergic cause of drug intolerance is hard to prove.

We hypothesized that psychometric scores: (i) would differ from those of the normal population for both groups; and (ii) would differ between the two groups, with worse scores for those being admitted to hospital for a challenge test.

METHODS

Patients and ethics

The study was approved by the ethics committees of the local medical council (no. 837.185.06 [5283]) and of the local university (no. 2008-304E-MA). All patients signed an informed consent form after being given written and oral information by the study physician (J. C. H.).

Included in the study were two groups of allergy inpatients. The first group were patients who were admitted to hospital for a challenge test for an alternative substance after likely or possible allergic or pseudoallergic reaction to a local anesthetic or analgesic (called the “challenge-test group”). The second group (called the “desensitization-therapy group”) were inpatients who received desensitization therapy because of a proven allergy to hymenoptera venom. These two groups were chosen because in the first an allergic cause is often difficult to prove and psychological factors could be involved in the clinical symptoms reported whereas the allergic origin of a hymenoptera venom allergic patient is easily proved by laboratory and skin tests. Diagnosis of hymenoptera venom allergy was based on a positive prick and radioallergosorbent test; diagnosis of drug intolerance was based on the typical medical history with urticaria, edema and/or vegetative symptoms after drug exposure. As is usual for drug intolerance, results from the prick or scratch test for the tested analgesics and/or local anesthetics were negative. Nevertheless, the patient was exposed to an alternative drug in the challenge test.

In a prospective cohort study design, all these patients of the Department of Dermatology, Ludwigshafen City Hospital, Ludwigshafen, from August 2006 to September 2007 and of the Department of Dermatology, University Hospital Mannheim, Mannheim, from September 2008 to July 2009 were asked to participate.

Questionnaires

Age, sex, consultation of psychological and/or psychiatric help at any time in life (yes/no), actual stress felt (yes/no) and total number of medications were recorded. The psychometric profile was assessed with the help of well-described psychometric screening instruments focusing on somatization,

depression, anxiety and, additionally, on HRQoL. The questionnaires were completed by the patients themselves but monitored for completeness afterwards. Questions with missing answers were asked again, face to face.

Initial screening for tendency to somatization was performed with the somatization subscale (12 items) of the Symptom Check List in the German version (SCL-SOM).^{19,20} Depression and anxiety were assessed with the depression and anxiety scale of the Hospital Anxiety Depression Scale in the German version (HADS, 7 items each).^{21,22} HRQoL was measured with a generic measure of HRQoL, the Short Form questionnaire in the abbreviated, validated German version (SF-12).²³

Scoring the scales

For analysis, a mean for the SCL-SOM was calculated, from answers coding 0 = “not at all” to 4 = “very strong”. The answers were added to give a total score and then divided by the number of items. The scores for the HADS dimensions anxiety and depression were calculated in accordance with the recommendations of the HADS.²² For SF-12, the two scores for the main dimensions physical health (physical component summary SF-PCS) and mental health (mental component summary SF-MCS) were calculated by using an SPSS syntax file.²³

Statistical evaluation

Missing answers were replaced with the most frequent answer of the respective scale. No more than one missing answer was allowed per scale; if more than one was missing the questionnaire was excluded. Cronbach's alpha or the split-half correlation, respectively, were calculated to estimate the reliability of the scales. The results from the challenge-test and desensitization-therapy groups were analyzed in two ways: (i) they were compared with values from representative samples of the German population; and (ii) the results from the challenge-test and desensitization-therapy groups were compared.

Comparison with the German population

The SCL-SOM mean scores were compared with the mean values for the German population evaluated in a representative sample (women 0.55, men 0.38).²⁴ We chose sex-specific and not age-specific mean

values for the German population because the SCL-SOM mean differed by only 0.08 between age groups 16–30 and 31–60 years, and sex seemed to be more important in this respect. For each participant, the difference between the observed value and the comparison value for the normal population was calculated. With a one-sample Student's *t*-test, the difference was tested to zero to assess whether the observed values differed statistically significantly in one direction from the comparison values (difference scores were tested by use of the Kolmogorov–Smirnov test for normal distribution).

The HADS scores were compared with a value calculated by use of the formula provided by the German norming study: HADS anxiety = $0.026 \times \text{age} + 0.69 \times \text{sex} + 3.09$ and HADS depression = $0.079 \times \text{age} + 0.15 \times \text{sex} + 0.73$ (sex: men “0”, women “1”).²⁵ For each participant, the difference between the observed and calculated HADS scores was calculated and again a one-sample Student's *t*-test to zero was performed. In addition, the percentage of participants exceeding a score of 10, described as indicative of non-normal anxiety or depression, was also calculated.

For SF-12, the age-dependent comparison values for the German population provided in the SF manual were taken, because age is more important than sex in this respect, especially for the SF-PCS.²³ Again, a difference was calculated for each group of participants and a Student's *t*-test was performed.

Between-group analysis

Between-group differences for the possible confounders age, sex, stress, psychological help and number of medications were tested (χ^2 -test, Student's *t*-test and Mann–Whitney *U*-test where appropriate). Because, according to the Kolmogorov–Smirnov test, all scores were in non-normal distribution, a non-parametric Mann–Whitney *U*-test was used to assess the significance of group differences. Differences between percentages for non-normal anxiety and/or depression scores were evaluated by use of the χ^2 -test.

All analyses were performed with SPSS version 16.0.1. The level of probability for statistical significance was set to $\alpha = 0.05$. Because of the explorative nature of the study design, alpha was not corrected.

RESULTS

During the study period, 127 patients met the study inclusion criteria. Eighteen patients were not reported to the principal investigator and were, therefore, not contacted, and two patients refused to participate, resulting in a total of 107 patients (84.3%). Although questions with missing answers were asked again immediately, in two HADS, two SF-12 and seven SCL-SOM one answer was missing and had to be replaced. In one SCL-SOM, more than two answers

were missing and the questionnaire was excluded from further analysis.

Details of the study groups are listed in Table 1. Of the 49 patients in the challenge-test group, only one patient reacted to the tested alternative drug. No significant difference occurred between the groups. Details of the main target variables are given in Table 2. Cronbach's alpha was 0.81 for SCL-SOM. The split-half correlation (Spearman–Brown-corrected) was 0.86 for HADS anxiety and 0.83 for HADS depression. For SF-12, the split-half correlation

Table 1. Details of the study groups and results from testing of the homogeneity of the groups

	Challenge-test group (<i>n</i> = 49)	Desensitization-therapy group (<i>n</i> = 58)	Test	Significance
Mean age (standard deviation)	51.9 (13.5)	52.6 (13.7)	Student's <i>t</i> -test	0.806
Sex (%)				
Men	24.5	37.9	χ^2 -Test	0.137
Women	75.5	62.1		
Stress (%)				
Yes	34.8	22.4	χ^2 -Test	0.162
No	65.2 (3 missing)	77.6		
Consultation for psychological help (%)				
Yes	23.4	10.3	χ^2 -Test	0.071
No	76.6 (2 missing)	89.7		
Median number of medications (25%/75% quartile)	1 (0/3)	0 (0/1)	Mann–Whitney <i>U</i> -test	0.094

The challenge-test group and desensitization-therapy group did not differ significantly in respect of age, sex, consultation for psychological and/or psychiatric help at any time in life, actual felt stress and total number of medications ($P > 0.05$). Explanation of median and 25%/75% quartiles: the 25% quartile cuts off the lowest 25% of the distribution, the 75% quartile cuts off the highest 25%. The median (50% quartile) represents the middle of the distribution when arranging all the data in order.

Table 2. Details of the scale scores and results of tests between the groups

	Challenge-test group (<i>n</i> = 49)	Desensitization-therapy group (<i>n</i> = 58)	Test	Significance
HADS anxiety median score (25%/75% quartile)	5 (3/9)	5 (2/8)	Mann–Whitney <i>U</i> -test	0.409
HADS depression median score (25%/75% quartile)	3 (1/7)	3 (1/5)	Mann–Whitney <i>U</i> -test	0.450
Percentage (<i>n</i>) of non-normal HADS anxiety scores (>10)	18.4 (<i>n</i> = 9)	12.1 (<i>n</i> = 7)	χ^2 -Test	0.363
Percentage (<i>n</i>) of non-normal HADS depression scores (>10)	4.1 (<i>n</i> = 2)	1.7 (<i>n</i> = 1)	χ^2 -Test	0.462
SCL-SOM median score (25%/75% quartile)	0.96 (0.42/1.42)	0.54 (0.33/0.92)	Mann–Whitney <i>U</i> -test	0.011
SF-MCS median score (25%/75% quartile)	49.2 (37.9/58.7)	54.3 (44.8/57.9)	Mann–Whitney <i>U</i> -test	0.373
SF-PCS median score (25%/75% quartile)	41.9 (30.7/51.7)	52.4 (41.0/55.5)	Mann–Whitney <i>U</i> -test	<0.001

Explanation of median and 25%/75% quartiles: the 25% quartile cuts off the lowest 25% of the distribution, the 75% quartile cuts off the highest 25%. The median (50% quartile) represents the middle of the distribution when arranging all the data in order. The challenge-test group and desensitization-therapy group differed significantly in respect of SCL-SOM and SF-PCS; the challenge-test group had a higher tendency to somatization (0.96–0.54, $P = 0.011$) and more impaired health-related quality of life (SF-PCS 41.9–52.4, $P < 0.001$). HADS, Hospital Anxiety Depression Scale; SCL-SOM, Somatization Scale of Symptom Check List; SF-PCS, physical component summary of SF-12; SF-MCS, mental component summary of SF-12.

Table 3. Comparison of study group scores with scores for the normal population

Group	Scale	Mean score differences between study groups and the German population (95% confidence interval)	Significance	Direction of difference between study group and German population
Challenge-test group (<i>n</i> = 49)	SCL-SOM (1 missing)	-0.52 (-0.71/-0.32)	<0.001	Higher level for study group
	HADS anxiety	-1.2 (-2.4/0.1)	0.062	Higher level for study group
	HADS depression	0.8 (-0.3/1.8)	0.165	Lower level for study group
	SF-PCS	7.2 (4.1/10.3)	<0.001	More impaired in study group
	SF-MCS	4.0 (0.7/7.2)	0.017	More impaired in study group
Desensitization-therapy group (<i>n</i> = 58)	SCL-SOM	-0.20 (-0.34/-0.07)	0.003	Higher level for study group
	HADS anxiety	-0.5 (-1.5/0.6)	0.378	Higher level for study group
	HADS depression	1.51 (0.6/2.4)	0.010	Lower level for study group
	SF-PCS	-1.0 (-3.5/1.4)	0.399	Less impaired in study group
	SF-MCS	1.4 (-1.0/3.9)	0.250	More impaired in study group

The table shows the differences between the scale scores for the study population and those for the normal population. The score for the study population was subtracted from the reference value for the population; negative values were indicative of higher scores in the study population. For example, in the challenge-test group, the mean SCL-SOM score was 0.52 higher than for the normal population, within a 95% confidence interval of 0.32–0.72. This difference was statistically significant ($P < 0.001$). HADS, Hospital Anxiety Depression Scale; SCL-SOM, Somatization Scale of Symptom Check List; SF-PCS, physical component summary of SF-12; SF-MCS, mental component summary of SF-12.

(Spearman–Brown-corrected) was 0.76 for SF-MCS and 0.82 for SF-PCS.

Comparison with the German population

In both groups, the tendency to somatization was significantly greater than in the population sample (Table 3). HRQoL was more impaired for both domains in the challenge-test group only, namely, for patients with drug intolerance. Median anxiety levels were no higher than in the normal population. In the challenge-test and desensitization-therapy groups, however, 18.4% and 12.1%, respectively, had a non-normal level of anxiety exceeding a score of 10 (Table 2). For depression, there was a trend toward lower scores in the desensitization-therapy group; only 1.7% of patients with hymenoptera venom allergies had non-normal depression (4.1% in the challenge-test group). In the German normal population, 10% exceeded a score of 10 with regard to depression and 5% (men)/10% (women) with regard to anxiety.

Between-group analysis

For patients with drug intolerance and those with hymenoptera venom allergies, SCL-SOM and SF-PCS scores were significantly different (Table 2). The challenge-test group had a higher tendency to somatization and more impaired HRQoL. There were no differences between anxiety and depression scores or in the mental health domain of HRQoL.

DISCUSSION

Both hypotheses could be accepted, meaning, first, that the psychometric profiles of patients with drug intolerance or hymenoptera venom allergy differ from those of the normal population and, second, that psychometric profiles differ between these two groups of patients. The results reveal that somatization is important in both investigated groups, and especially in patients with drug intolerance. Somatization is defined as expression of psychological distress as physical symptoms which often dramatically suggest a physical disorder. This confronts the clinician with the situation of not knowing whether the symptoms presented were mainly related to somatization or caused by the allergy. An allergic cause is easy to reveal in patients with hymenoptera venom allergy, but somatization can make it especially difficult to discriminate between allergic and psychosomatic symptoms for patients with drug intolerance. The clinician should therefore assess somatization as a matter of routine. In the event of high scores, a psychological consultation should be initiated. This may help to facilitate identification of symptoms which are primarily somatic or psychogenic. This is emphasized by the finding that these patients felt impaired in the physical health domain of HRQoL, matching the elevated somatization scores. Patients should therefore be informed about the association of allergies/pseudo-allergies and psychological disorders so they gain

motivation and lose inhibition in accompanying psychological therapy. It has been shown that patients with food intolerance and urticaria are significantly more motivated to accept psychosocial support than those with insect venom allergies and drug intolerance.²⁶ This could improve treatment, and may improve quality of life accordingly. Although depression was not frequently present in both groups, a substantial percentage of subjects had non-normal anxiety levels. Although the HADS questionnaire asks patients to answer the questions for the last week, elevated scores for anxiety could, of course, be affected by the fact they have been admitted for a challenge test with an alternative drug or for desensitization therapy, and must be interpreted within these limits. Screening for anxiety could therefore help to identify those patients who may benefit, during treatment, from therapy which reduces anxiety.

As far as the authors are aware, somatization and anxiety have not been investigated in patients with drug intolerance. Berino *et al.* examined a group of 50 patients with drug intolerance for the occurrence of depression, by using the Zung Depression Inventory, and hysteria, by using the Minnesota Multiphasic Personality Inventory (MMPI), reduced version. They found elevated scores for hysteria, especially in patients with milder reactions, and no significantly elevated scores for depression. Interestingly, they did not see a significant difference between patients with or without a positive reaction to placebo.²⁷ Our findings using the HADS depression questionnaire support this finding. It has been shown that of patients who attended allergy clinics because of a reaction to local anesthetics, only a minority could be proved to be truly allergic to the substance or the preservatives they contained.^{17,18} The authors concluded that the reactions had, therefore, to be psychogenic, driven by anxiety during a dental or surgical procedure; they did not, however, perform a psychometric evaluation. Knowledge of the increased anxiety of such patients should avoid reactions to medications, especially local anesthetics, being called “allergies” as first choice, leading to treatment with less effective anesthetics. Oude-Elberink *et al.* found increased anxiety scores measured by the Spielberger State-Trait Anxiety Inventory (STAI), in 29% of patients allergic to hymenoptera venom. In our patient group, only 12% of patients had a non-normal anxiety level.²⁸

Study strengths and weaknesses

The strength of the study is the prospective study design, including all potential subjects, without selection bias, and with an acceptable response. Furthermore, the availability of reference values from the normal population enables classification of the results in addition to the between-group analysis. A disadvantage of the study design is that all the assessments were only screening instruments which do not replace psychological or psychiatric diagnosis. However, previous studies have revealed that psychological diagnosis and the results of the screening instrument were highly correlated (e.g. for anxiety).⁶ Furthermore, the relatively small number of subjects limits the general nature of the finding and did not enable further analysis of the challenge-test group. It should be a matter of future research to assess possible differences between psychometric profiles of patients being admitted to hospital for a challenge test with and without reaction to a placebo test.

Conclusions

Bearing in mind the limitations of the study, screening for somatization and anxiety can be recommended for patients with allergic symptoms after drug intake, especially, and with hymenoptera venom allergy. Psychological consultation, if required, could consequently be of help to the patient, by monitoring and reducing psychological symptoms, and to the clinician, by possibly facilitating discrimination between allergic/pseudoallergic and psychosomatic symptoms.

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