Stress, Insomnia, and Chronic Idiopathic Urticaria — A Case-Control Study

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Background and Purpose: There is growing evidence that stress might play a crucial role in the pathogenesis of urticaria. This study examined the association between chronic idiopathic urticaria and stress from major life events and explored the validity of the biopsychosocial model of stress as it relates to urticaria.

Methods: A total of 75 consecutive cases with chronic idiopathic urticaria and 133 controls with tinea pedis who visited a dermatologic clinic for treatment were recruited for participation in this study. Subjects in both groups were assessed with a semi-structured questionnaire to determine the number and subjective weighting of major life events, somatic symptoms, insomnia, irregularity of daily life, perceived family support, ego-function, positive coping, and negative coping. Structural equation modeling was used to examine the influence of biologic, psychologic, and social factors on the development of urticaria. Cluster analysis was used to classify subjects according to risk of developing urticaria.

Results: In the 6 months preceding disease onset, patients with chronic idiopathic urticaria had significantly more life events, higher subjective weighting of impacts from life events, more somatic symptoms, more severe insomnia, less family support, more negative coping tendencies, and were younger in age. Good ego-function, coping strategies and family support were associated with decreased frequency of urticaria.

Conclusions: Stress is an important risk factor for the development of chronic idiopathic urticaria while positive coping tendencies and good family support appear to have preventative effects. Insomnia might be the most important psychosomatic symptom that is a predisposing factor for chronic urticaria.

Key words: Adaptation, psychological; Risk factors; Sleep disorders; Stress; Urticaria

J Formos Med Assoc 2005;**104**:254-63

Urticaria is a troublesome disease that manifests as wheals which are edematous, pink or red, usually pruritic, and surrounded by a bright red flare. The current clinical classification of urticaria is categorized into ordinary urticaria, physical urticaria, contact urticaria, urticaria vasculitis, and angioedema.[1] Physical urticarias include those induced by pressure, cold, vibration, sunlight (solar urticaria), water (aquagenic urticaria), exercise, emotional or heat stress (cholinergic urticaria), or stroking and rubbing (dermographism). Contact urticaria is defined as urticaria which is induced by biologic or chemical skin contact. Urticarial vasculitis is defined by vasculitis as shown by skin biopsy. Ordinary urticaria is defined as recurrent or episodic urticaria, which is not categorized above. The histologic features of the wheals consist of dermal edema, dilation of blood vessels, and a mild perivascular infiltrate. The perivascular infiltrate is composed mainly of monocytes and $CD4^+$ T lymphocytes. Other cells may also be found, including mast cells, eosinophils, and neutrophils.[2] Chronic urticaria is defined as the occurrence of widespread wheals daily or almost daily for at least 6 weeks.[3] The term chronic idiopathic urticaria indicates exclusion of urticarial vasculitis, predominant physical urticarias, and known causative foods or drugs. A previous study estimated that chronic urticaria was idiopathic in about 70% of patients.[4]

Stress was found to play a major etiologic role in many somatic and mental illnesses. In dermatology, the association between psychologic factors and dermatologic disorders has been noted for several decades.[5] Gupta et al[6] first reported that depression could modulate pruritic perception in chronic idiopathic

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Received: 15 March 2004 Revised: 24 May 2004 Accepted: 5 July 2004

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urticaria. Later, Fava et al[7] and Andrews[8] found that patients with chronic urticaria were exposed to significantly more stressful life events in the 4-6 months prior to disease onset. Badoux and Levy[9] further reported that patients with chronic idiopathic urticaria had more psychologic symptoms including somatization, obsessive-compulsive, anxiety, depression, hostility, paranoid ideation, and psychotism. These emotional disturbances were especially prominent in women compared with men.

Studies also showed that social support reduced or buffered the deleterious effects of stress by altering the perception of a situation or facilitating more appropriate coping.[10,11] In Taiwan, Chen et al[12] found that somatic symptoms and emotional disturbance were positively correlated with the number of life events but negatively correlated with good ego-function and family support. Moreover, they found that the severity of psychosomatic symptoms was positively associated with the number of life events and negative coping tendency.[13] Unfortunately, most of the aforementioned studies on chronic idiopathic urticaria only dealt with 1 of these major determinants and usually omitted to consider the complex reciprocal influences between them. Buffet[14] systematically reviewed the literature concerning psychologic factors associated with chronic urticaria during 1970-2002 and found that very few controlled studies were published and no study has evaluated psychological support, psychotherapies, behavioral therapies, technique of biofeedback and group therapies. He concluded that a complementary psychologic evaluation of patients suffering from chronic idiopathic urticaria is necessary.

In the present investigation, we endeavored to consider all of these possible psychologic factors and adopted the Stress Model[15] as a theoretical framework, which is summarized in Fig. 1. This model integrates biologic, psychologic, and social factors simultaneously. In this model, "stress" is a dynamic process generated from the interaction between life events and the person's coping reaction. When a life event happens, acting as a stressor, individuals cognitively appraise whether the event is threatening their existing resources. If environmental or outside demands are found to be overwhelming, they perceive themselves as being under stress. At almost the same time, the psychologic, physiologic and emotional reactions of the person under stress are automatically aroused. These automatized reactions interact with each other and are influenced by the person's personality traits, psychologic needs, and perceived social support.

In our clinical observations, patients with chronic idiopathic urticaria often had stressful life events and experienced a period of insomnia prior to disease onset. Moreover, antihistamines with a stronger sedative effect seemed more effective in treating patients with chronic idiopathic urticaria than those without such an effect. The purpose of this study was to examine the association between chronic idiopathic urticaria and stress from major life events and to explore the validity of the biopsychosocial mechanisms of the stress model using structural equation modeling. Finally, the influence of insomnia as a major psychosomatic symptom during the pathogenesis of chronic urticaria was also investigated.

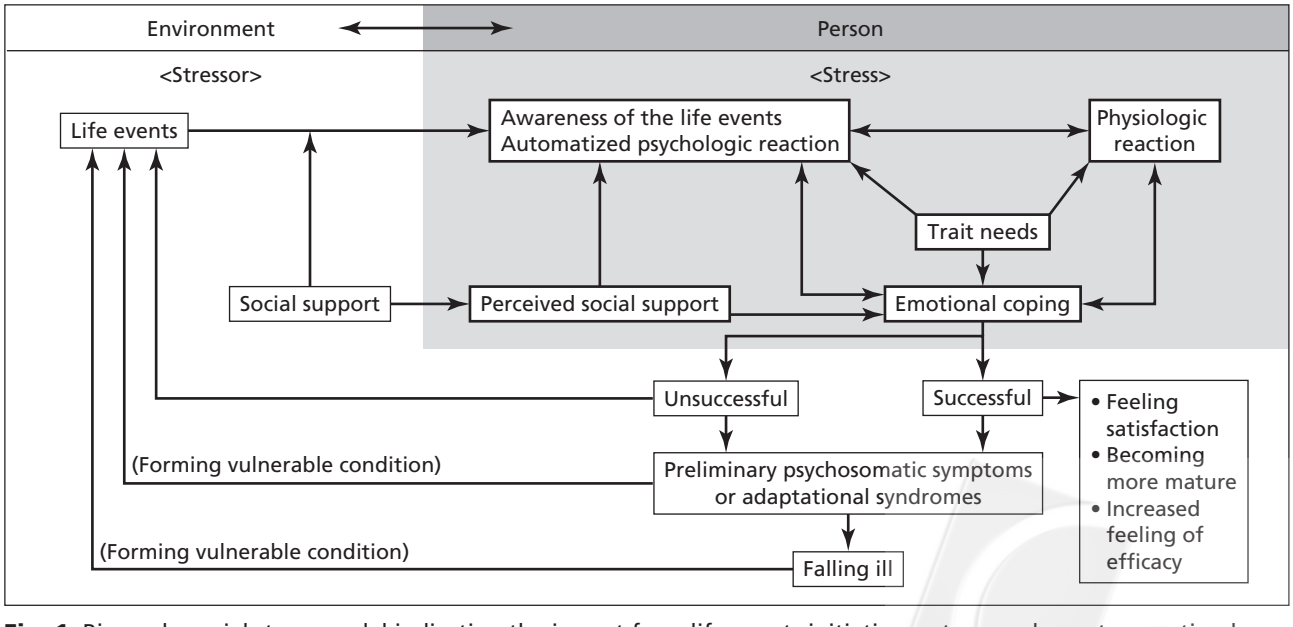

Fig. 1. Biopsychosocial stress model indicating the impact from life events initiating a stress and counter-reaction by an individual's coping strategies and social support.

Methods

Subjects

A total of 75 consecutive outpatients with chronic idiopathic urticaria who visited the Dermatological Clinics at National Taiwan University Hospital from October 1999 to February 2000 were enrolled as the case group. The diagnostic criteria for chronic idiopathic urticaria were as follows: 1) presence of skin lesions for longer than 6 weeks; 2) no known allergic or physical causes of urticaria. To rule out allergic or physical causes, all possible allergens — including medications, cold drinks, seafoods, hot water shower or bath, pregnancy, sunlight, and water, were all listed in the questionnaire. Patients with chronic urticaria were requested to recall the description events associated with the onset of urticaria. If a patient believed the onset of urticaria could be attributed to some allergic or physical causes, he/she was then excluded from the chronic idiopathic urticaria case group. In addition, 133 consecutive patients with tinea pedis who visited the same clinics were invited to serve as the control group. Tinea pedis patients with hyperhidrosis were excluded to prevent potential confounding from psychologic factors related to this condition. After examination by experienced dermatologists to confirm the diagnosis, all participants were immediately referred to a trained interviewer.

All subjects were asked to complete a semi-structured questionnaire with contents including Major Life Events Survey, Somatic Symptoms Checklist, Psychosomatic Symptoms Inventory, Insomnia Scale, Irregularity Index of Daily Life, Family Support Index, Ego-function Index, Positive Coping Checklist, and Negative Coping Checklist. Data were collected in a blind and independent manner. All of the above scales were pre-tested on 20 patients first. Items with unclear meaning identified in the pretest were replaced with a more definite description. The scoring methods for each specific questionnaire were based on both the prior knowledge and the final results of factor analysis and item analysis.

Somatic Symptoms Checklist

This checklist of symptoms, adopted from Cheng and Wu,[16] includes 41 general somatic complaints such as fatigability, weakness, neck soreness, lumbago, insomnia, muscle cramps, headache, dizziness, nausea, epigastralgia, loose stool, chest tightness, constipation, and palpitation, etc. The intensity of each somatic symptom was assessed for the 6-month period prior to disease onset. Respondents rated how frequently each symptom was experienced during the 6 months prior to disease onset on a 4-point scale ranging from 0 (never or none of the time) to 3 (more than once in a week). All ratings were summed to determine a total frequency score. The higher the score, the more frequent and severe the somatic complaints were during the 6 months prior to onset.

Major Life Events Survey

The Major Life Events Survey was administered to cover the 6-month period prior to the onset of dermatologic symptoms. This survey consists of 41 events such as loss of job, quarrel with boss or supervisor, sudden increase of one's occupational duty, aggravation of financial difficulty, retirement, change of school, facing a crucial examination, falling in love, getting married or divorced, pregnancy, hospitalization of oneself or spouse, etc. This instrument was modified from the study of Cheng and Wu,[16] and was designed for use by ethnic Chinese. Its clinical validity and reliability have been established in several studies in the Taiwanese population.[12,16,17] In this study, we also conducted a factor analysis before applying this instrument and found that its 3 major components were job, schooling, and family-related affairs. Besides indicating whether they had experienced each of the 41 events during the past 6 months prior to disease onset, subjects were also asked to rate the subjective feeling of impact of each event on a 4-point scale comprising 0 (not at all), 1 (mild), 2 (moderate), and 3 (severe). The total sum of all the ratings was used as an indicator representing the subjective impact of life events.

Insomnia Scale

This scale was applied to assess the severity of insomnia during the 6 months prior to disease onset. The insomnia scale was adopted from the scale used in Liu's study,[18] which was originally translated and modified from Coren's insomnia scale.[19] The scale was designed to measure self-reported sleep disturbance with 6 specific indices, including delayed sleep-onset latency, frequent night wakening, frequent nightmares, restlessness, early morning awakenings, and subjective feelings of tiredness upon awakening. Each item was assessed using a 5-point scale, ranging from "never" to "always". A higher score indicates a more disturbed sleep pattern. The internal consistency coefficient of this scale using Cronbach's alpha was 0.69 in this study.

Irregularity Index of Daily Life

Completing the Major Life Events Survey is often time-consuming and relatively inconvenient. As subjects' regular activities are often disturbed to some extent when they are facing stressful life events, we developed a new questionnaire to assess irregularity of daily life

and examined its correlation with the indicator of life events inventories. In this study, respondents were asked to rate the irregularity of activities in the 6-month period prior to disease onset, including: time of going to sleep, time of waking up, time of eating breakfast, time of eating lunch, time of eating dinner, time of arriving at the workplace, and time of leisure activities. Each activity was rated on a 5-point scale ranging from 0 (less than 15% irregularity) to 4 (more than 85% irregularity). A higher cumulative score indicated greater irregularity of life in the 6-month period prior to disease onset. The Cronbach's alpha coefficient of this instrument was 0.88 in this study.

Ego-function Index, Family Support Index, and Psychosomatic Symptoms Inventory

This integrated questionnaire was adopted from the research of Wu et al[20] and was composed of 3 subscales, including the Ego-function Index (9 items), the Family Support Index (10 items), and the Psychosomatic Symptoms Inventory (14 items). The Ego-function Index was used to assess the general coping and problem solving strategies in stressful circumstances. The Family Support Index was used to assess perceived family resources and support in daily life. The Psychosomatic Symptoms Inventory was derived and modified from Brief Symptom Rating Scale, and consisted of psychologic dimensions of somatization, obsession, depression, anxiety, hypoprosexia, notion of suicide, amnesia, hostility, phobia, and hypochondriasis. Respondents rated the frequency with which they agreed or disagreed with each statement on a scale ranging from 1 (never) to 4 (always). To determine the scoring method for each subscale, factor analysis was performed with principal axis extractions followed by oblique Promax rotation at first.

Items of the subscales were extracted in accordance with the factor loading and under supervision of the person who originally devised this scale. These 3 extracted subscales accounted for 61.3% of the total variance of the integrated total scale in this study. The results of this study corroborated the original construct validity of these 3 subscales. Cronbach's alphas of the 3 subscales were 0.81, 0.93, and 0.69, while that for total score was 0.75.

Ways of Coping Checklists

Subjects' general coping styles were assessed using the Ways of Coping Checklists, which were adopted from the research of Wu and Dum.[21] This scale consists of 37 items divided into 2 subscales: the Positive Coping Checklist and the Negative Coping Checklist. The Positive Coping Checklist can be used to determine how often good coping strategies were used to cope with stressors in previous experiences and the Negative Coping Checklist can be used to assess how often poor coping strategies were used. Respondents rated the degree to which they agreed or disagreed with each statement regarding their coping strategies used over the 6 months prior to the onset of symptoms.

A 4-point scale ranging from 1 (not at all like) to 4 (very much like) was used. A higher cumulative score of each subscale denotes greater predisposition to that type of coping strategy. Factor analysis with principal axis extractions followed by oblique Promax rotation was used to test the construct validity. Two factors, positive coping and negative coping, were successfully extracted and showed good construct validity. They accounted for 41% of the total variance. The internal consistency reliability using Cronbach's alpha coefficient was 0.72 for the overall scale and 0.88 *vs* 0.87 for the 2 subscales.

Statistical analysis

Because of the ordinal nature of our measurements, Mann-Whitney *U* test was used to determine the difference between the case and control groups. Spearman's rank-order correlation was used to examine the relation between ordinal scale variables. If variables were nominal dichotomous in nature, *phi* correlation was applied. Independent sample *t* tests were used to compare mean numbers of life events between groups. After looking at the frequency distribution for these indices, cut-off values were set for the high and low level groups for different scales or subscales. Mantel-Haenszel common odds ratios were calculated to examine the predictive effect for each factor.

All significant ($p < 0.05$) determinants in univariate analyses were then initially selected for the stepwise multivariate regression analysis. As we found that linear regression analysis was not suitable for the data because of the high degree of collinearity and reciprocal interaction, cluster analysis[22] was performed to determine the "high risk pattern", which may represent a higher odds ratio of developing chronic idiopathic urticaria. First, the extent of agglomeration and number of clusters were determined by a hierarchical cluster analysis using the between group linkage method. Then, subjects were grouped by the non-hierarchical K-means method. Values of determinants put into the cluster analysis were all standardized according to Z score.

Finally, structural equation modeling[23] was used to construct a framework, which could disclose the complex interaction between each biologic, psychologic, and social determinant.

Table 1. Demographic and clinical characteristics of the cases and controls.

	Chronic idiopathic urticaria	Control (tinea pedis)	*p* value (2-tailed)
Total number	75	133	
Female (%)	53 (70.7)	56 (42.1)	0.000*
Number of life events (± standard deviation [SD])			
Before onset of illness	1.5 (±1.7)	0.6 (± 1.1)	0.000†
After onset of illness	0.4 (±1.0)	0.2 (± 0.7)	0.277†
Mean duration to date (months) [± SD]	37.7 (± 58.9)	98.8 (± 127.3)	0.000†
Age (%)			0.000‡
≤ 29	27 (36)	13 (10)	
30-39	17 (23)	24 (18)	
40-49	18 (24)	37 (28)	
50-59	8 (11)	27 (20)	
≥ 60	5 (7)	32 (24)	
Education (%)			0.140‡
Junior high school (≤ 9 years)	12 (16)	22 (17)	
Senior high school (10-12 years)	24 (32)	27 (21)	
College or over (> 12 years)	39 (52)	83 (63)	
Marital status (%)			0.003*
Married	41 (55)	98 (74)	
Single	31 (41)	23 (17)	
Divorced or separated	2 (3)	3 (2)	
Death of spouse	9 (1)	9 (7)	
Employment status (%)			0.133*
Currently employed	50 (67)	83 (63)	
Retired	6 (8)	23 (17)	
Student	9 (12)	7 (5)	
Housewife	10 (13)	17 (13)	
Unemployed	0 (0)	2 (2)	
Household income (New Taiwan Dollars)			0.071‡
< 30,000	18 (24.3)	27 (20.5)	
30,000-49,000	23 (31.1)	31 (23.5)	
50,000-100,000	28 (37.8)	52 (39.4)	
> 100,000	5 (6.8)	22 (16.7)	

* Pearson chi-squared.
† *t* test.
‡ Mann-Whitney *U* test.

Results

Demographic characteristics

Cases with chronic idiopathic urticaria were significantly younger than controls (chi-squared test for trend, $p < 0.005$). The majority of cases were female, a significantly higher percentage than controls ($p < 0.05$). Patients in the control group had higher education, income, and a higher percentage were married and employed, as summarized in Table 1.

Reported life events and symptoms

Cases reported a significantly higher number of life events than controls in the 6 months prior to symptom onset. Moreover, cases had a significantly higher sum of subjective weighting scores of event impact than controls (Table 2). Compared with controls, cases also experienced significantly more severe somatic and

Table 2. Comparisons of mean rank score for different psychologic tests between cases and controls.

	Urticaria cases	Control group	*p* value
Subjective weighting of life events	125.8	92.5	0.000*
Somatic symptoms	117.1	96.6	0.018*
Score of insomnia	118.2	96.8	0.014*
Irregularity of daily life	90.8	81.9	0.262*
Perceived family support	87.1	113.4	0.002*
Psychosomatic symptoms	112.9	94.1	0.027*
Ego-function	99.8	104.8	0.560*
Positive coping	91.8	110.0	0.035*
Negative coping	74.1	56.3	0.007*

* Mann-Whitney *U* test.

Table 3. Crude odds ratios of different risk factors for urticaria.

	Cases (number)	Controls (number)	Odds ratio (95% CI)*
Gender			
Female	53	56	3.31 (1.81-6.06)
Male	22	77	
Age (years)			
< 40	44	37	3.68 (2.03-6.68)
≥ 40	31	96	
Number of events			
≥ 1	46	45	3.10 (1.72-5.58)
0	29	88	
Subjective weighting of events			
≥ 1	43	39	3.24 (1.79-5.85)
0	32	94	
Somatic symptoms			
≥ 27	34	36	2.21 (1.22-4.01)
< 27	41	96	
Insomnia			
≥ 21	12	5	4.88 (1.65-14.45)
< 21	63	128	
Family support			
< 30	37	40	2.33 (1.29-4.18)
≥ 30	37	93	
Psychosomatic symptoms			
≥ 21	34	34	2.33 (1.27-4.25)
< 21	40	93	
Positive coping			
< 60	56	78	2.15 (1.14-4.06)
≥ 60	18	54	
Negative coping			
≥ 32	33	32	2.46 (1.18-5.13)
< 32	18	43	

* Mantel-Haenszel common odds ratio estimate.
CI = confidence interval.

psychosomatic symptoms (especially insomnia), a more irregular daily life, perceived lower family support and had a tendency toward negative coping strategies.

Crude odds ratio of each determinant

Based on an evaluation of the frequency distribution of each risk factor, a threshold value of score was set and a crude odds ratio was calculated for each factor. As shown in Table 3, female gender, young age, confronting major life events, perceived low family support, low positive coping and high negative coping tendency were risk factors for urticaria. In particular, insomnia was found to be the most important factor with an odds ratio of 4.9 (95% confidence interval [CI], 1.7-14.5), which corresponded well to our clinical impressions.

Correlation analysis

Table 4 shows the Spearman's rank correlation matrices between each determinant. Urticaria onset was significantly correlated with the number of pre-onset events, the sum of subjective weighting scores of event impact, negative coping, insomnia, somatic symptoms, and psychosomatic symptoms. By contrast, older age, male gender, better coping strategies, and stronger family support were negatively associated with the onset of chronic idiopathic urticaria. These correlation associations were consistent with our theoretical hypothesis.

Multiple regression analysis

Initial stepwise regression analysis employed somatic symptoms as the dependent variable and set number of events, gender, score of family support, positive coping, negative coping, and insomnia as independent variables. The first model equation was as follows:

(Score of somatic symptoms) = 1.94 + 0.82 (insomnia) + 2.71 (number of events) + 0.42 (score of negative coping), with an $R^2 = 37.3\%$.

The score of psychosomatic symptoms was then employed as the dependent variable and the number of events, gender, age, and scores of family support, positive coping, negative coping, insomnia, and subjective weighting of events were entered into the regression. The selected best model was:

Table 4. Spearman rank correlation matrices for score results of different psychologic tests.

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
I. Numbers of life events	1												
II. Subjective weighting of events	0.94†	1											
III. Somatic symptoms	0.28†	0.29†	1										
IV. Score of insomnia	0.20†	0.26†	0.43†	1									
V. Irregularity of daily life	0.17‡	0.18‡	0.27†	0.31†	1								
VI. Psychosomatic symptoms	0.32†	0.34†	0.49†	0.61†	0.34†	1							
VII. Family support	–0.26†	–0.30†	–0.27†	–0.38†	–0.27†	–0.48†	1						
VIII. Ego-function	–0.05	–0.10	–0.27†	–0.44†	–0.22†	–0.46†	0.60†	1					
IX. Positive coping	–0.15‡	–0.16‡	–0.15‡	–0.23†	–0.21†	–0.40†	0.54†	0.59†	1				
X. Negative coping	0.22†	0.25†	0.38†	0.41†	0.35†	0.51†	–0.33†	–0.53†	–0.53†	1			
XI. Onset of urticaria*	0.31†	0.30†	0.17‡	0.17‡	0.09	0.16†	–0.21†	–0.04	–0.15‡	0.24†	1		
XII. Gender (male)*	–0.09	–0.12	–0.20†	–0.19†	0.01	–0.20†	0.16‡	0.06	–0.01	–0.13	–0.28†	1	
XIII. Age	–0.27†	–0.26†	–0.03	–0.06	–0.15‡	–0.17‡	0.16‡	0.05	0.23†	–0.30†	–0.36†	0.23†	1

* Correlation coefficients between nominal dichotomous variables are *phi* coefficients.
† $p < 0.01$ (2-tailed).
‡ $p < 0.05$.

Table 5. Number of life events and psychologic characteristics for 3 clusters of cases and controls.

	Cluster 1	Cluster 2	Cluster 3	*p* value (ANOVA)
Total numbers	93	95	20	
Numbers of events	0.5	0.9	3.1	0.000
Somatic symptoms	15.0	21.1	58.8	0.000
Insomnia	-0.3	6.6	20.3	0.000
Family support	32.8	28.9	24.7	0.000
Negative coping	26.1	34.5	40.4	0.000
Age	4.7	3.6	2.7	
No. of cases/no. of controls	16/77	46/49	13/7	0.000‡
Odds ratio*	1	4.5 (2.3-8.8)†	8.9 (3.1-25.9)†	

* Odds ratio = odds for urticaria in the cluster/odds for urticaria in cluster 1.
† 95% confidence interval.
‡ Pearson chi-squared test.
ANOVA = analysis of variance.

(Psychosomatic symptoms) = 17.75 + 0.32 (insomnia) – 0.22 (family support) + 0.16 (negative coping) + 0.59 (number of events), with an $R^2 = 54\%$.

Cluster analysis

Table 5 shows the summarized results of cluster analysis. Subjects were classified into 3 clusters based on the risk of developing urticaria and the identified features of each cluster. Cluster 3 was defined as the high-risk group and had an odds ratio of 8.9 (95% CI, 3.1-25.9) for developing chronic urticaria comparing with cluster 1, which was defined as the low-risk group. Cluster 2 was defined as middle risk and had an odds ratio 4.2 compared with cluster 1. Comparison of these clusters revealed that the high-risk group was characterized by younger age, more frequent major life events before disease onset, more somatic symptoms, suffering from more severe insomnia, receiving the least family support, and having the highest negative coping tendency in dealing with stressors (Fig. 2).

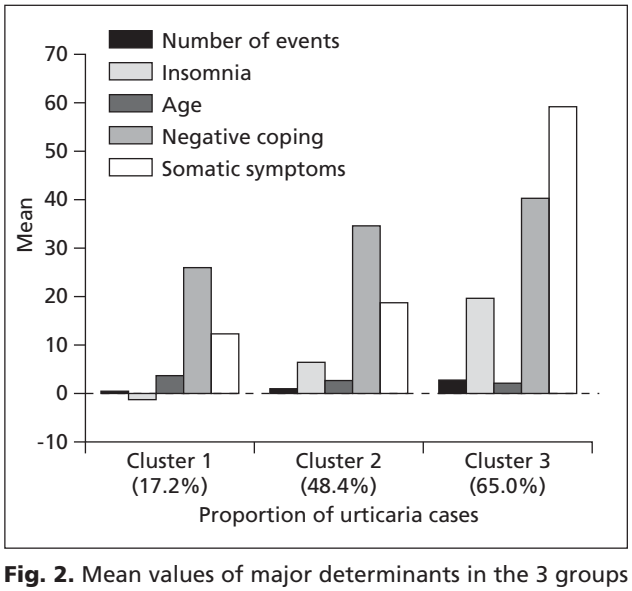

Fig. 2. Mean values of major determinants in the 3 groups identified by cluster analysis. Clusters based on different likelihoods of developing chronic idiopathic uticaria. Clusters 1, 2 and 3 indicate low, middle and high risks.

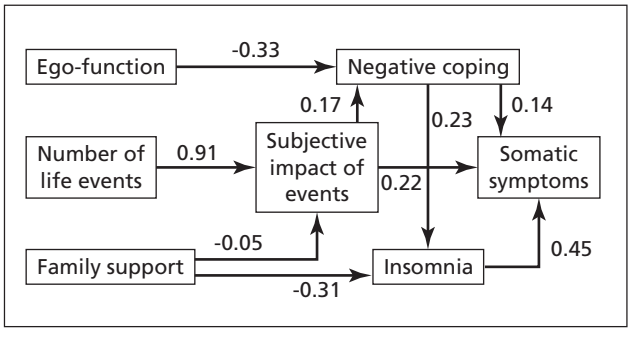

Fig. 3. Structural equation model showing the direction and magnitude of effect of each factor suggests a casual association between major life events and the development of somatic symptoms. χ^2 with 8 degrees of freedom = 7.35 ($p = 0.50$).

Structural equation modeling

Structural equation modeling with Linear Structural Relationships by the Method of Maximum Likelihood estimates[24] was applied to validate the conceptual framework of our study. The chi-squared statistic for goodness of fit was 7.35 with 8 degrees of freedom ($p = 0.50$). These results suggested an association between stress and the development of somatic symptoms. Negative coping tendency and insomnia aggravated the stress reaction, while good ego-function and family support seemed to counteract such a tendency, as shown in Fig. 3.

Discussion

This study showed that patients with chronic idiopathic urticaria were younger, encountered more life events before disease onset, subjectively felt a stronger impact from these life events, suffered from higher scores of somatic and psychosomatic symptoms, experienced less family support, and showed poorer

coping strategies than controls. A statistical association, however, does not necessarily imply a causal association and a careful scrutiny into alternative hypotheses should be carried out. A previous study found that about 30% of chronic urticaria was reported to be associated with foods and their additives, drugs, inhalants, infections, pressure, sunlight, cold, and heat.[25] In the selection of cases with chronic idiopathic urticaria, we deliberately excluded those with allergic diathesis and autoimmune diseases, by means of a detailed history review instead of checking serum immunoglobulin E (IgE), antinuclear antibody, C3 or C4. This was because studies suggested that total IgE might not be very useful in allergologic investigation without testing Anti-Fc epsilon RI alpha autoantibody,[26] and there was no consistent finding in levels of serum C3 and C4 for cases with chronic urticaria.[27,28] Hepatitis B virus, hepatitis C virus, or *Helicobacter pylori* infections have been suggested to be associated with some subsets of chronic urticaria.[29,30] Evidence for this, however, was not conclusive, and a routine screening was not recommended.[31,32] Despite detailed analysis of medical history that excluded patients with exposure to any known etiologic agents, some of the cases might still have been caused by unknown allergens. But a random misclassification would lead toward the null[33] and generally underestimate the effect of stress. These considerations suggest that these agents would have a limited confounding effect on our causal model.

In most life-event related studies, data collection usually involves retrospective reporting of events that might produce possible confounding. To reduce the likelihood of such a bias in the recalling of life events, we incorporated the findings of a comprehensive review of previous studies involving Taiwanese culture, and included only more important events for which the greatest percentage of the population would have a long-lasting memory, as mentioned in the Methods section. Trivial events were not included in the questionnaire in order to minimize the potential for recall bias, especially when the control subjects were also patients with skin disease. Our study subjects recruited from the dermatologic clinic included a higher proportion of females and younger people, which is consistent with previous reports.[34] This similarity of our findings to previous studies supports that the likelihood that selection bias was low in this study.

Another important finding of this study was the impact of insomnia on urticaria, which was rarely noted in previous studies. In our stepwise multiple regression analysis, insomnia was the first variable entered and it accounted for about 80% of the explainable variance in the model. The importance of insomnia was also supported by univariate crude odds analysis and cluster analysis. The structural equation model shown in Fig. 3 revealed that life events worked through negative coping strategy and poor family support to produce insomnia, which preceded the onset of other somatic symptoms. Although Alper claimed that the preponderance of published evidence supports equivalence in the efficacy of sedating and non-sedating antihistamines for chronic urticaria,[35] a trial from Germany involving 51 patients showed that the sedating antihistamine, azatadine, was more effective than the non-sedating antihistamine, terfenadine.[36] Thus, it appears that insomnia might be an important psychosomatic symptom that predisposes to the development of chronic urticaria and that treatment of insomnia might block the ongoing vicious cycle in a selected group of patents.

The pathogenic mechanisms of urticaria are not well understood, but the primary effector cell seems to be the mast cell or monocyte.[37] Release of mast cell mediators can cause inflammation and accumulation and activation of other cells, including eosinophils, neutrophils, and possibly basophils. Recent work has demonstrated that about one-third of patients with chronic idiopathic urticaria have circulating functional histamine-releasing anti-Fc epsilon RI alpha autoantibodies that bind to the high-affinity IgE receptor.[38] There are several findings suggesting mechanisms for the role of stress in urticaria. Stress was found to be associated with disease onset by activation of the sympathetic and adrenomedullary system and the hypothalamic-pituitary-adrenocortical (HPA) axis.[39] In acute stressful situations, both the adrenocortical and medullary systems are activated, leading to enhanced release of cortisol and catecholamines. But chronic stress may induce hyporesponsiveness of the HPA axis whereby cortisol secretion is attenuated and leads to increased secretion of inflammatory cytokines that are typically counter-regulated by cortisol.[40,41] Thus, chronic stress can result in some inflammatory disorders, such as chronic idiopathic urticaria, in which degranulation and mediator release from mast cells and possibly basophils were also reported.[42] Insomnia itself may further disturb the circadian rhythm of the secretion of cortisol[43] and precipitate the vicious cycle of chronic urticaria.

Our study found that female gender was an important risk factor for chronic idiopathic urticaria, with an odds ratio of 3.31 (95% CI, 1.81-6.06). These findings resemble those of other studies, which showed that chronic urticaria was twice as common in women as in men.[44,45] Since there has been no biologic hypothesis to support a gender predisposition for chronic urticaria, we looked for a possible mechanism from a psychosocial viewpoint. After

stratifying data by gender, we noted that females with urticaria had more somatic symptoms (60.6 *vs* 48.6, $p = 0.048$), more severe insomnia (61.6 *vs* 48.7, $p = 0.033$), less family support (46.2 *vs* 62.2, $p = 0.007$), and less positive coping (47.7 *vs* 59.9, $p = 0.042$) in comparison with female controls. In contrast, males with urticaria only showed a higher score of negative coping (37.6 *vs* 24.0, $p = 0.005$). Stratification of cases by age also revealed that young patients with urticaria (aged < 40 years) had more somatic symptoms (46.1 *vs* 43.9, $p = 0.033$) and less family support (34.0 *vs* 49.3, $p = 0.003$) compared with older controls. In contrast, older patients (aged ≥ 40 years) showed more severe insomnia (76.7 *vs* 59.9, $p = 0.028$) and higher scores of negative coping (37.5 *vs* 25.5, $p = 0.017$). These findings suggest that the influences of age and gender were associated with differences in social support and personal coping ability. When facing stressful life events, younger patients and females tended to obtain less family support and had poorer coping ability, which might have predisposed them to the development of urticaria. This analysis provides additional insight into the clinical management of chronic idiopathic urticaria.

In recent decades, life stress has been shown to be among the major determinants of skin disease. Psychosocial factors may interact synergistically with conventional risk factors. As there might be reciprocal and complex interactions among these factors, determination of the magnitude of their effects are problematic, and may not be adequately resolved by simple multiple regression analysis because of factor collinearity. In this study, we tried to define these multidimensional factors as a "risk pattern", and attempted to predict the onset of idiopathic chronic urticaria under specific risk patterns through cluster analysis. This method could provide impetus for developing algorithms that integrate psychosocial factors and conventional risk factors. Our findings suggest that the use of cluster analysis combined with structural equation modeling may be a useful tool to investigate the interaction of psychologic and conventional factors in the development of disease. Such an analysis is consistent with the biopsychosocial model, which postulates that stress coming from life events can produce somatic and psychosomatic symptoms, especially insomnia, if the affected person does not have a favorable coping strategy or perceives that family support is insufficient.

Conclusion

The results of this study provide support for the theory that stress is associated with the onset of chronic idiopathic urticaria, and that this risk is buffered by good ego-function, coping strategies, and family support. Our findings further suggest that insomnia might be the most important psychosomatic symptom that predisposes to the onset of urticaria.

ACKNOWLEDGMENTS: This work was supported by grants NHRI-GT-EX89P504P and NHRI-EX93-9204PP from the National Health Research Institutes. We appreciate the able assistance provided by Drs Wang, Wu, and Sun and the support provided by dermatologists of National Taiwan University Hospital.

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