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Report:

Investigation of stressful life events in patients with systemic sclerosis*

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Abstract: Objective: To assess the occurrence of stressful life events in the year before the initiation of systemic sclerosis. Methods: A consecutive series of 40 patients with systemic sclerosis (mean age (56.3±11.9) years, mean disease duration (4.3±3.1) years; 32 females and 8 males), including 28 with diffuse cutaneous scleroderma and 12 with limited cutaneous scleroderma, were evaluated. A control group of 40 healthy subjects free of systemic sclerosis also was included. Socioeconomic status was investigated and Paykel's interview for recent life events (a semi-structured research interview covering 64 life events) was conducted. Results: Patients with systemic sclerosis showed higher percentages of lower education (72.5%) and working class (82.5%), and reported more stressful life events ($P<0.05$), such as exits ($P<0.05$), undesirable events ($P<0.01$), and uncontrolled events ($P<0.001$), when compared with the control. More events that had an objective negative impact ($P<0.001$) were also reported in systemic sclerosis patients than in the control. These results are in accordance with a multifactorial model of pathogenesis in systemic sclerosis. Conclusion: We reported a strong relationship between stressful life events and the initiation of systemic sclerosis. Our findings are consistent with current understanding of the extensive links of behavioral responses to stress with neurophysiological and biochemical processes.

Key words: Systemic sclerosis (SSc), Life events, Stress, Pathogenesis
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INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease and a chronic and potentially life threatening condition characterized by vascular abnormalities and fibrosis of the skin and multiple organs (Steen and Medsger, 2000). Pain and functional impairment are common during its course. The skin changes are disfiguring, and immunologic disturbances are usually associated with these findings. Many factors, such as environmental factors, can lead to immunologic system disturbances and vascular changes. We hypothesize that social and psychological stresses may also trigger these disturbances and changes. However, few data on the prevalence of negative life events in patients with SSc are available. Only two studies evaluated the relationship between educational levels and SSc (Moser *et al.*, 1993; Edwards *et al.*, 2006). The two studies, conducted in the US and using self-reported educational levels, reported that the low level of formal education was a risk factor for adverse outcomes of SSc. The aim of the present study was to explore the relationship between stressful life events and the development of SSc, using Paykel (1997)'s interview method (a semi-structured research interview covering 64 life events).

PATIENTS AND METHODS

Patients

A total of 40 patients with SSc (mean age (56.3±11.9) years, mean disease duration (4.3±3.1) years; 32 females and 8 males), including 28 with

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diffuse cutaneous scleroderma and 12 with limited cutaneous scleroderma, were included in the study. Patients were admitted to the Department of Internal Medicine in the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, between December 2002 and December 2007 for a routine follow-up evaluation of SSc. Their diagnoses of SSc met the American College of Rheumatology criteria (Masi *et al*., 1980). Patients admitted for a recent complication related to organ involvement were not eligible for the study.

For those patients, the following epidemiological data were recorded: age, disease duration, previous psychopathology, current treatments, and socioeconomic status. Scleroderma was further categorized as diffuse or limited scleroderma as defined by LeRoy *et al*.(1988). Skin ulcers and arthritis were routinely examined during the physical examination. Interstitial lung disease was evaluated by lung function testing and computed tomography of the chest, and upper gastrointestinal tract involvement was examined by endoscope. The following laboratory tests were carried out: serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies, and anti-Scl 70 antibodies. Goldthorpe and Hope (1974)'s occupational classification was used to distribute the patients into two categories (middle-upper social class and working class), and evaluate their education levels (Archenholtz *et al*., 2001). A control group of 40 normal healthy subjects attending an outpatient clinic of our hospital was subsequently included, being matched for age (in decades), sex, marital status, and characteristics of non-communicable diseases such as hypertension and hyperlipidemia. All patients and control subjects gave informed consent after the procedures of the study were explained.

Investigation of life events

Paykel (1997)'s interview for recent life events covering 64 well defined life events was administered as a semi-structured research interview, with each event being carefully inquired about unless it clearly did not apply. All patients and control subjects were seen by the same interviewer. Detailed questioning was carried out to determine the exact nature and full circumstances of each event reported. On the basis of this account, two ratings were made: (1) the objective negative impact (contextual threat), in which raters made a judgment on the expected stressfulness of the event when its full nature and particular circumstances were taken into account, the subjective reaction of the patient was ignored; (2) independence, i.e., the likelihood that the event was not a consequence of the illness. The possibility of the events that occurred as the consequence of SSc was considered. The ratings concerned with objective negative impact and independence were made by an independent rater, taking into account the individual circumstances. The rater was unaware whether the life event had occurred in a patient or in a control subject. Paykel's interview for recent life events was administered in its independently validated Italian version (Baratta *et al*., 1985). The time period in which events were recorded was the year prior to the occurrence of SSc in patients and the interview for controls.

Statistical analysis

Data are presented as mean±*SD*. Statistical significance of differences between groups was calculated by Wilcoxon's rank sum test for independent samples and exact probability test. $P<0.5$ was chosen as the level of significance.

RESULTS

Patients' characteristics

Table 1 reports the main clinical and laboratory test features and family status. All 40 patients were on thoracic duct lymphatic drainage (TDLD) therapy (Huang and Zhu, 1991) with a satisfactory efficacy. None of the patients was receiving psychiatric care at the time of the study.

Number of life events

Table 2 shows life events that happened in the year prior to the occurrence of SSc in the patients and the interview for the control subjects. In all, SSc patients reported significantly higher numbers of life events than control subjects ($P<0.05$). When the events that were "almost certainly" or "probably" independent of illness were compared and those rated as "uncertain," "probably dependent," or "almost certainly dependent" were excluded, SSc patients reported more events than controls, although the

difference was not statistically significant (P=0.07). A further comparison was made on the objective negative impact of the events. Patients with SSc reported a significantly greater number of events rated as moderate, marked, or severe impact compared with controls (P<0.001).

Table 1 Demographic characteristics of the patients with systemic sclerosis (n=40)

Characteristics	Number of patients
Cutaneous involvement*	
Diffuse	28
Limited	12
Arthritis	7
Skin ulcers	6
Esophageal involvement	11
Pulmonary fibrosis (computed tomography)	18
Forced vital capacity <80%	11
Antinuclear antibodies	9
Anti-Scl 70 antibodies	8
Family status	
Spouse or living partner	25
Alone	15
Children at home	26
Paid job	24
≥13 years of education	11
Lower education	29
Middle-upper social class	7
Working class	33

* Serum creatinine (78±11) μmol/L; Erythrocyte sedimentation rate (20±12) mm/h; C-reactive protein (11±8) mg/L

Table 2 The number of life events in patients with systemic sclerosis (n=40) compared with controls (n=40)

	Number of life events		
	Total	IE	EWONI
Patients with SSc	1 (1~2)#	1 (0~1)	1 (0~1)
Controls	0.5 (0~1)	0 (0~1)	0 (0~0)
P*	<0.05	0.07	<0.001

#Data are expressed as median (interquartile range); *Wilcoxon's rank sum test; SSc: systemic sclerosis; IE: independent events; EWONI: events with objective negative impact

Categories of life events

Table 3 displays three categories of life events: (1) exits which were defined as a departure of the patient or subject from the social field (e.g., death, divorce), and entrances which were designated as an introduction of new person (e.g., birth of a child, marriage); (2) socially desirable or undesirable events; (3) controlled events (when the occurrence of an event was likely to be under one's control or was of one's choice) or uncontrolled events (when it was not likely to be under one's control or was against one's wish). Exits from social field (P<0.05), undesirable events (P<0.01), and uncontrolled events (P<0.001) were found to be significantly more frequent in patients with SSc than in controls.

DISCUSSION

Although what causes SSc yet is not very clear, many now agree that the disease may occur when the immune system becomes disordered, attacking the myelin surrounding nerve fibers. Focusing on biology, researchers suspect that these attacks may initially be triggered by infection with a virus, perhaps picked up early in life. However, social and psychological factors are well-documented to play a role in the causation of immune disorders, and there might be a connection of stress to SSc as well. In the current study, we found that the percentages of low education (72.5%) and working class (82.5%) were significantly higher in SSc group than in the control group (47.5% and 57.5%, respectively; P<0.05). SSc patients reported a significantly greater number of stressful life events than the normal control subjects, such as exits from the social field, undesirable events, and uncontrolled events. These results therefore lend support to previous uncontrolled literature (Brown and Harris, 1986), suggesting a trigger role for life events in SSc. These results may not only support previously

Table 3 Categories of life events in patients with systemic sclerosis (n=40) compared with controls (n=40) and the number of individuals reporting at least one event in any category

Category	Number of individuals					
	Entrances	Exits	Desirable events	Undesirable events	Controlled events	Uncontrolled events
Patients with SSc	4	13	4	28	7	23
Controls	3	4	6	12	5	6
P*	NS	<0.05	NS	<0.01	NS	<0.001

*Exact probability test; SSc: systemic sclerosis; NS: not significant

described associations between socio-economic status and adverse health outcomes (Brown and Harris, 1986; Edwards *et al*., 2006), but also suggest a susceptibility of a population under socio-psychological stresses to the initiation of SSc.

In the present study, we adopted Paykel (1997)'s interview method, a semi-structured research interview that has reportedly shown excellent reliability. In the administration of the interviews, all life events were clearly defined and carefully investigated, and a blind rater assessed the objective negative impact (ignoring patient's subjective reaction to events). As a retrospective study, one argue that patients with SSc in the current study might have been biased to report what happened socio-psychologically in seeking an explanation for their disorder, the so-called "effort after meaning" (Brown and Harris, 1986); however, these efforts may have secured to reduce the subjective error to its minimum.

Although in view of the methods used, the results of the present study should be considered suggestive of a causal relationship between stressful life events and SSc, the findings still lend themselves to several clinical implications. The last decade has witnessed increasingly extensive links of behavioral responses to stress with physiological and biochemical processes, including specific changes in neural, neuroendocrine, and immune systems, and a key factor in well-being is the person's neurochemical balance that affects the way the nervous system interprets and responds to challenge (McEwen and Stellar, 1993). Thus, it is possible that socio-psychological factors may play a causal role in SSc. As Theorell (1992) has emphasized the importance of socio-psychological programs in coping with difficult life situations, such kind of programs may be of potential value in patients with SSc. Similarly, since psychological well-being plays an important role in protecting the integrity of the organism against stressful life circumstances (Ryff and Singer, 1996), the potential role of well-being enhancing psychotherapeutic strategies (Markowitz *et al*., 2006) also deserves a further investigation in caring SSc patients.

In summary, we reported a strong relationship between stressful life events and the initiation of SSc, which is consistent with current understanding of the extensive links of behavioral responses to stress with neurophysiological and biochemical processes (Ma *et al*., 2006). Our findings should alert clinicians of the importance of socio-psychological factors in the diagnosis and treatment of SSc.

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References

Archenholtz, B., Nordborg, E., Bremell, T., 2001. Lower level of education in young adults with arthritis starting in the early adulthood. *Scand. J. Rheumatol.*, **30**(6):353-355. [doi:10.1080/030097401317148552]

Baratta, S., Colorio, C., Zimmermann-Tansello, C.H., 1985. Inter-rater reliability of the Italian version of the Paykel scale for stressful life events. *J. Affect. Disord.*, **8**(3): 279-282. [doi:10.1016/0165-0327(85)90027-8]

Brown, G.W., Harris, T., 1986. Establishing Causal Links: the Bedford College Studies of Depression. *In*: Katschining, H. (Ed.), Life Events and Psychiatric Disorder. Cambridge University Press, London, p.107-187.

Edwards, R.R., Goble, L., Kwan, A., Kudel, I., McGuire, L., Heinberg, L., Wigley, F., 2006. Catastrophizing, pain, and social adjustment in scleroderma: relationships with educational level. *Clin. J. Pain*., **22**(7):639-646. [doi:10.1097/01.ajp.0000210918.26159.94]

Goldthorpe, J.H., Hope, K., 1974. The Social Grading of Occupations. Oxford University Press, Oxford, p.235-238.

Huang, J.Z., Zhu, J. (Eds.), 1991. Thoracic Duct Lymphatic Drainage Therapy. Chinese Publishing House of International Broadcast, Beijing, p.217-223 (in Chinese).

LeRoy, E.C., Black, C., Fleischmajer, R., 1988. Scleroderma (systemic sclerosis): classification, subsets, and pathogenesis. *J. Rheumatol*., **15**(2):202-205.

Ma, Y., Li, H.C., Zheng, L.L., Yu, H.L., 2006. Hemodynamic changes in depressive patients. *J. Zhejiang Univ. Sci. B*, **7**(2):133-137. [doi:10.1631/jzus.2006.B0133]

Markowitz, J.C., Bleiberg, K.L., Christos, P., Levitan, E., 2006. Solving interpersonal problems correlates with symptom improvement in interpersonal psychotherapy: preliminary findings. *J. Nerv. Ment. Dis.*, **194**(1):15-20. [doi:10.1097/01.nmd.0000195314.80210.41]

Masi, A.T., Rodnan, G.P., Medsger, T.A., 1980. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum.*, **23**(5):581-590. [doi:10.1002/art.1780230510]

McEwen, B.S., Stellar, E., 1993. Stress and the individual: mechanisms leading to disease. *Arch. Intern. Med.*, **153**(18):2093-2101. [doi:10.1001/archinte.153.18.2093]

Moser, D.K., Clements, P.J., Brecht, M.L., Weiner, S.R., 1993. Predictors of psychosocial adjustment in systemic sclerosis. The influence of formal education level, functional ability, hardness, uncertain, and social support. *Arthritis Rheum*., **36**(10):1398-1405. [doi:10.1002/art.1780361012]

Paykel, E.S., 1997. The interview for recent life events. *Psychol. Med*., **27**(2):301-310. [doi:10.1017/S0033291796004424]

Ryff, C.D., Singer, B., 1996. Psychological well-being. *Psychother. Psychosom.*, **65**(1):14-23.

Steen, V.D., Medsger, T.A., 2000. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum.*, **43**(11):2437-2444. [doi:10.1002/1529-0131(200011)43:11<2437::AID-ANR10>3.0.CO;2-U]

Theorell, T., 1992. Critical life changes: a review of research. *Psychother. Psychosom.*, **57**(3):108-117.