The Effects of Daily Stress and Stressful Life Events on the Clinical Symptomatology of Patients With Lupus Erythematosus

MARIA I. PERALTA-RAMÍREZ, PHD, JUAN JIMÉNEZ-ALONSO, MD, JUAN F. GODOY-GARCÍA, PHD, AND MIGUEL PEREZ-GARCÍA, PHD, ON BEHALF OF THE GROUP LUPUS VIRGEN DE LAS NIEVES

Objective: The purpose of this study was to verify whether stress worsens the clinical symptomatology perceived by patients with lupus erythematosus. Toward this end, we considered two types of stressors—daily stress and high-intensity stressful life events. **Methods:** In 46 patients with systemic lupus erythematosus and 12 patients with chronic lupus discoid, we studied the stress they experienced daily for 6 months and their disease symptoms. During this period, we also analyzed the levels of C3 and C4 complements and anti-DNAn antibodies. The systemic lupus erythematosus activity (assessed by the Systemic Lupus Activity Measures) and cumulative organ damage (assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index) were also analyzed. **Results:** We did not find that high-intensity stressful life events produced a worsening of the symptomatology of the disease. However, using a time-series analysis (Box–Jenkins), we found that a high percentage of lupus patients (74.1%) perceived a worsening in their clinical symptomatology due to the effects of daily stress. Of this 74.1%, 53.4% worsened the same day they suffered the perceived daily stress, and the remaining 20.7% experienced an increase in symptoms both the same day and the following day. Subsequent Mann–Whitney analyses showed that the patients who worsened for 2 days because of the effects of stress had greater lupus activity, as evaluated by their levels of C3, C4, and anti-DNAn. **Conclusion:** Daily stress, and not stressful life events, worsened the clinical symptomatology perceived by lupus erythematosus patients. This increase extended at times to 2 days, and was associated with greater lupic activity. **Key words:** daily stressors, life events, time-series analysis, systemic lupus erythematosus.

SLE = systemic lupus erythematosus; **SLICC/ACR** = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; **SSLE** = Scale of Stressful Life Events; **DSI** = Daily Stress Inventory; **SLESI** = SLE Symptoms Inventory; **SLEDAI** = SLE Disease Activity Index.

INTRODUCTION

Systemic lupus erythematosus (SLE), prototype of the autoimmune diseases, is an affliction that can produce a broad spectrum of clinical manifestations and diverse immunological disorders. SLE is a syndrome whose clinical expression depends on the degree to which there is a convergence of an immune regulation disorder and a strong genetic base, hormonal influence, and various exogenous agents. These factors lead to a common pathogenic route, which is the formation of immune complexes. SLE can be manifested by general malaise, fever, fatigue, weight loss, skin rashes or joint inflammation, anemia, inflammation of the lymphatic glands, lowering of the defenses against infection, and cardiac, kidney, neurological, and pulmonary alterations. In chronic dermatological lupus, only the skin is affected; this condition can present rash erythemas, etc. The recent introduction of new immunological diagnostic methods (antinuclear antibodies, anti-DNA antibodies, complement fractions, etc.) has made it possible to recognize less severe forms of the disease, as well as its outbreaks and therapeutic guidelines.

Despite a large volume of research, there is still a lot that is unknown about the etiopathegenic mechanisms and treatment of SLE and its possible relationship to stress (1–11). Some studies give greater relevance to stressful life events (2,9,12), defining them as stressful events that are of great importance and intensity (death of a close family member, divorce, etc.). Other studies, however, argue that daily stressors, characterized by their low intensity and high frequency, most strongly influence the clinical evolution of patients with lupus (1,3,4,8,10). One of the first groups of researchers to use validated measures of daily stress in a longitudinal study was Weekking et al. (4). They carried out their study with 21 SLE patients and 20 patients with rheumatoid arthritis for 54 weeks. These researchers took measures every 6 weeks (9 times). They found that, although there wasn't a clear relationship between the laboratory data (such as the sedimentation speed of corpuscles and hemoglobin) and the subjective scores of physical and psychological status, there was evidence of a positive relationship between the number of daily stressors and the levels of creatinin and anti-DNA anti-bodies. Later, Adams et al. (1) carried out a study with 41 SLE patients for 56 consecutive days. The purpose of this study was to verify the possible relationships between stressful life events, daily stress, depression, anxiety anger, and the possible worsening of perceived SLE symptoms, using validated measures. These authors evaluated the SLE symptoms that might be worsened by the action of these psychological factors in certain areas (eg, joint pain, skin eruptions, etc.). They reached the following conclusions: (1) there is a positive correlation between daily stress and the worsening of SLE symptoms in 20% of the patients studied, with a lag equal to 1 (ie, the patients' symptoms worsened the day after experiencing the daily stress); (2) there is a great deal of variability among subjects; (3) daily stress carries more weight than

From the Department of Clinical Psychology, School of Psychology, University of Granada, Granda, Spain (M.I.P.-R., J.G.-G., M.P.-G.); and the Systemic Autoimmune Disease Unit, University Hospital "Virgen de las Nieves," Granada, Spain (J.J.-A.)

Address correspondence and reprint requests to Maria I. Peralta-Ramírez, Campus Universitario de Cartuja s/n, Facultad de Psicología de Granada, Universidad de Granada, 18071 Granada, España. E- mail: mperalta@ugr.es

Received for publication July 1, 2003; revision received April 15, 2004.

Other members of the Group Lupus Virgen de las Nieves: Drs. Laura Jáimez, Manuel Guzmán Úbeda, Miguel Ángel Ferrer, Antonio García Sánchez, Rafael Cáliz, Valentín García Mellado, Elena García Lora, Jorge Espelt, Jesús Tercedor, Juan Pasquau, José Manuel Osorio, Santiago Medialdea, MŞ Dolores López Segarra, MŞ Teresa Muros, Gonzalo Piédrola, Jesús Prieto, MŞ José Pimentel, Miguel Ángel Rosales, Pedro Luis Carrillo, José Mario Sabio, Encarnación Milla, David Esteva, Carmen Vera, Julián Muñoz, Nuria Navarrete, Pilar Macías, Concepción García–García, and Fernando Jaén.

DOI: 10.1097/01.psy.0000133327.41044.94

0033-3174/04/6604-0788

stressful life events in worsening SLE symptoms. Although this study presents daily measures of daily stress, it does not corroborate the stress–lupus relationship with biological measures. Furthermore, the statistical analysis used only provides information on lag equal to 1 and not on other lags. These two aspects improve in a study carried out by Shubert et al. (3), in which they evaluated the daily concentration of neopterin in the urine of a female lupus patient; they evaluated her daily stress each week. Likewise, data were gathered on stressful life events, emotional state, lifestyle, and subjective estimation of SLE activity. The results showed that moderately stressful incidents increased the concentration of neopterin ~1 day later, ie, with a lag of 1. These data coincide with those found by Adams et al. (1). This study used time-series analyses to determine the directionality and latency of the effect of the stress, and to investigate other possible "lags." A limitation on this study is the impossibility of generalizing the results, because only one SLE patient was involved.

On the other hand, Da Costa et al. (9) carried out a prospective study over 8 months, with the purpose of discovering the role of stressful life events, daily stress, and functional capacity in 42 women with SLE. They evaluated these patients twice—the first time when they took the baseline data and the second time 8 months later. Measures of stressful life events, daily stress, depression, functional incapacity, activity of the disease (systemic lupus activity measure revised [SLAM-R]), and damage caused by the disease (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SLICC/ACR]) were administered. In this study, they tried to relate stressful life events, daily stress, and functional incapacity in SLE patients. The data obtained suggest that the functional incapacity of these patients is more related to stressful life events than to daily stress, contrary to what had been found up to that point. One possible explanation for these results stems from the evaluation of daily stress, ie, it was carried out at two specific times. To measure daily stress reliably, it is advisable to use a period of time that is long enough for fluctuations to occur.

Finally, Pawlack et al. (10) carried out a study with the objective of verifying whether daily stress was associated with outbreaks in lupus patients. For 6 months, they evaluated the daily stress and the clinical and laboratory parameters of disease activity in 41 patients with lupus. The results showed an increase of outbreaks in patients with lupus who presented a greater amount of daily stress and, specifically, the patients who presented greater conflict in their social relationships and obligations. Although these authors point out the importance of daily stress (evaluated daily) as an exacerbater of lupus and provide a profile of the types of stressors that produce the greatest impact, the analyses they used did not allow them to predict the cause–effect process of this stress. Nor could they predict the latency time between the stressors and worsening of the disease.

The studies that have been carried out so far present some limitations. Although all of them use validated instruments, some use a methodology that does not make it possible to find out when the stressors affect worsening of the disease; others have done so in only one case ($N = 1$). On the other hand, we still do not know whether stressful life events or daily stress is related to the worsening of the patients. Therefore, the objective of this study will be to evaluate the life events and daily stressors in a group of patients with lupus and apply a statistical methodology that makes it possible to find out when stress affects lupus and in how many patients. To this end, for 6 months we evaluated 58 lupic patients, registering their daily stress and self-reported lupic symptomatology daily. During this 6-month period, we also took diverse biological parameters of lupic activity (anti-DNA, C3, and C4). Furthermore, we evaluated stressful life events, and related them to self-reported symptomatology over the subsequent 6 months.

PATIENTS AND METHODS

Study Population

Originally, 64 patients participated in this study, of which 6 were later rejected because they were found to have mixed connective tissue disease instead of lupus. Therefore, 58 lupus patients participated in the study, of which 50 were women and 8 were men. Forty-five patients met at least four ACR (14) criteria for classification as suffering from SLE, and 12 were found to be suffering from chronic dermatological lupus, as diagnosed by clinical history and anatomo-pathological study. The patients' mean age was 39.37 years (SD = 9.72), and their mean educational level was 10.7 years (SD = 3.44), which is equivalent to a Bachelor's degree. The mean duration of the illness was 9.1 years (SD = 6.38), the mean index of organ damage was 0.9 (SD = 1.06), and the mean of the index of lupus activity was 1.73 (SD = 3.2). All of the participants were patients at the Systemic Autoimmune Disease Unit at the University Hospital "Virgen de las Nieves" in Granada (Spain). They all could at least read and write, and none of them presented any associated mental illness at the time of the study, although there were two patients with psychiatric histories. All of these patients gave their signed informed consent to participate in this study. Of all the patients included, only three did not complete the entire stress and lupus evaluation. One patient only finished 1 month (30 days of evaluation), and the other 2 completed 4 months each (120 days of evaluation). In any case, their time series were analyzed and included in the study; including them did not interfere with the other measures, because each patient was analyzed individually.

Information Collected

Scale of Stressful Life Events

The Spanish version of Holmes and Rahe's Scale of Stressful Life Events (SSLE) (15) consists of 57 items that correspond to supposedly stressful experiences. From a list of stressful events, the subjects have to choose which event(s) has happened to them in the last 2 years and rate it on a Likert-type scale from 0 (it was not important to him or her) to 4 (it was very important to him or her). Later, this score is multiplied by the "life change units" that pertain to each item, and a total score is obtained. The Spanish version uses cut-off points determined by the normative data obtained in Spain (17). In this way, if a score greater than 1,000 is obtained, it means that in the last 2 years one has undergone an amount of stress greater than that experienced by the mean of the Spanish normative group. A score between 500 and 999 indicates that the amount of stress has been similar to that of the mean of the Spanish normative group, and a score of less than 500 signifies that the amount of stress experienced was less than the mean of the Spanish normative group.

Daily Stress Inventory

The translation and adaptation of the Brantley, Waggoner, and Jones Daily Stress Inventory (DSI) was carried out by Peralta (16) et al. For this adaptation, we used the responses to a complete version of the DSI given by a broad sample. We then created a 20-item version that comprised some items that remain identical (e.g., "I forgot something"), others that are worded in a

different way (eg, "gave up an undesirable habit: eating too much, smoking, etc" for "gave up a habit that was not good for him"), and others that grouped various items from the DSI with related criteria ("Had problems in his relationship with other people: was criticized, ignored, interrupted when speaking. . . "). This instrument measures stressful daily events and the degree of stress produced by each of them in the last 24 hours. It contains 20 items that are categorized from 0 to 6, depending on the degree of stress they caused, with 0 indicating that no stress was experienced and 6 indicating that the event caused panic. The instrument's reliability coefficient is 0.82, the Cronbach α-coefficient is 0.88, and its discriminant validity is 74.86% of correct classification. Therefore, the instrument presents high validity for detecting change (16).

SLE Symptoms Inventory

This inventory was elaborated by the group of medical specialists in the Systemic Autoimmune Disease Unit of the Internal Medicine Service at the University Hospital "Virgen de las Nieves" in Granada. It refers to 8 symptoms suggestive of SLE activity, such as loss of appetite, joint pain, general malaise, fever, tiredness or fatigue, skin rash, difficulty breathing, and abdominal symptoms. These items are categorized from 1 to 10 according to the degree of intensity of symptoms on that day. The SLE Symptoms Inventory (SLESI) was validated in the same sample by using the patient's medical report. A κ concordance index of 0.653 was found for difficulty breathing, 0.539 for joint pain, 0.465 for loss of appetite, 0.341 for general malaise, 0.279 for tiredness or fatigue, 0.311 for skin rash, and 0.234 for abdominal distress. Furthermore, during each patient's first month, the α Cronbach was calculated on a day that was selected randomly. The SLESI showed $\alpha = 0.8623$, which indicates high internal consistency and, therefore, a high degree of reliability.

The SLE Disease Activity Index (SLEDAI) (18) was used to assess lupus activity. It comprises 24 descriptors with pre-assigned severity weights. The total SLEDAI score can range from 0 (no activity) to 105 (maximum activity). The SLEDAI has been shown to be sensitive to change in lupus activity measured by the treating physician.

The SLE disease damage was measured with the SLICC/ACR Damage Index (19). The SLICC/ACR is a physician-rated index that assesses cumulative organ damage caused either by the disease or by complications of therapy. It includes the following 12 categories: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculo-skeletal, skin, premature gonadal failure, diabetes, and cancer. Total scores range from 0 (no damage) to 46 (maximum damage). SLEDAI and SLICC/ACR were evaluated only in the first weeks.

Serological Indicators of Activity

The determination of the levels of C3 and C4 complements was carried out with nephelometrics. When a patient with lupus presents an increase in disease activity, s/he consumes more complement. Therefore, a decrease in the complement levels is an indicator of activity. Specifically, normal levels of C3 lie between 79 and 152 mg/dl and the normal levels of C4 lie between 16 and 38 mg/dl. Scores lower than these values indicate an increase in lupic activity. The anti-DNAn was calculated by using the indirect immunofluorescence method with substrates of *Crithidia luciliae*. This is a specific method, with a medium sensitivity. An increase in anti-DNAn is associated with greater lupic activity. An anti-DNAn will be considered negative when the scores are between 0 and 100. Only 60% of patients with lupus present a positive anti-DNAn score (>100).

Procedure

During the first week, the patients were recruited by the internist at the outpatient clinic for autoimmune diseases. When the patient attended his routine check-up, s/he was informed about this study of the effects of stress and lupus, and s/he was invited to participate (90% agreed). If the patient agreed, s/he was given an appointment for the first session. In the first session, the study was explained in detail, and subjects were asked to sign the consent form (99% accepted). The subjects who accepted underwent the following: (1) a clinical interview to find out basic data like age, education level, and diverse emotional problems occurring in his or her life; (2) the SLEDAI and SLICC/ACR; (3) the SSLE; and (4) 31 copies of the 20-item version of the DSI and 31 copies of the SLESI. They were informed that they would have to complete the DSI and SLESI at the end of the day every day for 6 months (This was done by all the patients, except the three who left the evaluation early). Each month they were provided with 31 DSI questionnaires and 31 SLESI questionnaires, personally if they lived in Granada or by mail if they lived outside of Granada. Furthermore, every 15 days they were telephoned in order to resolve any doubts about completing the questionnaires, and they were encouraged to continue to fill them out.

Coinciding with a routine medical check-up, the levels of C3 and C4 complements and anti-DNAn antibodies were measured on at least two occasions. This medical check-up could occur at any time during the 6 months of the study.

Statistical Analyses

In order to verify the first objective of whether stressful life events (SSLE) worsened the clinical symptomatology perceived by patients with lupus erythematosus, a one-way ANOVA was carried out. The mean of the clinical symptomatology of lupus during the next 6 months was the dependent variable, and the score obtained on the SSLE was the factor. These SSLE scores were categorized into 3 groups: (1 = below the Spanish normative group mean; 2 = equal to the Spanish normative group mean; 3 = above the Spanish normative group mean) (17). The first hypothesis was that stressful life events (SSLE) worsened lupus symptomatology.

The second objective was to study whether stress predicted a worsening in the self-reported clinical symptomatology of lupus. To test this, 58 multivariate time-series analyses—one for each patient—were carried out. These analyses are also called dynamic regressions using transference analyses (20). These analyses provided us with the prediction of the evolution of one time-series (daily self-reported symptoms) based on another (daily stress). The transference analysis is based on time analyses of stochastic processes, which make it possible to find a statistical model of auto-regressive behavior, influenced by previous values of the variable like the auto-regressive model and the moving averages variable. To carry out a transference analysis between daily stress ("input" series) and the worsening of daily self-reported symptomatology ("output" series), the auto-regressive-integrated-moving-average model of the stress series was applied to itself, and the result provided the residuals of the stress series. Second, the auto-regressive-integrated-moving-average model of the stress was applied to the self-reported symptoms series and, as before, the residuals were obtained, but in this case from the self-reported symptoms series. Finally, a transference analysis was carried out between the residuals of the stress series ("input" series) and those of the self-reported symptoms series ("output" series). This process was carried out for each of the

patients studied, thus establishing 58 transference analyses. The statistical packet used for this analysis was the interactive time series modeling package (19). As a function of the obtained results of this analysis (transference analysis, Table 1), the patients were categorized into one of the following three groups: (G1) patients with increased clinical lupus symptomatology due to the effect of that day's stress; (G2) patients with increased clinical lupus symptomatology due to the effect of 2 days' stress; and (G3) patients for whom stress does not predict a change in clinical lupus symptomatology. Our hypothesis was that the same relationship would not be found in all the patients, because the heterogeneity of this relationship had already been demonstrated by Adams et al. (1).

To study what differentiates lupus patients whose clinical symptomatology increases due the effects of daily stress from those patients whose symptoms do not increase due to its effects (Objective 3), we decided to use a variance analysis to test whether diverse demographical factors determine this difference. In addition, Mann–Whitney analysis was carried out to compare by pairs, because this analysis compares the differences between means of the variables organized by ranges. This analysis is appropriate because of the unequal variance of the variables analyzed. Three nonparametric analyses were carried out for each of the clinical variables to see whether there were differences between the three groups. The relation stress and clinical symptomatology of lupus patients was the factor with three levels and the average amount of daily stress, C3, C4, anti-DNA, SLEDAI, and SLICC were the dependent variables. Our hypothesis was that the patients whose condition worsened because of the effects of stress would have greater levels of stress and present greater lupic activity.

RESULTS

Stressful Life Events and Increased Clinical Symptomatology

The results found by using variance analysis did not show statistically significant differences between the score obtained on the stressful life events questionnaire filled out by the patients and the average of the clinical symptomatology of lupus [$F(2,55) = 0.044$; $p < .978$].

Daily Stress and Worsening of Clinical Symptomatology

To test this objective, 58 transference analyses were carried out—one for each of the patients studied. The results showed that daily stress significantly predicted the increase in clinical

TABLE 1. Statistical Transference Analysis Coefficients for Each of the Lupus Patients Studied

Subjects	$X(t)$	$X(t-1)$	Subjects	$X(t)$	$X(t-1)$
1	0.120		30	0.263	
2	0.230	0.114	31	0.307	
3	0.118		32	0.074	
4	0.090		33	0.353	
5	NS		34	0.350	0.196
6	0.169	0.131	35	0.186	0.099
7	NS		36	0.307	
8	NS		37	NS	
9	0.179		38	NS	
10	0.455		39	NS	
11	0.335		40	0.430	0.239
12	NS		41	0.371	0.234
13	NS		42	0.082	0.094
14	0.194		43	NS	
15	0.388		44	0.804	
16	0.137		45	0.373	
17	0.322	0.290	46	NS	
18	0.159		47	NS	
19	0.258		48	NS	
20	NS		49	0.431	
21	0.341		50	0.178	
22	0.613		51	0.385	
23	0.271		52	0.026	0.011
24	0.453		53	0.357	
25	0.350		54	0.348	
26	0.331		55	0.292	0.236
27	NS		56	NS	
28	0.149	0.186	57	0.141	0.099
29	0.205		58	0.283	

NS, Non-significant coefficients.
$X(t)$, Coefficient of worsening of symptoms as a result of the daily stress the same day.
$X(t-1)$, Coefficient of worsening of symptoms as a result of the daily stress from the same day and the previous day.

symptomatology of lupus in 74.1% of the patients studied (Table 1). In all of the analyses carried out, we found a positive sign whereby the increase in stress produces an increase in the clinical symptomatology of lupus. To find out how daily stress affects clinical symptomatology, the delays in the transference functions were analyzed. The results showed that in 31 (53.4%) patients, the increase in clinical symptomatology was predicted by an increase in daily stressors on the same day (lag = 0) (G1), in 12 (20.7%) patients the increase in clinical symptomatology was predicted by an increase in daily stressors the day before and the same day (lag = 0,1) (G2), and in 15 (25.9%) patients the daily stress experienced did not predict any increase in the self-reported clinical symptomatology (G3) (Table 2).

What Differentiates the Patients in Whom Daily Stress Is Associated With an Increase in Symptoms From Those in Whom It Is Not?

Once the relationship between daily stress and the increase in clinical symptomatology was demonstrated by means of transference analysis, we studied the possible differences in demographic parameters, daily stress, and levels of C3, C4, and anti-DNAn on SLICC and SLEDAI indices between the patients who got worse and those who remained stable. For this purpose, and using the results found in the transference functions (from the previous section), all the patients were classified into the following three groups: (G1) patients for whom the clinical symptomatology of lupus was predicted by the same day's stress; (G2) patients for whom the increase in clinical symptomatology was predicted by stress on the same day and on the previous day; and (G3) patients whose clinical symptomatology did not worsen due to the effects of daily stress.

Effect of Demographic Variables on the Relationship Between Stress and the Increase in the Clinical Symptomatology

The results found by using variance analysis indicated that the three stress/symptom groups did not differ significantly in age [$F(2,55) = 0.292$; $p < .748$] or educational level [$F(2,55) = 2.63$; $p < .081$].

The Role of the Amount of Stress in the Relationship Between Stress and the Worsening of Clinical Symptomatology

The results of the Mann–Whitney nonparametric analysis showed that there were no statistically significant differences between the three groups (G1, G2, and G3), although the ranges of daily stress of G1 and G2 patients (19.8 and 19.7) were greater than those of G3 patients (11). Thus, although not statistically significant, the daily stress of the groups in which this stress predicts an increase in lupus symptoms is greater than in the group of lupus patients whose clinical symptomatology did not worsen as a result of the stress. This finding suggests that the amount of stress perceived by these patients could be one of the factors involved in the previously described stress–lupus relationship.

Relationship With Lupus Activity

The results obtained from the Mann–Whitney nonparametric analysis showed that there were statistically significant differences in the anti-DNAn variable and the three groups (G1, G2, and G3), with G2 showing higher levels of anti-DNAn than G1 ($p < .03$) and G3 ($p < .025$) (Table 3). On the other hand, there are nearly statistically significant differences between G2 and G3 ($p < .065$) on the C3 variable, with G2 showing lower levels of C3. Although there were no statistically significant differences found in the parameter of C4 activity, it can be seen that the range of the G2 group (8.3) is inferior to the ranges of the G1 and G3 groups (15.3 and 15.4). Keeping in mind that these parameters (C3 and C4) can be useful markers of lupus activity, these results suggest that patients in the G2 group had greater lupus activity than those in the other groups (Table 3).

Along other lines, to test whether the influence of daily stress on the clinical symptomatology reported was related to the SLEDAI and SLICC/ACR, 6 Mann–Whitney nonparametric tests were carried out. The results did not show statistically significant differences between those patients whose symptomatology worsened and those whose symptoms did not.

DISCUSSION

The results of our study suggest that daily stress is related to the appearance of clinical symptomatology perceived by patients with lupus, but this relationship does not exist with

TABLE 2. Influence of Daily Stress on the Appearance of Clinical Manifestations in Lupus Patients

	N	Lag(0) *N* (%)	Lag(0,1) *N* (%)	No Relationship Stress–Lupus *N* (%)
Total population	58	31 (53.4%)	12 (20.7%)	15 (25.9%)
SLE	46	24 (52.2%)	9 (19.5%)	13 (28.3%)
CLD	12	7 (58.3%)	3 (25%)	2 (16.6%)

SLE, systemic lupus erythematosus; CLD, chronic lupus discoid; *N*, number of patients.
Lag (0) = increase in SLESI values was predicted by an increase in the same-day DSI values.
Lag (0,1) = Increase in SLESI values was predicted by an increase in previous day and same-day DSI values.

TABLE 3. Levels of C3–C4 Complement and Anti-DNAn in Patients with Lupus Erythematosus According to Whether Daily Stress Worsened or Not

Variable	Ranges of the Groups			Mann–Whitney	Significance
	G1	G2	G3		
C3	85	74	87.5	G1–G2 = 60.5	NS
				G2–G3 = 17	0.068
				G1–G3 = 61	NS
C4	15.3	8.3	15.4	G1–G2 = 55.5	NS
				G2–G3 = 22	NS
				G1–G3 = 88.5	NS
Anti-DNAn	49	110	55	G1–G2 = 28	0.025
				G2–G3 = 13	0.03
				G1–G3 = 94	NS

G1, Patients whose reported symptomatology increased the same day as the perception of daily stress; G2, patients whose reported symptomatology increased for 2 days; G3, patients whose self-reported symptomatology did not worsen as a result of daily stress.
C3, C3 complement (mg/dl); C4, C4 complement (mg/dl); Anti-DNAn, Normal in healthy subjects is absence of anti-DNAn, but 0–10 v/ml are admitted as normal values, and between 10 and 15 are considered ambiguous. Expressed as title, it is significant from 1/10 on.
NS, Not significant.

stressful life events. Furthermore, we found that there are lupus patients who do not worsen as a result of daily stress, patients who worsen the same day, and patients whose clinical symptomatology worsens for 2 days after suffering an increase in the amount of daily stress. On the other hand, the results show that the patients in whom stress produces a greater clinical effect after 2 days of stress have greater lupic activity, as rated by biological markers.

There are two possible explanations for the results obtained with regard to stressful life events and worsening of the clinical symptomatology of lupus. The first is determined by the evaluation instrument. This questionnaire (SSLE) has been criticized because it supposes that all the eventful changes in life are stressful, regardless of how desirable they are for those who experience them. However, it has been pointed out that the desirable changes seem less stressful than the undesirable ones, or at least they are not related to the later development of negative consequences associated with the stress. A second explanation is related to time, ie, it is difficult to detect the effect of stressful events that occurred a long time before the evaluation of symptomatology (up to 2 years).

These results provide information on the relationship between daily stress, the clinical evolution of the illness, and the time delay of the effect of this stress. It is noteworthy that there are three groups that are quite differentiated by this relationship—the lupus patients in whom stress has no effect, the lupus patients whose symptoms worsen the same day of the increase in daily stress, and the lupus patients who worsen 2 days after the stress is produced. Based on the results, it seems that the patients who worsen distinguish themselves from those who do not in the amount of lupic activity immune parameters, such as C3 and anti-DNA. Specifically, the patients who worsened after 2 days as a result of daily stress showed greater lupus activity—indicated by the study of the levels of C3 complements and anti-DNAn antibodies—than the patients who worsened for only 1 day or did not worsen at all. However, no significant differences were found between the three groups (G1, G2, and G3) on the SLEDAI and SLICC/ACR. One possible explanation is that both measures were taken at a moment before the evaluation of daily stress and symptoms. Therefore, any possible variation was not detected during the evaluation process.

These results lead us to think that in the G1 group, patients probably do not experience a real worsening of clinical symptoms, but rather a perception of worsening because of the effect of stress. In future studies, it would be interesting to investigate the role these lupic symptoms play in the perception of stress in these patients.

These results have an impact on the question of whether it is daily stress, stressful life events, or both, that produce an aggravation of the illness (10,11), and they suggest the importance of daily stress compared with stressful life events. Thus, the results of our study coincide with and complete the short-term studies in which daily evaluations of daily stress and lupus activity (1,4) are carried out. Specifically, the study by Adams et al, (1) presents some similarities to ours, because it used the same instrument to measure daily stress (with daily measurements) and a longitudinal design. However, there are some differences; in our study, the tracking period was longer (180 vs. 59 days) and involved a greater number of patients. Furthermore, a statistical analysis was carried out that makes it possible to capture the time relationship between stress and the worsening of lupus symptoms. The above-mentioned authors also found a relationship between daily stress and lupus in 20% of patients the day after suffering from increased stress. For this purpose, they used regression analysis and moved the time series (clinical symptomatology) 1 day with regard to the time series of daily stress. However, with this procedure it is not possible to study the duration of the effect of stress on the lupus symptoms and the moment when it occurs. This is probably the main reason the authors did not detect a worsening on the same day. With regard to other studies, one of the main criticisms received by the study that evaluated daily stress and neopterin (3) has been that, although

the statistical analyses are very precise, the study was carried out with a very small sample, which makes it difficult to generalize the results. In our study, we used the same statistical design and found a high degree of agreement between the results in a sample of 58 patients over a longer tracking period.

Currently, the mechanisms through which daily stress could produce a worsening in the clinical symptoms of lupus patients are not known. One of the possible explanatory hypotheses would be the activation of prolactin, a hormone involved in the developmental course of lupus. Thus, diverse studies have shown that one of the consequences of facing stressful situations is an increase in the levels of prolactin in the blood (22), and that patients who have more lupus symptoms present higher blood levels of prolactin (23).

Although this study has shown that in at least 20% of patients, daily stress worsens reported SLE symptomatology, we must keep in mind that the illness itself can increase this stress, because living with the disease is stressful in itself.

One of the limitations of our study is the directionality of the effect of stress on the clinical symptomatology, because even though transference analysis established a prediction relationship between stress and an increase in clinical lupus symptoms, it is also possible that the opposite is true. The lupus symptomatology may produce stress; it is commonly accepted that chronic disease itself is a daily stressor. In future studies, it would be especially interesting to be able to test whether an increase in the worsening of these patients' symptomatology also produces an increase in the amount of daily stress they perceive.

In summary, this study of 58 patients who were monitored daily for 6 months suggests a time relationship between daily stress and worsening of the symptomatology of lupus sufferers. Future studies should examine the importance of prolactin in the relationship between stress and lupus, and the possible beneficial effects of a psychological approach to stress in patients with SLE.

Our thanks to Ana Rosales and Paqui for their technical assistance, to the patients who kindly participated in this study during the 6-month period of daily monitoring, and to the doctors who sent their lupus patients to our unit for study.

REFERENCES

1. Adams SG, Dammers PM, Saia TL, Brantley PJ, Gaydos GR. Stress, depression and anxiety predict average symptom severity and daily symptom fluctuation in systemic lupus erythematosus. J Behav Med 1994;17:459–77.
2. Dobkin PL, Forti PR, Joseph L, Esdaile JM, Danoff DS, Clarke AE. Psychosocial contributors to mental and physical health in patients with systemic lupus erythematosus. Arthritis Care Res 1998;11:23–31.
3. Schubert C, Lampe A, Rumpold G, Fuchs D, König P, Chamson E, Schüssler G. Daily psychosocial stressors interfere with the dynamics of urine neopterin in a patient with systemic lupus erythematosus: an integrative single-case study. Pychosom Med 1999;61:876–82.
4. Wekking EM, Vingerhoets AJJ. Daily stressors and systemic lupus erythematosus: a longitudinal analysis-first findings. Psychother Psychosom 1991;55:108–13.
5. Dobkin PL, Da Costa D, Fortín PR. Living with lupus: a prospective pan-Canadian study. J Rheumatol 2001;28:2442–8.
6. Dostal C, Marek J, Moszkorzova L. Effects of stress on serum prolactin levels in patients with systemic lupus erythematosus. Ann N Y Acad Sci 2002;966:247–51.
7. Ward MM, Marx AS, Barry NM. Psychological distress and changes in the activity of systemic lupus erythematosus. Rheumatology 2002;41: 184–8.
8. Schubert C, Lampe A, Geser W. Daily psychosocial stressors and cyclic response patterns in urine cortisol and neopterin in a patient with systemic lupus erythematosus. Psychoendoneuroendocrinology 2003;28:459–73.
9. Da Costa D, Dobkin PL, Pinard L, Fortin PR, Danoff DS, Esdale JM, Clarke AE. The role of stress in functional disability among women with systemic lupus erythematosus: a prospective study. Artrritis Care Res 1999;12:112–9.
10. Pawlack CR, Witte T, Heiken H, Hundt M, Schubert J, Wiese B, Bischoll-Renken A, Gerber K, Licht B, Goebel MU, Heijnen CJ, Schumidt RE, Shedlowski, M. Flares in patients with systemic lupus erythematosus are associated with daily psychological stress. Psychother Psychosam 2003;72:159–65.
11. Wallace DJ. Does stress or trauma cause or aggravate rheumatic disease. Baillières Clin Rheumatol 1994;8:149–59.
12. Picardi A, Abeni D. Stressful life events and skin diseases: disentangling evidence from myth. Psychother Psychosom 2001;70:118–36.
13. Schubert C, Geser W, Noisternin B. Stressful life events and skin diseases: an additional perspective from research on psychosomatic dynamics in systemic lupus erythematosus. Psychother Psychosom 2002; 71:123–6.
14. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25: 1271–7.
15. González de Rivera JL, Morera A. La valoración de sucesos vitales: adaptación española de la escala de Holmes y Rahe. Psiquis 1983;4:7–11.
16. Peralta MI, López F, Godoy JF, Godoy D, Sánchez MB, Pérez M. Validación de la detección de cambio del inventario de estrés cotidiano. Psicología Conductual 2002;10:343–54.
17. Labrador JF. El estrés: Nuevas técnicas para su control. Madrid: Planeta DeAgostini; 1996.
18. Bombardier C, Gladman DD, Urowitz MB. The development and validation of the SLE Disease Activity Index (SLEDAI). Arthritis Rheum 1992;35:630–40.
19. Gladman D, Urowitz MB, Goldsmith C, Fortin P, Ginzler E, Gordon C. The reliability of the SLICC/ACR damage index in patients with SLE. Arthritis Rheum 1997;40:809–13.
20. Box GEP, Jenkins G. Time-Series Analysis: Forecasting And Control. San Francisco: Holden-Day; 1976.
21. Blockwell PJ, Davis RA. ITMS: an interactive time series modelling package for the PC. New York: Springer-Verlag; 1991.
22. Heesen C, Schulz H, Schmidt M. Endocrine and cytokine responses to acute psychological stress in multiple sclerosis. Brain Behav Immun 2002;16:282–7.
23. Straub RH, Georgi J, Helmke K, Vaith P, Lang B. In polymyalgia rheumatica serum prolactin is positively correlated with the number of typical symptoms but not with typical inflammatory markers. Rheumatology 2002;41:423–9.