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Research Article

Stressful life events at the onset and during the evolution of systemic sclerosis

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Objective: Stressful life events, such as Childhood Adverse Events (CAE) and Recent Stressful Events (RSE) may play a role in the pathogenesis of autoimmune disorders. The present study investigated their occurrence in Systemic Sclerosis (SSc).

Methods: 110 SSc patients and 110 controls were enrolled. Stressful events assessment included a semi-structured interview and the Childhood Experience of Care and Abuse Questionnaire (CECA-Q). A normative evaluation of RSE was made by means of the Paykel's scoring of life events. The clinical status of patients with a very early diagnosis of Systemic Sclerosis (VEDOSS) during the first year after the diagnosis was evaluated in order to detect patients with a significant clinical worsening.

Results: All investigated CAE were more frequently reported in SSc patients compared to controls, although with a significant difference only for the events "loss of mother" ($p<0.05$) and "sexual abuse" ($p<0.05$). SSc patients reported higher occurrence of at least one RSE ($p<0.01$), number of RSE ($p<0.01$), and stress load (mean total Paykel's score) ($p<0.01$) in the year prior to the diagnosis compared to the year prior to the interview for controls. This was particularly true for severe and independent RSE ($p<0.001$). VEDOSS subjects who worsened during the first year after the diagnosis, compared to those who did not, reported a higher impact of severe and independent RSE in the same year ($p<0.05$).

Conclusions: CAE may represent potential predisposing factors for SSc, while the occurrence of RSE may play a role in the onset and worsening of the disease.

Keywords: systemic sclerosis • psychology • autoimmune diseases • inflammation • VEDOSS

Introduction

Systemic Sclerosis (SSc) is a disabling and chronic connective tissue disease characterized by widespread small vessel vasculopathy, progressive fibrosis of the skin and of multiple internal organs, and production of autoantibodies [1-4]. Recently, new classification criteria for SSc have been defined [5]. Through a score system considering seven items (besides skin involvement), these criteria classify as SSc patient who has a score ≥ 9, allowing to identify SSc patients since the earliest stages of the disease. A definition of "Very Early Diagnosis of Systemic Sclerosis" (VEDOSS) has also been proposed [6,7], indicating as VEDOSS patients those characterized by a score of 9 or less and having Raynaud's Phenomenon (RP), puffy fingers, disease-specific autoantibodies and/or pathognomonic microvascular alterations (detectable by capillaroscopy) [8]. Despite the many advances made in the understanding of SSc pathogenic mechanisms, many aspects of the disease remain largely unknown.

It has been proposed that psychosocial factors, namely stressful life events, may play a role in the pathogenesis of autoimmune disorders [9-12], especially if occurred during childhood [13-15] or during the few months prior to the onset of the disorder itself [16,17]. In fact, as repeatedly reported [18-20], early stress can interfere with the development of the Hypothalamic-Pituitary-Adrenal (HPA) axis and lead to an altered stress-response system (hence vulnerable to later stressful situations [21]. The deleterious effect of stress in autoimmune rheumatic disorders may be mediated by an inadequate response to stressors [22-26] and to chronic inflammation [27,28] due to a dysfunctional production of stress hormones by the HPA axis.

Consistently with this view, Childhood Adverse Events (CAE) and Recent Stressful Events (RSE) have been respectively proposed as predisposing and precipitating factors for SSc [14,29]. Although both an excess of RSE [30] and a deficit of the anti-inflammatory stress-response system [31] have been reported in SSc,

few studies have addressed the role of stressful life events in this disease, and none of them evaluated both CAE and RSE at the same time. For this reason, the aim of the present study was to specifically investigate the presence of stressful life events in SSc and to evaluate its relationship with the course of the disease.

Methods

This observational, cross-sectional study has been conducted on 110 adult patients with SSc classified according to 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [5] and referred to the Scleroderma Unit of the University Hospital in Florence (Italy) during a 1-year period, excluding those with neurological and/or cognitive impairment, or not fluent Italian. The clinical sample has been enrolled to obtain two homogeneous subgroups based on a different score and then stage of the disease: a group consisting of 55 consecutive patients with very early SSc and a score ≤9 [6-8], and a group consisting of 55 consecutive patients with established disease, score > 9 [5]. Exclusion criteria were: age <18 years or >75 years, pregnancy, substance abuse and/or addiction, presence of other chronic inflammatory or autoimmune disorders, inability to give informed consent.

A control group of 110 subjects (matched for age, gender and education to the clinical group) was selected using a case-control method from a pool of 1077 subjects drawn from the general population and randomly recruited from the lists of the Italian National Health System (99.7% of the citizens are included in the list of the NHS).

Interviewers

Four clinical psychologists were the interviewers. All of them underwent an intensive training program, comprising:

- Attending the Psychiatry and Rheumatology units and participating to the routine clinical work for at least 8 weeks
- Being trained and supervised in the administration of clinical interviews and rating scales
- Fulfilling the assessment forms with videotaped interview
- Discussing the assessment inconsistencies
- Measuring the inter-rater agreement (vs. the scores given by the supervisor) on all the other-administered interviews/scales used in the study (see below) every six months.

Qualified psychiatrists supervised the entire training process and did not certified the interviewers until the achievement of a fully satisfactory reliability.

Instruments

At enrollment, both patients and control subjects underwent a complete assessment of medical history and clinical status performed by fully qualified rheumatologists. The assessment also included a face-to-face interview with a clinical psychologist and the administration of self-report questionnaires. Adverse events during childhood and early adolescence (before the age of 15 years) were studied by means of the structured interview for early trauma (other-administered) included in the Florence Psychiatric Interview (FPI) [32] and of the Childhood Experience of Care and Abuse Questionnaire (CECA-Q) (self-administered) [33]. The subject's answers were recorded, and the circumstances in which the events took place and their causes were fully investigated. Although interviewers were aware of the patient or control status of the subjects, the reports, recorded in detail, were submitted (with patients and control subjects randomly mixed) to two assessors who were not involved in the interviews and were blind as to whether a given account referred to a patient or to a control subject. Thus, any element by which the assessors could identify whether the subject was a patient or a control was omitted.

Assessment of childhood adverse events

For the purpose of this study, the presence of CAE was evaluated as follows:

- *Loss*: Whenever the death of or separation (for one year or more) from parents was reported.
- *Divorce*: Serious conflict between parents (divorce, or legal or *de facto* separation).
- *Severe illness of the child*: Severe and chronic illness of the child sufficient to interfere with the development of normal social relationships (e.g. pediatric cancer, diabetes, malformations, long periods of hospitalization, etc.)
- *Sexual* or *physical abuse*: Whenever the CECA-Q or the interview showed the occurrence of physical and/or sexual abuse.

The division of the accounts into "events" and "non-events" was made by the assessors on the basis of previously established cut-off points.

For example, "separation" had to be continuous and of at least one-year duration. Whenever the consequences of a childhood event appeared in another event (e.g. separation from a parent consequent upon divorce), only the original event was taken into account. The procedure for retrospectively collecting and assessing Recent Stressful Events (RSE) has been described in detail elsewhere [34]. Briefly, patients and control subjects were given a semi-structured interview, derived from that by Brown and Harris [35], which extensively and systematically explored RSE, as well as the circumstances and the context in which they occurred.

For the purpose of this study, RSE occurred within one year *before* the diagnosis for the clinical group (or before the interview in the case of control subjects) and within one year *after* the diagnosis for VEDOSS patients, were taken into account.

Assessment of recent stressful events

In regard to RSE, in order to obtain a normative measure of recent stress for each subject, the assessors had to decide the following:

- Whether a given occurrence, as elicited by the interview, would fit any of the items on the list included in the Scale for Recent Life Events (SRLE) by Paykel et al. [36]. This list is made up of 61 events, ranked in descending order of severity. A weighted score (Paykel's score), obtained through a calibration study, is connected with each event. The most severe event ("death of child") has a score of 19.33; the 20th event (which we considered the cut-off point to distinguish *severe* from *non-severe* events), is "loss of personally valuable object" and has a score of 14.07; and the last (61st) event ("child married with respondent's approval) has a score of 2.94. A subject was considered to have experienced a *severe* event when any of the top 20 events on the Paykel's list [36] had occurred.
- Whether the event could be dependent, i.e., under the control of the subject (in other words, whether the behavior of the subject could have determined the occurrence of the event). For instance, an event such as "sudden stroke of father" was considered unlikely to be determined by the subject and was thus assessed as *indep9endent*. On the other hand, events such as "marital separation" and "loss of job because of absenteeism" were considered *dependent*, since they were possibly secondary to disordered behavior on the part of the subject.

On the basis of this procedure it was possible to obtain several normative measures of recent stress for each group (i.e. number of subjects with at least one event, number of subjects with at least one *severe* and *independent* event, mean number of events, mean number of *severe* and *independent* events, mean weighted score for all events and for *severe* and *independent* events).

Assessment of disease progression since early phases of disease

The clinical assessment of the very early SSc patients group included an evaluation of the disease progress by investigating the presence of *significant clinical worsening* during the first year after the diagnosis. A *significant clinical worsening* was defined as a worsening of the skin and internal organ involvement detected by:

- Modified Rodnan skin total score (mRSS) for skin thickness [37].
- Capillaroscopy (microvascular involvement).
- Evaluation of digital ulcers.
- Pulmonary function test (reduction of carbon monoxide diffusing capacity or DLCO) and chest Computed Tomography (i.e. ground glass or fibrosis) for lung involvement.
- Echocardiography (i.e. pulmonary arterial hypertension, diastolic disfunction).
- Esophageal manometry (gastrointestinal involvement).
- Creatinine clearance (renal function).

Ethics

Informed consent was obtained from all patient's prior the procedure and the study was approved by our local ethical committee, conforming to the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed by means of the Statistical Package for Social Sciences (SPSS) for Windows (release 20.0, IBM, 2011). The values of normally distributed variables were expressed as mean ± SD, whereas the values of skewed variables were expressed as median values [quartiles]. Student t test, independent variables Mann–Whitney U tests, and χ^2 test were performed when appropriate. Predictive value of RSE and CAE in the development of disease

progression was tested with logistic regression and expressed in OR (95% CI).

Results

In the SSc sample the mean age was 52.1 ± 14.0 years (mean illness duration 7.1 ± 9.0 years) and the female gender was predominant (with a F:M ratio of 6.86:1). Clinical characteristics are reported in Table 1. As expected, given the case-control design of the study, the clinical and control groups did not differ for age (52.1 ± 14.0 *vs.* 51.9 ± 13.8 years old, p=0.900), gender (87% of the subjects were females in both groups) and level of education (11.2 y ± 4.0 *vs.* 11.2 ± 4.1, p=0.894). The two clinical subgroups did not differ in terms of gender and level of education, although, as expected, patients with full-blown SSc were significantly older than the ones with very early SSc (56.6 ± 10.9 vs. 47.6 ± 15.3 years, p=0.001) and had a longer duration of the illness (10.6 ± 10.5 *vs.* 3.5 ± 5.3 years, p<0.001).

Table 1. Clinical characteristics of VEDOSS and established SSc.

	VEDOSS patients	Established SSc
Raynaud's Phenomenon	55 (100%)	48 (87.27%)
Puffy fingers	22 (40%)	15 (27.27%)
ANA positivity	36 (65.45%)	49 (89%)
ACA positivity	16 (29%)	25 (45.45)%
Scl-70 positivity	3 (5.4%)	20 (36.36%)
NVC pattern: early	7 (12.72%)	14 (25.45%)
NVC pattern: active	8 (14.55%)	12 (21.81%)
NVC pattern: late	3 (5.45%)	15 (27.27%
SKIN involvement	0	53 (96.36)%
ILD	0	8.8 (16%)
DU	12 (21.81%)	30 (54.54%)
GER	14 (25.45%)	9 (16.36%)

ANA: Anti-Nuclear Antibodies; ACA: Anti-Centromere Antibodies; Scl-70 70: anti-Scl 70 antibodies; NVC: Nailfold Video Capillaroscopy; ILD: Interstitial Lung Disease; DU: Digital Ulcers, GER: Gastro Esophageal Reflux,

Childhood adverse events

The results obtained from the evaluation of CAE in the sample are summarized in Table 2. A significantly higher number of patients reported to have experienced at least one CAE compared to controls. More in detail, all of the investigated CAE were more frequently reported by patients compared to controls, even though a significant difference was obtained only for the events "loss of mother" and "sexual abuse". No significant difference in terms of occurrence of CAE was obtained from the comparison between the SSc and the VEDOSS subgroups, nor any CAE or specific CAE was significantly predictive of disease worsening in the year after diagnosis (p=NS).

Recent stressful events

The presence of RSE in the sample is summarized in Table 3. Paykelìs score did not correlate with disease duration at the time of the interview, nor with mRSS at baseline (r=-0.181, p=0.159). A higher number of patients reported the occurrence of at least one RSE compared to controls (in the year before the diagnosis for the former, in the year preceding the interview for the latter). A higher number of patients reported at least one *severe* and *independent* RSE compared to controls. Overall, patients reported a significantly higher number of RSE than controls. In particular, patients reported a higher number of *severe* and *independent* RSE, whereas the comparison for *non-severe* or *dependent* RSE did not attain statistical difference (data not shown). In regard to the normative assessment of RSE, higher mean weighted scores (Paykel's score) were found in patients compared to controls both when considering all events and when the comparison was limited to *severe* and *independent* RSE (Table 3). No significant difference in terms of RSE load was found between the established

Table 2. Presence of Childhood Adverse Events. Comparison between patients and controls, and between Systemic Sclerosis and Very Early Diagnosis of Systemic Sclerosis.

Childhood Adverse Events	Controls N=110 n (%)	Patients N=110 n (%)	p	SSc N=55 n (%)	Very Early SSc N=55 n (%)	P
Any type	38 (34.5)	62 (56.3)	0.001	30 (54.5)	32 (58.2)	0.701
Loss of mother	6 (5.4)	15 (13.6)	0.039	6 (10.9)	9 (16.4)	0.405
Loss of father	14 (12.7)	21 (19.1)	0.197	9 (16.4)	12 (21.8)	0.467
Divorce of parents	7 (6.3)	11 (10.0)	0.325	5 (9.1)	6 (10.9)	0.751
Severe illness of the child	9 (8.2)	18 (16.4)	0.064	12 (21.8)	6 (10.9)	0.122
Sexual abuse	1 (0.9)	7 (6.3)	0.031	2 (3.6)	5 (9.1)	0.241
Physical abuse	0 (0.0)	3 (2.7)	0.081	0 (0.0)	3 (5.5)	0.079

Childhood Adverse Events: Adverse events occurred during the first 15 years of life; SSc: Systemic Sclerosis

Table 3. Presence of Recent Stressful Events (stressful events occurred within one year before the diagnosis of Systemic Sclerosis or before the interview in the case of control subjects). Comparison between patients and controls, and between established Systemic Sclerosis and very early SSc.

Recent Stressful Events		Controls N=110	Patients N=110	p	SSc N=55	Very early SSc N=55	p
Number of subjects with at least one event	Any type (%)	47 (42.7)	70 (63.6)	0.002	34 (61.8)	36 (65.5)	0.692
	Severe and independent (%)	22 (20.0)	46 (41.8)	0	24 (43.6)	22 (40.0)	0.699
Mean number of events	Any type (M ± SD)	0.58 ±0.81	1.08 ± 1.34	0.001	0.98 ± 1.15	1.18 ± 1.50	0.435
	Severe and independent (M ± SD)	0.21 ±0.43	0.61 ± 0.86	0	0.62 ± 0.83	0.60 ± 0.89	0.912
Mean Paykel's score	Total (M ± SD)	7.15 ±9.80	14.05 ± 18.12	0.001	13.70 ± 16.34	14.40 ± 19.88	0.841
	Severe and independent (M ± SD)	3.30 ±6.81	9.46 ± 13.30	0	9.93 ± 13.17	8.99 ±13.52	0.712

Recent Stressful Events: stressful events occurred within one year before the diagnosis of Systemic Sclerosis (or before the interview in the case of control subjects); SSc: Systemic Sclerosis; VEDOSS: Very Early Diagnosis of Systemic Sclerosis; M: Mean; SD: Standard Deviation; Paykel's score: normative assessment of recent stressful events as derived by the Paykel's weighted scoring of stressful life event

SSc and patients with an early disease in any of the ways it was measured.

Recent stressful events and progression of disease

Among all patients, RSE load was significantly predictive of disease progression in the year after diagnosis (OR 1.040, 95% CI 1.012-1.070, p=0.005). When analyzing the two patients' groups separately, 18 VEDOSS patients (32.7%) showed a *significant clinical worsening* during the first year *after* the diagnosis. No significant difference in terms of presence and number of RSE was found between very early SSc patients with and without a significant worsening (data not shown), whereas the normative assessment of *severe* and *independent* RSE showed a higher mean weighted score (Paykel's score) in patients who worsened compared to those who did not (15.39 ± 18.21 vs. 5.87 ± 9.34, p<0.05). In particular, Paykel's score was significantly predictive of disease progression in the VEDOSS (OR 1.068, 95%CI 1.014-1.125, p=0.013) and not in the established SSc (OR 1.026, 95% CI 0.992-1.060, p=0.138) patients. Moreover, when specifically analyzing the type of disease progression, RSE load significantly predicted the development of gastro-esophageal involvement only (OR 1.061, 95% CI 1.008-1.116, p=0.024).

Discussion

Despite the growing body of evidence suggesting the possible role of stress in the etiopathogenesis of SSc [10-12] and of individual response to in stress in the natural history of this disease [38,39], few studies have specifically addressed and focused on stressful life events [30,31]. In the present SSc sample, the mean age was around 50 years and the female gender was predominant (with a F:M ratio of 6.86:1). This is in line with current epidemiological evidence on SSc reporting a peak age of onset in the forties and a female-to-male incidence ratio between 1:1 and 14:1 [40]. While patients did not differ from controls in terms of age, sex, education and marital status, the subgroup of patients with defined SSc was significantly older and had a longer duration of illness compared with the very early SSc subgroup. This was somehow expected, given the natural history and the current classification of SSc [5].

Childhood adverse events

The number of SSc patients who reported at least one CAE was significantly higher than the number of controls. This result seems to support the previous literature on the possible role of early stress in increasing vulnerability to autoimmune disorders [10-12,15,29], and is in line with previous evidence indicating CAE as predictors of adult inflammation [13] and risk factors for rheumatic disorders [14]. Specifically, a greater occurrence of the childhood events "loss of mother" and "sexual abuse" was reported by patients compared to controls. Interestingly, a large body of preclinical work on maternal separation and recent studies on adults with childhood parental loss have consistently documented the relationship between loss events and adult HPA axis dysfunction [25]. Moreover, unlike other forms of childhood stress, "loss of mother" is a discrete and objective event that may be minimally influenced by recall bias or subjective judgments. On the other side, among

the most common CAE, sexual abuse is the one considered to have the strongest association with experiencing multiple other forms of childhood trauma [41]. No significant difference in terms of occurrence of CAE was obtained from the comparison between the established SSc and the very early SSc patients, sharing the same predisposing factors [5-8].

Recent stressful events

SSc patients reported a significantly higher occurrence of at least one RSE, number of RSE and stress load (as assessed by the mean total Paykel's score) in the year prior to the diagnosis compared with the year prior to the interview for controls. Although all types of RSE were investigated, for the purpose of this study, only stressful events being *severe* and *independent* at the same time were taken into account. For what concerns severity, we focused on stressful events severe enough to warrant a high probability that they would not be ignored (specifically, the 20 most severe events on the Paykel's list). In fact, it is unlikely that occurrences such as death or hospitalization of a close relative, severe personal disease, divorce, and loss of job would not be reported when systematically investigated. For what concerns independency, in order to minimize subject- and disorder- related confounding factors, we focused on stressful events which were unlikely to be determined by the subject's behavior or by the consequences of the illness. On the basis of this procedure, we found a significantly greater occurrence of *severe* and *independent* stressful events, in terms of presence of at least one event, number of events, and mean Paykel's score in the year prior to the diagnosis of the patients group compared with the reference year of controls. These results seem to support previous literature suggesting a precipitating role of stressful life events in SSc [11,12,16,17,29]. In particular, these findings are in line with the results of the only available study on the occurrence of RSE in SSc, reporting higher number of total uncontrolled and negative impact RSE [30] in the year prior to the diagnosis of SSc patients compared to year prior to the interview for controls. No significant difference in terms of RSE load was found between the established SSc and very early SSc patients in any of the way it was measured.

Recent stressful events and disease progression

In order to investigate the possible relationship between stressful life events and SSc course, we evaluated the disease progress of the patients group during the first year after the diagnosis. In fact, given the chronic and progressive nature of SSc [1,2], a significant clinical worsening in the first year of early and subclinical illness may be less expected (and possibly more related to intervening factors) than it would be in later stages. Our results indicate that the VEDOSS patients who significantly worsened during the first year of illness, compared with those who did not, reported a significantly higher stress load during the same year, as indicated by the mean Paykel's score of *severe* and *independent* RSE. Moreover, Pakel's score was predictive for disease progression, in particular regarding the development of gastro-esophageal involvement. This is in line with the results of Lepri et al. who detected esophageal and anorectal involvement since the early phases of the disease [42]. Since the exact timing of clinical worsening is impossible to determine and the exact timing of RSE was not taken into account, the present study is unable to detect causal relationships between higher stress load and worse illness course in the very early SSc subgroup. We can only speculate that if a negative influence of RSE on very early SSc course exists, then it could mainly involve *severe* and *independent* RSE.

Limitations

The present study has some limitations:

- The retrospective evaluation of stressful life events is based on the subjective reports of the participants and may be susceptible to recall bias (memory distortions, search for meanings).
- Socio-economic and housing contexts were not evaluated, although it is known that disrupted contexts can lead to adverse events and worse illness prognosis [43,44].
- The exact timing of stressful life events has not been taken in to account; it is however likely that different stressful events exert different effects at different ages and times [45].
- The limited very early SSc sample size. On the other hand, the presence of statistically significant results, in spite of the small sample, indicates the clinical relevance of the present findings.
- The cross-sectional nature of this study does not allow to detect any causal relationship between stress and SSc. We can only speculate that the relationship between stressful life

events and SSc is multifactorial, complex, and possibly bidirectional.

On the other hand, this study is the first, as far as we know, to comprehensively explore the presence of stressful life events in a large sample of SSc patients, taking into account both early and recent events at the same time.

Conclusion

In conclusion, our study suggests a meaningful association between stressful life events and SSc onset and course. In particular, CAE may represent potential predisposing factors for SSc, while the occurrence of RSE may play a role in the onset and evolution of the disease. Our data highlight the need to comprehensively explore stressful life events in the evaluation of SSc patients, regardless of their assignment to a full-blown stage. Large, prospective studies are warranted in order to clarify the causal relationship between stressful life events and systemic sclerosis.

Declaration of conflict of interest

All the authors declare that have not conflict of interests for the manuscript.

Conflict of interest

None.

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