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Concise report

Late-onset systemic sclerosis—a systematic survey of the EULAR scleroderma trials and research group database

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Abstract

Objective. The clinical course of SSc depends on subtype, organ involvement and age. Few data are reported on patients suffering from late-onset SSc.

Methods. We analysed data from 8554 patients prospectively followed in the EULAR Scleroderma Trials and Research (EUSTAR) group database. Late-onset SSc was defined as onset of non-RP disease features at or beyond 75 years of age. Disease characteristics, clinical features, disease course and mortality were evaluated.

Results. A total of 123 patients with SSc onset at or beyond 75 years of age were identified. Compared with patients <75 years they had more frequently limited than diffuse SSc and a higher prevalence of anti-centromere autoantibodies. Fewer old patients had digital ulcers. The modified Rodnan's skin score, the prevalence of lung fibrosis and renal crisis did not differ significantly between groups. Pulmonary hypertension (PH) measured by echocardiography was more prevalent in the late-onset group, as well as arterial hypertension and diastolic dysfunction. Late-onset SSc remained a positive predictor for PH in multivariate analyses. No significant difference of the two groups in skin score or diffusion capacity was observed during follow-up. Mortality due to SSc was higher in the late-onset group, but the survival time from diagnosis was longer compared with the younger patients.

Conclusion. Late-onset SSc shows a distinct clinical presentation and outcome. Patients with late-onset SSc suffer more frequently from the limited subtype and PH, but fewer patients have digital ulcers. PH may in part be determined by underlying cardiovascular disease.

Key words: Systemic sclerosis, Scleroderma, Late onset, EULAR Scleroderma Trials and Research, Geriatric, Elderly.

CLINICAL SCIENCE

Introduction

SSc is a heterogeneous CTD. Whereas vasculopathy in the form of digital ulcers or pulmonary hypertension (PH) is the leading clinical feature in the limited form, diffuse SSc is associated with progressive fibrosis of skin and inner organs. The clinical presentation also depends on age. Patients with juvenile-onset SSc have less skin involvement and lower mortality but suffer more frequently from overlap syndromes, notably with skeletal muscle involvement [1]. In contrast, patients with onset of RP above the mean age suffer more frequently from digital ulcers, lung fibrosis, PH and diastolic heart failure [2]. The mean age at onset of first non-RP in the EULAR

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Scleroderma Trials and Research (EUSTAR) database was reported as 44.8 years for diffuse SSc and 47.9 years for limited SSc [2]. In a North American SSc cohort study, white patients had an older age at diagnosis (55.5 years) compared with black patients (43.8 years) [3]. Among white patients, the peak incidence was between 65 and 74 years in women and >75 years in men [3]. The incidence of SSc >75 years is around 20 cases per million per year, which is 2–4% of all SSc cases [3].

Data indicate that a late age at onset of SSc is associated with more aggressive disease [4]. In fact, the risk of death increases by 5% for each 1-year increase in age at diagnosis [3]. The number of patients >75 years at diagnosis in previous studies, however, is low and naturally occurring comorbidity in the elderly certainly influences survival analysis. Only small SSc cohorts or case series have focused on late-onset SSc. Whereas some cases presented with a more severe disease course compared with patients <60 years, a more benign course, especially concerning skin involvement, has been reported by others [5–7]. Despite more severe lung involvement and a delayed diagnosis in the late-onset group, the disease remained stable in patients >75 years old [7]. In this study, we describe disease characteristics, progression and mortality of late-onset SSc in a larger patient cohort by analysing the large collection of the EUSTAR database.

Patients and methods

Data sample

We reviewed the minimal essential data set of the EUSTAR database. The recruitment, structure and content of the database have been described previously [2]. For SSc classification, American College of Rheumatology (ACR) criteria and clinical subsets were defined according to LeRoy *et al*. [8]. All participating centres have obtained ethics committee approval and enter data for all consecutively consenting patients.

Definitions

Late-onset SSc was defined as age ⩾75 years at onset of first non-RP. This age cut-off has been chosen as representative of geriatric patients and in accordance with previous studies [7]. First onset of non-RP was chosen to assess specifically the first occurrence of manifest organ involvement.

Data analysis

Patients were dichotomized according to age (<75 or ⩾75 years) and data analysed cross-sectionally at study entry. We analysed follow-up and survival data in all patients with ⩾1 follow-up visits. Both ACR criteria positive and negative patients were included in the main data set in order to keep atypical or early SSc cases in the analysis. As a sensitivity analysis, we repeated our analysis limited to the subset patients with positive ACR criteria only.

Dyspnoea was defined as New York Heart Association (NYHA) Grade 3 or 4, arterial hypertension as blood pressure >140 mmHg systolic or >90 mmHg diastolic. Pulmonary fibrosis was diagnosed by CT. Lung restriction was defined as vital capacity <80%. PH (defined as systolic pulmonary artery pressure >40 mmHg), diastolic dysfunction and reduced left ventricular ejection fraction (LVEF) were diagnosed according to echocardiographic results reported by the cardiologist. Patients without tricuspid regurgitation were considered as not having PH. For disease course analysis, endpoints were defined as relative diffusing capacity for carbon monoxide (DL_{CO}) decline of ⩾25% from baseline or modified Rodnan skin score (mRSS) decline of ⩾3 points, which corresponded to 25% of the median baseline mRSS in the cohort.

Statistical analysis

Discrete variables are expressed as counts and continuous variables as medians and interquartile ranges (IQRs). Two-group comparison was performed with Wilcoxon–Mann–Whitney tests and a Kruskal–Wallis one-way analysis of variance was used for multiple-group comparisons. Associations of late-onset SSc and other factors with PH were calculated in logistic regression models. We used unadjusted and multivariate models adjusted for confounders and report odds ratios (ORs). Effect modification of late-onset SSc for the association of diastolic dysfunction and PH was tested by including an interaction term into the multivariate regression model. Since the frequency of missing data was low (<2–5% per variable and <10% for the multivariate model), we only present a complete case analysis and did not perform imputation of missing data. All testing was two-tailed and $P < 0.05$ was considered statistically significant. All calculations were performed using Stata 11.0 (Stata Corp., College Station, TX, USA).

Results

Basic description

At the time of data censoring (1 June 2009), 8554 patients were included in the EUSTAR database. One hundred and twenty-three patients with a late onset of non-RP at an age of ⩾75 years were identified. Of these, 74.3% fulfilled the ACR criteria for SSc, whereas ACR criteria were fulfilled in 84.4% of the patients <75 years ($P = 0.002$; Table 1). The median disease duration both of RP [4.4 (IQR 2–14) *vs* 10.1 (IQR 4–20) months; $P \leqslant 0.01$] and non-RP [2.1 (IQR 0.8–3.0) vs 6.8 (IQR 2.8–14.3) months; $P \leqslant 0.01$] at diagnosis was lower in the late-onset group. The median disease duration of non-RP symptoms at study inclusion was also lower in the late-onset group [30 (IQR 15–48) *vs* 75 (IQR 36–144) months; $P = 0.01$].

Significantly more patients in the ⩾75 years group had limited SSc (74.1 *vs* 58.2%: $P = 0.001$), whereas 17.8 *vs* 32.5% suffered from diffuse disease ($P = 0.001$). The late-onset group had a higher proportion of positive anticentromere autoantibodies (54.2 *vs* 33.4%; $P < 0.001$). Anti-Scl70 autoantibodies were more prevalent in the younger group (32.3 *vs* 23.0%; $P = 0.034$). ANA positivity was similar in both groups (94.2 *vs* 92.1%; $P = 0.4$). Significant differences for the same covariates were also found in the subsets of ACR criteria-positive patients.

Table 1 Demographic features at inclusion according to SSc onset by age at first non-RP disease feature

Disease characteristics	Age <75 years	Age ⩾75 years	*P*-value
Total number of patients	8431	123	
Demographic characteristics			
Average age at inclusion, median (IQR)	55 (45.6–64.8)	79.6 (78.2–81.7)	<0.0001**
Sex: female, %	86.4	89.3	0.36
Clinical characteristics			
Clinical subtype, %			
Limited	58.2	74.1	0.001**
Diffuse	32.5	17.8	0.001**
Other	9.1	8	0.67
Disease history			
Age at onset of RP, years (IQR)	41 (28–52)	75 (64–78)	<0.01
Age at onset of non-RP, years (IQR)	45 (33–56)	78 (76–80)	<0.01*
Disease duration of non-RP at diagnosis, months (IQR)	6.8 (2.8–14.3)	2.1 (0.8–3.0)	<0.01
Duration of RP at diagnosis, months (IQR)	10.1 (4.4–20.4)	4.4 (2.2–14.5)	<0.01
ARC criteria fulfilled	84.4	74.3	0.002*
Autoantibody status, %			
Anti-centromere	34.4	54.2	<0.001**
Anti-Scl-70	32.3	23	0.034*
ANA	92.1	94.2	0.4

*Significant; **highly significant.

Clinical features

The median mRSS was similar in both age strata (7 *vs* 7; $P = 0.57$; Table 2). The late-onset group had significantly less digital ulceration (22.1 *vs* 30.1%; $P = 0.03$). Patients with late-onset SSc had higher rates of arterial hypertension (40.6 *vs* 20.2%; $P < 0.001$), abnormal diastolic function (29 *vs* 16.1%; $P < 0.001$) and conduction blocks (21.8 *vs* 9.7%; $P < 0.001$). PH was more prevalent in the late-onset group (35 *vs* 20%; $P < 0.001$), whereas there was no difference in median DL_{CO} between the groups (45 *vs* 53%; $P = 0.3$); the late-onset group did not suffer more frequently from dyspnoea (40.9 *vs* 34.3%; $P = 0.13$). Similar results and statistical significant differences were also found in the subset of ACR criteria-positive patients, except for creatine kinase (CK) elevation, which was similar in both groups.

To investigate whether late-onset SSc was an independent risk factor for PH, we calculated logistic regression analysis (supplementary data are available at *Rheumatology* Online). Late-onset SSc was a significant predictor for PH with an unadjusted OR of 2.1 (95% CI 1.5, 3.1). In addition, we found reduced LVEF [OR 4.78 (95% CI 3.90, 5.86)], abnormal diastolic function [OR 3.4 (95% CI 3.0, 3.8)], lung fibrosis [OR 2.7 (95% CI 2.5, 3.1)], conduction block [OR 2.64 (95% CI 2.2, 3.0)] and arterial hypertension [OR 1.82 (95% CI 1.55, 2.14)] to be significant univariate predictors for PH. All those factors remained independent predictors for PH in multivariate logistic regression analysis. We found no evidence for effect modification of late-onset SSc (*P* of interaction term = 0.2), indicating that diastolic dysfunction is a risk factor for PH in all age groups.

Table 2 Prevalence of clinical features in patients aged ⩾75 *vs* <75 years

Parameter	Age <75 years	Age ⩾75 years	*P*-value
MRSS, median (IQR)	7 (3–14)	7 (3–12)	0.57
Synovitis, %	15.8	15.5	0.94
Joint contracture, %	30.1	26.4	0.38
Digital ulcer, %	31.3	22.1	0.03*
Tendon friction rubs, %	10.5	10	0.84
Muscle weakness, %	25.7	21.4	0.28
Muscle atrophy, %	12.8	10.6	0.46
Proteinuria, %	5.8	6.7	0.68
RP, %	95.2	92.6	0.19
Conduction block, %	9.7	21.8	<0.001**
Diastolic function abnormal, %	16.1	29.6	<0.001**
Diastolic failure, %	5.8	6.7	0.68
PH (echocardiographic), %	20	35	<0.001**
Lung restrictive defect, %	30.7	29.8	0.83
Lung fibrosis, %	36.4	30.1	0.16
Oesophageal symptoms, %	67.0	59.8	0.09
Intestinal symptoms, %	23.2	26.2	0.77
Renal crisis, %	2.2	0.82	0.29
Dyspnoea, %	34.3	40.9	0.127
Palpitation, %	23.8	21.3	0.50
CK elevation, %	8.2	3.3	0.05*
Arterial hypertension, %	20.2	40.6	<0.001**
Elevated acute phase reaction, %	29.9	44.5	0.001**
DL_{CO} (% of normal), median (IQR)	53 (−76)	45 (−73)	0.30
Reduced left ventricular function, %	5.2	6.3	0.6

*Significant; **highly significant.

Disease course

All patients with ⩾1 follow-ups were analysed with respect to the course of DL_{CO} and mRSS. Severe and moderate impairment of DL_{CO} (defined as a DL_{CO} <50 and <65%) were found in 20 and 22% of late-onset patients, compared with 20 and 27% of control patients. During the follow-up, 17% of late onset and 11% of control patients had a decline of at least 25% from baseline DL_{CO} ($P = 0.38$). Late-onset patients had lower median mRSS at study inclusion [4 (IQR 3, 7) *vs* 7 (IQR 4, 13); $P = 0.002$], which was also confirmed in multivariate analysis adjusted for disease duration ($P = 0.02$). The decline of ⩾3 points in mRSS was also similar in both groups (28% in late-onset patients *vs* 34% of control patients; $P = 0.4$).

Overall and disease-specific mortality

The overall mortality in the 4081 patients with available follow-up information was 6.9% (22% in the late-onset group and 6.7% in the early-onset group; $P < 0.001$). Overall, 178 (63%) deaths were attributed to SSc. The SSc-specific mortality rate was 12.2% in late-onset patients with a median survival time of 49 months (IQR 22, 92 months) and significantly lower in early-onset patients (4.3%; $P = 0.01$), but with a shorter median survival of 41 months (IQR 22, 73 months).

Discussion

This study aimed to characterize clinical features, disease progression and mortality in late-onset SSc. Unlike that reported in previous studies, SSc in the late-onset group was diagnosed earlier then in the control group, which might be due to a higher frequency of medical consultation or less extensive and invasive diagnostic investigation in this subgroup [7]. Patients with a late onset suffered more frequently from limited SSc and had significantly higher rates of anti-centromere autoantibodies. Despite the higher prevalence of limited disease, they had fewer digital ulcers. This suggests a milder disease course in late-onset SSc patients, but might be biased by a shift of patients with mild disease into the late-onset group and the shorter disease duration at study inclusion, respectively. Conversely, PH was more prevalent in late-onset SSc. However, diastolic dysfunction, arterial hypertension and conduction blocks, which were also more prevalent in the late-onset group, can lead to left ventricular hypertrophy, and thus result non-specifically in PH [9]. Unfortunately, right heart catheterization was performed in none of the late-onset patients. The data set in the present form did not allow us to determine whether the higher frequency of diastolic dysfunction and conduction blocks in the late-onset group was caused by left-ventricle hypertrophy or cardiac fibrosis due to SSc. Also, false-negative results from echocardiography due to the absence of detectable tricuspid regurgitation jet cannot be excluded, although there are no data to suggest that this would affect elderly SSc patients more than younger patients. The course of both ILD and skin involvement remained stable in the majority of both groups. This is in line with previous reports of a stable course of signs in elderly SSc, but low mRSS values especially found in limited SSc are relatively unsensitive and therefore only of limited value as a marker for disease progression [7].

ACR criteria were fulfilled in fewer patients in the late-onset group. This might indicate that, apart from an earlier study inclusion, older SSc patients suffer from a more atypical disease course, possibly influenced by co-medication or comorbidities, such as atherosclerosis. Studies in patients with late-onset SLE have shown similar results where they more frequently had RP, arterial hypertension, organ damage and a higher mortality [10]. Conversely, and in accordance with the present findings, the clinical course of late-onset SLE was described as less aggressive [10]. It is also noteworthy that RP in the elderly has different characteristics and pathogenic mechanisms compared with younger individuals [11, 12].

As expected, more patients died in the older group. Taken into account the international nature of the EUSTAR database, mortality could not be compared with an available age-matched control group. Unexpectedly, in patients whose death was attributed to SSc, the median survival time was longer in the older patients, furthermore suggesting a more protracted course of SSc in the elderly.

Limitations of this study include missing information concerning treatment modalities and co-medication, and a possible bias related to differences in diagnostic work-up and treatment of younger compared with older patients. Inter-individual and centre bias might also influence the results.

Taken together, limited disease and PH measured by echocardiography are more prevalent in the elderly, but these patients suffer less from digital ulcers. SSc-unrelated left heart hypertrophy has to be considered especially in late-onset SSc before the diagnosis of PH can effectively be made and treatment started.

Rheumatology key messages

- Limited disease is more prevalent, yet digital ulcers are less prevalent in late-onset SSc.
- PH in late-onset SSc is influenced by underlying cardiovascular comorbidity.
- The time from diagnosis to death is longer in late-onset SSc.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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