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Factors affecting survival in juvenile systemic sclerosis

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Objectives. To determine whether demographic, clinical and immunological features may predict the outcome in juvenile SSc (JSSc).
Methods. Clinical and laboratory characteristics of patients with JSSc collected from paediatric rheumatology centres worldwide were analysed. First, univariate tests identified those features significantly related with fatal outcome, and then multivariate logistic regression analysis was applied to determine the predictors of mortality.
Results. One hundred and thirty-four patients from 40 centres were eligible for the analysis. Sixteen patients died and a rapidly fatal course was observed in most of them: 4/16 died within 1 yr after diagnosis and 10/16 within 5 yrs. At the moment of diagnosis, patients with poor outcome showed a significantly higher frequency of internal organ involvement, particularly cardiac, respiratory and gastrointestinal systems. No significant difference emerged for entity of skin, vascular and musculo-skeletal involvement, nor for auto-antibodies profile and laboratory tests. Multivariate analysis showed the following factors to be significant predictors of mortality: fibrosis on chest X-rays [odds ratio (OR) 11.2], raised creatinine levels (OR 22.7) and pericarditis (OR 41.3), while a short disease duration at diagnosis conferred protection (OR 0.3).
Conclusions. All patients with JSSc and fatal outcome were affected by the diffuse form of the disease, and most of them showed a very rapid progression and early signs of internal organ involvement. This suggests that, in children, SSc may have two possible courses: a rapid development of internal organ failure leading to severe disability and eventually to death, or a slow course of the disease with lower mortality.

Key words: Scleroderma, Mortality, Systemic sclerosis, Child, Outcome.

Introduction

SSc is uncommon in children, as paediatric cases account for only 3% of all cases. Therefore, apart from the two recent large studies [1, 2], only small case series describing the clinical features of the juvenile form of the disease have been published [3, 4].

In adults with SSc, several features are associated with a poor survival, while to date, in the juvenile form, no study on large samples have been performed to identify predictors of outcome by using statistical analysis.

Herein, we performed univariate and multivariate analysis to verify whether demographic, clinical and immunological features of a large cohort of patients with juvenile SSc (JSSc), included in the Paediatric Rheumatology European Society (PRES) international database, may predict the outcome of the disease.

Methods

In a previous study, we described demographic, clinical and laboratory characteristics of patients with JSSc retrospectively collected from paediatric rheumatology centres worldwide, as part of a multiphase project, supported by the PRES [1].

Since there were no classification criteria specific for JSSc at that time, contributors were asked to report all their patients affected by SSc according to the ACR preliminary criteria [5] and to define organ involvement at the time of onset and/or diagnosis and any time during the follow-up. Patients with overlap syndrome (OS) and MCTD were excluded from the analysis. The distinction between diffuse or the limited form of the disease on the basis of skin involvement was established according to the criteria proposed by LeRoy *et al*. [6], with skin thickening above the elbows, on the trunk or above the knees identifying the diffuse disease and skin thickening of the distal extremities the limited disease.

A special form was developed for collection of data on the following items:

(i) Demographics (gender, age at the first signs or symptoms of the disease, age at diagnosis).
(ii) Family history for connective tissue or other autoimmune diseases, as based on the medical history.
(iii) Participants were asked to use the following recommendations to define organ involvement. Skin involvement was determined by the presence of skin induration, PIP to MCP and/or MTP joints, oedema or sclerodactyly. Peripheral vascular system involvement was diagnosed by any one of the following: Raynaud's phenomenon, digital infarcts, digital pitting, abnormal nail-fold capillaries and capillaroscopy findings (such as megacapillaries and avascular areas). Lung involvement was defined by the presence of dyspnoea and any one among abnormal chest X-rays or high-resolution CT, reduced DL_{CO} and FVC, according to the normal values defined in each centre and to the patient's age. Cardiac disease was diagnosed by the presence of arrhythmias or pericarditis, heart failure or pulmonary hypertension, diagnosed by echocardiogram and/or cardiac catheterization. Musculo-skeletal involvement was defined by the presence of muscle weakness, arthritis, arthralgia or tendon friction rubs. Gastrointestinal tract involvement was determined by dysphagia, gastroesophageal reflux, diarrhoea or weight loss. Renal disease was identified by the presence of raised creatinine levels, proteinuria, renal crisis or persistent arterial hypertension, according to the normal values defined in each centre and to the patient's age. Nervous system involvement was determined by the report of seizures, peripheral neuropathy and abnormal brain MRI.
(iv) Abnormal laboratory parameters at the time of diagnosis and/or anytime after diagnosis including: white blood cell (WBC) count, haemoglobin, platelets, ESR, CRP, creatine

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kinase (CK), lactic dehydrogenase (LDH), Immunoglobulin G, A, M (IgG, IgA, IgM, respectively) and complement fractions C3 and C4. Abnormal values were referred to the normal range of laboratory standards of each participating centre.

(v) Serum autoantibodies, ANA, anti-dsDNA, SCL-70, ACA or other ENA autoantibodies, aCL, LAC and RF. Abnormal values were referred to the normal range of laboratory standards of each participating centre.

In order to standardize the data acquisition, detailed instructions on collection form compilation were included in the material sent to each centre (see supplementary data, available at *Rheumatology* Online). Before the analysis was completed, we accurately revised the characteristics of the patients and asked the principal investigators at the participating centres to verify the reliability of the data in order to improve their quality.

In particular, we solicited the contributors to verify how many patients were lost to follow-up in order to make sure that all deaths included in the analysis were real.

Statistical analysis

Differences in categorical variables among surviving and deceased patients were statistically tested using Pearson's χ^2-test or Fisher's exact test, where appropriate, while unpaired Student's *t*-test was applied to assess differences between means. A *P*-value <0.05 was considered significant. The association between variables at diagnosis and during the disease course and mortality were assessed using bivariate analysis. The strongest independent predictor variables were identified by logistic regression analysis. All analyses were performed by using SPSS® Release 14.0 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier curve was constructed to estimate survival using as time 0 the date of diagnosis of SSc.

Results

Between January 2002 and March 2005 we collected data on 159 patients with JSSc from 55 centres worldwide, but complete data on vital status were available for 134 patients from 40 centres (24 European, 6 North American, 7 South American and 3 Asian), the remaining patients being lost to follow-up. The majority of patients (122/134) were affected by the diffuse form of the disease.

The mean follow-up was 9.6 yrs (median 7.6 yrs, range 0.4–44.5 yrs). Out of 134 patients, 16 (11.9%) deceased and the causes of death were: cardiac failure in 10, 2 of whom had pulmonary hypertension, renal failure in 2 (1 also having pulmonary hypertension), respiratory failure in 2 and infection in 2 patients.

Among deceased patients, none was affected by the limited form of the disease; as far as geographical distribution, 10 were from European, 5 from South American and 1 from North American centres.

The F:M ratio was 2.2:1 *vs* 5.2:1 in the group of deceased and alive patients, respectively, without statically significant difference. In deceased patients, the disease occurred at 10.4 yrs of age (median 10.9 yrs, range 5.1–15 yrs), which was slightly later than that in surviving patients (8.5 yrs; median 8.8 yrs, with range 0.3–16 yrs), but this was not statistically significant.

The first sign of the disease was defined as the first symptom attributable to SSc. The time interval between first sign of the disease (for example, RP and/or skin sclerosis) and diagnosis was significantly shorter in patients with fatal outcome (average 12.6 *vs* 25.3 months, median 6.1 *vs* 12 months with ranges 0–71.9 and 0–240.5 months, respectively, $P < 0.001$) (Table 1). Indeed, the fatal course of the disease was rapid in most patients and slower in others, as death occurred after a mean 4 yrs from diagnosis, with median 2.8 yrs and a range from 13 days to 18.1 yrs. In particular, 10/16 patients (62.5%) died within 5 yrs from diagnosis, 5/16 (31.25%) within 5–10 yrs and only 1 (6.25%) after >10 yrs. Moreover, 4/16 patients (25.0%) died within the first year after diagnosis, all of cardiac failure. This observation is confirmed by the Kaplan–Meier survival curve (Fig. 1), which shows that the survival rate at 5 yrs from diagnosis is 88.0%, at 10 yrs 85.2%, remains stable at 15 yrs and decreases at 79.1% after 20 yrs. The mean survival time in our cohort of patients with JSSc is 42.55 yrs (95% CI 40.95, 44.14). As shown in Fig. 1, overall mortality in our cohort of children with diffuse JSSc is lower than the one reported in a series of adult patients with diffuse subtype [7].

The first analysis was aimed to identify possible factors present at diagnosis that could identify patients that will present a poor outcome. As shown in Table 2, the presence, at the moment of diagnosis, of signs and symptoms of internal organ involvement, particularly cardiac, such as arrhythmias, pericarditis and heart failure was significantly associated with increased mortality. Indeed, presence of basal crackles and gastroesophageal reflux were significantly more frequent at diagnosis in deceased patients. No statistically significant difference was observed for vascular, renal and musculo-skeletal system involvement between patients who deceased and others, as well as for extension of skin involvement.

By evaluating the overall course of the disease, similar results for cardiac, pulmonary and gastroesophageal involvement were

TABLE 1. Comparison of main demographic features of surviving and deceased patients with JSSc

	Alive	Deceased	*P*
Patient no., %	118 (88.1)	16 (11.9)	
Gender F:M ratio, %	5.2:1	2.2:1	NS
Male	19 (16.1)	5 (31.3)	
Female	99 (83.9)	11 (68.7)	
Age at onset, yrs			
Mean	8.5	10.4	NS
Median	8.8	10.9	
Range	0.3–16	5.1–15	
Disease duration at diagnosis, months			
Mean	25.3	12.6	<0.001
Median	12	6.1	
Range	0–240.5	0–71.9	
Follow-up, yrs			
Mean	10.4	4.0	0.001
Median	9.0	2.9	
Range	1.5–44.5	0.4–18.0	

NS = $P > 0.05$.

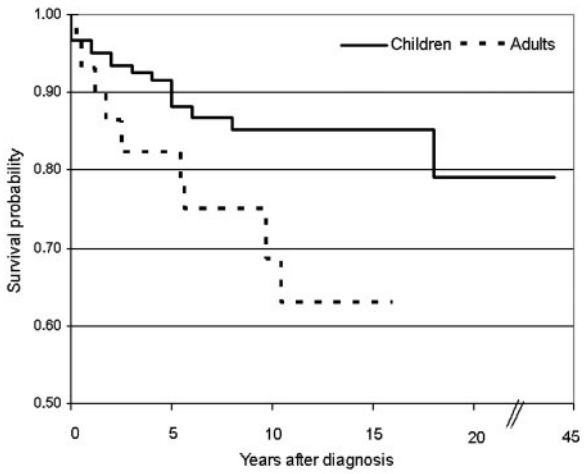


FIG. 1. Kaplan–Meier survival curve from diagnosis of the disease in patients with diffuse JSSc from our cohort and from a group of adult patients with diffuse subset (adapted from Ref. [6]). Note the lower mortality rate in the juvenile form both at short- and long-term follow-up.

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TABLE 2. Comparison of main clinical features at diagnosis and during the overall disease course in surviving and deceased patients with JSSc (134 patients)

	At diagnosis			Overall course		
	Alive Positive/tested (%)	Deceased Positive/tested (%)	*P*	Alive Positive/tested (%)	Deceased Positive/tested (%)	*P*
Skin						
Sclerodactily	74/116 (63.8)	7/16 (43.8)	NS	87/116 (75.0)	10/16 (62.5)	NS
Induration proximal to MCP	78/114 (68.4)	12/16 (75.0)	NS	96/115 (83.5)	14/16 (87.5)	NS
Induration distal to MCP	79/113 (69.9)	12/16 (75.0)	NS	92/114 (80.7)	13/16 (81.3)	NS
Peripheral vascular system						
RP	92/117 (78.6)	15/16 (93.8)	NS	101/117 (86.3)	15/16 (93.8)	NS
Digital infarcts	27/107 (25.2)	7/16 (43.8)	NS	36/107 (33.3)	9/16 (56.3)	NS
Positive capillaroscopy	44/81 (54.3)	4/10 (40.0)	NS	67/81 (82.7)	6/10 (60.0)	NS
Respiratory system						
Dyspnoea	12/115 (10.4)	4/15 (26.7)	NS	19/115 (16.5)	6/15 (40.0)	0.03
Basal crackles	3/116 (2.6)	3/16 (18.8)	0.02	8/116 (6.9)	6/16 (37.5)	0.001
Abnormal chest X-rays	14/105 (13.3)	5/15 (33.3)	NS	31/105 (29.5)	12/15 (80.0)	0.0001
Reduced DL_{CO}	13/69 (18.8)	1/12 (8.3)	NS	32/70 (45.7)	8/12 (66.7)	NS
Reduced FVC	19/88 (21.6)	2/14 (14.3)	NS	49/90 (54.4)	10/14 (71.4)	NS
Cardiac involvement						
Pericarditis	4/116 (3.4)	3/16 (18.8)	0.03	8/117 (6.8)	8/16 (50.0)	0.0001
Heart failure	0/114 (0.0)	4/16 (25.0)	<0.001	4/115 (3.5)	8/16 (50.0)	0.0001
Arrythmias	1/117 (0.9)	2/16 (12.5)	0.03	4/116 (3.4)	4/16 (25.0)	0.008
Pulmonary hypertension	2/84 (2.4)	2/14 (14.3)	NS	5/83 (6.0)	6/14 (42.9)	0.001
Muskulo-skeletal system						
Muscle weakness	17/114 (14.9)	5/16 (31.3)	NS	30/114 (26.3)	7/16 (43.8)	NS
Arthritis	27/115 (23.5)	6/16 (37.5)	NS	35/115 (30.4)	8/16 (50.0)	NS
Arthralgia	34/117 (29.1)	6/15 (40.0)	NS	47/117 (40.2)	9/15 (60.0)	NS
Gastrointestinal system						
Dysphagia	13/115 (11.3)	3/16 (18.8)	NS	24/115 (20.9)	9/16 (56.3)	0.002
Gastroesophageal reflux	11/110 (10.0)	5/16 (31.3)	0.03	30/110 (27.3)	12/16 (75.0)	0.0001
Diarrhoea	4/115 (3.5)	0/16 (0.0)	NS	11/115 (9.6)	4/16 (25.0)	NS
Weight loss	22/116 (19.0)	3/15 (20.0)	NS	33/116 (28.4)	7/15 (46.7)	NS
Renal system						
Raised serum creatinine	1/115 (0.9)	1/16 (6.3)	NS	3/115 (2.6)	4/16 (25.0)	0.004
Hypertension	2/116 (1.7)	0/16 (0)	NS	4/116 (3.4)	1/16 (6.3)	NS
Nervous system						
Seizures	1/116 (0.9)	0/16 (0.0)	NS	1/116 (0.9)	2/16 (12.5)	0.04

NS = $P > 0.05$.

obtained (Table 2). In this analysis, an increase of creatinine level was much more frequent in the deceased patients (25.0 *vs* 2.6%, $P = 0.004$) while the only one recorded renal crisis occurred in a surviving patient. Also CNS involvement was more consistent in deceased patients, as shown by the frequency of seizures (12.5 *vs* 0.9% $P < 0.05$).

No statistically significant differences between the two groups of patients were observed for laboratory tests and autoantibody profile.

To identify independent predictors, multivariate analysis was performed utilizing logistic regression (step-wise method). Due to the retrospective nature of the study, and to the small number of deceased patients, the multivariate analysis was performed using clinical characteristics that at diagnosis and during the overall course of the disease were significantly related with fatal outcome. Disease duration at diagnosis, gastroesophageal reflux, dyspnoea, pulmonary fibrosis on chest X-rays, heart failure, arrhythmia, pericarditis and raised serum creatinine level were included in the multivariate analysis. The best-fitting model for prediction of poor outcome included fibrosis on chest X-rays [odds ratio (OR) 11.1; 95% CI 1.3, 90.3; $P = 0.02$], raised creatinine levels (OR 22.7; 95% CI 1.3, 369.0; $P = 0.02$) and pericarditis (OR 41.3; 95% CI 4.7, 360.3; $P = 0.001$), while a short time interval between disease onset and diagnosis seems to be protective (OR 0.3; 95% CI 0.09, 0.99; $P = 0.05$). Although the high range of 95% CI limits due to the little number of deceased patients, comparing our predictions to the obtained outcomes, the model appears rather reliable with a sensitivity equal to 69.2% and a specificity equal to 97.0%. Overall, 92.4% of the 79 selected cases for the analysis were correctly classified. The classification table concerning predicted and observed cases shows for the model a 81.8% positive predictive value and a 94.1% negative predictive value.

Discussion

To our knowledge this is the first report focusing on the identification of factors affecting survival in a large cohort of children with SSc. The participation in the data collection of centres from all over the world with a good response rate make this study representative, although ethnic or geographical bias could have been introduced [1]. Moreover, our choice to exclude SSc patients that did not satisfy ACR classification criteria, those lost to follow-up and those with overlap features may have narrowed the population studied.

In general, as previously reported, the survival rates in children are higher than in adults as probably explained by the development of comorbid conditions in older patients.

Previous studies in adults demonstrated that factors most related with mortality were severity of internal organ involvement and extension of skin disease. In particular, in two prospective studies of 237 and 264 adult patients, the presence of cardiac, pulmonary, gastrointestinal or renal involvement within the first year of presentation was associated with a poor survival [8–10]. Indeed, the importance of the dcSSc subset as risk factor for higher mortality was also reported in large studies in adults [7, 10, 11]. The extension of skin involvement was not significant in our analysis probably because in children a clear-cut differentiation between the various subsets is difficult as the limited cutaneous form is extremely rare [1]. Moreover, no validated skin score for children is available and the usual

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parameters for adult skin scores cannot necessarily be extrapolated to a paediatric population, as shown by a recent publication in which healthy children have increased skin scores, according with the modified Rodnan skin score [12]. Furthermore, in our study, probably for the small number of deceased patients, no relationship was found between serological features, age at onset, gender and mortality, while in adult series the presence of anti-topoisomerase I antibodies, an older age and the male gender have been associated with poorer survival [7, 9, 11].

In our cohort, using multivariate analysis, we observed that fibrosis on chest X-rays, raised creatinine levels and pericarditis are strongly and independently predictive of death, while a short time interval between disease onset and diagnosis seems to be protective. In children with SSc, cardiac involvement as prominent feature associated with fatal outcome was previously described by other authors [2, 13].

The only available data on outcome of large numbers of children with SSc appear similar to ours for the lower mortality compared with adults and for the significance of internal organ involvement in patients with fatal outcome [2, 14]. However, in the first report, the studied population also included children with OS and MCTD, which differ from SSc for some clinical and serological features [2] and, in the second one, the evaluation of organ involvement was based only on the judgement of the referring physician and not from objective data [14].

Indeed, in our cohort of patients, those with fatal outcome showed a significantly shorter time interval between onset of disease and diagnosis. This observation suggests that in patients with fatal outcome the clinical manifestations were very severe since the onset of the disease, allowed an earlier diagnosis and lead rapidly to death, as showed by the fact that most of the deaths occurred in the first 5 yrs after diagnosis.

Based on these observations we could speculate that in children SSc may have two possible evolutions: few children have a rapid development of internal organ failure leading to severe disability and eventually to death, while other patients experience a slow insidious course of the disease with lower mortality. The milder course was not only related to the presence of limited cutaneous involvement (as all patients with the limited subtype presented a good outcome) but indeed, a substantial group of patients (106 patients) with diffuse SSc, without severe onset, had a mild course and good prognosis. Further prospective studies are needed to confirm these preliminary observations.

Rheumatology key messages

- First report on identification of factors affecting survival in children with SSc by statistical analysis.
- Most cases of JSSc with fatal outcome show rapid progression and early internal organ involvement.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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