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Concise Report

Clinical science

Systemic sclerosis sine scleroderma is more aggressive in children than in adults

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Abstract

Objectives: To compare the clinical and laboratory features of paediatric SSc *sine scleroderma* (ssJSSc) with adult-onset ssSSc.

Methods: Demographic, clinical and laboratory data of ssJSSc, retrospectively retrieved from our hospital medical records, case reports from the literature and from the Pediatric Rheumatology European Society JSSc registry, were compared with the Padua cohort of adult patients with ssSSc. Patients were defined as having ssSSc if they never had skin involvement but all the following features: (i) RP and/or digital vasculopathy, (ii) positive ANA, (iii) internal organs involvement typical of scleroderma and (iv) no other defined CTD.

Results: Eighteen juvenile and 38 adult-onset ssSSc patients, mean disease duration 5.8 and 9.7 years, respectively, entered the study. The frequency of females affected was significantly lower in ssJSSc (38.9% *vs* 89.5%, $P<0.0001$). When compared with adults, ssJSSc displayed fewer SSc-specific capillaroscopy abnormalities (68.8% *vs* 94.7%, $P=0.02$) while having significantly higher vascular (digital pitting scars, ulcers 35.3% *vs* 10.5%, $P=0.042$), respiratory (50.0% *vs* 23.7%, $P=0.02$) and cardiac (50.0% *vs* 2.6%, $P<0.0001$) involvement. The outcome was significantly worse in ssJSSc as six patients (33%) died ($n=3$) or reached an end-stage organ failure ($n=3$) in comparison with only two deaths (5.3%) in the adult cohort. ACA were significantly lower in children (20.0% *vs* 68.4%, $P=0.001$) while no difference was noted for other SSc-specific autoantibodies.

Conclusion: Compared with adults where ssSSc generally has an indolent course, children present with aggressive disease that heralds a worse prognosis characterized by high cardiorespiratory morbidity and mortality.

Keywords: scleroderma, cardiomyopathy, digital ulcers, juvenile systemic sclerosis, pulmonary arterial hypertension.

Rheumatology key messages

- Little is known about difference between SSc *sine scleroderma* in children (ssJSSc) and in adults (ssSSc).
- We compared the clinical and laboratory features of ssJSSc with adult-onset ssSSc.
- SsJSSc presents a more aggressive course and a worse prognosis than in adults.

Introduction

SSc is a multisystem CTD that presents with skin thickening and widespread fibrosis of internal organs, along with vascular manifestations such as RP and digital ulcers. The disease is rare, with a reported incidence varying between 8 and 56 cases per million persons per year, with juvenile-onset forms (JSSc) accounting for only 5% of total cases [1–3]. The 2007 ACR/ Pediatric Rheumatology European Society (PRES)/ PRINTO classification criteria for JSSc require the presence of skin induration proximal to MCP joints and at least 2 of 20 minor criteria [4]. Seemingly, according to the most recent 2013 ACR/EULAR classification criteria for adult SSc, a typical skin presentation is sufficient for the diagnosis [5]. Based on the extent of skin involvement, two distinct disease subsets are identified, dcSSc and lcSSc [6], which are characterized by different clinical feature and associated autoantibody profiles, as well as different prognosis [7]. Nonetheless, up to 10% of adult patients with SSc, despite the presence of typical visceral and vascular involvement, lack the pathognomonic skin manifestations (i.e. skin thickening) and therefore represent a third subset called *sine scleroderma* (ssSSc) [8–14]. In children, this entity has been seldom described. In a recent paper, including a small cohort of juvenile-onset ssSSc patients (ssJSSc), we highlighted a longer delay in diagnosis, a

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more severe cardiac involvement and worse outcome than reported in classic JSSc [15]. The present study aimed to compare the clinical features and the outcome of ssJSSc and adult ssSSc and to identify possible predictors of severe outcome in the two groups.

Methods

We conducted a retrospective study collecting demographic, clinical and laboratory data of both adult and juvenile ssSSc cases. Patients were defined as having ssSSc if they satisfied all the following criteria over the course of the disease: (I) RP or a peripheral vascular equivalent such as digital pitting scars, digital-tip ulcers or scleroderma-specific nailfold capillaries (NFC) pattern [16] (II) positive ANA, (III) any one of the following: distal oesophageal hypomotility, pulmonary interstitial fibrosis, pulmonary arterial hypertension, cardiac involvement typical of scleroderma or renal failure consistent with scleroderma renal crisis, and (IV) exclusion of other defined CTD [8]. Internal organ involvement was defined on the basis of previously reported features [15]. In particular, a regular cardiorespiratory assessment was provided for all, adult and paediatric patients, both at the time of diagnosis and, periodically, thereafter. Cardiac assessment included echocardiography with pulmonary arterial pressure evaluation. Respiratory assessment included chest X-ray, high-resolution CT, and cardiopulmonary testing including diffusing capacity of carbon monoxide and forced vital capacity. Only patients with at least 3 years of follow-up after the diagnosis of ssSSc were included. Data on ssJSSc were retrieved from the Electronic Medical Records (EMRs) of JSSc patients followed at the Pediatric Rheumatology Unit at the University Hospital of Padova since 2000, from two case reports from the literature [17, 18] and from the PRES international registry on JSSc [19], which included data of 153 patients followed in 55 centres (32 European, 8 North American, 11 South American and 4 Asian). In this registry, ssJSSc patients were identified as those with no mention of skin involvement but satisfying the Poormoghim criteria [8]. Data on adult ssSSc patients followed at the Division of Rheumatology of the University Hospital of Padova since 2008 were collected from the EMRs. Standard descriptive statistics was used to characterize demographic and clinical features of the enrolled patients. Comparison between juvenile and adult clinical features was performed using Chi-squared test and Fisher's exact test for qualitative variables or Mann–Whitney *U* test for quantitative variables. A binary logistic regression model by Wald test (backward-stepwise method) was applied to identify predictors of severe outcome in both cohorts and defined as death or end-stage organ failure (ESOF). Statistical significance was considered for *P*-values <0.05. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

A written informed consent was obtained by patients or legal representatives. According to the Padua University Hospital policy, approval from the Ethics Committee was not needed because all information were anonymously collected.

Results

We identified 38 adult and 18 juvenile ssSSc cases. Adult patients were predominantly females (34 patients, 89.5%), and had a mean disease duration of 9.7 ± 6.7 years and a mean age at diagnosis of 49.1 years (Table 1). The ssJSSc cohort included five patients currently followed at our centre and already reported [15], two case reports from the literature [17, 18] and 11 additional patients identified in the PRES Registry. In the ssJSSc cohort, only seven patients (38.9%) were females, a proportion significantly lower than in the adult cohort ($P < 0.001$), mean disease duration was 5.8 ± 3.5 years and mean age at disease onset 9.9 ± 3.4 years. A consistent delay in diagnosis was observed both in ssJSSc (19.6 months) and adult ssSSc (13.9 months). Importantly, disease outcome at the time of the last evaluation was significantly worse in paediatric ssSSc as six patients (33%) deceased ($n = 3$) or reached an ESOF ($n = 3$), in comparison with two deaths (5.3%) in the adult cohort ($P = 0.01$). In the ssJSSc cohort, cardiac arrest was the cause of death in all three deceased patients. Among those who reached ESOF, isolated cardiomyopathy was already present at the time of diagnosis in one patient who underwent cardiac transplantation 4 years after the disease onset. The other two patients developed end-stage cardiorespiratory failure due to concomitant interstitial lung disease (ILD) and cardiomyopathy with dysrhythmia. As for the adult ssSSc cohort, sudden cardiac arrest in one patient and right heart failure due to pulmonary arterial hypertension (PAH) in another patient were the causes of death.

In terms of organ involvement, as shown in Table 1, ssJSSc patients had significantly higher respiratory involvement (55.6% *vs* 23.7%, $P = 0.02$), in terms of ILD and more frequent cardiac involvement when compared with adults (50.0% *vs* 2.6%, respectively, $P < 0.0001$). No difference between the two groups was noted in the frequency of RP (juvenile 94.4% *vs* adult 97.4%), PAH (16.7% *vs* 7.9%), gastrointestinal (61.1% *vs* 68.4%) and musculoskeletal manifestations (16.7% *vs* 18.4%). Digital pitting scars/digital ulcers (DPS/DU) were more frequent in ssJSSc (35.3% *vs*

Table 1. Comparison between paediatric and adult-onset SSc *sine scleroderma*

	Juvenile ssSSc ($n = 18$)	Adult ssSSc ($n = 38$)	*P*
Female sex (%)	7 (38.9)	34 (89.5)	<0.001
Age at diagnosis (years, range)	9.9 (3–17)	49.1 (22–73)	
Disease duration at last evaluation (years)	5.8 (3.5)	9.7 (6.7)	0.025
Delay in diagnosis (months)	19.6 (17.3)	13.9 (8.1)	n.s.
Severe outcome	6 (33.3)	2 (5.3)	0.01
Organ involvement			
RP	17 (94.4)	37 (97.4)	n.s.
DPS/DU	6 (35.3)	4 (10.5)	0.042
Respiratory	9 (50.0)	9 (23.7)	0.019
Renal	0 (0.0)	0 (0.0)	n.s.
Cardiac	9 (50.0)	1 (2.6)	<0.001
Gastrointestinal	11 (61.1)	26 (68.4)	n.s.
Musculoskeletal	3 (16.7)	7 (18.4)	n.s.
2013 ACR/EULAR criteria	8 (44.4)	23 (60.5)	n.s.
SSc-specific NFC pattern	11/16 (68.8)	36 (94.7)	0.02
ANA	17/17 (100)	36 (94.7)	n.s.
SSc-specific autoantibodies	9/15 (60.0)	30 (78.9)	n.s.
Anti-topo I	5/15 (33.3)	5 (13.2)	n.s.
ACA	3/15 (20.0)	26 (68.4)	0.001
Anti-RNA polymerase III	1/15 (6.7)	1 (2.6)	n.s.

Values are numbers (%) or mean (± S.D.). DPS: digital pitting scars; DU: digital ulcers; ssSSc: SSc *sine scleroderma*; NFC: nailfold capillaroscopy;

10.5%, $P = 0.042$). Renal manifestations were not present in either adult or paediatric patients. Interestingly, when the 2013 ACR/EULAR classification criteria were applied, 23 (60.5%) adults and 8 (44.4%) children had a score >9, considered for defined SSc. A significant lower frequency of scleroderma-specific pattern on NFC (68.8% *vs* 94.7%) was noted in the ssJSSc cohort. Autoantibodies profile showed that ACA were significantly lower in children than in adults (20.0% *vs* 68.4%, $P = 0.001$) while no difference was noted for anti-topo I and RNA polymerase III. The application of a binary logistic regression analysis did not identify any significant predictors of death/ESOF between single or combined demographic, clinical and laboratory parameters in both cohorts. However, cardiac involvement showed a trend toward significance in the paediatric cohort (odds ratio 8.0, 95% CI 0.66–97.3, $P = 0.103$).

Discussion

In this study, we compared the clinical and laboratory features of adult and paediatric patients with ssSSc, highlighting some key differences in terms of organ involvement and disease outcome. ssSSc in adults is a well-known entity although its exact characterization is still a subject of debate. In various reported cohorts, the characteristics of adult scleroderma patients without cutaneous involvement have been compared with those with 'classic' dcSSc and lcSSc forms [8–13]. In most studies, it emerges that the features of ssSSc are more similar to those of lcSSc, in terms of both organ involvement and disease severity, appearing more indolent compared with dcSSc. This seems to be confirmed in our cohort of adult patients as well, where we also observed a high prevalence of positivity for ACA, typical of lcSSc [9]. Some authors argue that ssSSc can be considered a milder form of lcSSc [8, 9] although several other studies have reported relevant differences between ssSSc and lcSSc, allowing for the identification of ssSSc as a subtype on its own [10–14].

As we previously reported in a smaller series of patients, ssJSSc is much more frequent in males (61%) than in both adult ssSSc (10%) and even classic JSSc (25%) [15]. This would make a male patient without skin features more notable for cardiopulmonary evaluation if they had RP and/or digital ulcers and ANA positivity. This is less true for respiratory involvement as it is significantly more present in ssJSSc than in adults (50% *vs* 23%) but it has also a high frequency in classic juvenile forms (59%), therefore representing a characteristic of juvenile-onset disease *per se* [15].

Interestingly, a recent study from the European Scleroderma Trials and Research (EUSTAR) cohort identified a better survival as discriminating feature between ssSSc and the other SSc subtypes. In ssSSc, in fact, the survival rate was 92.8%, which is similar to our results in adults where the mortality was 5.2% [14]. This finding is strikingly different from what we observed in our ssJSSc cohort, where extremely severe disease outcomes were present in one-third of cases, with a mortality rate of 17%. This difference is likely explained by the different pattern of organ involvement that characterizes the two cohorts. In fact, paediatric patients have a much higher cardiac and respiratory involvement compared with adults [19] and, in fact, deaths and ESOF were essentially due to cardiorespiratory failure. The occurrence of ssSSc in adults is considered underestimated in clinical practice because of the absence of any skin involvement associated to mild disease manifestations [13]. In children, ssJSSc also is probably underestimated despite the fact that the clinical manifestations are not mild, as in adults. In fact, before the diagnosis of ssJSSc, most of our paediatric patients were followed by various paediatric specialists for isolated respiratory, cardiac or gastrointestinal manifestations and RP has been the index of suspicion for an underlying connective tissue disorder. Another aspect that distinguishes ssJSSc from the adult-onset forms is the more rapid progression of the microangiopathic dysfunction, confirmed by the higher frequency of DPS/DU. On the contrary, our adult cohort and other studies have highlighted that in adult ssSSc the frequency of DPS/DU is even lower than that reported in lcSSc [10, 11, 13, 20]. In our adult ssSSc cohort, patients show a rather slower course that represents a useful prognostic factor at diagnosis in individual patients [13, 20, 21]. The enlargement of our previously reported cohort [15] with data obtained from the PRES international registry allowed us to confirm that ssJSSc in children is a highly aggressive disease compared with the adult form. This contrasts with what was generally found in the comparison between adult and paediatric forms of 'classic' SSc, as the latter typically tends to have a better prognosis with less frequent organ involvement and mortality rate [22]. As for the debate on whether or not ssJSSc should meet the 2013 ACR/EULAR classification criteria, our data confirm that, when more inclusive criteria are applied [5], less than half of paediatric patients and only 60% of adult ssSSc actually met the 2013 ACR/EULAR criteria. This was predictable, considering that the presence of cutaneous manifestations is the item that carries the highest weight in the classification scoring, being potentially usable alone to confirm the diagnosis. However, patients who did not meet the minimum criteria had other key non-criterion disease-specific findings (i.e. typical involvement of the distal esophagus) that led to the diagnosis. Our findings underline the distinct nature of ssSSc in children and emphasizes that in the presence of typical scleroderma manifestations such as RP, ILD, PAH and/or cardiomyopathy, in the absence of cutaneous involvement, ssJSSc should always be considered. This suspicion should be confirmed by checking for SSc-specific autoantibodies and typical capillaroscopy changes. A diagnostic delay, more pronounced in ssJSSc, might be an additional factor contributing to the worse disease outcome observed in paediatric patients as they are identified late in the disease course when organ complications are already advanced. Possible limitations of the present study include its retrospective nature and the heterogeneous sources of the data on paediatric patients. As for the first point, we adopted strict diagnostic criteria proposed for adults [8] and a prolonged observation period of at least 3 years, as cut-off, to exclude early lcSSc patients. Our choice was also justified by the need to identify homogeneous criteria to compare our cohort with other adult series. The retrospective nature of the study allowed both of these requirements to be met. As for the second aspect, since ssJSSc is quite a rare condition, it was necessary to draw from multiple sources to obtain a proper number of cases to make our results more reliable. This was also warranted by the quality of the academic centers and physicians that provided the cases and by the completeness of the PRES registry data themselves. Lastly, despite the rather large cohort of children with ssJSSc, considered the rarity of the condition, the sample size was still too small and the power of the estimates of the logistic regression analysis

obtained from the model was therefore limited. In conclusion, our study shows that ssSSc in children follows a much more aggressive course than in adults and is characterized by high cardiorespiratory morbidity and mortality. When evaluating patients with possible scleroderma manifestations such as RP, isolated cardiomyopathy, PAH or ILD, ANA with SSc-specific autoantibodies and NFC pattern should be promptly looked for in order to achieve an earlier diagnosis and treatment.

Data availability

Additional unpublished data from the study are available by sending an e-mail to Francesco Zulian (francescozulian58@gmail.com).

Contribution statement

F.Z. and E.Z. are the senior authors. F.T., E.Z. and F.Z. designed the study. G.M., A.M. and F.T. performed the systematic literature review. A.M., G.M., M.B. and B.M. contributed with patients to the study. C.G. reviewed the radiological imaging of each patient. F.V. performed the statistical analysis. F.T. wrote the first draft of manuscript and all the other co-authors revised and approved the final version of the manuscript.

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