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Concise report

Juvenile and young adult-onset systemic sclerosis share the same organ involvement in adulthood: data from the EUSTAR database

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Abstract

Objective. The aim of the present study was to explore the long-term outcome and clinical characteristics of adult patients with juvenile onset in the EULAR Scleroderma Trials and Research (EUSTAR) cohort and compare them with adult patients with onset between 20 and 40 years of age.

Methods. From the EUSTAR SSc cohort two patient groups were analysed: patients with juvenile SSc (jSSc) who are adults at present, and patients diagnosed between the age of 20 and 40 years (aSSc). Demographic data of the patients, organ involvement and outcome of the disease were examined using the Minimal Essential Data Set database system.

Results. From 5000 patients in the EUSTAR cohort, 60 patients (1.2%) with jSSc and 910 patients (18%) with aSSc were selected according the inclusion criteria. In the jSSc group, the mean age of disease onset was 12.4 years (range 2–15.9 years), and in the aSSc group, the mean age was 32 years (range 20–40 years). Disease subsets were similar. The antibody profile was also comparable except for ACAs, which were positive in 5% of the jSSc group and 26.9% of the aSSc group ($P < 0.005$). Organ involvement (lung, kidney, joint, muscle and heart) was similar in the two groups of patients at the time of the last follow-up.

Conclusion. The subset distribution in the jSSc and aSSc cohorts was found to be similar. Only the frequency of ACAs was significantly lower in the jSSc, which supports the hypothesis that the SSc patients with paediatric onset in the adult cohort may represent a distinct subgroup of the complete cohort of paediatric patients.

Key words: juvenile scleroderma, juvenile systemic sclerosis, systemic sclerosis, outcome, prognosis, organ involvement, diffuse subtype, limited subtype, antibody profile, EUSTAR.

CLINICAL SCIENCE

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Introduction

Juvenile SSc (jSSc) is a rare disease in childhood, with an estimated incidence of 0.05 per 100 000 [1] and a prevalence of ~1 in 1 000 000. It has been hypothesized that ~10% of all SSc patients develop the disease before the age of 16 years but nothing is known about whether puberty has any influence on the incidence. One of the major problems that has to be discussed frequently with a jSSc patient and his/her family is the long-term outcome of the disease. Obviously survival of the affected patient is a pivotal problem, and it is known that the 5-year survival of jSSc patients ranges between 95% [2] and 93% [3] according to the two existing multinational retrospective paediatric surveys. Approximately 90% of the patients in

these paediatric cohorts are affected by the diffuse form of SSc; this appears to be a different disease pattern compared with the adult cohorts. However, at present, only few data are available addressing the long-term outcome of these patients from youth to adulthood. Therefore the purpose of our study was to explore the long-term outcome and clinical characteristics of adult patients with juvenile onset SSc (jSSc) and compare them with young adult-onset SSc (aSSc) patients from the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) [4].

Methods

Up to April 2006, 5000 patients were registered in the EUSTAR database [4]. Patients were classified according to the ACR preliminary classification criteria [5], and the subset was defined according to the LeRoy criteria [6]. In this database, data of the patients were collected in the Minimal Essential Data Set (MEDS) [MEDS parameters and video coaching material are also available at the EUSTAR website (http://www.eustar.org)] [4], which has been established by a consensus process of the EUSTAR members. It covers demographic aspects, disease duration, organ involvement and laboratory data. Patient data were extracted from this database, selecting subjects with the first non-Raynaud presentation before the age of 16 years. This group was split into early-onset jSSc, onset of first non-Raynaud symptoms before the age of 10 years (prepubertal) and late-onset (pubertal) jSSc with age of onset after the age of 10 years. (The mean age of girls starting puberty reaching Tanner stage 2 is between 9.5 and 9.7 years [7], and for boys with systemic JRA it is 10.8 years [8]. This explains the cut-off at the age of 10 years.) We chose as comparison patients who had the first non-Raynaud presentation between 20 and 40 years of age. Demographic data, organ involvement, laboratory data and outcome of these patients were evaluated according to the guidelines of the MEDS database [4]. A comparison with previous published series was performed using the Student's *t*-test for statistical analysis with the significance set at $P < 0.05$.

Results

Sixty patients (1.2% of the whole EUSTAR cohort) with jSSc (juvenile onset, age of onset before the age of 16 years) were identified, 55 females and 5 males (female : male = 11 : 1). Interestingly, when we divided patients by age of onset before or after the age of 10 years, the male/female ratio was significantly different between the two groups ($P = 0.012$). It was 1 : 2.75 before 10 years of age compared with 1 : 21.5 between 10 and 16 years of age (Table 1). The disease subset distribution also differed: patients with prepubertal onset had an increased proportion of diffuse subset patients: 60% compared with 35% ($P = 0.192$). None of the prepubertal patients had ACAs ($P = 0.673$). The modified Rodnan skin score was significantly higher in patients with prepubertal onset: 17.5 compared with 10.7 in those with onset after the age of 10 but < 16 years ($P = 0.027$). Interestingly, patients with prepubertal onset had less gastrointestinal involvement ($P > 0.05$). The proportions of patients with pulmonary fibrosis were similar. The mean age at disease onset in the whole jSSc group was 12.4 years (range 2–15.9) with a mean disease duration of 17.6 years (1.8–54.8).

The aSSc (adult-onset) group, age of onset between 20 and 40 years, consisted of 910 patients (representing 18% of the EUSTAR cohort). In all, 810 of the patients were females and 100 were males (male : female = 1 : 8.1). Mean age at disease onset was 32 years (range 20–40). The mean disease duration was 12.5 years (2–47.5). The disease was active according to EUSTAR activity score [4] at the time of last follow-up in 26.6% of jSSc patients and 24.8% of aSSc patients. In jSSc, 59 (98%) of the 60 patients were alive at the last follow-up and 1 was lost to follow-up. In aSSc, 898 (99%) patients were alive at the last follow-up, 7 died and 5 were lost to follow-up (Table 2). The distribution of the disease subsets was statistically not different. In the whole jSSc group, 42% of patients had a diffuse subset, 49% had a limited subset and 9% had an overlap syndrome. In aSSc, 38.2% of patients had a diffuse subset, 53.1% had a limited subset and 8.7% had an overlap syndrome (Table 2).

The antibody profile was also comparable with regard to the presence of ANA: 90% in the jSSc group and 92.8% in the aSSc group. Anti-Scl-70 was positive in 40% of the jSSc and 40.7% of aSSc patients. There was a significant difference in the frequency of ACAs, 5% in the jSSc group and 27.8% in the aSSc group ($P < 0.005$) (Table 2). Organ involvement showed a similar pattern in the two groups of patients at the time of the last follow-up (Table 3), with no significant difference in any of the evaluated and affected organs.

Discussion

Our study shows interesting differences in prepubertal- and pubertal-onset patients with adult jSSc. Prepubertal children have a significantly increased proportion of male patients and significantly higher mean modified Rodnan skin score (Table 1). The main difference between jSSc and aSSc patients is the significantly decreased frequency of ACAs in the jSSc patients. Scalapino *et al.* [9] and Foeldvari *et al.* [13] found a similar decreased frequency of ACAs in a similar study looking at paediatric-onset patients in adulthood (Table 4). It could be hypothesized that this reflects the predominance of the diffuse subset in childhood, persisting only in the antibody profile but not in the amount of skin involvement. As adult patients were characterized by the physician currently treating them, they could have had diffuse-onset disease in childhood. In our jSSc cohort, the number of patients with anti-Scl 70 was 40% compared with 33% in the Royal Free cohort [12] and 23% in the Pittsburgh cohort [9]. Despite the difference in antibody expression, we could not demonstrate significant differences regarding organ involvement between the groups in the EUSTAR cohort. These results are in contrast to the data from Scalapino *et al.* [9], in which the study groups were

Table 1 Characteristics of patients with first non-Raynaud symptoms before the age of 10 and between 10 and 16 years of age

Characteristics of patients and organ involvement	First non-Raynaud <10 years of age	First non-Raynaud >10 years of age	*P*
Number of patients	15	45	–
Age at disease onset, mean (range), years	7.57 (2–10)	13.79 (10–16)	–
Sex (female/male)	4 (26)/11	1 (2.2)/44	0.012
Disease duration, years	17.8	17.15	–
Alive	15	45	–
ACR criteria fulfilled	13/15	40/45	–
Disease subset[a]			
Diffuse	9 (60)/15	15 (36)/42	0.192
Limited	5 (33)/15	23 (55)/42	0.300
ANA positive	12 (80)/15	42 (93)/45	0.159
ACA positive	0 (0)/15	3 (6.8)/44	0.673
Anti-Scl 70 antibody positive	6 (40)/15	18 (40)/45	1.000
Raynaud's	14 (93)/15	43 (95)/45	1.000
Digital ulceration	4 (28)/14	17 (38)/45	0.281
Modified Rodnan skin score, median (range)	16 (2–36)	7 (0–42)	0.027
Active at last follow-up	3 (20)/15	14 (31)/45	–
Proteinuria	1 (6.6)/15	1 (2)/44	0.585
Renal hypertension	1 (6.6)/15	4 (9)/45	1.000
Renal crisis	0 (0)/15	0 (0)/45	–
Arthritis	1 (6.6)/15	5 (11)/45	1.000
Contractures	6 (40)/15	12 (27)/45	0.347
Muscle weakness	2 (13)/15	10 (10)/45	0.712
Gastrointestinal involvement			
Oesophagus	6 (40)/15	30 (66)/45	0.126
Stomach	1 (6.6)/15	9 (20)/45	0.426
Colon	1 (6.6)/15	8 (18)/44	0.568
Pulmonary fibrosis	3 (20)/15	11 (24)/45	1.000
Pulmonary hypertension	2 (13)/15	6 (14)/44	1.000

Data are represented as *n* (%)/total *n*, unless otherwise mentioned. [a]Some data missing, therefore not 100%.

defined as onset of disease before the age of 16 years and young adults with onset of disease between 16 and 40 years of age. They found significant differences in organ involvement: the mean modified skin score at presentation and the frequency of renal crisis were lower in the juvenile-onset group, whereas skeletal muscle involvement was twice as frequent in the juvenile-onset group [9]. Unlike our study, the Pittsburgh survey also found a significantly higher proportion of jSSc patients with overlap syndrome and this observation was confirmed in the population of the Royal Free cohort [13].

Although disease duration at last follow-up was similar in the Pittsburgh survey and our cohort, the survival of our paediatric patients was not different from the adult-onset patients; survival was worse in the paediatric group in the Pittsburgh cohort [9]. The survival rate in the Royal Free cohort at 5, 10, 15 and 20 years was 100, 98, 95 and 82%, respectively, comparable to that of the EUSTAR cohort. One of the explanations for these differences could be that the recruitment of patients in the Pittsburgh cohort started in 1960, whereas in the EUSTAR cohort and Royal Free cohort the patients were followed and treated more recently. During this time period the mortality of SSc changed significantly [10], with a better outcome in the current era. Another explanation is the difference in ethnic background of the study populations. This is pointed out in a publication from the Pittsburgh group when comparing the Pittsburgh cohort with a French cohort, where the patients are predominantly Caucasian, with a less severe disease course in the latter [11]. The Caucasian ethnic pattern is also prevalent in the EUSTAR cohort.

The subset distribution in favour of dSSc is unique to this juvenile SSc cohort [3], whereas the adult juvenile-onset patients in all three cohorts have a subset distribution similar to that of adult-onset SSc patients, but the Royal Free cohort and the Pittsburgh cohort consist of a significant proportion of patients (37%) with overlap features [13]. The adult prepubertal-onset patients show a similar increased diffuse subset dominance. This change in the subset distribution over time from paediatric to adult jSSc patients is presumably the result of a survival bias of the limited subset or of decreased skin involvement of diffuse patients over time.

It is noteworthy that the antibody profile is similar in the juvenile-onset cohorts in adulthood (Table 4), with a low number of patients with ACAs, a feature that appears to be predominant in jSSc patients. In the publication from

Table 2 Characteristics of the adult jSSc and aSSc patients from the EUSTAR cohort

Characteristics of patients and organ involvement	Adult jSSc (age of diagnosis <16 years of age)	aSSc (age at diagnosis between 20 and 40 years of age)	*P*
Number of patients	60	910	–
Sex (female/male)	55 (92)/5	806 (89)/100	0.744
Age at disease onset, mean (range), years	12.4 (2–15.9)	32 (20–40)	–
Disease duration, mean (range), years	17.6 (1.8–54.8)	12.5 (2–47.5)	–
Alive, *n*	59 (1 lost to follow-up)	898 (5 lost to follow-up)	–
Disease subset			
Diffuse	24 (42)/57	344 (38.2)/900	0.055
Limited	28 (49)/57	478 (53.1)/900	0.056
Overlap	5 (9)/57	78 (8.7)/900	0.071
Modified Rodnan skin score, median (range)	9 (0–42)	9 (0–43)	0.697
ANA positive	54 (90)/60	838 (92.8)/903	0.642
Anti-Scl 70 antibody positive	24 (40)/60	361 (40.7)/886	0.639
ACA positive	3 (5)/59	245 (27.8)/880	0.000
Active disease at last follow-up, %	26.6	24.8	–

Data are represented as *n* (%)/total *n*, unless otherwise mentioned.

Table 3 Clinical characteristics of the juvenile onset and young adult-onset SSc EUSTAR cohort

Organ involvement	Adult jSSc cohort (age at onset <16 years of age) (*n* = 60)	aSSC cohort (age at onset between 20 and 40 years of age) (*n* = 910)	*P*
RP	95	95.1	1.000
Digital ulcers	35	41.3	0.208
Pulmonary hypertension	13.3	14.4	1.000
Pulmonary fibrosis	23.3	36	0.058
Hypertension	8.3	11	0.727
Renal crisis	0	2	0.707
Proteinuria	3.3	5.8	0.556
Oesophageal involvement	60	65.2	0.509
Gastric involvement	16.7	26.1	0.228
Intestinal involvement	15	22.4	0.210
Synovitis	10	15.4	0.558
Joint contractures	30	36.9	0.574
Muscle weakness	20	24.2	0.615
Tendon friction rub	8.3	12.2	0.574

Data are represented as percentages, unless otherwise mentioned.

the Pittsburgh cohort, the assessment and comparison with the EUSTAR cohort for each organ system is difficult due to lack of recorded data. However, hypertension appears to occur more often in the adult juvenile cohort and synovitis occurs more often in the paediatric-age juvenile cohort.

The strengths of our data consist in the large number of cases collected and examined by experts in the field using a pre-designed survey tool. A weakness is that it is a cross-sectional survey at many centres without standardized assessment of organ involvement and serology.

Our study presents one of the largest adult jSSc patient cohorts compared with an adult cohort of aSSc patients. Interestingly, the antibody profile with the low frequency of ACAs persists into adulthood. The subset pattern of the jSSc cohort in adulthood resembles that of adult-onset patients in all other ways. Interestingly, we could even show some differences in patients with disease onset before and after 10 years of age; especially interesting is the higher rate of males aged <10 years. The survival bias is presumably related to the higher rate of death in the juvenile-onset diffuse SSc patients between the paediatric age and the time of observation in the EUSTAR cohort or to the decreasing skin involvement over time. To gain knowledge regarding the disease between the paediatric and adult cohorts, the prospective Juvenile Systemic Scleroderma Inception Cohort Project (ww.juvenile-scleroderma.com) could help, where new-onset jSSc

TABLE 4 Comparison of juvenile-onset patients in the EUSTAR, Pittsburgh and Royal Free cohorts [7, 12]

	EUSTAR cohort ($n = 60$)	Pittsburgh cohort ($n = 111$)	Royal Free cohort ($n = 52$)
Age at disease onset, mean (range), years	12.4 (2–15.9)	NA	14.0 (5–15.9)
Disease duration, mean (range), years	17.64 (1.8–54.8)	17.2	
Sex (male/female), *n/n*	5/55	19/92	13/39
Disease subset diffuse, %	40	35	46
Overlap	NA	29	37
Disease subset limited, %	46.7	40	54
Survival, %	Last follow-up 98% at 17.64 years	89% at 5 years, 69% at 20 years	100% at 5 years, 82% at 20 years
Lost to follow-up, %	2	NA	22
ANA positive, %	90	97	92
Anti-Scl 70 positive, %	40	23	33
ACA positive, %	5	0	2
RP, %	95	96	100
Pulmonary hypertension, %	13.3	3.6	13
Pulmonary fibrosis, %	23.3	9	54
Renal crisis, %	0	3.6	2
Hypertension, %	8.3	NA	NA
Proteinuria, %	3.3	NA	NA
Synovitis, %	10	NA	NA
Muscle weakness, %	20	NA	NA
Tendon friction rub, %	8.3	NA	NA

NA: in the publication, data not published.

patients with a disease course of <18 months are followed prospectively.

Rheumatology key messages

- The subset distribution of jSSc patients in adulthood and the aSSc cohort was similar.
- Only the frequency of ACAs was significantly lower in jSSc patients than in adult-onset SSc patients.

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