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Are diffuse and limited juvenile systemic sclerosis different in clinical presentation? Clinical characteristics of a juvenile systemic sclerosis cohort

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Abstract

Introduction: Juvenile systemic sclerosis is an orphan disease. Currently, the majority of juvenile systemic sclerosis cohort studies are retrospective in design without standardized assessment. This study was conducted prospectively to investigate the difference in manifestations of limited cutaneous juvenile systemic sclerosis and diffuse cutaneous juvenile systemic sclerosis subtypes. An additional aim was to compare these data to other juvenile systemic sclerosis cohorts and a large adult systemic sclerosis cohort.

Methods: Patients fulfilling the Paediatric Rheumatology European Society juvenile systemic sclerosis classification criteria were included. Clinical characteristics and patient-related outcomes were assessed.

Results: In all, 88 patients with a mean disease duration of 3.5 years were enrolled, 72.5% with diffuse cutaneous juvenile systemic sclerosis with a mean modified Rodnan Skin score of 18 and 27.5% with limited cutaneous juvenile systemic

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sclerosis with mean modified Rodnan Skin score of 9. The mean age at the onset of Raynaud's and first non-Raynaud's symptoms was similar in both groups, approximately 9 and 10.5 years. Active digital tip ulcerations were present in 29% diffuse cutaneous juvenile systemic sclerosis and none in the limited cutaneous juvenile systemic sclerosis subjects ($p = 0.005$). Of those with cardiopulmonary testing, 3% of diffuse cutaneous juvenile systemic sclerosis and 23% of limited cutaneous juvenile systemic sclerosis group had cardiac involvement ($p = 0.015$), and 41% diffuse cutaneous juvenile systemic sclerosis and 22% of the limited cutaneous juvenile systemic sclerosis group had pulmonary involvement ($p = 0.009$). Physician global disease damage assessment was higher in the diffuse cutaneous juvenile systemic sclerosis group compared to the limited cutaneous juvenile systemic sclerosis group: 35 and 15 ($p = 0.021$).

Discussion: The majority of this international juvenile systemic sclerosis cohort had diffuse cutaneous juvenile systemic sclerosis (72.5%) with more frequent vascular and pulmonary involvement compared to the limited cutaneous group, who had increased cardiac involvement. Our cohort reflects prior findings of published juvenile systemic sclerosis cohorts and emphasizes a difference in the presentation compared to adult-onset systemic sclerosis.

Keywords

Juvenile scleroderma, juvenile systemic sclerosis, organ involvement, patient-related outcomes, diffuse cutaneous subset, limited cutaneous subset

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Introduction

Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. The estimated incidence rate is 0.27 (95% confidence interval (CI): 0.1–0.5) per million children according to a cross-sectional study by Herrick et al.[1] The estimated prevalence is 3 per million children based on data from the US claims data base.[2] To date, there have been a low number of studies characterizing the clinical features of jSSc. In addition, the majority of published case series have been retrospective. The exception is the prospective jSSc cohort from the University of Pittsburgh.[3] The two largest retrospective cohorts include 153[4] and 135 jSSc patients,[5] respectively. Both cohorts are multicentre and multinational cross-sectional surveys with cross-sectional chart review in design. In addition, there are also some smaller monocentric retrospective cohorts reported.[6–8] The assessment of organ involvement was not standardized in most of these studies and differs across the studies.

We present data of our cohort enrolling jSSc patients who were assessed by a standardized protocol at time of enrolment, reflecting good clinical practice. We provide a summary characterization of demographic and organ manifestations, with a focus on the differences between the diffuse and limited cutaneous subtypes of jSSc within this cohort and compare these findings to the literature.

Methods

Study procedure

The coordinating study centre of the jSSc inception cohort is based at the Hamburger Centre of Paediatric and Adolescent Rheumatology. Initially, the study was planned to enrol only patients with new onset jSSc, a disease duration of less than 18 months after onset of first non-Raynaud's organ involvement and the patient fulfilling the Paediatric Rheumatology European Society (PRES) classification criteria for jSSc.[9] Patients have to be under the age of 18 years at time of the inclusion into the cohort. The cohort started enrolment in January 2008, but due to slow recruitment the inclusion criteria were modified in 2014 to include all patients diagnosed with jSSc,[9] irrespective of the disease duration. The study was continuously advertised at international meetings and through the paediatric rheumatology mailing list. The included patients are prospectively followed every 6 months for at least 60 months with a standardized assessment. Approval from the coordinating ethical review board for this project was received in 2007, with an amendment addressing the expanded inclusion criteria approved in May 2014. The enrolment period for this publication was from January 2008 to April 2016.

Measurements

Patient's sociodemographic characteristics, comorbidities and SSc clinical characteristics were collected at baseline. This study was conducted under minimal financial support. Therefore, there was no opportunity to conduct teaching sessions for standardization of assessments. Organ involvement was assessed using a standardized clinical research form (CRF) for each organ system. Patients were classified into diffuse (dcSSc) and limited cutaneous subset (lcSSc).[10] Antinuclear antibody (ANA) positivity was defined as ANA $\geq$ 1:80. Anti-Scl-70 and anticentromere and other extractable nuclear antigen (ENA) antibodies were also assessed. Elevated erythrocyte sedimentation rate (ESR) was defined as ESR > 20 mm/h. Elevated C-reactive protein (CRP) was defined by CRP > 5 mg/L.

Forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) were considered decreased

when <80% of expected value was recorded. Pulmonary hypertension (PH) was screened by echocardiogram via estimates of pulmonary artery pressure by measuring the tricuspid regurgitation velocity (<2.8 m/s normal). Interstitial lung involvement was considered, if FVC was decreased <80% and/or high-resolution computed tomography (HRCT) of the lungs showed signs of interstitial lung disease (ILD), and other causes of FVC decrease were excluded by the treating physician. Cardiac involvement was defined as an abnormal echocardiogram finding, such as pericardial effusion, abnormal ejection fraction, left ventricular (LV) or right ventricular (RV) diastolic dysfunction or abnormal electrocardiography (ECG) finding. Renal involvement was considered, when there was a history of prior hypertension, hypertension was present at the baseline visit, or when a positive urinary sediment with significant proteinuria or renal crisis occurred prior or at the time of enrolment. Renal crisis was defined as acute severe hypertension (>150/85), acute renal failure (>30% reduction in estimated glomerular filtration rate), microangiopathic haemolytic anaemia and an elevated creatinine.[11] Gastrointestinal (GI) involvement was assessed by reported symptoms: diarrhoea (>3 stools/day), constipation (stooling < than once every 3 days), reflux symptoms, and by evaluation with barium swallow, oesophageal scintigraphy, endoscopy and colon scintigraphy based on the decision of the treating clinician. Skin involvement was assessed by the modified Rodnan Skin score (mRSS).[12] Nailfold capillary changes were assessed by different methods, including dermatoscope and microscope, and it was queried as normal or abnormal, and the pattern could be commented.[13] Musculoskeletal involvement was clinically assessed by total joint count and assessment of muscle strength. All organ evaluation methods were conducted locally at the discretion of the treating physician.

Patient-reported outcomes

Patient-related outcomes included several visual analogue scales (VAS), scores 0–100, regarding the impact of the disease on the patient in regard to global disease activity, global disease damage, Raynaud's activity and ulceration activity. Patient/parent assessment of functional ability was collected through the Childhood Health Assessment Questionnaire (CHAQ).

Physician assessment

Physician global assessment via VAS scales, scores 0–100, was ascertained regarding global disease activity, global disease damage and ulceration activity.

Statistical analyses

Statistical analyses were conducted using SAS software version 9.4. Categorical variables were reported by absolute and relative frequencies and continuously distributed variables by means and standard deviations. Comparison between patients with diffuse and limited cutaneous subtype of jSSc was performed using chi-square test for categorical variables and linear regression analysis for continuously distributed variables, with robust estimated standard errors for the regression coefficients. A p value of <0.05 was considered to be statistically significant.

Results

Demographics

A total of 80 patients from 26 participating centres from 17 countries were enrolled. The geographic distribution of the centres includes 16 from Europe, 4 from South America, 2 from North America and 4 from Asia. The characteristics of the patients are summarized in Tables 1–9. Patient demographics and the subtype distribution are summarized in Table 1. In all, 58 patients (72.5%) were classified as dcSSc and 22 as lcSSc (27.5%). Patients with overlap features were included within the diffuse cutaneous juvenile systemic sclerosis (dcjSSc) and limited cutaneous juvenile systemic sclerosis (lcjSSc) groups, 6 within the dcSSc and 5 within the lcSSc.

The majority of subjects were Caucasian females in both the dcSSc and lcSSc subtypes (Table 1). The mean age at onset of Raynaud's symptoms was 9.0 years in the dcjSSc and 10.4 years in lcjSSc group ($p = 0.446$), and the mean age at onset of first non-Raynaud's symptom was 9.4 in dcjSSc and 10.9 in lcjSSc ($p = 0.30$). The mean disease duration at the time of enrolment was 3.7 years in the dcjSSc and 3.0 years in lcjSSc subjects, with a mean age at enrolment of 13.1 years (dcjSSc) and 13.9 years (lcjSSc).

Growth parameter assessment of the total cohort ($n = 80$) using standardized scores for paediatric age and sex showed in 18% a body mass index (BMI) standard deviation score (SDS) < –2, in 36% a height SDS < –2 and in 39% a weight SDS < –2. Tanner developmental stages were age appropriate.

Laboratory evaluation and antibody profile

ANA positivity was present in 79% and 76% of the dcjSSc and lcjSSc patients tested for ANA positivity, respectively. The frequency of anti-Scl-70 was similar in both groups, approximately 30%, while there was a difference in the anticentromere positivity, 6% in the dcjSSc and 15% in the lcjSSc. Antibodies to other specific ENA's, such as RNA Polymerase III, Pm-Scl and Th/To were not assessed. General inflammatory markers, such as ESR and CRP, were not commonly elevated (Table 1).

Organ manifestations

Skin and vascular changes. The mRSS at enrolment (Table 1) was 18.2 in the dcjSSc and 9.1 in lcjSSc ($p = 0.004$). Capillary abnormalities were found in 62% in the dcjSSc and 55% in

Table 1. Clinical characteristics of the patients at the time of inclusion into the cohort: demographic, subtype distribution, antibody profile and distribution of cutaneous and vascular involvement.

	Whole group (N = 80)	Diffuse subtype (N = 58)	Limited subtype (N = 22)	p value between diffuse and limited
Female-to-male ratio	4.3:1 (65/15)	4.8:1 (48/10)	3.4:1 (17/5)	0.667
Ethnicity				
Caucasian	71 (89%)	51 (88%)	20 (91%)	0.710
African	4 (5%)	4 (7%)	0 (0%)	
Indian	3 (4%)	1 (2%)	2 (9%)	
Mean disease duration (years), mean (SD)	3.5 (3.1)	3.7 (3.2)	3.0 (2.5)	0.590
Mean age of onset of Raynaud's symptoms (years), mean (SD)	9.4 (4.0), 8 non-Raynaud	9.0 (3.8), 5 non-Raynaud	10.4 (4.3), 3 non-Raynaud	0.446
Mean age of onset of non-Raynaud's symptoms (years), mean (SD)	9.9 (4.1)	9.4 (3.7)	10.9 (4.6)	0.300
Autoantibody positivity				
ANA	78% (60/77)	79%* (44/56)	76%* (16/21)	0.937
Anti-Scl-70	31% (24/77)	30% (17/56)	33% (7/21)	0.856
Anticentromere	9% (4/46)	6% (2/33)	15% (2/13)	0.363
Inflammatory markers				
ESR elevated (>20 mm/h)	26% (20/76)	30% (17/57)	16% (3/19)	0.344
CRP elevated (>5 mg/L)	16% (11/70)	17% (9/52)	11% (2/18)	0.590
Cutaneous				
Mean modified Rodnan skin score	15.7 (0–51); n = 79	18.2 (0–51); n = 57	9.1 (0–24); n = 22	0.004
Vascular				
Raynaud's phenomenon	90% (72/80)	91% (53/58)	86% (19/22)	0.878
Nailfold capillary changes	60% (48/80)	62% (36/58)	55% (12/22)	0.757
History of ulceration	50% (39/78)	60% (34/57)	23% (5/22)	0.068
Active ulceration	26% (10/56)	29% (10/34)	0% (0/22)	0.005

SD: standard deviation; ANA: antinuclear antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

the lcjSSc patients (Table 1). Data were limited to provide summary results regarding nailfold capillary pattern. History of fingertip ulceration was fairly common in dcjSSc (60%), compared to 23% in lcjSSc (p = 0.068), with active open ulcerations in one-third of the dcjSSc and none in the lcjSSc group (p = 0.005).

Cardiopulmonary disease was assessed by ECG, cardiac ultrasound, HRCT and/or pulmonary function tests. There were no patients with documented cardiac magnetic resonance imaging (MRI). The frequency of testing is documented in Table 2, which was limited in part due to young age of testing. In general, 70% of the jSSc patients had an ECG, 60% had an echocardiogram, 60% had PFTs with FVC, only 35% with DLCO and 56% with HRCT performed. Of the 18 patients with FVC under 80%, 7 had a proven ILD on HRCT, 6 of the 16 in the diffuse subtype group and 1 of the 2 in the limited subtype group. *ILD* was identified by HRCT in 56% (n = 18) dcjSSc subjects and 23% (n = 3) in lcjSSc group (p = 0.128) in those with imaging. Decreased FVC%, less than 80% predicted, occurred in 44% in the dcjSSc and in 15% in lcjSSc (p = 0.180). The DLCO parameter of the PFTs was assessed less frequently (n = 28 of total cohort), and it was lower than 80% predicted in approximately 50% of both diffuse and limited jSSc subjects. The mean distance walked in the 6-min walk test was 392 m in the dcjSSc group and 504 m in the lcjSSc group (p = 0.391); however, this information was only available in 21 patients (Table 2).

Any cardiopulmonary involvement, defined as either cardiac involvement, PH or ILD, occurred in 47% of the dcjSSc and 55% in the lcjSSc patients, given constraints of those tested. While cardiac involvement was more prevalent in lcjSSc than in dcjSSc (23% vs 3%), pulmonary involvement was more common in dcjSSc, than in lcjSSc (41% vs 23%; Table 2). The most common cardiac manifestations were conduction abnormalities, which occurred in 2 dcjSSc (first-degree atrioventricular (AV) block, incomplete right bundle-branch block (RBBB)) and 2 lcjSSc (atrial arrhythmia, supraventricular extrasystole) patients, followed by 1 lcjSSc subject each with the following: pericarditis, mitral insufficiency and tricuspid insufficiency.

The frequency of *PH* detected in those with echocardiograms performed was 14% (n = 4) in dcjSSc and 13% (n = 1) in lcjSSc (Table 2). No data on right heart catheterization were reported.

Renal involvement (Table 3). No patients had hypertension at the initial visit or had a history of SSc renal crisis prior to enrolment.

GI involvement (Table 3) was assessed by specific tests in 45% in the dcjSSc and 50% in the lcjSSc group based on

Table 2. Clinical characteristics of the patients at the time of inclusion into the cohort: cardiopulmonary involvement.

	Whole group (N = 80)	Diffuse subtype (N = 58)	Limited subtype (N = 22)	p values between diffuse and limited
Number of patients assessed for cardiopulmonary involvement	81% (65/80)	78% (45/58)	91% (20/22)	0.666
ECG done	71% (57/80)	67% (39/58)	82% (18/22)	0.605
Cardiac US done	59% (47/80)	50% (29/58)	82% (18/22)	0.206
FVC done	60% (48/80)	62% (36/58)	55% (12/22)	0.757
DLCO done	35% (28/80)	33% (19/58)	41% (9/22)	0.640
HRCT done	56% (45/80)	55% (32/58)	59% (13/22)	0.868
Pulmonary				
FVC < 80%	37% (18/48)	44% (16/36)	15% (2/12)	0.180
DLCO < 80%	53% (15/28)	53% (10/19)	56% (5/9)	0.937
6-min walk test **(**mean (SD))	419.3 m (138.2); n = 21	392.6 m (141); n = 16	504.6 m (85); n = 5	0.391
Interstitial lung disease Assessed by HRCT	47% (21/45)	56% (18/32)	23% (3/13)	0.128
Total pulmonary involvement	36% (29/80)	41% (24/58)	22% (5/22)	0.009
Cardiac				
Pulmonary hypertension Assessed by US	11% (5/47)	14% (4/29)	13% (1/18)	0.603
Total cardiac involvement	9% (7/80)	3% (2/58)	23% (5/22)	0.015

ECG: electrocardiography; US: ultrasound; FVC: forced vital capacity; DLCO: diffusing capacity of the lungs for carbon monoxide; HRCT: high-resolution computed tomography; SD: standard deviation.

Table 3. Clinical characteristics of the patients at the time of inclusion into the cohort: renal and gastrointestinal involvement.

	Whole group (N = 80)	Diffuse subtype (N = 58)	Limited subtype (N = 22)	p values between diffuse and limited
Renal				
Assessed by urine test	6% (5/80)	7% (4/58)	5% (1/22)	0.714
Proteinuria	4	4	0	–
Erythrocyturia	1	0	1	–
Hypertension Assessed by RR	0% (0/80)	0% (0/58)	0% (0/22)	–
Gastrointestinal				
Number of patients assessed for gastrointestinal involvement	46% (37/80)	45% (26/58)	50% (11/22)	0.803
Endoscopy done	15% (12/80)	17% (10/58)	9% (2/22)	0.425
Oesophageal scintigraphy done	9% (7/80)	7% (4/58)	14% (3/22)	0.389
Barium swallow done	26% (21/80)	24% (14/58)	32% (7/22)	0.599
Colon scintigraphy done	0% (0/80)	0% (0/58)	0% (0/22)	–
Total gastrointestinal involvement	33% (26/80)	38% (22/58)	18% (4/22)	0.212
Oesophageal involvement	69% (18/26)	68% (15/22)	75% (3 /4)	0.909
GI beside oesophageal	31% (8/26)	32% (7/22)	25% (1/4)	0.093

RR: relative risk.

the treating clinician's judgement. Of those with diagnostic testing, GI involvement was present in 38% of dcjSSc and 18% of lcjSSc group (p = 0.212), with the majority having oesophageal involvement in both groups. The most commonly used assessment was barium swallow. Approximately one-third of the subjects had other GI manifestations, such as diarrhoea and constipation.

Musculoskeletal involvement (Table 4) was present in 58% in dcjSSc and 73% in lcjSSc group. In both subsets, joint contractures dominated with 42% in dcjSSc and 55% in lcjSSc (p = 0.542), while swollen joints were rarely observed. Muscle weakness occurred in 17% in the dcjSSc and 27% in the lcjSSc group (p = 0.553), and creatine kinase (CK) was elevated in 21% in the dcjSSc and in 8% in the lcjSSc group (p = 0.36). Only in 2 patients with dcjSSc, CK elevation coincident with muscle weakness, and 6 patients had muscle weakness without any CK elevation.

Table 4. Clinical characteristics of the patients at the time of inclusion into the cohort: musculoskeletal involvement.

	Whole group (N = 80)	Diffuse subtype (N = 58)	Limited subtype (N = 22)	p values between diffuse and limited
Musculoskeletal	62% (49/79)	58% (33/57)	73% (16/22)	0.563
Joint manifestation				
Patients with swollen joints	35% (17/49)	36% (12/33)	31% (5/16)	0.724
Number of joints with pain on motion	43% (21/49)	39% (13/33)	50% (8/16)	0.482
Patients with contractures	45% (35/77)	42% (23/55)	55% (12/22)	0.542
Muscle manifestation				
Muscle weakness	20% (9/46)	17% (6/35)	27% (3/11)	0.553
Muscle weakness and joints' contractures	13% (6/46)	11% (4/35)	18% (2/11)	0.616
Muscle weakness with no contractures	7% (3/46)	6% (2/35)	9% (1/11)	0.713
Tendon friction rub	10% (7/70)	11% (6/53)	6% (1/17)	0.515

Table 5. Clinical characteristics of the patients at the time of inclusion into the cohort: patient-related outcomes.

	Whole group N = 80 Mean (min–max)	Diffuse subtype N = 58 Mean (min–max)	Limited subtype N = 22 Mean (min–max)	p values between diffuse and limited
Patient global disease activity	44 (0–100) n = 40	44 (0–100) n = 36	46 (30–55) n = 4	0.891
Patient global disease damage	42 (0–90) n = 39	42 (0–90) n = 35	34 (0–50) n = 4	0.482
Patient Raynaud activity	30 (0–100) n = 64	32 (0–100) n = 53	21 (0–75) n = 11	0.525
Patient ulceration activity	17 (0–100) n = 67	19 (0–100) n = 55	11 (0–57) n = 12	0.355
CHAQ	0.4 (0–2.5) n = 51	0.4 (0–2.5) n = 40	0.4 (0–1.25) n = 11	0.722
Physician global disease activity	38 (0–90) n = 44	40 (0–90) n = 36	25 (5–50) n = 8	0.370
Physician global disease damage	32 (0–80) n = 43	35 (0–80) n = 36	15 (0–45) n = 7	0.021
Physician ulceration activity	15 (0–83) n = 69	17 (0–83) n = 56	10 (0–57) n = 13	0.579

CHAQ: Childhood Health Assessment Questionnaire.

Neurologic involvement was observed in only one patient in each subset; a dcSSc patient with carpal tunnel syndrome and an lcSSc patient with a demyelinating sensorimotor axonal polyneuropathy.

Patient-reported outcomes and global assessment

The mean patient global disease activity score assessed by a visual analogue (VAS) score (0–100) was 44 in the dcjSSc and 46 in lcjSSc (Table 5). The mean patients' global disease damage was 42 in the dcjSSc and 34 in lcjSSc (p = 0.482). Raynaud's activity assessed by a VAS score (0–100) was 32.0 in the dcjSSc and 21 in the lcjSSc group (p = 0.525). Patients' ulceration activity assessed by a VAS score (0–100) was 19 in the dcjSSc and 11 in the lcjSSc group (p = 0.355). The mean CHAQ score was 0.4 in both subtypes.

Physician global assessment

Table 5 describes the physician global assessments. The disease activity global and digital ulcers VAS assessments were not significantly different between the dcjSSc and lcjSSc groups, while the global disease damage physician assessment was significantly higher in the dcjSSc group (35 vs 15; p = 0.021). In the lcjSSc group, patients/parents judged the disease activity and disease damage higher than the treating physician (Table 5).

Subanalyses of cohort

Differences in the clinical presentation according to gender

A subanalysis was performed to examine for gender differences. Results are described in Table 6. The majority

Table 6. Clinical differences in the patients' characteristics in the cohort according gender.

	Female (N = 66)	Male (N = 14)	p value
Diffuse subtype	48 (72.7%)	10 (71.4%)	0.982
Diffuse overlap	6	0	
Limited subtype	18 (27.3%)	4 (28.6%)	
Limited overlap	5	0	
Caucasian	59 (89.4%)	12 (85.7%)	0.834
African	4 (6.1%)	2 (14.3%)	
Indian	2 (3%)	0 (0%)	
Yemenite	1 (1.5%)	0 (0%)	
Mean disease duration (years)	3.6 (±3.1)	3.3 (±2.9)	0.671
Mean age of onset of Raynaud's symptoms (years)	9.4 (±4.1) 8 non-Raynaud	9.3 (±3.9) 0 non-Raynaud	0.913
Mean age of onset of non-Raynaud's symptoms (years)	10.0 (±4.1)	9.1 (±3.9)	0.834
Disease-modifying drugs	75.8% (50/66)	85.7% (12/14)	0.418
6-Minute Walk Test (mean, SD)	441.4 m (±116.1) n = 18	286.7 m (±179.8) n = 3	0.035
Musculoskeletal	55.4% (36/65)	92.9% (13/14)	0.009
Total contractures	38.1% (24/63)	78.6% (11/14)	0.006
Tendon friction rub	6.7% (4/60)	33.3% (3/9)	0.013
Patient global disease activity	41.9 (0–100); n = 34	58.3 (30–80); n = 6	0.041
Physician global disease activity	34.3 (0–90); n = 38	58.3 (30–80); n = 6	0.037
Physician global disease damage	26.2 (0–70); n = 37	68.3 (40–80); n = 6	0.001

SD: standard deviation.

Table 7. Clinical differences in the patients characteristics in the cohort according anti-Scl-70 positivity or negativity.

	Anti-Scl-70 negative N = 53	Anti-Scl-70 positive N = 24	p value
Female-to-male ratio	5.6:1 (45/8)	3:1 (18/6)	0.628
Diffuse subtype	39 (73.6%)	17 (70.8%)	0.867
Diffuse overlap	5	0	
Limited subtype	14 (26.4%)	7 (29.2%)	
Limited overlap	4	0	
Caucasian	49 (92.4%)	20 (83.3%)	0.834
African	4 (7.5%)	2 (8.3%)	
Indian	0 (0%)	1 (4.2%)	
Yemenite	0 (0%)	1 (4.2%)	
Mean disease duration (years)	3.7 (±3.1)	3.4 (±3.0)	0.671
Mean age of onset of Raynaud's symptoms (years)	9.5 (±3.8) 6 non-Raynaud	9.7 (±4.1) 1 non-Raynaud	
Mean age of onset of non-Raynaud's symptoms (years)	9.8 (±4.0)	10.3 (±4.0)	0.846
Disease-modifying drugs	71.7% (38/53)	87.5% (21/24)	0.129
ANA	75.5% (40/53)	86.4% (19/22)	0.294
Anticentromere	6.1% (2/33)	15.4% (2/13)	0.312
CRP elevated (>5 mg/L)	8.5% (4/47)	35% (7/20)	0.007
Abnormal findings in HRCT	58.1% (18/31)	23.1% (3/13)	0.034
Number of joints with decreased range	57.7% (30/52)	29.2% (7/24)	0.021

ANA: antinuclear antibody; CRP: C-reactive protein; HRCT: high-resolution computed tomography.

of the cohort was female (82.5%). Dichotomizing the cohort into male and female demonstrated similar predominance of dcSSc seen in the total cohort (72%), as well as similar disease onset and duration, although the male patients were slightly younger at the presentation of the first non-Raynaud's symptoms with a mean age of 9.1 years versus 10.0 years. Clinical variables were assessed between the two sexes for differences. The majority of organ manifestations were similar; however, there were a few clinical items that demonstrated

Table 8. Clinical differences in patient characteristics in the cohort according to age at inclusion under the age of 10 years and over the age of 10 years.

	<10 years at first visit N = 16	> 10 years at first visit N = 64	p value
Female-to-male ratio	3:1 (12/4)	5.4:1 (54/10)	0.688
Diffuse subtype	14 (87.5%)	44 (68.7%)	0.574
Diffuse overlap	0	6	
Limited subtype	2 (12.5%)	20 (31.2%)	
Limited overlap	1	4	
Caucasian	14 (87.5%)	57 (89.1%)	0.972
African	1 (6.25%)	5 (7.8%)	
Indian	0 (0%)	2 (3.1%)	
Yemenite	1 (6.25%)	0 (0%)	
Mean disease duration (years)	2.3 (±1.8)	3.9 (±3.2)	0.539
Mean age of onset of Raynaud's symptoms (years)	4.3 (±2.3) 0 non-Raynaud	11.0 (±3.0) 8 non-Raynaud	0.027
Mean age of onset of non-Raynaud's symptoms (years)	4.8 (±2.1)	11.2 (±3.3)	0.074
Disease-modifying drugs	81.2% (13/16)	76.6% (49/64)	0.688
Telangiectasia	54.5% (6/11)	21% (8/38)	0.030
Gastrointestinal beside oesophageal	12.5% (2/16)	1.6% (1/64)	0.039
Physician global disease activity	57.9 (10–90); n = 7	33.7 (0–80); n = 37	0.037

Table 9. Medication at the time of inclusion into the cohort.

	Whole group	Diffuse subtype	Limited subtype	p value
Number of patients	**80**	**58 (72.5%)**	**22 (27.5%)**	
Medication	86% (62/71) 9 patients – no data	86% (44/51) 7 patients – no data	90% (18/20) 2 patients – no data	0.671
Corticosteroids	58% (36/62)	61% (27/44)	50% (9/18)	0.410
Biologic and nonbiologic DMARDs				
Methotrexate	56%(35/62)	54%(24/44)	61%(11/18)	0.636
Mycophenolate mofetil	18% (11/62)	18% (8/44)	17%(3/18)	0.887
Azathioprine	2% (1/62)	2% (1/44)	0% (0/18)	0.519
Cyclophosphamide	8% (5/62)	11% (5/44)	0% (0/18)	0.136
CQ/HCQ	16% (10/62)	14% (6/44)	22% (4/18)	0.404
Adalimumab	0% (0/62)	0%	0%	–
Tocilizumab	2% (1/62)	0% (0/44)	6% (1/18)	0.115
Rituximab	3% (2/62)	2% (1/44)	6% (1/18)	0.507
Non-DMARDS				
Bosentan	18% (11/62)	23% (10/44)	6%(1/18)	0.108
PDE5 inhibitors	6% (4/62)	7% (3/44)	6% (1/18)	0.886
Prostanoids	2%(1/62)	0% (0/44)	6% (1/18)	0.115
Ca channel blockers	40% (25/62)	43% (19/44)	33% (6/18)	0.473
ACE inhibitors	25 (1/62)	0% (0/44)	6% (1/18)	0.115
AT1 receptor blockers	2% (1/62)	2% (1/44)	0% (0/18)	0.519
Anticoagulants	2% (1/62)	2% (1/44)	0% (0/18)	0.519

The percentage refers to the relative proportion of patients with diffuse or limited subtype.

a significant difference, pointing towards more severe disease in male patients compared to female patients. These include the 6-min walk distance (268.7 m/441.4 m; p = 0.035), number of patients with musculoskeletal involvement (92.9%/55.4%; p = 0.009), number of patients with joint contractures (78.6%/38.1%; p = 0.006) and number of patients with tendon friction rubs (33.3%/6.7%; p = 0.013; Table 6). There were significant differences regarding the patient-related outcomes and physician global assessment also between male and female patients, including physician global disease activity (58.3%/34.3%; p = 0.037), physician global disease damage (68.3%/26.2%; p = 0.001) and patient-related disease damage (58.3%/41.9%; p = 0.041; Table 6).

Differences in the clinical presentation according to anti-Scl-70 positivity and anti-Scl-70 negativity

In both dcSSc and lcSSc subjects, approximately 30% of the patients are anti-Scl-70 positive. A subanalysis dichotomizing the cohort into anti-Scl-70 positive versus negative was performed to evaluate whether certain clinical features are more strongly associated with Scl-70 antibody positivity in jSSc. Results are summarized in Table 7. Approximately 70% of the patients were classified as diffuse subtype in both groups. There is no significant difference between the groups regarding demographics, age of onset or disease duration at the time of entering the cohort (Table 7). Only a few clinical variables differed significantly between the Scl-70 positive and negative patients. This included a higher CRP in the anti-Scl-70 group (35%/8.5%; $p=0.007$) and a higher percentage of those with an abnormal HRCT (58.1%/23.1%, $p=0.034$) and number of joints with decreased range (57.7%/29.2%; $p=0.021$) in the anti-Scl-70 negative group (Table 7).

Differences in clinical presentation according to the age below 10 years or more than 10 years at the time of inclusion in the cohort

To examine whether a younger age of onset within the jSSc cohort has an impact on clinical features, a subanalysis was performed comparing those enrolled into the cohort under the age of 10 years ($n=16$) versus 10 years or older ($n=64$; Table 8). Although not reaching statistical significance, the proportion of patients with diffuse subtype is much higher under the age of 10 years, with 87.5% having dcSSc, compared to the overall cohort (72%), and $\geqslant$10 years onset (68%). More overlap features were present in the older age group. The mean age of onset was significantly lower in the below 10 years group, with 4.3 years compared to 11.00 years ($p=0.027$), as expected, though with a longer disease duration until enrolment in the older subgroup (3.9 vs 2.9 years). Two clinical characteristics varied significantly between the two groups, the number of patients with telangiectasias (54.5%/21%; $p=0.03$) and with GI involvement beside oesophageal involvement (12.5%/1.6%; $p=0.039$), both being more prevalent in the younger age group. The judgement of the physician regarding global disease activity was significantly higher in the younger patients (57.9/33.7; $p=0.037$; Table 8).

Treatment at the time of inclusion into the cohort

Medication at the time of enrolment was available for 86% of the cohort and is described in Table 9. In general, over half were on corticosteroids and/or methotrexate, followed by mycophenolate mofetil and hydroxychloroquine regarding disease-modifying antirheumatic drug (DMARD) therapy, with only three patients on a biologic DMARD. Calcium channel blockers were the most common vasodilator utilized (40%), followed by a variety of vasodilator agents.

Discussion

We present enrolment data of the first 80 patients included in our prospective international jSSc registry. Given the estimated low incidence rate of jSSc, our cohort of 80 patients is sizable. Interestingly, compared to adult patients, where approximately 30%–40% have diffuse subset,[14,15] we report a higher proportion of patients with 72.5%. This number is between two previously published paediatric cohorts with 90%[4] and with 35%[3] (Table 10). This subset distribution seems to be a characteristic of the paediatric patients, with the predominance of the diffuse subset demonstrated even more vividly in those with younger age of onset in our subanalysis (81% in those below the age of 10 years at enrolment). Organ involvement was similar in this young group of dcjSSc compared to older onset jSSc. The autoantibody profile in jSSc might not correlate as strongly to cutaneous disease subtype as there was an equal amount of subjects with positive antitopoisomerase (30%) in the lcSSc and dcSSc groups, which is more classically associated with dcSSc subtype in adult SSc. As seen in prior jSSc cohorts, anticentromere positivity has a low frequency in jSSc.[3–5] This 'crossing over' of autoantibodies between classical subsets is demonstrated in adult SSc patients in a similar frequency, as described in the large EUSTAR cohort of 7655 patients,[16] where 23% of lcSSc patients have anti-Scl-70 positivity and 7.2% of the dcSSc patients have anticentromere positivity. The caveat in jSSc is the overall lack of identified specific autoantigens. Most jSSc cohorts will demonstrate a high ANA positivity, but typically 40% or less have combined Scl-70 or centromere positivity;[3,4] therefore, basing certain clinical features with autoantibody positivity may be limited. Our subanalysis evaluating for differences in clinical presentation in anti-Scl-70 positive and negative paediatric patients found surprisingly a significantly higher number of patients with interstitial lung disease in the anti-Scl-70 negative group.

In the paediatric population, the female-to-male ratio is much less dramatic, with 4.8:1 in the dcjSSc and 3.4:1 in the lcjSSc group, compared to the adult SSc population with a 6:1 ratio,[17] 4:1 for dcSSc and 10:1 for lcSSc.[16] In the younger age group, we found an even lower ratio of 3:1, which would suggest that hormonal influence in the puberty and after in adult females is a risk factor to develop SSc. In adult SSc, male patients tend to have a more severe disease.[17] We confirmed this observation in jSSc, finding significantly higher rating for physician global disease activity, physician global disease damage and patient rating of physician global disease activity. Clinical features more prevalent in jSSc males include musculoskeletal

Table 10. Comparison of the different paediatric cohorts focused on diffuse subset patients, compared to a large international adult SSc cohort, EUSTAR (n = 7655).[16]

	Cohorts								
	Paediatric						Adult		
	Inception Cohort Total n = 80	dcSSc n = 58	lcSSc n = 22	Foeldvari et al.[5] n = 135	Martini et al.[4] n = 153	Scalapino et al.[3] n = 111	EUSTAR Meier[16] Total n = 7655	dcSSc n = 2838	lcSSc n = 4481
Demographics									
Age onset (years)									
Onset of RP	9.4	9.0	10.4	8.8*	8.1*	11.1*	42.2	42.2	42.1
Onset Non-RP	9.9	9.4	10.9	–	–	–	45.9	44.2	47.2
Follow-up (years)	3.5	3.7	3.0	5.0	3.9	14.4	ND	ND	ND
Sex Female:male	4.3:1	4.8:1	3.4:1	2.8:1	3.6:1	4.1:1	6.1:1	4:1	10:1
Ethnicity (Caucasian, %)	89	88	91	Mostly Caucasian	ND	92%	89.2	84.5	92.1
Subtype (%)									
Diffuse (dcSSc)	72.5	–	–	ND	91	35	37.1	–	–
Limited (lcSSc)	22.5	–	–	ND	9	36	58.5	–	–
Overlap	14% (11)	10% (6)	23% (5)	ND	ND	26% (29)	4	–	–
Organ involvement (%)									
Skin									
mRSS (mean)	15.7	18.2	9.1	ND	ND	19.4	8	16	6
Vascular									
Raynaud	90	91	86	72	84	97	96.3	96.1	96.6
Nailfold capillary changes	60	62	55	ND	39.9	ND	90.9	92.2	90.1
Digital infarcts/ulceration	50	60	23	28.6	29	ND	36	42.4	32.7
MSK									
Joint contracture	45	42	55	79	27	82	32.1	48.7	21.9
Muscle weakness	20	17	27	ND	24.2	32	25	33.5	18.9
GI tract	33	38	18	65	69	74	67+	70+	66+
Oesophageal	22.5	26	13.6	47	31	ND	67.3	69.5	66.4
Pulmonary	36	41	22	50	42	55	60.6	64.1	52.0
Pulmonary hypertension	11	7	5	ND	7.2	7	21.1	22.1	20.7
Abnormal HRCT/fibrosis	26	31	14	ND	23.5	ND	51.9	64.1	43.5

Table 10. (Continued)

	Cohorts								
	Paediatric						Adult		
	Inception Cohort Total n = 80	dcSSc n = 58	lcSSc n = 22	Foeldvari et al.[5] n = 135	Martini et al.[4] n = 153	Scalapino et al.[3] n = 111	EUSTAR Meier[16] Total n = 7655	dcSSc n = 2838	lcSSc n = 4481
Reduced DLCO	19	17	22.7	ND	27.5	ND	–	–	–
Reduced FVC	22.5	27.5	9	ND	41.8	16 severe FVC < 50	–	–	–
Cardiac	9	3	23	44	29	17	37.0	42.1	33.7
Renal									
Proteinuria	5	7	0	13	4.6	4	6.1	8.4	4.4
Hypertension	0	0	0	ND	2.6	4	20.6	20.3	21.2
Renal crisis	0	0	0	0.7	0.7	4	2.1	4.0	1.0
Autoantibodies (%) positive of those tested									
ANA positive	75	76	72	ND	80	97	93.4	93.5	93.7
Anticentromere	5	3.4	9	ND	7.1	8	32.3	7.2	48.2
Anti-Scl-70	30	29	31.8	ND	34	20	36.8	59.8	23.2

ND: not done; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; mRSS: modified Rodnan Skin score; MSK: musculoskeletal; GI: gastrointestinal; HRCT: high-resolution computed tomography; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; ANA: antinuclear antibody.
*Unknown if onset RP or non-RP.

domains of weakness, joint contractures and tendon friction rubs. The gender gap described in the large EUSTAR cohort also observed significant musculoskeletal burden in males compared to females, characterized by muscle atrophy and CK elevation.[18,19]

Despite the preponderance of dcSSc disease subtype in this jSSc cohort compared to adult-onset SSc, renal crisis was not observed in our cohort with a mean disease duration of 3.5 years, compared to 4%–6% frequency in adult patients.[16,19] We also found a lower rate of patients with CRP elevations than expected in an adult population, where one-quarter of the patients have CRP elevation,[16,20] especially early in the disease course. Interestingly, anti-Scl-70 positivity correlates with elevated CRP in our cohort.

Within our juvenile-onset SSc cohort, we observed a few main differences between the diffuse and limited subsets. This includes a higher mRSS, more frequent active ulcerations and pulmonary involvement (mainly consisting of ILD identified by HRCT) in the dcSSc subjects, which mirrors adult SSc cohort data.[21] On the contrary, a higher frequency of cardiac involvement was reported in the lcjSSc subjects, consisting mostly of conduction defects. These subjects tended to also have musculoskeletal organ involvement, supporting an underlying myopathy of both peripheral muscle and cardiac skeletal muscle as demonstrated by Scalapino et al.[3] jSSc cohort and Quartier et al.[21] observations in jSSc. The frequency of PH, around 7%, was similar between the two subsets, and in the other large paediatric cohorts (Table 10), whereas in adult SSc, it is approximately 20%.[16] Although our findings are only a reflection of the true frequency in these subtypes as cardiac and pulmonary testing was not obtained on all subjects.

This is the first prospective study in a large international jSSc patient population, where patient-reported outcomes and physician global assessment data are reported. We demonstrated significantly more damage impact in dcjSSc compared to lcjSSc patients when physicians globally score the patient, presumably physician rating is strongly influenced by the mRSS and the higher ulceration activity. Of interest, children interpret a higher disease activity and severity impact on their VAS compared to the physician's treating them, especially in the lcSSc subtype. jSSc overall does have a more severe impact on general function, as measured by the universally validated and accepted CHAQ instrument, with a mean CHAQ score of 0.4, which is in the same range as juvenile idiopathic arthritis (JIA) patients before starting anti-TNF therapy,[22] higher than juvenile dermatomyositis (JDM; 0.25)[23] and juvenile onset systemic lupus erythematosus (jSLE; 0.25)[24] captured in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) cohort.

There are several prospective SSc registries for adult patients,[25] but ours is the first multicentre international prospective registry in paediatrics with standardized data collection forms, including current assessment methods. The only large prospective paediatric study including 111 patients collected from 1960 to 2003 is single-centre-based study, and the evaluation methods of the patients' organ involvement over such large time period changed significantly.[3]

The secondary aim of this publication was to compare our findings with other historic large paediatric-onset SSc cohorts,[3–5] which are summarized in Table 10. Since our jSSc cohort was predominantly dcSSc subtype, a large EUSTAR adult-onset SSc cohort that contains a large dcSSc patient population was chosen as a comparison[16] (Table 10).

The age of onset, disease duration, female:male ratio and ethnicity is comparable to other historic jSSc cohorts.[3–5] Joint involvement in the paediatric cohorts ranges from 27% to 82%, with our cohort in the middle range with 42.4%, similar in range as the adult comparison. Raynaud's activity is almost universal in all paediatric jSSc cohorts,[3–5] and the higher frequency of nailfold capillary abnormalities and digital ulcers in our cohort is likely secondary to the emphasis placed on these variables in the CRFs, reaching closer to true frequency, which also matches the adult populations. However, the GI involvement is lower in our cohort, and we surmise secondary to the low number of patients with formal GI investigation (46%). We continue to observe less patients with decreased DLCO, FVC and pathologic HRCT of the lung in the paediatric cohorts (Table 10). PH occurs in 7% of the paediatric patients across all cohorts, compared to 22% in the adults. Renal involvement is low in all jSSc cohorts (4%–13%), with renal crisis being extremely rare (⩽4%). Interestingly, hypertension is very low or not observed in the paediatric patients. This could be explained by the missing comorbid conditions in this age group. Muscular involvement ranges from 10% to 32% in the paediatric patients and has been associated with cardiac involvement in the Scalapino et al.[3] cohort as in our cohort.

Our study provides some very unique and interesting blanket of data on jSSc subjects early in the disease course with a mean disease duration of 3.5 years. However, the study has limitations. The results may be interpreted with some caution due to the small sample size and in particular in subgroup analyses. This is a cohort study and the participating clinicians report according to their standard of care in jSSc in the CRF. Performance of additional organ evaluation was not mandatory due to the observational study design and ethical reasons. In consequence, the results of specific organ manifestation screenings include a remarkable proportion of missing data and may be slightly biased to patients with a more severe organ involvement; however, the similarity of organ involvement pattern compared to other jSSc cohorts is reassuring.

Declaration of conflicting interests

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