ARE DIFFUSE AND LIMITED JUVENILE SYSTEMIC SCLEROSIS DIFFERENT IN CLINICAL PRESENTATION?

CLINICAL CHARACTERISTICS OF A JUVENILE SYSTEMIC SCLEROSIS COHORT

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Manuscript word count:

ABSTRACT:

Introduction:

Juvenile systemic sclerosis (jSSc) is an orphan disease. Currently the majority of jSSc cohort studies are retrospective in design without standardised assessment.

This study was conducted prospectively to investigate the difference in manifestations of limited cutaneous (lcjSSc) and diffuse cutaneous (dcjSSc) subtypes. An additional aim was to compare these data to other historic jSSc cohorts and a large established adult onset SSc cohort.

Methods:

Patients fulfilling the PRES jSSc-classification criteria were included. Clinical characteristics and patient related outcomes were assessed.

Results:

Eighty patients were enrolled, 72.5% with dcjSSc with a mean modified Rodnan Skin Score (mRSS) of 18(SD), and 27.5% lcjSSc with mean mRSS of 9(SD). Mean disease duration at enrolment was 3.7 and 3.0 years in dcjSSc and lcjSSc patients, respectively. The mean age at onset of Raynaud's and first non-Raynaud's symptoms was similar in both groups, approximately 9 and 10.5 years old, respectively. Active digital tip ulcerations were present in 29% dcjSSc and none in the lcjSSc subjects(p=0.005). Of those with cardiopulmonary testing, 3% of dcjSSc and 32% of lcjSSc group had cardiac involvement (p=0.024), and 41% dcjSSc and 22% of the lcjSSc group had pulmonary involvement (p=0.009). Physician global disease damage assessment was higher in the dcjSSc compared to the lcjSSc group, 35 and 15 respectively (p=0.021).

Discussion:

The majority of this international jSSc cohort had diffuse cutaneous disease (72.5%), which associated 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 jSSc cohorts and emphasizes a difference in the presentation compared to adult onset SSc.

Key words:

Juvenile scleroderma

Juvenile systemic sclerosis

Organ involvement

Patient related outcomes

Diffuse cutaneous subset

Limited cutaneous subset

Introduction

Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. The estimated incidence rate is 0.27 (95% 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 has been a low number of studies characterising 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. Additionally, 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 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 standardised 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). ANA positivity was defined as ANA $\geq$ 1:80. Anti-Scl70 and anti-centromere and other extractable nuclear antigens (ENA) antibodies were also assessed. Elevated ESR was defined as ESR > 20 mm/hr. Elevated CRP was defined by CRP > 5mg/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 (< 2.8m/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, 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 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 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 to 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 to 100, were 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, continuously distributed variables by means and standard deviations. Comparison between patients with diffuse and limited cutaneous subtype of jSSc were performed using Chi^2-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 centers from 17 countries were enrolled. The geographic distribution of the centers 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. Fifty-eight patients (72.5%) were classified as dcSSc and 22 as lcSSc (27.5%). Patients with overlap features were included within the dcjSSc and 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 time of enrolment was 3.7years 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), respectively.

Growth parameter assessment of the total cohort (n =80) using standardized scores for paediatric age and sex showed 18% had a BMI > 2SD below the mean, 36% had a height > 2 SD below the mean and 39% had a weight > 2SD below the mean. 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. The frequency of anti-Scl 70 was similar in both groups, approximately 30%, while there was a difference in the anti-centromere 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 erythrocyte sedimentation rate and C-reactive protein, 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 in 62% in the dcjSSc and 55% in 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 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. Seven of 18 patients with FVC under 80% had a proven ILD on HRCT, 6 of the 16 in the diffuse subtype group and one of 2 in the limited subtype group. *Interstitial lung disease* 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), it was lower than 80% predicted in approximately 50% of both diffuse and limited jSSc subjects. The mean distance walked in the 6 Minute 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, pulmonary hypertension or interstitial lung disease, 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 (32% 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 (1st degree AV block, incomplete RBBB) and 4 lcjSSc (2 sinus arrhythmias, 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 was reported.

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

Gastrointestinal involvement (Table 3) was assessed by specific tests in 45% in the dcjSSc and 50% in the lcjSSc group based on the treating clinician's judgment. Of those with diagnostic testing, gastrointestinal 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 CK was elevated in 21% in the dcjSSc and in 8% in the lcjSSc group (p=0.36). Only in 2 patients with dcjSSc were CK elevation coincident with muscle weakness, 6 patients had muscle weakness without any CK elevation.

Neurologic involvement was observed in only one patient in each subset; a dcSSc patient with carpal tunnel syndrome, and a 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 gender

A subanalysis was performed to examine for gender differences. Results are described in Table 6. The majority 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 with a mean of 9.1 years versus 10.0 years of age. 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 a significant difference, pointing towards more severe disease in male patients compared to female patients. These include the 6 minute walk distance (268.7m/441.4m; 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 anti-Scl70 positivity and anti-Scl70 negativity

In both dcSSc and lcSSc subjects, approximately 30% of the patients are anti-Scl70 positive. A subanalysis dichotomizing the cohort into anti-Scl70 positive vs. negative was performed to evaluate if certain clinical features are more strongly associated with Scl70 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 (Table7). Only a few clinical variables differed significantly between the Scl70 positive and negative patients. This included a higher CRP in the anti-Scl70 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 at age under 10 years or over 10 years at the time of inclusion in the cohort.

To examine if 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) vs 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, with 87.5% having dcSSc, compared to the overall cohort (72%), and $\geq$10 years onset (68%). More overlap features were present in the older age group. The mean age of onset was significantly lower in the under 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 gastrointestinal involvement beside oesophageal involvement (12.5%/1.6%; p=0.039), both being more prevalent in the younger age group. The judgment 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 are described in Table 9. In general, over half were on corticosteroids and/or methotrexate, followed by

mycophenolate mofetil and hydroxychloroquine regarding DMARD therapy, with only 3 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 to 40% have diffuse subset (14, 15), we report a higher proportion of patients with dcjSSc (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 <age 10 at enrolment). Organ involvement was similar in this young group of dcjSSc compared to older onset jSSc. The auto-antibody profile in jSSc might not correlate as strongly to cutaneous disease subtype as there was an equal amount of subjects with positive anti-topoisomerase (30%) in the lcSSc and dcSSc groups, which is more classically associated with dcSSc subtype in adult SSc. As seen in prior jSSc cohorts, anti-centromere 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-Scl70 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-Scl70 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 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 to 6% frequency in adult patients (16, 20). 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, 21), especially early in the disease course. Interestingly anti-Scl70 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(22). 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 observations in jSSc (22). The frequency of suspected pulmonary hypertension by echocardiography, 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 JIA patients before starting anti-TNF therapy (23), higher than JDM (0.25) (24) and jSLE (0.25) (25) captured in the CARRA cohort.

There are several prospective SSc registries for adult patients (26), 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%, our cohort in the middle range with 42.4%, similar in range as the adult comparison. Raynaud's is almost universal in all paediatric jSSc cohorts (3-5), 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. On the other hand, the gastrointestinal involvement is lower in our cohort, 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 ($\leq$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(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 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.

Acknowledgement:

All authors have nothing to disclose regarding this publication. None of the authors received financial support for this project. No commercial support for the last 5 years, before a nonrestricted start up grant from Actelion form 20.000 €.

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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 (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 (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
Anti-centromere	9% (4/46)	6% (2/33)	15% (2/13)	0.363
Inflammatory markers:				
ESR elevated (>20 mm/hr)	26% (20/76)	30% (17/57)	16% (3/19)	0.344
CRP elevated	16% (11/70)	17% (9/52)	11% (2/18)	0.590

(>5 mg/l)				
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

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 Minute Walk Test **(**mean (sd))	419.3m (138.2) n=21	392.6m (141) n=16	504.6m (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:				
Suspected pulmonary hypertension assessed by US	11% (5/47)	14% (4/29)	13% (1/18)	0.603
Total Cardiac involvement	12% (9/80)	3% (2/58)	32% (7/22)	0.024

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

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:				
Number of 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
Number 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

Table 6.

Clinical significant differences in the patients characteristics in the cohort according gender

	Female **N=66**	**Male** **N=14**	**P-Werte**
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 (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 (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)	441.4m (±116.1) n=18	286.7m (±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

Table 7. Clinical significant differences in the patients characteristics in the cohort according anti-Scl70 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 (years)	9.5 (± 3.8) 6 non-Raynaud	9.7 (± 4.1) 1 non-Raynaud	
Mean age of onset of non-Raynaud´s (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
Anti-centromere	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

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

	< 10years at first visit N=16	> 10years 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 (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 (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 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 patient no data	86% (44/51) 7 patient 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
Anti-coagulants	2% (1/62)	2% (1/44)	0% (0/18)	0.519

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								
	Pediatric						**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 (yrs)	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's	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
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	12	3	32	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

*unknown if onset RP or Non-RP; ND = Not done