Chapter 10
Juvenile Systemic Sclerosis

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Keywords Care for children • Diagnosis • Incidence • jSSc • Juvenile systemic sclerosis • Prevalence • Special issues

Juvenile systemic sclerosis (jSSc) is a rare multisystem connective tissue disease. Approximately 5–10% of all adults with systemic sclerosis (SSc) report the onset of the disease during childhood. It has a variety of clinical manifestations, sometimes different from the adult form. Mixed connective tissue disease (MCTD) and overlap syndromes have features of jSSc and sometimes even fulfill the criteria of jSSc [1]. It is important to differentiate it from juvenile localized scleroderma, which is much more common in the pediatric population, it occurs in 4.7–20 per 100,000, and it is 10 times more frequent than jSSc. It has in most cases a more benign course with the exception of pansclerotic morphea [2]. Localized scleroderma rarely evolves into systemic sclerosis in childhood, although in adults it is well recognized that cases of systemic sclerosis may also demonstrate localized scleroderma.

jSSc is characterized by pathologic thickening and tethering of the skin. It is considered that fibrosis is a consequence of a vasculopathy of the small vessels system, associated with altered endothelial cell function [3], which leads to fibrotic changes of the skin and other organs. Alterations of the immune system, genetic and environmental factors are part of the pathogenesis. Several recent publications review this topic extensively [4–7]. Triggers of the disease are still unclear. A positive family history of SSc is the strongest known risk factor for SSc [8]. This chapter will be focused on clinical characteristics and outcome of jSSc in the childhood, and on the clinical presentation and outcome of jSSc patients in adult cohorts of SSc patients. The specific clinical features of jSSc will be compared to the adult onset systemic sclerosis (aSSc). Unfortunately there is no evidence-based data regarding treatment of jSSc patients. Most of the therapeutic suggestions are derived from the adult literature, and the current therapeutic recommendations of the EULAR/EUSTAR [9, 10], summarizes the current state of evidence-based expert opinion on SSc management.

Incidence and Prevalence

Juvenile systemic sclerosis (jSSc) is a rare autoimmune disease. There are no good data regarding prevalence and incidence. According to a study in Finland around 0.05 per 100,000 is the incidence of the disease [11] and according to a current study from the UK 0.27 (95% CI 0.1–0.5) [12]. According to a current study from Spain [13], where SSc was defined according the Le Roy and Medsger criteria [14] and/or the ACR criteria [15], the overall age- and sex-adjusted annual incidence was 2.3 per 100,000 population aged 15 year and older, the lowest incidence is in the age range 15–44 years with 0.7 per 100 000 people. It is assumed that 5–10% of the patients with systemic sclerosis first develop the disease in childhood.

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J. Varga et al. (eds.), *Scleroderma: From Pathogenesis to Comprehensive Management*,
DOI 10.1007/978-1-4419-5774-0_10,

Classification

For a long time, there were no specific classification criteria for pediatric patients with jSSc. In an effort of the Paediatric Rheumatology European Society (PRES) juvenile scleroderma working group, a new definition for the classification was developed (Table 10.1). This new classification was reached over a Delphi process involving pediatric and adult rheumatologist as pediatric and adult dermatologist specialized in systemic sclerosis. This classification was recently published and it is accepted by the ACR too [1]. The acceptance by the ACR was a very important step to create a common language to classify these patients in most parts of the world. The major expected advantage of this classification criteria is that patients with juvenile systemic sclerosis can be classified earlier, they need to have as major organ involvement the typical skin involvement of the systemic sclerosis in the limited form [16], and two other scleroderma-specific organ manifestation (see Table 10.1 and the publication for detailed description of the organ involvement [1]). It is different from the preliminary adult classification criteria because here, only skin and pulmonary features listed [15] as possible minor criteria. The prospective validation of the childhood criteria is in process, it is part of the prospective juvenile systemic scleroderma inception cohort project: www.juvenile-scleroderma.com. There are ongoing initiatives to update and improve classification criteria for adult SSc, and these are likely to become more similar to those of juvenile SSc.

Diagnosis and Assessment of the Patient

A key clinical goal is earlier detection and diagnosis of jSSc. The typical facial appearance of a child with juvenile onset systemic scleroderma is shown in Fig. 10.1. Raynaud's phenomenon is the presenting symptom in 75% of the patients at time of diagnosis [17] and sclerodactyly is another key feature at onset, but is present only in 37% [17]. Capillaroscopy is not prospectively validated in jSSc patients, in adult studies, it seems to be a valid tool for the diagnosis of SSc specific Raynaud's. In the largest retrospective pediatric study [17], only 10% of patients had capillary changes at disease onset, and 25% at diagnosis of jSSc, although we do not know the number of reporting centers that reviewed capillary changes routinely,

Table 10.1 The provisional classification criteria for juvenile systemic sclerosis

Major criteria	Minor criteria
• Induration[a]/Sclerosis[a]	• Vascular changes[a] • Pulmonary involvement[a] • Gastrointestinal involvement[a] • Renal involvement[a] • Cardiovascular involvement[a] • Musculoskeletal involvement[a] • Neurologic involvement[a] • Serology[a]

[a]Typical for systemic sclerosis – defined in the publication (Zulian et al. [1])

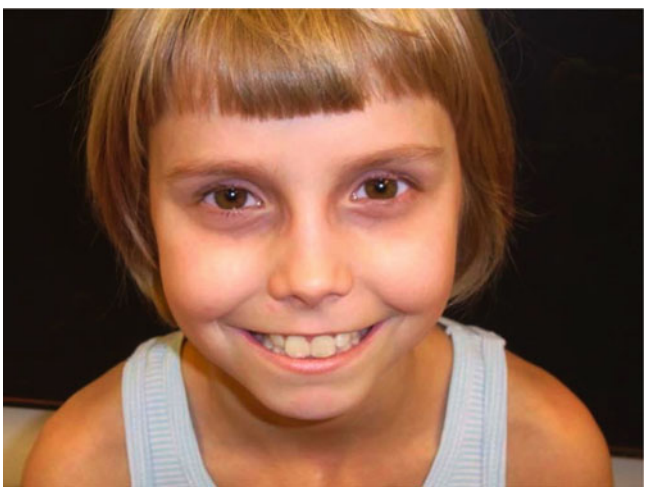

Fig. 10.1 Classical facial appearance of a child with juvenile-onset systemic scleroderma

and what kind of capillaroscopy they used. Video capillaroscopy is the most sensitive for changes, the handheld dermatoscope or ophthalmoscope is a routinely applicable device to see changes, but not for quantitative changes prospectively [18]. Another problematic issue regarding capillaroscopy was pointed out in two studies, where it was shown, that capillary changes in the pediatric age group behave differently from adults, and capillary dimension needs to be age-adjusted, as arterial and venous dimension begin to rise with age [19, 20]. For skin changes, it was shown to, that in the modified Rodnan skin score, which is validated in adults, the applicability cannot automatically be transferred to the pediatric patients. The skin score in healthy children seems to be dependent from the Tanner stage as from the body mass index (BMI) [21]. The durometer, a handheld device, can help to make more objective measures in children. The results of a pilot study were presented at the EULAR meeting 2010 (Foeldvari et al.). A durometer can differentiate between healthy and sclerotic skin, but it has problems to operate, if a bony structure underlies directly under the skin, like fingers, the face, and forefoot.

The 6-min walk test (6MWT) is a well-established primary outcome measure in adult treatment studies for pulmonary hypertension, an important organ involvement in jSSc, is not validated on jSSc patients. There are studies in which they looked at development of norm values of 6MWT in children [22, 23], but the range for the different age groups in the two studies differs significantly; therefore a current study looks at the same issue too (Foeldvari et al., abstract EULAR 2010). It seems to be that the length of the lap and the physical condition correlates with the distance that can be walked in 6 min. Pulmonary function is one of the main dominators of the walk distance in jSSc patients. A current study showed the pulmonary function tests in jSSc patients correlate well with the high-resolution computed tomography findings [24].

There is no specific antibody, which always has to be present to prove the diagnosis. Because most paediatric patients have a diffuse subset, therefore anti-Scl70 is more frequent, it occurs in around 34% [17], and anticentromere antibodies are around 0–7% [17, 25]. Inflammatory markers as sedimentation rate or CRP are elevated only in 34–8% and 12.6% of patients, respectively.

Biologic markers of disease or certain organ involvement are gaining increasing interest, because they enable us to diagnose and follow certain organ involvement or disease activity noninvasively. There a is pilot study regarding anti-KL6 as a serum marker, to evaluate the interstitial lung involvement in children with jSSc [26] and there is a study regarding the prognostic value of B-type natriuretic peptide in children with pulmonary hypertension [27–29].

Clinical Presentation of Patients with Juvenile Systemic Scleroderma

jSSc is an orphan disease, and up till the beginning of the 1990s, only single-case reports and single-case series were published. The first larger cross-sectional cohort based on a multinational survey of a pediatric rheumatologist was published in 2000 [30]. The first prospective data collection of jSSc patients was started recently. In this prospective data collection (www.juvenile-scleroderma.com), only patients with early jSSc, less than 18 months after the first non Raynaud's are included, and prospectively followed with a standardised assessment protocol. Already 20 patients are included in this cohort.

The first large multicentre cross-sectional case collection [30] gained data from 135 jSSc patients. A main surprise of this study was that the mean age of the disease inset of the patients was 8.8 years significantly younger than previously expected. The male:female ratio was 1:2.85, which differs from the adult cohort, with a larger female part of patients. The patients were followed in the mean for 5 years. In the other multicenter cross-sectional study, data of 153 patients were collected and the mean age at disease onset was 8.1 years. The organ involvement at last followed is presented in Table 10.2. Both groups had 63.5–79% joint involvement, followed by 65–69% gastrointestinal involvement. Pulmonary involvement occurred 50–1.8%, not to mention the most common organ involvement in this cohorts. In the cohort of Foeldvari et al., 16% of the patients had central nervous system involvement, which seems to be unique. Renal involvement was relatively low with 13–9.8%. Interestingly in both cohorts, just 1 patient with CREST syndrome was reported; this is part of the limited subtype spectrum. In the cohort of Martini et al., the subtype of the disease was assessed too, and surprisingly, 90.8% of the patients showed a diffuse subtype. In none of the cohorts is data regarding the modified Rodnan skin score is existing, which reflects that pediatric rheumatologist are not familiar to assess this.

The antibody distribution fits to this finding, because only 7.1% of the patients were anticentromere positive in the cohort of Martini et al. In the cohort of Foeldvari et al. no patient was anticentromere antibody positive, despite typical pitting fingertip scars that are reminiscent of a CREST pattern of limited scleroderma in an adult patient (Fig. 10.2).

It has to be mentioned that the population of both cohorts overlap and in both surveys, the evaluation of the organ involvement was not standardised. Both studies are based on retrospective multicentre data evaluation, but despite that, the results from both surveys show comparable results. The results from other recently published monocentric case series, from Japan with 61 patients [31], from South America with 23 cases [32], and from Asia with 23 cases [33], confirmed most of the

Table 10.2 Organ involvement of the patients in the two paediatric multicentre cross-sectional studies

Organ involvement	Foeldvari et al. $n=135$ (%)	Martini et al. $n=153$ (%)
Skin	135 (100)	116 (75,8)*
Joints	106 (79)	97(63,5)
GI tract	88 (65)	106(69)
Only oesoph.	63 (47)	47(31)
Pulmonary	68(50)	64(41,8)
Cardiovasc.	60 (44)	44(28,8)
CNS	21 (16)	4 (3)
Renal	17 (13)	15 (9,8)
Muscular	13 (10)	37(24,2)
Raynaud's	97 (72)	128(83,7)
Calcinosis	36 (27)	28(18,3)
Sjögren's syndr.	7 (5)	?
CREST	1	?

75.8 skin induration; 66 % sclerodactyly; 44.1 % edema

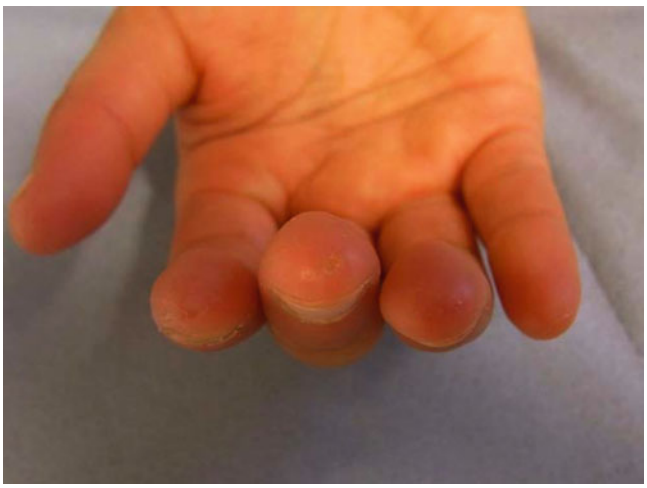

Fig. 10.2 Scarring on the finger tips associated with severe secondary Raynaud's in jSSc

previous findings. There seems to be some ethnic differences in the east Indian population [33], 39% of the patients showed a limited subtype; in all other case series, the diffuse subtype dominated with 90.9 up to 100%. The prevalence of the anti-centromere antibody positivity was from 0% to 7.1%, this specificity of the pediatric cohorts were confirmed.

Comparison of the Largest Pediatric Cohort of jSSc with a Large Adult Cohort with Diffuse Subset jSSc

As 90% of the pediatric patients have a diffuse subset, it is reasonable to compare these patients [17] with adult onset patients with a diffuse subset to see the differences in presentation. The patients from the EUSTAR cohort published by Walker et al. [34] are a good group to compare (Table 10.3), where 1,349 patients with diffuse subset are presented. These adult patients had a mean disease duration of 7.4 years compared to 3.9 years in the paediatric cohort. In the adult population digital infarcts, pulmonary involvement, gastrointestinal involvement, hypertension, muscle weakness, and tendon friction rub were more frequent. Part of the difference could be explained by the difference in disease duration, but the pediatric cohort had a mean disease duration of 3.9 years, which covers the first 4 years of the disease, were most of the new onset organ involvement evolves. Interestingly, the prevalence of anticentromere antibodies in the adult-diffused population is 6%, which is in the same range as the prevalence of the anticentromere antibody in the pediatric cohorts.

Table 10.3 Comparison of the largest paediatric cohort with the EUSTAR adult cohort

	Paediatric cohort [17]	EUSTAR-diffuse subtype [34]
Skin		
Edema	43.8	
Sclerodactyly	66.0	
Skin induration	75.8	100
Calcinosis	18.3	
Peripheral vascular system		
Raynaud's phenomenon	83.7	96
Digital infarcts	28.6	43
Digital pitting	37.9	
Abnormal nailfold capillaries	39.9	
Positive capillaroscopy	51.0	
Respiratory system		
Dyspnea	17.7	45
Abnormal chest X-rays	28.8	53
Abnormal chest HRCT	23.5	
Reduced DLCO	27.5	64
Reduced FVC	41.8	
Cardiac involvement		
Pericarditis/Arrhythmias	9.8	13
Heart failure	7.2	17
Pulmonary hypertension	7.2	22
Musculoskeletal system		
Muscle weakness	24.2	37
Arthritis	27.5	21
Arthralgia	36.0	
Tendon friction rubs	10.5	22
Gastrointestinal system		
Dysphagia	24.2	68
Gastroesophageal reflux	30.1	68
Diarrhea	10.5	
Weight loss	27.5	
Renal system		
Raised creatinine/proteinuria	4.6	9
Renal crisis	0.7	4
Hypertension	2.6	19
Nervous system		
Seizures	2.6	
Peripheral neuropathy	1.3	
Abnormal brain MRI	2.6	

Outcome of the Patients in the Pediatric Cohorts

In both cohorts the survival of the patients after 5 years of the disease course between 90% and 95%. Most patients in the cohort of Foeldvari et al. died in the first 2 years of the disease on a multisystem involvement. The eight patients, who died, showed a higher rate of pulmonary (75%), cardiovascular (100%), central nervous system (38%), and renal involvement (50%). The male-to-female ratio was 1:1, the median age at disease onset 10.5 years. Interestingly the fatal cases of the cohort of Martini et al. [35] had a male:female ratio of 1:2.2, and a mean age of 10.4 years at disease onset. Mean time until death was 4.6 years, four of them in the first 12 months. The patient who died had a significantly shorter time interval to diagnosis with 8.8 months compared to 23 months in the survivals. Patients with fatal outcome showed here to a higher rate of pulmonary, gastrointestinal, and cardiac involvement. All had diffuse subtype.

Special Issues in the Care for Children with jSSc

Even that we have no evidence based data on the treatment of jSSc. The approach in the treatment and rehabilitation of these patients differs from the adult patients. The care involves the [31] patient and the parents/caregivers. The patient can not give consent to the treatment/rehab-plan, but only an assent. The understanding of the treatment by the patient is essential. The support of the concept by the parents and caregivers is essential too. Sometimes the patients and parents/caregivers have different fears and hopes regarding the side effects of the treatment and side effects of the disease.

Outcome of Pediatric Onset Juvenile Systemic Sclerosis Patients into Adulthood

We have currently three larger patient populations to look at long-term prognosis. One is a retrospectively evaluated cohort from the Pittsburgh centre [25] looking at patients diagnosed in childhood and followed into the adulthood. There are two other patient populations were in an adult scleroderma cohort, patients with juvenile onset, but still followed in these cohorts, were identified [36, 37]. In Table 10.4 the characteristics of the three patients cohorts in adulthood are compared with the pediatric patients in childhood. The sex distribution changed in the Pittsburgh as in the EUSTAR cohort to a male:female ratio of 1:5–10 compared to 1:3.6 in the pediatric aged cohort. The disease distribution changed to the adult pattern with 35–40% diffuse subtype and 46.7–61% limited subtype. The large portion of patients with overlap feature in the Royal free cohort seems to be a survival advantage. The mean disease duration of the pediatric patients in the adult cohort is 17.2–21.15 years, compared to 3.9 years of the patients in the juvenile-aged cohort. The shift in the disease subset pattern could present presumably a survival bias. Patients with diffuse subset have more severe disease and could have died earlier in the disease course and the patients with limited subset survived. Despite of this disease subset distribution, the prevalence of the anticentromere antibodies persisted in the low range with 5–6.5%. This finding proposes another possible explanation for the change in disease distribution, that would be, that if pediatric onset patients are seen late in their disease course, the diffuse skin involvement in the survivals evolves into a limited skin involvement. The observation of Peter Merkel in the pooled SCTC population about the natural course of the skin involvement, the decrease of the modified Rodnan skin score over time independent of the treatment, would support this hypothesis. The explanation could be a mixture of both hypotheses. Interestingly, the proportion of patients with pulmonary hypertension is lower than expected compared to the EUSTAR population, where it is around 20%. Unfortunately, not all organ involvement is described in detail in the different populations, so it is not possible to have a complete comparison.

We are missing the data on patients between the cohort of patients in childhood and cohort of patients in adulthood. The prospective inceptions cohort project – www.juvenile-scleroderma.com – hopefully will help to gain this missing data.

Table 10.4 Comparison of juvenile onset patient characteristics in adulthood with the characteristics of patients in juvenile cohort in childhood (right column)

	jSSc in EUSTAR ($n=60$)	jSSc royal free ($n=57$)	jSSc Pittsburgh ($n=57$)	jSSc PRESS ($n=153$)
Mean age at disease onset	12.4 (2–15.9)	13.06 (5-16)	?	8.1 (0.4–15.6)
Disease duration	17.64 (1.8–54.8)	21.15 (3-58)	17.2	3.9 (0.2-18.1)
Sex (male /female)	5/55	11/35	19/92	33/120
Disease subtype diffuse (%)	40	39	35	90.9
Disease subtype limited (%)	46.7	61	40	9.1
Overlap features	NN	43.5	NN	NN
Outcome	59 (98%)	97% /15Y//93% /20Y)//83%25Y	(89(5y)//74(20Y)	112/127(88) 15/127(12) 26
-lost to follow up(%)	1 (2%)	NN	NN	(17%)
ANA positive	90%		97	80.7%
Anti-Scl 70 positive	40%	26	23	34%
Anti-centromere positive	5%	6.5	0	7.1%
Raynauds phenomenon (%)	95	NN	96	83.7
Pulmonary hypertension (%)	13.3	15	3.6	7.2
Pulmonary fibrosis (%)	23.3	47	9	23.5
Renal crisis (%)	0	2	3.6	0.7

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