Scleroderma in children: an update

Francesco Zulian, Giorgio Cuffaro, and Francesca Sperotto

Purpose of review
Scleroderma, in its localized and systemic presentation, represents the third most frequent rheumatic condition in childhood after juvenile idiopathic arthritis and systemic lupus erythematosus. Early diagnosis, appropriate assessment and effective treatment are crucial to improve the long-term outcome.

Recent findings
Recent studies, concerning histopathology and clinical associations with other conditions, open new horizons on the etiopathogenesis of scleroderma. New developments have been also reached in the field of outcome measures. In juvenile localized scleroderma (JLS), new techniques such as Doppler and laser Doppler imaging have shown their usefulness for the daily monitoring of the patients. In juvenile systemic sclerosis (JSSc), a new severity score has been developed and needs to be validated in future trials. Finally, a randomized, double-blind controlled trial, a multicenter consensus statement and long-term follow-up studies have confirmed the important role of methotrexate (MTX) for the treatment of JLS.

Summary
Studies over recent years highlighted the role of imaging as outcome measures for JLS and introduced a severity score for JSSc. New studies on MTX confirmed its important role for the treatment of JLS.

Keywords
juvenile localized scleroderma, juvenile systemic sclerosis, outcome measures, treatment

INTRODUCTION

Juvenile scleroderma is a clinical entity that may manifest in young individuals with specific epidemiological and clinical features. The two main forms of the disease are juvenile localized scleroderma (JLS) and juvenile systemic sclerosis (JSSc). These conditions share common pathophysiologic features which are mainly characterized by inflammation and fibrosis of the skin. In JLS, fibrosis involves restricted areas of the skin, whereas in JSSc it also affects the internal organs.

Contributions to the literature over the last years have provided further information on etiopathogenesis, potential outcome measures and treatment.

LOCALIZED SCLERODERMA

JLS is the most frequent form of scleroderma in childhood. A recent epidemiological study [1] in the United Kingdom reported an incidence rate of 3.4 cases per million children per year, the vast majority represented by the linear subtype.

Etiopathogenesis

The pathogenesis of JLS is still unknown, although it has been shown that the interaction between inflammatory, fibrotic and vascular components seems to play a crucial role.

A recent histopathology study on individuals with active JLS showed similar cellular infiltration in children and in adult patients. By the immunostaining technique, the authors showed lack of $CD34^+$ dermal dendritic cells and increased Factor XIIIa1 cells (dermal dendrocytes) in the areas of fibrosis. This could reinforce the hypothesis that both transformation of $CD34^+$ fibrocytes to $CD34^-$ myofibroblasts and increase of Factor XIIIa+ cells acting in cross-linking the newly formed collagen and matrix molecules contribute to the fibrotic process [2].

Another pathology study, involving 73 patients with JLS, reported a significant perineural inflammation. This finding was observed in half of the patients and has been proposed as a possible

Division of Pediatric Rheumatology, Department of Pediatrics, University of Padua, Padua, Italy

Correspondence to Francesco Zulian, MD, Professor and Chief, Division of Paediatric Rheumatology, Department of Paediatrics, University of Padua, Padua, Italy. Tel: +39 498213583; e-mail: zulian@pediatria.unipd.it

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KEY POINTS

- Scleroderma may manifest in young individuals as juvenile localized scleroderma, in which fibrosis involves just restricted areas of the skin, and juvenile systemic sclerosis, which also affects the internal organs.
- Contributions to the literature over recent years have provided further information on potential outcome measures and treatment.
- New techniques such as Doppler and laser Doppler imaging have been shown to be useful for the monitoring of patients with juvenile localized scleroderma.
- A randomized, double-blind controlled trial, a multicenter consensus statement and long-term follow-up studies have confirmed the role of methotrexate for the treatment of juvenile localized scleroderma.
- The first severity score for pediatric patients with systemic sclerosis has been developed and needs validation in future trials.

histologic marker specific for JLS, in addition to other known features such as the prevalent fibrosis at dermal level in comparison with the subcutaneous layer involvement, and the intense inflammation [3].

The autoimmune nature of the disease has been confirmed by the recent case reports describing association of JLS with other autoimmune conditions. Firoz *et al.* [4] reported the case of an 11-year-old girl presenting JLS associated with type 1 diabetes and celiac disease. Other authors presented the case of a 7-year-old girl with JLS associated with Sjögren syndrome and precocious puberty. The authors' concluded that the co-occurrence of precocious puberty was considered as a mere coincidence, whereas Sjögren syndrome and JLS could be associated [5].

The case of a 4-year-old girl with JLS associated with Turner's syndrome has opened new horizons on the possible role of the X chromosome mosaicism. According with the authors' opinion, Turner's syndrome was the main triggering factor for the very early presentation of JLS in this patient and has also probably contributed to the treatment resistance [6]. Two mechanisms involving the X chromosome may be implicated in the dysregulation of immune response. Autoreactive T cells may fail to be tolerated by self-antigens encoded by one of the two X chromosomes and, in target tissues, these autoreactive T cells may stimulate B cells expressing the target X-encoded antigen, thereby inducing an autoimmune response. Alternatively, X-encoded genes may be involved in immune system homeostasis, and dysregulation may affect B and T cells directly [7].

Clinical aspects

The heterogeneous clinical manifestations of localized scleroderma and the rarity of the disease itself highly influence the promptness and the accuracy of the diagnosis.

Recent studies evaluated the access to care and the degree of diagnostic of delay of patients with JLS. The latter was estimated lasting as much as 11.1 months (range 2–79 months). Indeed, none of the 50 patients was correctly diagnosed at presentation, as in 44% there was no diagnosis, in 20% it was atopic dermatitis, 8% melanocytic nevus, 6% fungal infection or others [8]. Other studies confirmed that a prolonged interval time between the first manifestation of JLS and the definitive diagnosis adversely affects the final outcome and underscored the need to raise awareness among primary care physicians to consider scleroderma earlier and to refer patients to the specialists [9,10].

A high incidence of odontostomatologic abnormalities was reported in patients with linear scleroderma of the face. They consisted of dental malocclusion, overgrowth of the anterior lower third of the face, gnathologic alterations, dental roots abnormalities and temporomandibular joint involvement [11▪]. This study proposed cone-beam computed tomography as a useful technique to evaluate and monitor soft and hard tissue changes in JLS.

Outcome measures

An open issue for JLS is to establish and validate objective outcome measures to monitor the disease activity (Table 1) [12–20]. Along with traditional instruments to evaluate disease activity such as thermography, computerized skin scoring or MRI, few studies [16–18] have recently assessed the role of ultrasound as either Doppler or laser Doppler applications, confirming the previous evidence. The rationale for using these tools is that superficial blood flow has been shown to correlate with disease activity. A case–control study involving 51 patients (104 JLS lesions) evaluated the performance of the ultrasound Doppler technique in comparison to the standard histological examination. The ultrasound Doppler technique, using compact 7–15 MHz linear probes, showed high sensitivity and specificity for assessing the disease activity. The most accurate sonographic signs of lesion activity were increased subcutaneous tissue echogenicity and increased cutaneous blood flow [18].

Table 1. Imaging in localized scleroderma

Instrument	No. of patients	No. of raters	Explored parameters	Performance	References
Computerized Skin Score	10	10	Extension	Interrater agreement 95%, intrarater agreement 91–93%	[12]
Thermography	40	2	Activity	Sensitivity 92%, specificity 68%	[13]
Ultrasonography	6	1	Activity, extension (depth)	Useful to detect skin involvement depth, operator dependent, difficult to standardize	[14]
Laser Doppler flowmetry	41	1	Activity	Sensitivity 80%, specificity 77%	[15]
Laser Doppler imaging	20	2	Extension	Positive predictive value 73% Negative predictive value 94%	[16]
Ultrasound disease activity (U-DA)	21	2	Activity	Increased echogenicity and vascularity in active lesions ($P=0.0010$)	[17]
Color Doppler ultrasound	51	1	Activity	Sensitivity 100%, specificity 98,8%, positive predictive value, 95.7% negative predictive value 100%	[18]
Magnetic resonance imaging	43	N/A	Extension (depth)	Useful to detect musculoskeletal involvement	[19]
Magnetic resonance imaging	N/A	N/A	Extension (depth)	Useful to detect skin involvement depth, expensive procedure, Invasive (sedation need)	[20]

Another retrospective study [17] compared the construct validity of two proposed measures, the ultrasound disease activity (UDA) and the Tissue Thickness Score (TTS) on 52 JLS lesions from 21 patients to define their performance in detecting active lesions. Whereas UDA resulted to be useful to identify an active lesion, TTS did not.

As for laser Doppler imaging (LDI), a recent prospective study [16] evaluating a small cohort of patients with JLS confirmed this tool as effective and useful in predicting the disease progression (positive predictive value 84% and negative predictive value 94%).

It is well known that extracutaneous manifestations occur in approximately one-fourth of the patients with JLS and are mainly characterized by musculoskeletal involvement [21]. Recently, a study involving 43 patients confirmed this observation by reporting musculoskeletal MRI abnormalities in 74%. The most frequent findings were subcutaneous septal and fascial thickening, synovitis and tenosynovitis. Perifascial enhancement, myositis and enthesitis were less frequently shown. Interestingly, the highest prevalence of musculoskeletal involvement was seen in patients with pansclerotic morphea [19].

Treatment

The lack of knowledge in JLS influences not only the diagnosis, but also the treatment approach. A cross-sectional study has shown that therapeutic decision-making in JLS is largely determined by the specialty of the provider rather than by the disease characteristics. Therefore, many treatments with little or no proven efficacy are often used, whereas others with proven efficacy are underused: dermatologists prescribe topical steroid in 68.2% of the cases, but methotrexate (MTX) in only 4%; conversely, only 8% of the patients managed by the rheumatologists are treated with topical therapy, whereas 38.8% use MTX [10].

MTX still represents the cornerstone for the treatment of the majority of JLS subtypes (Table 2) [22,23▪,24,25▪,26].

Recently, the first randomized controlled trial (RCT) in JLS, comparing a 12-month course of oral MTX (15 mg/m^2) for 12 months, associated with

Table 2. New treatments proposals for juvenile localized scleroderma

Author (reference)	Year	Study design	Treatment	Regimen	No. of patients	Follow-up	Result	Assessment
Zulian [22]	2011	Double-blind, placebo RCT	MTX + PDN	MTX 15 mg/m^2/week oral (max. 20 mg) + PDN 1 mg/kg/day (3 months, max. 50 mg)	70	12 months	Effective (67.4%)	Skin Score Rate, thermography
Li [23▪]	2012	Consensus treatment plan	MTX	MTX 1 mg/kg/week s.c. (max. 25 mg)	Ongoing study	N/A	Ongoing study	Clinical judgment imaging
			MTX + i.v. MPDN	MTX 1 mg/kg/week s.c. (max. 25 mg) + i.v. MPDN 30 mg/kg/dose (max. 1 g) for 3 months				
			MTX + oral PDN	MTX 1 mg/kg/week (max. 25 mg) s.c. + oral PDN 2 mg/kg/day (max 60 mg)				
Mirsky [24]	2012	Retrospective	MTX ± PDN	MTX 0.3–5 mg/kg/week oral/s.c. for at least 3 months ± i.v. or oral corticosteroids	90	N/A	Relapse after 6 months Tx (>29%)	Clinical judgment
Zulian [25▪]	2012	Prospective, open-label extension	MTX + PDN	MTX 15 mg/m^2/week for at least 12 months + oral PDN 1 mg/kg/day (max. 50 mg) for the first 3 months	65	40 months range 3–72	Effective (73.8%)	New lesions, Skin Score Rate, thermography
Pope [26]	2011	Prospective, open-label	Imiquimod	5% Topic cream (3 times/week first month, 5 times/week next 8 months)	9	12 months	Effective	Thickening (VAS), DIET Score, ultrasonography

DIET, dyspigmentation/induration/erythema/telangiectasia; i.v., intravenous; MPDN, methylprednisolone; MTX, methotrexate; PDN, prednisone; RCT, randomized controlled trial; s.c., subcutaneous; VAS, visual analog scale.

a 3-month course of oral prednisone (1 mg/kg/day, maximum dose 50 mg), with placebo has been published [22]. MTX was effective and well tolerated in more than two-thirds of patients. New lesions appeared in only 6.5% of MTX-treated patients compared with 16.7% of the placebo group. The open-label extension part in the same cohort of patients also reported the long-term efficacy of MTX. In particular, among 65 patients treated with MTX, 73.8% were responders, 15.4% relapsed by 24 months since MTX start, and 10.8% were lost to follow-up. Among the responders, 73% maintained clinical remission off-medication for a mean of 25 months and 27% were in clinical remission on medication [25▪]. According to these results, MTX treatment should be continued for at least 24 months to ensure a prolonged and sustained disease remission.

Similar conclusions were drawn in a retrospective study [24] reporting a high incidence of relapse in patients treated with shorter MTX course, suggesting that longer treatments may help reducing the relapse rate.

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) group have recently proposed a consensus treatment plan for JLS in order to limit the variability in medication use and to address the methods of assessment. These recommendations, that include both MTX and corticosteroids in various combinations, will allow future comparative effectiveness studies and enable the development of evidence-based guidelines for the treatment of JLS [23▪]. The group agreed on three different approaches that are summarized in Table 2.

For the milder form of JLS (circumscribed or plaque morphea), a new topical treatment, 5% imiquimod cream, has been recently proposed [26]. Imiquimod is an immunomodulator that inhibits human fibroblast to produce both collagen and glycosaminoglycans by increasing interferon-alpha and interferon-gamma levels. This topical agent was shown to be effective in decreasing the thickening of scleroderma lesions and well tolerated for the pediatric use. Unfortunately, as reported by the authors themselves, the study [26] was not blinded, was small sample sized and not placebo controlled.

An open issue in localized scleroderma concerns the surgical treatment of facial deformities. In the past, this treatment approach has been highly debated, considering both conservative therapy and orthopedic–orthodontic or maxillofacial ones. A recent study on a case series of 17 patients with JLS of the face (Parry–Romberg syndrome or scleroderma *en coupe de sabre*) confirmed the potential usefulness of the surgical treatment, mainly including fat injections, bone paste cranioplasty and Medpor implants. All individuals, evaluated by a multidimensional questionnaire on the psychosocial effects of the surgical interventions, supported the benefits of this treatment, would consider repeated surgery and recommend surgery to other patients with en coupe de sabre and Parry Romberg syndrome [27]. Unfortunately, the timing on when these procedures should be performed and how to establish complete disease remission to avoid unpleasant side-effects are still unclear.

SYSTEMIC SCLEROSIS IN CHILDREN

JSSc is a potentially life-threatening condition, with an incidence rate of 0.27 cases per million children per year [1]. JSSc can manifest as a diffuse or as limited cutaneous forms. The diffuse cutaneous JSSc presents a widespread and rapid progressive skin thickening and involves internal organs, such as lung, heart and kidney, early on. The limited cutaneous JSSc is characterized by a restricted and nonprogressive skin thickness, limited to the distal extremities, and can be accompanied by pulmonary manifestations, arterial hypertension or malabsorption. JSSc may also manifest as an overlap syndrome, sharing common characteristics with other connective tissue diseases, such as dermatomyositis or systemic lupus erythematosus [28,29]. The features and the severity of the clinical manifestations closely influence the disease outcome.

Clinical aspects

Although the clinical aspects are undoubtedly heavier than the localized form, JSSc onset can be insidious and significant delay in diagnosis can be observed. A retrospective study [9] on 89 patients with systemic sclerosis, including 16 with JSSc, revealed that the median time from the first symptom to diagnosis was 7 months (range 2–50). This finding clearly shows the difficulty in recognizing systemic sclerosis in children, highlighting the need to improve knowledge and awareness of this rare condition.

To properly identify the distinct features of SSc in childhood, recent studies searched for the possible differences between juvenile and adult onset forms of SSc. A study compared the clinical characteristics of 52 adults with juvenile-onset SSc from a single-center cohort (JSSc) with a cohort of 954 adult-onset SSc. Results showed more frequent overlap syndromes among the JSSc cohort (37%) compared with the adult-onset group (18%) and a lower frequency of diffuse cutaneous SSc in the JSSc group than in the adult-onset one. The study also confirmed the previous studies [30] on survival that reported significantly better survival among the individuals with juvenile forms (98 vs. 75%) [31].

Table 3. The Juvenile Systemic Sclerosis Severity Score (J4S)

	0 Normal	1 Mild	2 Moderate	3 Severe	4 End stage	Maximum score
General[a]	BMI > to the baseline value Hb >11.5 g/dl	BMI <1st centile Hb 10–11.4 g/dl	BMI <2nd centile Hb 9–9.9 g/dl	BMI <3rd centile Hb 7–8.9 g/dl	BMI <4th centile Hb <7 g/dl	4
Vascular	No RP	RP requiring vasodilators	Digital tip scars	Digital tip ulcerations	Digital gangrene	4
Skin	MRSS 0	MRSS 1–14	MRSS 15–29	MRSS 30–39	MRSS >40	4
Osteoarticular[b]	No articular involvement		Presence of limited range of motion (ROM)		Presence of arthritis and/or tendon friction rub	2
Muscle[b]	Normal proximal muscle strength	cMAS 39–51	cMAS 38–26	cMAS 13–25	cMAS 0–12	2
Gastrointestinal[a]	Normal proximal GI tract investigations	GI symptoms Distal esophageal hypoperistalsis GERD at 24-h Ph-metry or scintiscan	Medium and high esophageal hypoperistalsis	Malabsorption syndrome	Hyper alimentation	4
Respiratory[a,c]	DLCO >80% FVC >80% Normal HRCT sPAP <30 mmHg	DLCO 70–79% FVC 70–79% Alveolitis on HRCT sPAP 31–45 mmHg	DLCO 50–69% FVC 50–69% Fibrosis on HRCT sPAP 46–75 mmHg	DLCO <50% FVC <50% Fibrosis on X-ray sPAP >75 mmHg	O_2 dependence	8
Cardiac[a,c]	Normal EKG LVEF >50%	EKG conduction defect LVEF 45–49%	Arrhythmia LVEF 40–44%	Arrhythmia requiring treatment LVEF 30–40%	CHF LVEF <30%	8
Renal[d]	Creatinine clearance (GFR): >90 ml/min	Creatinine clearance (GFR): 75–89 ml/min	Creatinine clearance (GFR): 50–74 ml/min	Creatinine clearance (GFR): 10–49 ml/min	ESRF	4

CHF, congestive heart failure; cMAS, childhood muscle activity score; DLCO, diffusing capacity for carbon monoxide; EKG, electrocardiogram; ESRF, end-stage renal failure; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; Hb, hemoglobin; GI, gastrointestinal; HRCT, high-resolution computed tomography; LVEF, left ventricular ejection fraction; MRSS, modified Rodnan Skin Score; sPAP, estimated pulmonary artery systolic pressure by Doppler echo; RP, Raynaud phenomenon. Modified from [32▪▪].

[a]Either one of the following parameters defines the score.

[b]Each score should be multiplied by 0.5 to obtain the final score.

[c]Each score should be multiplied by 2 to obtain the final score.

[d]GFR: male 0–12 years = 0.55 × height (cm)/creatinine (mg/dl); male 12–18 years = 0.7 × height (cm)/creatinine (mg/dl); female 0–18 years = 0.55 × height (cm)/creatinine (mg/dl); male >18 years = (weight in Kg × 140) − age (years)/72 × creatinine (mg/dl); female >18 years = [(weight in Kg × 140) − age (years)/72 × creatinine (mg/dl)] × 0.85.

Outcome measures

As JSSc is one of the most severe conditions in pediatric rheumatology, it is crucial to objectively establish its severity in daily practice. A feasible instrument to evaluate JSSc severity in children has recently been reported in a multicenter study coordinated by the research group of the Padua University. The study was aimed to set up a reliable instrument to assess the disease severity of JSSc, in order to determine the best therapeutic choice and regimen. The authors proposed a simple score, named J4S (Juvenile Systemic Sclerosis Severity Score), composed by 16 indices grouped into 9 sections corresponding to general and specific organ system involvement (Table 3) [32▪▪]. This multidimensional score includes growth parameters, skin and internal organs involvement, and takes into account the great variability of the clinical manifestations of the disease. J4S should be validated in prospective studies and will have an important role both in the standardization of the clinical approach to the disease and in the daily clinical practice to guide the decision-making process [32▪▪].

CONCLUSION

New developments over the last 2 years have provided important information concerning the epidemiological characteristics, pathogenic mechanisms and clinical features of JLS and JSSc. Unfortunately, there was no significant news about the treatment of JSSc, although several studies, including a RCT, underscored the essential role of MTX for the treatment of JLS.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- ▪▪ of outstanding interest

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