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An updated overview of Juvenile systemic sclerosis in a French cohort

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Abstract

Background Systemic sclerosis encompasses a range of disorders characterized by vascular and connective tissue abnormalities. Although rare in pediatrics, juvenile systemic sclerosis (jSSc) is a severe and life-threatening condition that significantly impacts children's development. This study aimed to provide an overview of JSSc in France over the past decade.

Methods Patients with disease onset before the age of 16 were included following a request for observations sent via email to member practitioners of the SOFREMIP (French pediatric Rheumatology society).

Results Our study included 18 patients from 8 different French centers. While our cohort exhibited a balanced distribution between limited and diffuse subsets of the disease, we observed a higher prevalence of the diffuse subset in children above the age of 10. Skin induration was the most reported symptom, while Raynaud's phenomenon was present in 61% of the children at initial clinical evaluation. All children tested positive for antinuclear antibodies, with anti-Scl70 being the most common specificity, even among children with limited cutaneous subsets. Interestingly, we found a high sensitivity of the ACR / EULAR criteria for diagnosing jSSc in our cohort with 83% of patients meeting these criteria, except for 3 children who presented with overlap syndromes. Despite the frequent use of corticosteroids at the onset, no deaths or renal crises were reported. Three patients received treatment with biological agents, specifically Rituximab and Tocilizumab.

Conclusion JSSc is a rare but severe disease requiring rapid, specialized, and multidisciplinary care. Further studies are needed to validate proper diagnosis criteria including overlap syndromes and evaluate the use of biotherapies in children.

Keywords Scleroderma, Systemic, Juvenile systemic sclerosis, Autoimmune disease, Biological therapy

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Background

Juvenile systemic sclerosis (jSSc) is a rare condition. In 2005, the incidence rate of children diagnosed with the disease in the UK and Ireland was 0.27 per million per year [1]. In different series reporting cases of jSSc, the mean age at diagnosis was between 8 and 12 years, and female to male ratio was approximately 3:1 [2, 3].

The pathophysiology of this condition remains unclear. Innate and adaptive immune system abnormalities lead to tolerance breakdown associated with autoantibodies and cell-mediated autoimmunity, that is responsible for inflammation at different stages of the disease. Endothelial dysfunction and fibroproliferative vasculopathy are hallmarks of SSc, associated with ischemic signs and excessive collagen formation in the extracellular matrix, caused by fibroblast dysfunction [4, 5]. SSc is thought to be a multifactorial disease, implicating genetic and environmental factors [6]. Familial segregation of several cases of SSc is not common, although the risk of a first-degree relative developing SSc is 15-folds higher than in unaffected controls [7].

SSc is divided into several subtypes, according to skin involvement. When the extent of scleroderma is proximal to knees and elbows, it is called "diffuse" SSc, otherwise it is considered "limited". There is also a rare form of SSc, without skin sclerosis, commonly referred to as 'systemic sclerosis sine scleroderma' [8]. Another feature referred to as "overlap syndrome", especially common in children, associates different symptoms specific to SSc and other connective tissue diseases such as dermatomyositis, Sjogren's syndrome, systemic lupus erythematosus (SLE) or juvenile arthritis [9]. In terms of overall prognosis, a recent study shows a 98% survival at 10 years from disease onset in the pediatric population as compared with 75% in adults [10].

Clinical presentation varies among patients. Raynaud phenomenon (RP) is frequent in children with jSSc (75% at the onset of the disease and 84% in the overall course) [3]. Symmetrical skin change is the second most common feature [3]. Musculoskeletal involvement is also common in children with jSSc, presenting as morning stiffness, arthralgia, joint contractures, tendon friction rubs, or arthritis [3]. Myositis and elevated creatine kinase levels are more frequent in overlap syndromes [11]. Gastrointestinal symptoms are also common, including gastrointestinal reflux disease, alternation of constipation and diarrhea, and signs of malabsorption, which can lead to malnutrition and have a significant impact on growth [12]. Respiratory findings are found in approximately 50% of those children, manifesting as dry cough or dyspnea, due to parenchymal damage or pulmonary arterial hypertension (PAH) reflecting microcirculation impairment [12, 13]. Although rarely documented in diffuse jSSc, cardiac involvement appears to be statistically much more frequent in the limited form of jSSc (3% and 23%, respectively, according to recent data from the inception cohort) [13]. Regarding renal involvement, only 1 child out of the 153 included in the historical series of jSSc experienced a scleroderma renal crisis [3].

Regarding the different subsets, recent data from the international jSSc inception cohort show that patients with diffuse jSSc generally present a more severe disease with greater lung involvement, as demonstrated in adults [14]. Unexpectedly, children with overlap syndrome were shown to exhibit a higher prevalence of muscular impairment but also, an even more frequent pulmonary involvement [15].

The literature on the management of jSSc is very scarce. However, the SHARE group (Single Hub and Access point for pediatric Rheumatology in Europe) has proposed guidelines for the management of jSSc in 2021, depending on the severity of the disease and the extent of organ involvement [16]. More recently, an article based on expert opinions and a comprehensive literature review aims to broaden the guidelines to encompass additional aspects of the disease and ensure recommendations align with the most current information [17]. It ranges from cold protection measures to vasodilator and / or immunosuppressive drugs like oral corticosteroids, conventional immunosuppressives, or more recently biological therapies, especially Rituximab and Tocilizumab, based on studies conducted in adult patients.

In our study, we provide an overview of jSSc in children treated in Reference Centers for pediatric rheumatology in France over the past decade. We present data on epidemiology, clinical and immunological features, also with up-to-date therapy options and follow up.

Methods

We conducted a study on juvenile-onset systemic sclerosis cases occurring below the age of 16 years, treated in French Reference Centers for pediatric rheumatology over the past 10 years. Practitioners were contacted three times by email via the SOFREMIP (French society for the study of pediatric inflammatory diseases) mailing list, to identify potential participants based on their diagnosis of SSc.

Epidemiological, clinical, and biological data were gathered retrospectively from consultation and hospitalization records from the initial contact to the most recent evaluation at the center. Demographic characteristics were described, including familial history of systemic sclerosis or other autoimmune disease. Organ involvement and time to onset after diagnosis were reported, along with clinical manifestations and relevant biological, functional, and imaging data.

The presence or absence of a RP was noted, in association with capillaroscopy findings when it was performed,

specifying the pattern according to the Cutolo classification [18]. Concerning cutaneous involvement, the degree of sclerosis and the presence of finger edema, active digital ulcers, pitting scars, digital infarcts, telangiectasia, calcinosis, livedo, or chilblains was evaluated as precisely as possible. The potential extent of skin sclerosis beyond the elbows and knees allowed for the classification of patients into both different subtypes (limited and diffuse jSSc). Joint and tendinous involvement was specified, including arthralgia or arthritis, synovitis, tendon friction rubs and tendinous retraction (abnormal reduction in length of a tendon which tends to pull the attached muscle tissue with shortening of the muscle fibers). Muscle pain, myositis, strength loss, specific muscular MRI hypersignals (when performed) were sought. Pulmonary involvement was defined in the presence of a respiratory functional impairment (a decrease in forced vital capacity < 80%, indicative of a restrictive lung syndrome, and/or a decrease in DLCO < 80%, indicating a diffusion disorder) and/or a diffuse interstitial lung disease pattern on high-resolution CT scanner. Dyspnea, as a multifactorial condition, was also systematically assessed as a subjective symptom reported by the patients, regardless of any objective pulmonary involvement observed on imaging and pulmonary function tests. Cardiac disease was diagnosed based on symptoms of cardiac insufficiency, the elevation of biological markers (troponin, nt-pro-BNP), a pathological EKG, echocardiography, or MRI during follow-up. It was subclassified into SSc-specific cardiac involvement or pulmonary arterial hypertension (PAH). Gastro-intestinal involvement was defined by symptoms of pyrosis or reflux, abdominal pain, occlusion or pseudo-occlusion, digestive hemorrhage. Renal involvement was defined in the case of an isolated proteinuria, persistent arterial hypertension (according to age standards), or the occurrence of a scleroderma renal crisis. Neurological disease was notified in case of seizure, peripheral neuropathy, or abnormal magnetic resonance imagery (MRI) findings. Patients were eventually screened for general symptoms, such as fever, asthenia, anorexia, weight loss or growth failure.

The main therapeutic classes used at diagnosis or during follow-up were recorded.

Because there is no consensus regarding the classification criteria for jSSc, we also assessed the sensitivity of the 2013 ACR/EULAR classification criteria during the initial clinical evaluation in our study population [9].

We compared the distribution between the diffuse and limited cutaneous subset of the disease and the age at diagnosis using a Chi-square test.

The study was approved by the University Hospital of Strasbourg ethics committee (CE-2022-13).

Results

A total of 42 French centers involved in the care of children with rheumatological conditions (Reference Centers and Competence Centers in pediatric rheumatology) were contacted, with 3 emails sent to each center (126 emails in total). Out of the 42 centers, a response was received from 25. Out of the 25 centers that responded to our emails, 17 did not have patients with jSSc at the time of inclusion.

Eighteen children with diagnosis of jSSc were included, from 8 different centers: 6 from Alsace (4 Strasbourg and 2 Mulhouse), 4 from Bicêtre hospital in Paris, 3 from Robert Debré hospital in Paris, 2 from Marseille, and 1 each from Nancy, Bordeaux and Annecy. The main demographic and clinical characteristics of the patients are summarized in Table 1. The sex ratio confirms the female predominance of SSc in children. About one third of the patients had a family history of autoimmune condition (dermatomyositis, type 1 diabetes, acute polyradiculonevritis, and 2 multiple sclerosis). Median time to diagnosis after the onset of symptoms was 9 months.

RP was present at diagnosis in 61% of the patients and during the overall course of the disease in 72%. Skin induration was the most frequent skin lesion (15/18 patients, 83%). Rodnan's score had been assessed in 13 patients, with a mean score of 11/51 (range 0 to 26). Capillaroscopy was performed in 15 cases and showed a pathogenic pattern for all the patients: 3 patients with a "scleroderma pattern" without precision, 4 patients with nonspecific pathological patterns suggestive of organic microangiopathy, and following the Cutolo classification, 1 patient with an early-stage, 3 patients with an active-stage and 4 patients with late-stage scleroderma pattern.

Eight patients (44%) had articular involvement. This manifestation was consistently observed at the disease's onset, and none of the children developed it during the follow-up period.

Muscular involvement was reported in 3 patients with 2 of them diagnosed with overlap syndrome (systemic sclerosis and dermatomyositis), associating muscular pain and rhabdomyolysis. Full-body MRI was performed in one of those patients and was described as pathogenic (signs of myositis), while muscular biopsy was inconclusive.

Gastrointestinal manifestations were present in 14 patients (78%), mostly abdominal pain for 9 patients (50%), pyrosis for 8 (44%), esophageal dysmotility in 6 cases (33%), diarrhea and vomiting for 3 (17%) and 2 patients (11%), respectively. In all cases, these manifestations were present at the time of diagnosis, except for one child who developed digestive obstruction during the follow-up period.

Dyspnea was a common symptom, occurring in 12 cases (67%). All children underwent pulmonary function

Table 1 Main demographic and clinical characteristics of the cohort. Results are presented into absolute values, and as a percentage of the overall cohort in parentheses. The information was gathered for each of the patients, unless otherwise specified. Familial history of autoimmune disease is known for 16 patients. AI, autoimmune disease; DM, dermatomyositis, F/M, female to male, MCP, metacarpophalangeal joint; RP, Raynaud phenomenon

Demographic characteristics		**Clinical presentation**	
Sex		Cutaneous involvement	18/*18* (100)
Female	16 (89)	*RP*	13 (72)
Male	2 (11)	*Skin induration*	15 (83)
F/M ratio	8:1	*Scleroderma proximal to MCP*	10 (56)
Familial history of AI disease ($n=16$)	5 (31)	*Digital ulcerations*	13 (72)
1st degree	3 (19)	*Nailfold changes*	13 (72)
2nd degree	2 (11)	*Telangiectasia*	9 (50)
Age at diagnosis (years)		*Livedo*	5 (28)
Median	10	*Calcinosis*	4 (22)
Range	4–15	*Chilblain*	3 (17)
Duration of symptoms before diag. (months)		*Digital infarction*	2 (11)
Median	9	Articular involvement	8/*18* (44)
Range	1–24	*Synovitis*	5 (28)
Duration of follow-up (years)		*Arthritis*	4 (22)
Median	4,5	*Tendinous retraction*	4 (22)
Clinical presentation		Muscular involvement	3/*18* (17)
Limited	10 (56)	Gastro-intestinal involvement	14/*18* (78)
Diffuse	8 (44)	*Abdominal pain*	9 (50)
Overlap syndromes	5 (28)	*Pyrosis / reflux*	8 (44)
DM	4 (22)	*Diarrhea*	3 (17)
Lupus	2 (11)	*Vomiting*	2 (11)
Sjögren	1 (6)	*Digestive occlusion*	1 (6)
		Esophagal dysmotility	6 (33)
		Pulmonary involvement	14/*18* (78)
		Dyspnea	12 (67)
		Intersitial lung disease	7 (39)
		Restrictive lung disease	10 (56)
		Low CO-transfer	9 (50)
		Pulmonary arterial hypertension	1 (6)
		Cardiac involvement	6/*18* (33)
		Pericarditis	3 (17)
		Myocarditis	2 (11)
		Renal crisis	0/*18*

tests (PFT), and 17 out of 18 also had at least one thoracic CT scan, typically performed during the initial assessment. Restrictive lung disease was prevalent in PFT (10 patients, with 56% of total cases), with the identification of scleroderma-associated interstitial lung disease on CT scans in 7 patients (39% of cases). One patient had PAH. In two cases, pulmonary involvement was not present at onset but appeared after two years of follow-up.

A cardiac ultrasound was performed in all patients and generally repeated as part of the follow-up. Pericarditis was reported in 3 patients (17%), including one child presenting with overlap syndrome involving SLE. Two other patients had scleroderma-specific myocardial involvement, with pathogenic MRI showing inflammation and fibrosis, resulting in end-stage heart failure requiring cardiac transplant in one case.

Isolated proteinuria was found in 2 patients, but there was no history of arterial hypertension or scleroderma renal crisis in our cohort.

Although not systematically reported by the medical practitioners, growth retardation was very frequent in this cohort (7 out of 15 patients experienced some degrees of failure to thrive). Ten children experienced anorexia at least at one point, and 7 patients had significant weight loss (39%). Asthenia, a non-specific manifestation, was also very common. There was no death reported in our cohort during follow-up.

Regarding the subsets of the disease, there was a slight predominance of the limited cutaneous involvement in our cohort, observed in 10 out of 18 patients, especially among children below the age of 10 (Table 2). Five patients had overlap syndromes, dermatomyositis for 3 of them, one had SLE, and another had Sjögren's syndrome. Although comparing subgroup data is challenging due to the small sample size of our study, children with the diffuse subset of jSSc appeared to have a lower proportion of joint and muscle involvement but a higher frequency of pulmonary and cardiac involvement, and a higher Rodnan's score. Growth retardation also appeared to be more frequent in the diffuse subset of jSSc. Regarding autoantibodies, anti-Scl70 or topoisomerase I antibodies were predominantly detected in children with the diffuse subset of the disease. However, in the limited cutaneous subset, about one-third of cases also exhibited anti-Scl70 antibodies, along with other specificities such as anti-centromere and other rare autoantibodies not included in the ACR / EULAR classification criteria. Strong immunosuppressant drugs including conventional and biological DMARDs such as mycophenolate, cyclophosphamide, rituximab, and tocilizumab also appeared to have been used more frequently in cases of diffuse jSSc.

Fifteen patients (83%) met the ACR / EULAR criteria for the diagnosis of SSc (listed in appendix S1).

Table 2 Repartition between the diffuse and limited cutaneous subset of the disease in our cohort and specific data concerning overlap syndromes (including patients with diffuse and limited jSSc). Results are presented into absolute values, and as a percentage of the subgroup in parentheses. The values and proportions presented in this table refer to the entire patient cohort unless otherwise stated. Data are compared using the Chi-square test ($p < 0,05$). ANA, antinuclear antibodies; CO, carbon monoxide; GI, gastro-intestinal; jSSc, juvenile systemic scleroderma; mRSS, modified Rodnan skin score; SD, standard deviation

	Diffuse cutaneous subset *n* = 8	**Limited cutaneous subset *n* = 10**	***p***	**Overlap syndromes * *n* = 5**
Age ≤ 10 (*n* = 14)	3	9	0,019*	
Age > 10 (*n* = 6)	5	1		
Mean mRSS (+/- SD)	*n* = 7 16.4 (+/- 6.18)	*n* = 6 5.5 (+/- 6.92)		*n* = 4 5
Articular involvement	4 (50)	7 (70)		2 (40)
Muscular involvement	1 (13)	3 (30)		2 (40)
GI involvement	7 (87)	7 (70)		3 (60)
Pulmonary involvement	7 (87)	7 (70)		4 (80)
Restrictive lung disease	6 (75)	3 (30)		3 (60)
Interstitial lung disease	4 (50)	3 (30)		2 (40)
Low CO transfer	6 (75)	4 (40)		
Pulmonary hypertension	1 (13)	0		0
Cardiac involvement	5 (62)	1 (10)		2 (40)
Growth retardation	*n* = 5 4 (80)	*n* = 9 3 (33)		*n* = 5 3 (60)
Antibodies				
ANA	8	10		5 (100)
Anti-Scl70	*n* = 7 5 (71)	3 (30)		2 (40)
Anti-centromeres	*n* = 7 0	2 (20)		0
Anti-PmScl	*n* = 7 0	2 (20)		2 (40)
Anti-fibrillarin	*n* = 7 1 (14)	1 (10)		0
Anti-Ku	*n* = 7 0	1 (10)		1 (20)
Treatments used				
Corticosteroids	8 (100)	6 (75)		5 (100)
Methotrexate	4 (50)	6 (75)		4 (80)
Mycophenolate	6 (75)	2 (25)		2 (40)
Cyclophosphamide	1 (13)	0		0
Rituximab	2 (25)	0		0
Tocilizumab	2 (25)	0		0

* Please note that the 5 overlap syndromes include 1 patient with diffuse jSSc and 4 patients with limited jSSc

Inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were elevated in 3 patients (19%) at diagnosis. Antinuclear antibodies, the hallmark of systemic autoimmunity, were positive in all children with a titer exceeding 1:80. Anti-topoisomerase 1 or Scl-70, present in 10 out of 18 patients, was the most frequent autoantibody, even among children with limited cutaneous subset. Other specificities for extractable nuclear antigens (ENA) autoantibodies are described in Table 3. The patients with overlap syndromes showed positivity for autoantibodies directed against Pm/Scl in 2 cases and Ku in an additional case. Two patients did not present any scleroderma-specific antibody (12%). Anti-polymerase III antibody was not identified in our cohort.

Most patients (83%) received immunosuppressive therapy, with corticosteroids used in all but one case. The disease-modifying antirheumatic drugs (DMARDs) used in our cohort are listed in Table 4. Three patients were treated with a biological agent. Two patients were treated with rituximab, and 2 were treated with tocilizumab (one sequentially receiving both treatments). Association of immunosuppressive drugs (one DMARD and at least one biological agent) was described in 3 patients (17%).

Vasodilators were commonly used, mostly calcium channel blockers in 10 patients (56%). Anti-endothelin was used in 1 patient and iloprost in 2 patients for severe and complicated RP. Another PAH drug was used in 1 patient in the cohort. Nintedanib, an anti-fibrotic drug

Table 3 Main immunological characteristics of the cohort. Results are presented into absolute values, and as a percentage of the overall cohort in parentheses. The values and proportions presented in this table refer to the entire patient cohort unless otherwise stated. ANA, antinuclear antibodies; ds-DNA, double-stranded DNA; RNP, ribonucleoprotein

ANA	18 (100)
Scleroderma-specific antibodies ($n=17$)	16 (89)
Scl-70	8 (47)
Centromere	2 (12)
RNA pol III	0
Pm/Scl	2 (12)
Fibrillarin	2 (12)
Ku	1 (6)
Other autoantibodies	
SSA (n = 17)	1 (6)
SSB (n = 17)	1 (6)
RNP (n = 16)	3 (19)
ds-DNA (n = 16)	2 (13)

Table 4 Main therapeutics used in our cohort, during follow-up. Results are presented into absolute values, and as a percentage of the overall cohort in parentheses. AAS, acetylsalicylic acid; ASCT, autologous stem cell transplant; IVIg, intravenous immunoglobulins; NSAI, nonsteroidal anti-inflammatory; PAH, pulmonary arterial hypertension

Immunosuppressors / modulators	**15 (83)**
Corticosteroids	14 (78)
Methotrexate	10 (56)
Mycophenolate	8 (44)
Cyclophosphamide	1 (6)
Hydroxychloroquine	4 (22)
Biologicals	3 (17)
Rituximab	2 (11)
Tocilizumab	2 (11)
IVIg	3 (17)
Vasodilators	11 (61)
Anticalcic	10 (56)
Bosentan	1 (6)
Iloprost	2 (11)
PAH treatment	1 (6)
Anti-fibrotic nintedanib	1 (6)
ASCT	0
Organ transplant	1 (6)
AAS	4 (22)
NSAI	2 (11)
Proton pump inhibitors	10 (56)

validated for use in adults with scleroderma-associated interstitial lung disease, was used in one case [19]. Cellular therapy (autologous stem cell transplant) was not reported in our cohort, but a patient needed emergency heart transplant because of acute end-stage heart failure due to scleroderma-related myocarditis.

Discussion

We describe in this article the first cohort of jSSc cases in the French pediatric population. While larger cohorts of jSSc have been published previously, our study provides a detailed overview of the demographic and clinical aspects of the disease, as well as the treatments modalities over the past decade. A selection bias cannot be ignored, and it is likely attributable to a lack of response during the inclusion period, which further explains the geographical recruitment heterogeneity in our study. Indeed, we only present data from 25 out of the 42 centers contacted, with 17 of them not responding, which is one of the major limitations of our study.

In our cohort, the median age at diagnosis was consistent with other published works. On the other hand, we observe a female-to-male ratio of 8, which is more imbalanced than what has been demonstrated in the largest pediatric cohorts where it typically ranges around 4 [3, 13]. The limited cutaneous scleroderma pattern was more frequent in children enrolled in our study, while the diffuse pattern was reported in the literature in around 70% of cases [3, 20]. Besides, we found in our cohort a significant association between an older age at diagnosis (after 10) and the diffuse pattern of the disease. These results need to be confirmed by larger studies.

Although there have been reports of severe cases and rapid fatal outcomes in some children, it is worth noting that no deaths occurred in our cohort [3]. Of course, our study does not permit to consider survival rate, considering our relatively small population.

Median time to diagnosis was approximately 9 months from initial clinical symptoms, albeit with a high disparity ranging from 1 to 24 months. This duration is quite comparable to what was described in one of the largest jSSc cohort published almost 20 years ago, showing a one-year median duration of symptoms before diagnosis [3]. It remains sometimes much too long, owing to the extreme rarity of the disease and the variety of clinical presentations at diagnosis. Implementing a rapid screening process and assessment could allow improved outcomes by early initiation of management and prevention of irreversible organ damage. According to the latest recommendations, children presenting with RP should undergo clinical examination, nailfold capillaroscopy and antinuclear antibody (ANA) testing in a pediatric rheumatology center [16].

As previously published, RP was one of the most prevalent clinical features during follow-up. Yet, it was present in only 61% of cases at diagnosis, this number is much lower than in the largest cohort of jSSc published by Foeldvari et al., which reported RP in 90% of children at the time of diagnosis [13]. Even if our data may underestimate the number of patients with RP due to a reporting bias at the time of the initial consultation, especially in

the case of young children, we believe that the absence of RP does not rule out the possibility of jSSc in cases of compatible clinical presentation. The modified Rodnan's score is not validated in pediatrics, due to physiological variation with body mass index and Tanner stage, but has shown some value in monitoring skin involvement in adult patients, and correlates with organ damage and survival rate when performed in a standardized way [21, 22]. In our study, only 13 out of 18 patients underwent Rodnan's score assessment at diagnosis, which constitutes a limitation of our work. Systematic assessment of this score would be interesting in children, allowing future studies to validate its relevance in the pediatric population.

In our cohort, we identified a proportion of patients with joint and muscle involvement similar to what has been reported in the literature, where the prevalence reaches 50% [13]. The diffuse cutaneous subset was associated in our cohort with a higher frequency of pulmonary involvement, including more diffuse interstitial lung disease and functional involvement (restrictive lung disease or decreased CO diffusion), as demonstrated in the largest published cohorts of jSSc [13]. Conversely, other authors found a higher proportion of cardiac involvement (mainly conduction disorders) in children with limited jSSc, which we did not find in our cohort where cardiac involvement was observed in 62% of children with diffuse jSSc versus 10% of children with limited jSSc [10, 13]. The analysis is, of course, limited due to the small number of patients within the subgroups. Yet, our results seem to be consistent with the data found in adult cohorts [23].

In most cases, significant organ involvement was present at diagnosis, but we report two cases of respiratory involvement that appeared after two years, making close follow-up necessary in all children. No case of renal crisis was reported in our cohort, which argues for the possibility of an early use of corticosteroids in the initial phase of the disease.

One might think that jSSc would be associated with a more pronounced genetic susceptibility than adult-onset scleroderma, mirroring other juvenile-onset connective tissue diseases like SLE [24]. Interestingly, approximately one third of our patients had family history of autoimmune disease, but none had SSc. This could be related to the small number of children in our cohort. We could also hypothesize that several genetic variants are responsible for an increased susceptibility for autoimmune conditions in children, with different clinical manifestations correlated to other secondary factors, like environmental or microbiological factors for example, the so-called "second-hits" [25].

The 2013 ACR / EULAR criteria for SSc in adults should also become a standard for diagnosis in the pediatric population, as they were met for 86% of the children recently evaluated for systemic sclerosis in the Padua jSSc cohort [26], and show a similar sensitivity in our cohort. According to them, the presence of skin thickening proximal to metacarpophalangeal joints is sufficient for the diagnosis of systemic sclerosis [9]. They should be preferred to the criteria proposed in 2007 for the pediatric population, coming from PRES / EULAR / ACR expert consensus (listed in appendix S2), as they have a lower sensitivity, inducing a risk of diagnostic delay [26, 27]. In our study, the only 2 patients who did not meet those 2013 ACR / EULAR criteria had overlap syndromes, with respectively anti-Pm/Scl and anti-Ku autoantibodies that are still excluded from those criteria, yet prototypic of scleromyositis. Several studies published in adults indeed suggest integrating these rare antibodies into classification criteria, in order to correctly diagnose and classify patients with authentic forms of SSc needing appropriate treatment [28]. We acknowledge that patients with overlap syndromes, showing features of myositis or other connective tissue disease, may have a different presentation than children with "isolated" scleroderma.

More generally, recent position from the SHARE expert group recommends assessing any child presenting with RP with at least a capillaroscopy and ANA testing. A child with an abnormal finding resembling scleroderma pattern on capillaroscopy or a positive ANA testing should be referred to a pediatric rheumatology specialist for follow up, even if the EULAR / ACR criteria are not fully met [16]. A recent work published by Foeldvari in 2023 suggests evaluating every child presenting with jSSc using a system based on 12 domains. This could potentially enhance the screening for organ involvement at diagnosis, thereby improving therapeutic management, as well as enhancing the reproducibility of children assessment in clinical studies [29].

Corticosteroids were the most frequent immunosuppressive drugs used in our population, with a good safety profile, followed by methotrexate and mycophenolate mofetil. The SHARE expert group indeed considers that the introduction of a systemic immunomodulatory treatment should always be considered at the time of jSSc diagnosis, with subsequent use of methotrexate and then switching for mycophenolate mofetil after 6 months if symptoms do not improve, in the aim of corticosteroid sparing.

Biological therapies (tocilizumab and rituximab) were used in 3 patients in our cohort, while they are only very recently mentioned in the latest guidelines [17]. Interestingly, one patient under tocilizumab treatment showed impressive improvement of her cutaneous, articular, and pulmonary involvement within one year of follow-up. Further studies are needed to confirm those promising results.

Conclusion

This study presents a characterization of an 18-patient French cohort diagnosed with pediatric systemic sclerosis. Epidemiologically, our cohort exhibited similarities to previously described cases of jSSc in the literature. Noteworthy, our work evokes an association between an age above 10 at diagnosis and the diffuse subset of the disease. Additionally, our findings confirm the high sensitivity of the 2013 ACR / EULAR criteria in diagnosing JSSc, enabling earlier and more appropriate diagnosis and management compared to previous criteria developed in children. No scleroderma renal crisis was described in our work despite the frequent use of corticosteroids, especially at the time of diagnosis. Finally, the increasing use of biological therapies in children, sometimes with convincing results, should lead to larger studies in this population to decipher their indications in jSSc.

Abbreviations

ANA	Antinuclear antibody
DMARD	Disease-modifying antirheumatic drug
ENA	Extractable nuclear antigen
jSSc	Juvenile systemic sclerosis
RP	Raynaud phenomenon
PAH	Pulmonary arterial hypertension
SHARE	Single Hub and Access point for pediatric Rheumatology in Europe
SLE	Systemic lupus erythematosus

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the University Hospital of Strasbourg ethics committee (CE-2022-13).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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