

Systemic sclerosis in children

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Juvenile systemic sclerosis, although rare in children, represents one of the most severe chronic rheumatic conditions in pediatric rheumatology practice. In this review, the various clinical, laboratory and therapeutic aspects of systemic sclerosis in children will be presented. The overall outcome of this disease and the main distinctive features between childhood-onset and adulthood-onset disease will also be discussed.

Juvenile systemic sclerosis (JSSc) is a chronic multisystem connective tissue disease characterized by the symmetrical thickening and hardening of the skin, associated with fibrous changes in internal organs, such as the esophagus, intestinal tract, heart, lungs and kidneys, arthritis and myositis.

Classification

To date, no classification criteria are available for children. According to the 1980 American Rheumatism Association criteria for adults, systemic sclerosis (SSc) classification requires the presence either of the major criterion (fibrosis/induration involving areas proximal to the metacarpophalangeal or metatarsophalangeal joints) or of two minor criteria (sclerodactyly, digital pitting scars or bibasilar pulmonary fibrosis) [1]. This classification was designed to be specific rather than sensitive to minimize false-positive ascertainment. Subsequently, the widespread use of nailfold capillary microscopy, more precise autoimmune serologic tests and early detection of Raynaud's phenomenon in patients who, years later, developed SSc, has raised the need for a more comprehensive classification.

As a result of these issues and with the lack of an acceptable classification for pediatric patients, a multicenter multinational project, sponsored by the Pediatric Rheumatology European Society was performed to define nomenclature and criteria that allow the classification of homogeneous groups of patients with JSSc on the basis of their clinical features and laboratory parameters. By using consensus-based methodologies, the preliminary classification criteria that define a patient as having JSSc were identified and are in the process of being validated (Box 1). According to this classification, a patient aged less than 16 years shall be said to have JSSc if the one major and at least two of the 20 minor criteria are present [2].

Epidemiology

In general, SSc has an estimated annual incidence ranging from 0.45 to 1.9 per 100,000, and a prevalence of approximately 15–24 per 100,000 [3]. Onset in childhood is very uncommon: children under 16 years of age account for less than 5% of all cases [4], and fewer than 10% of all patients develop SSc before the age of 20 [5–8]. The onset occurs at a mean age of 8.1 years and the peak age is between 10 and 16 years [4,8]. The disease is almost fourfold more frequent in females, and there is no racial predilection [8].

Interestingly, the mean time between the first sign of the disease and the first physician diagnosis of JSSc has been reported as being between 1.9 and 2.8 years, with a range of between 0 and 12.2 years [4,8]. The result of this is underdiagnosis and a somehow insidious onset of this disease.

Clinical presentation

The clinical features at the onset of the disease mainly include Raynaud's phenomenon and skin induration (Figure 1). Raynaud's phenomenon is the first sign of the disease in 70% of patients and in 10% it is complicated by digital infarcts. It is more common in the fingers (Figure 2), but can be observed in the toes, ears, lips, tongue and the tip of the nose. Raynaud's phenomenon can be complicated by digital ulcers (Figure 3).

Proximal skin induration develops later and is the second most frequent symptom, being present in 41% of the patients at onset [8]. Cutaneous changes characteristically evolve in a sequence beginning with edema, followed by induration and resulting in marked tightening and contracture. The skin becomes waxy in texture, tight, hard and bound to subcutaneous structures. This is particularly noticeable in skin of the digits and face where the characteristic expressionless appearance of the skin may be the first clues to diagnosis appear (Figure 4).

Keywords: autoantibodies, classification, mortality, organ involvement, systemic sclerosis, treatment

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Box 1. Preliminary criteria for the classification of juvenile systemic sclerosis.

A patient, aged less than 16 years, shall be classified as having juvenile systemic sclerosis if the one major and at least two of the 20 minor criteria are present:

Major criterion

- Proximal sclerosis/induration of the skin

Minor criteria

Skin

- Sclerodactyly

Vascular

- Raynaud's phenomenon
- Nailfold capillary abnormalities
- Digital tip ulcers

Gastrointestinal

- Dysphagia
- Gastro-oesophageal reflux

Renal

- Renal crisis
- New onset arterial hypertension

Cardiac

- Arrhythmias
- Heart failure

Respiratory

- Pulmon fibrosis (high-resolution computed tomography/x-ray)
- Diffusion capacity for carbon monoxide
- Pulmonary hypertension

Musculoskeletal

- Tendon friction rubs
- Arthritis
- Myositis

Neurological

- Neuropathy
- Carpal tunnel syndrome

Serology

- Antinuclear antibodies
- Systemic sclerosis selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillar, anti-polymyositis-scleroderma, antifibrillin or anti-RNA polymerase I or III)

Other presenting complaints include arthralgia, arthritis and, although less frequently, muscle weakness, dyspnoea and calcinosis (Figure 1). Unlike adults, telangiectasia is rarely present in children with JSSc. Examination of the periungual nailfold with an ophthalmoscope may demonstrate capillary dropout, tortuous dilated loops and, occasionally, distorted capillary architecture [9,10].

Interestingly, nailfold capillaries changes are reported in 10% of patients at the onset of the disease, in 25% at diagnosis and in 40% in the overall disease course [8].

From a practical point of view, the association of Raynaud's phenomenon and skin changes, eventually with some signs of internal organ involvement or capillary abnormalities, are the key diagnostic features.

Organ involvement during the disease course

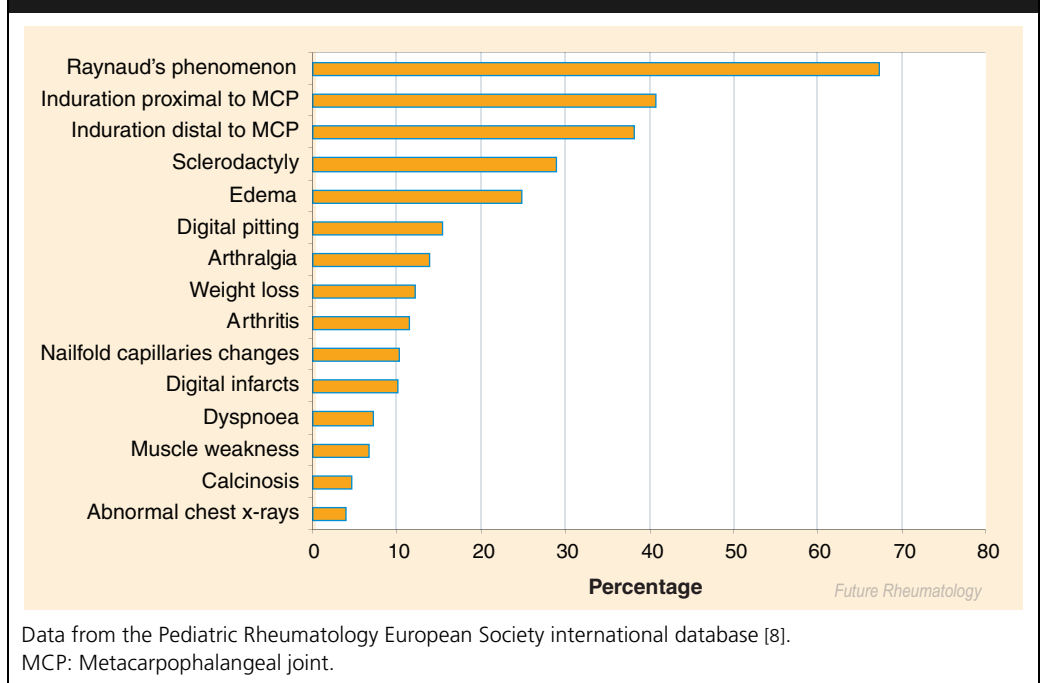
In children with JSSc, visceral organ involvement can be widespread and is associated with significant morbidity.

Gastrointestinal involvement occurs in 30–74% of children with JSSc [4,8]. Most affected patients have esophageal dysfunction, resulting in gastro-oesophageal reflux and dysphagia. Manometry, esophageal scintigraphy and intraesophageal 24-h pH monitoring provide more sensitive indicators of diminished lower esophageal sphincter tone and gastroesophageal reflux [11]. Large bowel involvement is less frequent and presents as alternating complaints of constipation and diarrhea, bloating or abdominal discomfort. Lactulose breath tests to evaluate bacterial overgrowth, endoscopy or colon scintigraphy are useful tools to evaluate this portion of intestinal tract.

Pulmonary involvement, although frequently asymptomatic, can be present as a dry, hacking cough to dyspnea on exertion [12]. Unlike adults, interstitial pulmonary fibrosis, a devastating complication, is not frequently reported in children with JSSc [4,8]. If we consider the various manifestations of lung involvement, such as bilateral basilar interstitial fibrosis on chest radiograph or high-resolution computed tomography, restrictive lung disease, pleuritis, pleural friction rub or pleural effusion, abnormal diffusion capacity for carbon monoxide (DLCO) or pulmonary arterial hypertension, the frequency of this complication ranges between 40 and 55% [4,8].

The classic radiographical features of interstitial lung disease consist of symmetric, reticulonodular shadowing, most pronounced at the lung bases. High-resolution computed tomography (HRCT) may reveal pulmonary disease even in the presence of a normal chest radiograph. In children, HRCT findings include groundglass opacification, subpleural micronodules, linear opacities and honey combing [13,14].

In addition, pulmonary diffusion (DLCO) and spirometry are sensitive measures of involvement of the respiratory tract. Pulmonary vascular

Figure 1. Clinical features at disease onset in 153 children with systemic sclerosis.

disease occurs very rarely, either independent or as a result of pulmonary fibrosis, and echocardiography is important in detecting early pulmonary hypertension [4,8].

Cardiac involvement is present in 17% of patients and represents a primary cause of morbidity among children with JSSc [4,15,16]. Cardiac fibrosis results in conduction defects, arrhythmias and impaired ventricular function. Pericardial effusions are common but are not usually of hemodynamic significance. In addition, pulmonary hypertension caused by pulmonary vascular disease can lead to myocardial damage and right heart failure. Cardiorespiratory complications are the leading cause of death in children with JSSc [4,8,15,16].

Severe cardiomyopathy is rare and usually associated with diffuse cutaneous disease and features of polymyositis. An aggressive immunosuppressive treatment is effective on muscle, skin and lung involvement but does not impair the progression of myocardial dysfunction and heart transplantation might be eventually considered [17].

There are limited data on the prevalence of renal involvement in children with JSSc. In a case series of children with systemic sclerosis, approximately 10% had some kind of renal involvement, including either increased urinary protein excretion (5%) or raised creatinine level [8]. Acute renal crisis has rarely been reported, with a frequency ranging between 0.7 and 4% [4,8]. Although renal

involvement in children appears to be not so severe as in adults, the abrupt onset of accelerated hypertension with acute renal failure (scleroderma renal crisis) remains one of the most severe and life-threatening complications of JSSc.

Is childhood-onset systemic sclerosis different from the adulthood-onset disease?

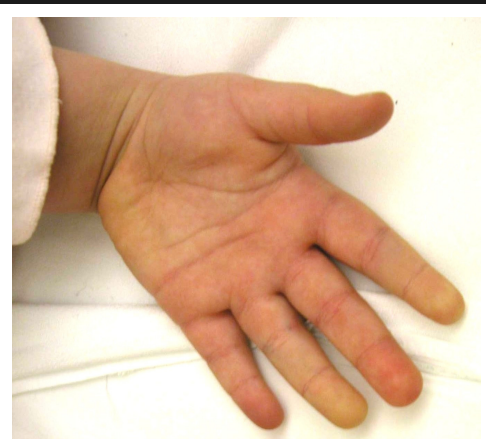
As known, SSc in adults is present in two varieties: the diffuse cutaneous (dc)SSc and limited cutaneous (lc)SSc. In lcSSc, cutaneous induration is restricted mainly to the digits and the extremities up to the elbow and knee.

Overall, cases of lcSSc account for approximately a half to two-thirds of the adult patients with scleroderma [18].

A comparison with an adult series is difficult because in children the lc form, which is by far the most frequent in adults, is definitely rare. However, it has now been shown that a substantial number of patients with childhood-onset SSc have their diagnosis confirmed either during adolescence or as young adults [4]. Therefore, it is possible that the limited subset might be underdiagnosed in younger children because of the lack of a full clinical picture.

Table 1 summarizes the comparison of some clinical and laboratory characteristics, present in the overall disease course, of children and adults reported in two large, multicenter studies [8,18].

Figure 2. Classic Raynaud's phenomenon in a 4-year-old girl.



Note the ischemic changes (blanching phase) of the second and fourth fingers and the cyanosis (bluish phase) of the fifth finger.

As shown, arthritis is slightly more common in children while interstitial lung involvement is less frequently seen than in adults. For other internal organs, a similar pattern of involvement has been seen in adult and pediatric patients, with the exception of gastroesophageal dysmotility, which has been reported in approximately 30% of children and 80% of adults with dcSSc, arterial hypertension and musculoskeletal symptoms that are much more common in adults [8,18]. On the contrary, in a recent report, muscle inflammation was observed in up to 38% of children with SSc and was a distinguishing feature from adulthood SSc [4]. These results could be influenced by the fact that the population examined in this study included children with both overlap syndrome and mixed connective tissue disease, which are known to have a more frequent muscle involvement.

Other differences with SSc in adults can be seen in the prevalence of Raynaud's phenomenon and skin sclerosis, which are less frequent in the pediatric age group.

Laboratory

Approximately a quarter of patients have chronic anemia or, less commonly, macrocytic anemia due to malabsorption of vitamin B12 or folate. Leukocytosis is not prominent but correlates with the degree of visceral or muscle disease. Patients with myositis will have elevated levels of creatine kinase [4,8].

High titers of antinuclear antibodies (ANAs) are commonly found, with a frequency of 80% in children with JSSc [8]. The prevalence of both

antitopoisomerase I (ScI-70) and anticentromere antibodies is lower in children compared with adults (Table 1). Interestingly, a high proportion of ANA-positive children, ranging from 20 to 34%, have none of the SSc-specific reactivities [4,8]. No significant difference between the adulthood and childhood form has been reported for rheumatoid factor and anticardiolipin antibodies [8,18].

Management

Since very little information is available on the treatment of SSc in childhood, part of the following considerations are based upon reports on adults and the personal opinion of the authors.

The nonpharmacological measures include physiotherapy to help maintain functional ability, muscle strength and joint movement while preventing flexion contractures and the use of corrective splints to treat or prevent contractures [19].

General skin care includes avoiding irritating or drying substances and the daily application of lanolin or water-soluble cream as an emollient.

Patients and parents should be told to avoid cold and trauma since they can exacerbate symptoms. These children are also susceptible to hyperpigmentation from sunlight and have difficulty in dissipating heat through sclerotic skin.

The pharmacological management of patients with JSSc is challenging, since no drug has been shown to be of unequivocal benefit in either

Figure 3. Pitting of the fingertips.



Note a small ulceration of tip of the right third finger and shiny, tightly stretched skin over the fingertips.

Figure 4. Classical expressionless appearance of a 10-year old girl with systemic sclerosis.



Note also the waxy, translucent appearance of the skin in the upper trunk.
(Courtesy of Ruben Cuttica, MD, Argentina).

children or adults with SSc. According to the experience in adult patients with SSc, therapy can be distinguished as:

- Disease-modifying therapy, directed at controlling the underlying disease process and includes immunomodulatory and antifibrotic agents;
- Organ-targeted therapy, directed towards complications specifically affecting the organs.

Disease-modifying therapy

The following is a summary of the agents that are currently used as disease-modifying therapy. The limited data on their use in pediatric patients with JSSc derive primarily from studies of adults.

Glucocorticoids are generally ineffective, except for the early inflammatory stage of muscle involvement or in the early, edematous phase of the cutaneous disease [20,21]. Since higher doses, which in children are equivalent to more than 1 mg/kg/day prednisone, appear to be associated with an increased frequency of renal crisis [22], their use should be accompanied by vigilant monitoring of renal function.

Methotrexate, a proven effective drug for juvenile idiopathic arthritis, demonstrated clinical benefit in adult SSc documented by skin score and pulmonary function [23,24].

D-penicillamine is an antifibrotic agent whose role in the treatment of SSc is unclear, as most studies have been either retrospective or poorly controlled. In a randomized, placebo-controlled

trial, D-penicillamine appeared to be ineffective in the treatment of SSc [25]. The results of this trial do not support the indication of D-penicillamine therapy for SSc.

Cyclophosphamide in combination with corticosteroids is efficacious in some patients, but controlled studies in children have yet to be performed. Similarly to adult experience, cyclophosphamide is used in combination with corticosteroids for children with fibrosing alveolitis who do not yet have advanced fibrosis [Personal experience].

Mycophenolate mofetil in combination with antithymocyte globulin has been successfully used for early diffuse scleroderma [26]. More recently, its use has been extended to also benefit early scleroderma lung disease [27]. The apparent safety and tolerability of this drug makes it a potential choice as an immunomodulatory drug for maintenance. However, its role needs to be defined by controlled clinical trials.

Since tumor necrosis factor (TNF)- α antagonizes a number of profibrotic cytokines, including transforming growth factor- β 1, it was postulated that its blockade would be beneficial in SSc. A pilot study treating ten patients with early diffuse SSc suggests that treatment with soluble TNF- α receptor antagonist (etanercept) is well tolerated, although conclusions regarding efficacy would be premature [28].

Autologous hemopoietic stem cell transplantation (HSCT) represents one of the most aggressive recent approaches to therapy for JSSc [29]. The rationale for this therapy is that ablation of self-reactive lymphocyte clones, responsible for the autoimmune process, may block pathogenesis of the disease. A multicenter study in adults reported that HSCT improved skin score in nearly 70% of patients, did not affect lung function but halted pulmonary hypertension. However, disease progression occurred in 19% of patients, while 17% died of complications related to the procedure [30]. Similar results have been recently reported by the European Group for Blood and Marrow Transplantation and the European League Against Rheumatism (EBMT/EULAR) registry. In this study, a durable clinical response was observed in two-thirds of the patients and treatment-related mortality was 9% [31]. As a result of this considerable mortality rate, HSCT has to be carefully considered for SSc patients, especially in children.

Organ-targeted therapy

Raynaud's phenomenon is a difficult complication to treat. The most widely used vasodilator agents are the calcium channel blockers (CCB).

Table 1. Main distinctive features of childhood- and adult-onset systemic sclerosis.

Distinctive feature	Childhood-onset SSc (%) n = 153 [8]	Adult-onset SSc (%) n = 290 [18]	Significance
Clinical subtype			
Limited cutaneous SSc	9.1	59.7	p < 0.001
Diffuse cutaneous SSc	90.9	40.3	p < 0.001
Signs and symptoms			
Edema	46	54	NS
Skin induration	76	95	p < 0.001
Raynaud's phenomenon	84	91	NS
Reduced DLCO	27	58	p < 0.001
Abnormal HRCT	23	n/a	–
Arthritis	27	17	NS
Heart failure	7	3	NS
Arterial hypertension	3	17	p < 0.001
Gastroesophageal reflux	30	79	p < 0.001
Autoantibodies			
Autonuclear antibodies	81	94	p < 0.01
Anti-topoisomerase	34	43	NS
Anticentromere	7	23	p < 0.001
Rheumatoid factor	17	23	NS
Anticardiolipin antibodies	15	10	NS
Mortality rate (5 years) (Data taken from [4,8,15,16,18,42,43].)	6–12	22–32	–

DLCO: Diffusion capacity for carbon monoxide; HRCT: High-resolution computed tomography; n/a: Not available; NS: Not significant; SSc: Systemic sclerosis.

Nifedipine is the most widely recommended, although this priority may change as new agents are developed. In several controlled trials it has been well tolerated, reduced the frequency and severity of Raynaud's phenomenon and promoted healing of cutaneous ischemic ulcers [32,33]. Intermittent infusions of prostacyclin or its analogs have been reported to be safe and effective in the treatment of Raynaud's phenomenon and ischemic digits of children with JSSc and other connective tissue diseases [34].

In the past, renal involvement was the leading cause of mortality in patients with SSc. The angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril and losartan) have brought about remarkable improvement for effective long-term control of blood pressure and stabilization of renal function [35]. Whether or not prior ACE inhibition is successful in protecting patients from developing scleroderma renal crisis is not entirely clear. Certainly, patients on ACE inhibitors have developed this complication [36].

If a child suffering from alveolitis has respiratory symptoms and abnormal or declining pulmonary function, and HRCT shows ground-glass picture, we suggest initiating therapy with low-dose prednisone (0.2–0.4 mg/kg/day) plus daily oral (1–2 /kg/day) or monthly intravenous pulse cyclophosphamide (500–750 mg/m²/month) [37,38]. An alternative pharmacological approach may be azathioprine (1–3 mg/kg/day to a maximum dose of 100 mg/day). Treatment should be continued for at least 6–12 months before reaching a decision about efficacy.

If HRCT reveals a predominantly reticular pattern, it is likely that fibrotic pulmonary fibrosis disease is present. If bronchoalveolar lavage suggests the presence of active alveolitis, then treatment is similar to the previous one. In the absence of any evidence for active inflammatory process, we recommend standard general supportive therapy, such as supplemental oxygen, control of gastroesophageal reflux and preventive measures such as annual influenza vaccination.

Executive summary**Classification**

- The preliminary classification criteria for juvenile systemic sclerosis (JSSc) have been recently defined. A patient, aged less than 16 years, shall be said to have JSSc if diffuse skin induration and at least two among a list of 20 minor criteria are present.

Epidemiology

- JSSc is very uncommon: children under 10 years of age account for less than 2% of all cases and 10% of all patients develop SSc before the age of 20.

Clinical presentation

- In children, JSSc presents with Raynaud's phenomenon and/or skin tightening and thickening of the hands and face. Other presenting complaints include arthralgia, arthritis and, although less frequently, muscle weakness, dyspnoea, dysphagia and calcinosis.
- Visceral organ involvement can be widespread and is associated with significant morbidity.
- During the course of the disease: 30–74% have gastrointestinal involvement as esophageal dysfunction, abdominal discomfort constipation or diarrhea, 40–55% have pulmonary involvement, frequently asymptomatic or as interstitial pulmonary fibrosis or pulmonary hypertension, 17% have cardiac involvement and renal involvement is present in less than 10%.

Distinctive features with adulthood-onset SSc

- In children, the limited cutaneous form of SSc, which is the most frequent form in adults, is definitely rare.
- Arthritis is slightly more common in children, while Raynaud's phenomenon, skin induration, lung and gastrointestinal involvement are more frequent in adults.
- Children have a significantly lower prevalence of antinuclear antibodies (ANA) and anticardiolipin (ACA) positivity than adults, while in a third of ANA-positive children no SSc-specific autoantibodies are present.

Management

- Nonpharmacological measures: physiotherapy and corrective splints general skin care.
- Disease-modifying therapy:
 - Glucocorticoids for the inflammatory stage of muscle involvement or in the early edematous phase of the cutaneous disease.
 - Careful monitoring of the renal function is mandatory.
 - Methotrexate shows clinical benefit on skin and pulmonary function.
 - Cyclophosphamide in combination with corticosteroids for fibrosing alveolitis.
 - Mycophenolate mofetil is a potential choice for maintenance.
 - Autologous hemopoietic stem cell transplantation, the most aggressive therapeutic approach for JSSc, is indicated for the more refractory cases. Owing to the considerable treatment-related mortality (9%), this approach has to be carefully considered for children.
- Organ-targeted therapy:
 - Raynaud's phenomenon: calcium channel blockers, intermittent infusions of prostacyclin or its analogs.
 - Renal involvement: angiotensin-converting enzyme inhibitors (e.g., captopril and losartan).
 - Alveolitis: low-dose prednisone (0.2–0.4 mg/kg/day) plus cyclophosphamide, daily oral (1–2 mg/kg/day) or monthly intravenous pulse (500–750 mg/m²/month).
 - Pulmonary arterial hypertension: continuous prostacyclin infusions, endothelin-1 receptor antagonist (bosentan).
 - Myositis, serositis: prednisone (0.3–0.5 mg/kg/day).
 - Arthritis or tenosynovitis: nonsteroidal anti-inflammatory drug.
 - Isolated skin involvement: methotrexate in combination with low-dose glucocorticoids.

Prognosis

- Skin tightness and joint contractures inevitably lead to severe disability.
- The skin may eventually soften years after onset of the disease.
- Overall mortality rate at 5 years in JSSc is still approximately 6–12%, but is better than in adults (22–32%).
- Most common causes of death are cardiac failure, end-stage renal failure, respiratory failure, infections and hypertensive encephalopathy.

If pulmonary fibrosis is complicated by pulmonary arterial hypertension (PAH), continuous prostacyclin infusions (or analogs such as epoprostenol) have been used with good results [39,40]. Recently, an endothelin-1 receptor antagonist, bosentan, was demonstrated to be safe and effective in the treatment of PAH [41]. It should be

mentioned, however, that in this study only a minority of patients had PAH associated with SSc. The oral formulation and the potential use for other vascular complications represent important factors for its use in JSSc.

The treatment of gastroesophageal reflux is based mainly on the use of prokinetics, such as

domperidone and proton pump inhibitors. The management of low intestinal tract involvement has focused on symptom control and nutritional support to prevent weight loss and malnutrition, while the bacterial overgrowth syndrome is treated with antibiotics, such as metronidazole, ciprofloxacin and doxycycline.

For myositis and serositis, use of low-dose prednisone (0.3–0.5 mg/kg/day) is recommended. For arthritis or tenosynovitis, nonsteroidal anti-inflammatory drugs can be effective.

When isolated skin involvement is present, methotrexate in combination with low-dose glucocorticoids is recommended.

Course of the disease & prognosis

Generally, the prognosis of JSSc is poor. Skin tightness and joint contractures inevitably lead to severe disability [42]. It has been reported that the skin may eventually soften years after the onset of the disease. The most common causes of death in children are related to the involvement of the cardiac, renal and pulmonary systems. Cardiomyopathy, although rare, can be one of the causes of early death, especially in children [17]. Interstitial lung disease and renal failure or acute hypertensive encephalopathy supervenes as a potentially fatal outcome in a few children and seem more likely to occur early in the disease course [15,16].

Survivorship has not been determined in any large series of children due to the rarity of this disease, and very few retrospective data are available

[4,15,16]. The overall mortality rate at 5 years is approximately 6–15% and appears to be better than in adults where it ranges between 25 and 32% [3,43] (Table 1). The causes of death in JSSc include cardiac failure (67%), end-stage renal failure (13%), respiratory failure (10%), infections (7%) and hypertensive encephalopathy (3%) [15,16].

Conclusions

JSSc is a rare disease in children. In comparison to adult-onset disease, JSSc appears to be less severe: children have less internal organ involvement, less specific autoantibody profile and better long-term outcome. A multicenter and multispeciality collaboration is needed to better define the pattern of organ involvement and to standardize the clinical approach to this threatening disease.

Future perspective

The next decade will see a rapid increase in our knowledge about the natural history and pathogenesis of SSc in children. Many efforts have been made during the last few years to improve clinical research collaboration both in Europe and in North America.

As soon as disease activity and damage outcome measures are defined and validated for children, we should be able to measure accurately the effects of new drug regimens in controlled clinical trials and to better compare patient groups.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

- Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum.* 23, 581–590 (1980).
- Zulian F, Woo P, Athreya BH *et al.*: The PRES/ACR/EULAR provisional classification criteria for juvenile systemic sclerosis. *Arthritis Care Res.* (2007) (In press).
- Describes an international project aimed to define a provisional set of classification criteria for systemic sclerosis (SSc) in children on the basis of clinical data from real patients following a consensus-based methodology.
- Mayes MD, Lacey JV, Beebe-Dimmer J *et al.*: Prevalence, incidence, survival and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum.* 48(8), 2246–2255 (2003).
- Scalapino K, Arkachaisri T, Lucas M *et al.*: Childhood onset systemic sclerosis: classification, clinical and serologic features, and survival in comparison with adult onset disease. *J. Rheumatol.* 33, 1004–1013 (2006).
- Interesting description of the clinical features of childhood-onset SSc followed at one center and a comparison with those of adult-onset cases.
- Kornreich HK, King KK, Bernstein BH *et al.*: Scleroderma in childhood. *Arthritis Rheum.* 20, 343–350 (1977).
- Medsgger TA Jr: Epidemiology of systemic sclerosis. *Clin. Dermatol.* 12, 207–216 (1994).
- Black CM: Scleroderma in children. *Adv. Exp. Med. Biol.* 455, 35–48 (1999).
- Martini G, Foeldvari I, Russo R *et al.*: Systemic sclerosis in childhood: clinical and immunological features of 153 patients in an International Database. *Arthritis Rheum.* 54(12), 3971–3978 (2006).
- Comprehensive study describing the clinical and immunological features of SSc in a group of 153 children from a multicenter, multinational database sponsored by the Pediatric Rheumatology European Society.
- Spencer-Green G, Schlesinger M, Bove KE *et al.*: Nailfold capillary abnormalities in childhood rheumatic diseases. *J. Pediatr.* 102, 341–366 (1983).
- Dolezalova P, Young SP, Bacon PA, Southwood TR: Nailfold capillary microscopy in healthy children and in childhood rheumatic diseases: a prospective single blind observational study. *Ann. Rheum. Dis.* 62, 444–449 (2003).

11. Weber P, Ganser G, Frosch M *et al.*: Twenty-four hour intraoesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease. *J. Rheumatol.* 27, 2692–2695 (2000).
12. Eid NS, Buchino JJ, Schikler KN: Pulmonary manifestations of rheumatic diseases. *Pediatr. Pulmonol. Suppl.* 18, 91 (1999).
13. Koh DM, Hansell DM: Computed tomography of diffuse interstitial lung disease in children. *Clin. Radiol.* 55, 659–667 (2000).
14. Seely JM, Jones LT, Wallace C *et al.*: Systemic sclerosis: using high-resolution CT to detect lung disease in children. *Am. J. Roentgenol.* 170, 691–697 (1998).
15. Foeldvari I, Zhavania M, Birdi N *et al.*: Favourable outcome in 135 children with juvenile systemic sclerosis: results of a multi-national survey. *Rheumatology (Oxford)* 39, 556–559 (2000).
- **Survey, involving 34 pediatric rheumatology centers, showing a favorable outcome in most patients with childhood-onset juvenile (J)SSc and a significantly better survival than in the adult SSc patients.**
16. Martini G, Vittadello F, Athreya BH *et al.*: Mortality in juvenile systemic sclerosis: data from the Padua International Database of 153 patients. *Arthritis Rheum.* 52(9), S533 (2005) (Abstract).
17. Quartier P, Bonnet D, Fournet JC *et al.*: Severe cardiac involvement in children with systemic sclerosis and myositis. *J. Rheumatol.* 29, 1767–1773 (2002).
- **Description of a subset of JSSc patients with severe cardiomyopathy and myositis refractory to the usual immunosuppressive regimen.**
18. Della Rossa A, Valentini G, Bombardieri S *et al.*: European multicentre study to define disease activity criteria for systemic sclerosis. I. Clinical and epidemiological features of 290 patients from 19 centres. *Ann. Rheum. Dis.* 60, 585–591 (2001).
- **Multicenter cross-sectional study describing clinical features and assessment of adult patients with SSc.**
19. Alpiner N, Oh TH, Hinderer SR, Brander VA: Rehabilitation in joint and connective tissue diseases. 1. Systemic diseases. *Arch. Phys. Med. Rehabil.* 76 (Suppl. 1), S32–S40 (1995).
20. Clements PJ, Furst DE, Campion DS *et al.*: Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic considerations. *Arthritis Rheum.* 21, 62–71 (1978).
21. Takehara K: Treatment of early diffuse cutaneous systemic sclerosis patients in Japan by low-dose corticosteroids for skin involvement *Clin. Exp. Rheumatol.* 22(Suppl. 33), S87–S89 (2004).
22. Steen VD, Medsger TA Jr: Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum.* 41, 1613–1619 (1998).
23. van den Hoogen FH, Boerbooms AM, Swaak AJ *et al.*: Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br. J. Rheumatol.* 35, 364–372 (1996).
24. Pope JE, Bellamy N, Seibold JR *et al.*: A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum.* 44, 1351–1358 (2001).
25. Clements PJ, Furst DE, Wong WK *et al.*: High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double blind, randomized, controlled clinical trial *Arthritis Rheum.* 42, 1194–1203 (1999).
26. Stratton RJ, Wilson H, Black CM: Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma. *Rheumatology (Oxford)* 40, 84–88 (2001).
27. Lioussis SNC, Bounas A, Andonopoulos AP: Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology (Oxford)* 45, 1005–1008 (2006).
- **Pilot study showing the efficacy of mycophenolate mofetil associated with small doses of corticosteroids in patients with diffuse SSc and recent alveolitis.**
28. Ellman MH, MacDonald PA, Hayes FA: Etanercept as treatment for diffuse scleroderma: a pilot study. *Arthritis Rheum.* 43, S392 (2000) (Abstract).
29. Wulffraat NM, Sanders LA, Kuis W: Autologous hemopoietic stem-cell transplantation for children with refractory autoimmune disease. *Curr. Rheumatol. Rep.* 2, 316–323 (2000).
30. Binks M, Passweg JR, Furst D *et al.*: Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. *Ann. Rheum. Dis.* 60, 577–584 (2001).
- **Comprehensive report on the treatment of SSc with bone marrow transplantation.**
31. Farge D, Passweg J, van Laar JM *et al.*: Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. *Ann. Rheum. Dis.* 63(8), 974–981 (2004).
- **Study showing a durable clinical response in two-thirds of SSc patients treated with autologous stem cell transplantation with 9% treatment-related mortality.**
32. Rodeheffer RJ, Rommer JA, Wigley F *et al.*: Controlled double-blind trial of nifedipine in the treatment of Raynaud's phenomenon. *N. Engl. J. Med.* 308, 880–883 (1983).
33. Sauza J, Kraus A, Gonzalez-Amaro R *et al.*: Effect of the calcium channel blocker nifedipine on Raynaud's phenomenon. A controlled double blind trial. *J. Rheumatol.* 11, 362–364 (1984).
34. Zulian F, Corona F, Gerloni V *et al.*: Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases. *Rheumatology (Oxford)* 43, 229–233 (2004).
- **The favorable experience on the use of iloprost for the treatment of critically ischemic digits and Raynaud's phenomenon resistant to common vasodilators in children with connective tissue diseases.**
35. Steen VD, Costantino JP, Shapiro AP *et al.*: Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann. Intern. Med.* 113, 352–357 (1990).
36. Steen VD, Medsger TA Jr: Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum.* 41, 1613–1619 (1998).
37. White B, Moore WC, Wigley FM *et al.*: Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann. Intern. Med.* 132, 947–954 (2000).
38. Denton CP, Black CM: Combination therapies for systemic sclerosis. *Springer Semin. Immunopathol.* 23(1–2), 109–129 (2000).
39. Kuhn KP, Byrne DW, Arbogast PG *et al.*: Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am. J. Respir. Crit. Care Med.* 167, 580–586 (2003).
40. Badesch DB, Tapson VF, McGoon MD *et al.*: Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann. Intern. Med.* 132, 425–434 (2000).

41. Rubin LJ, Badesch DB, Barst RJ *et al.*: Bosentan therapy for pulmonary arterial hypertension. *N. Engl. J. Med.* 346, 896–903 (2002).
42. Bottoni CR, Reinker KA, Gardner RD *et al.*: Scleroderma in childhood: a 35-year history of cases and review of the literature. *J. Pediatr. Orthop* 20, 442–449 (2000).
43. Bulpitt KJ, Clements PJ, Lachenbruch PA *et al.*: Early undifferentiated connective tissue disease: III. Outcome and prognostic indicators in early scleroderma (systemic sclerosis). *Ann. Intern. Med.* 118(8), 602–609 (1993).

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