

Scleroderma in Children

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Juvenile scleroderma syndromes are multisystem autoimmune rheumatic diseases whose unifying characteristic is the presence of hard skin and onset before 16 years of age. They can be separated into two main categories: localized scleroderma (morphea) in which there is skin sclerosis but no vascular or internal organ involvement, and systemic sclerosis, in which there is diffuse skin sclerosis involving many sites of the body together with internal organ involvement.

Juvenile systemic sclerosis

Juvenile systemic sclerosis is a chronic multisystem connective tissue disease characterized by sclerodermatous skin changes and widespread abnormalities of the viscera. In this condition the symmetrical fibrous thickening and hardening of the skin accompany fibrous changes in internal organs, such as esophagus, intestinal tract, heart, lungs, and kidneys.

Classification

According to of the 1980 American College of Rheumatology classification criteria for adults, the diagnosis of systemic sclerosis requires the presence of either the major criterion (diffuse scleroderma involving areas proximal to the metacarpophalangeal or metatarsophalangeal joints) or of two minor criteria (sclerodactyly, digital pitting scars, bibasilar pulmonary fibrosis) [1]. This classification was designed to be specific rather than sensitive to minimize false-

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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 systemic sclerosis, have shown the need for a more comprehensive classification.

Because of these issues and the lack of an acceptable classification for pediatric patients, a multicenter multinational project, sponsored by the Pediatric Rheumatology European Society (PRES), was organized to define nomenclature and criteria that allow the classification of homogeneous groups of patients with juvenile systemic sclerosis on the basis of clinical features and laboratory parameters. As a final step of this 3-year project, a consensus conference, including pediatric and adult rheumatologists and dermatologists, was convened in Padua, Italy, June 3 through 6, 2004. By using both Delphi and Nominal Group Technique methodologies, the preliminary classification criteria that define a patient as having juvenile systemic sclerosis were identified and are in the process of being validated (Box 1) [2].

Epidemiology

In general, systemic sclerosis has an estimated annual incidence from 0.45 to 1.9 per 100,000 and a prevalence of approximately 15 to 24 per 100,000 [3]. Onset in childhood is uncommon: children under 10 years account for fewer than 2% of all cases, and it has been estimated that fewer than 10% of all patients develop systemic sclerosis before the age of 20 years [4–7]. No racial predilection or peak age of onset has been determined for children [8]. More accurate epidemiologic data are lacking.

Etiology and pathogenesis

The cause of systemic sclerosis is unknown despite significant advances in the understanding of the pathogenetic mechanisms [9]. The disease can be represented as tripartite process in which dysfunction of the immune system, endothelium, and fibroblasts are mutually involved in a complex process characterized prominently by fibrosis.

Cellular immunity plays a major role in the initiation of scleroderma. This role is clearly indicated by the presence of mononuclear cell infiltrates in early lesions, altered function of T-helper and natural killer cells, and release of various cytokines, chemokines, and growth factors. The early infiltrates of mononuclear cells release several cytokines and chemokines that in turn have effects on both endothelial cells and fibroblasts. Several growth factors, such as transforming growth factor β (TGF- β) and connective tissue growth factor, have also been noted in scleroderma skin. They stimulate the synthesis of extracellular matrix components and promote fibrosis [10–13]. Several cytokines (interleukins [IL]-1, -2, -4, -6, -8, and -12) are increased in scleroderma serum or in scleroderma

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

Sclerosis/induration
Sclerodactyly
Raynaud's phenomenon

Minor criteria

Vascular
Nailfold capillaries changes
Digital ulcers
Gastrointestinal
Dysphagia
Gastroesophageal reflux
Renal
Renal crisis
New-onset hypertension
Cardiac
Arrhythmias
Heart failure
Respiratory
Pulmonary fibrosis (High-resolution CT/radiograph)
Pulmonary diffusion (DLCO)
Pulmonary hypertension
Muskuloskeletal
Tendon friction rubs
Arthritis
Myositis
Neurologic
Neuropathy
Carpal tunnel syndrome
Serologic
Antinuclear antibodies
Systemic sclerosis-specific antibodies (Scl-70, Anticentromere, PM-Scl)

skin (IL-4, -6, and -8) [14–17]. Specific cytokines such as tumor necrosis factor (TNF) promote fibrosis. Others, such as interferon- γ , are potent suppressors of collagen synthesis (Fig. 1).

Evidence that endothelial cells are damaged is provided by the elevated levels of factor VIII-related antigen, reduced plasma angiotensin-converting enzyme

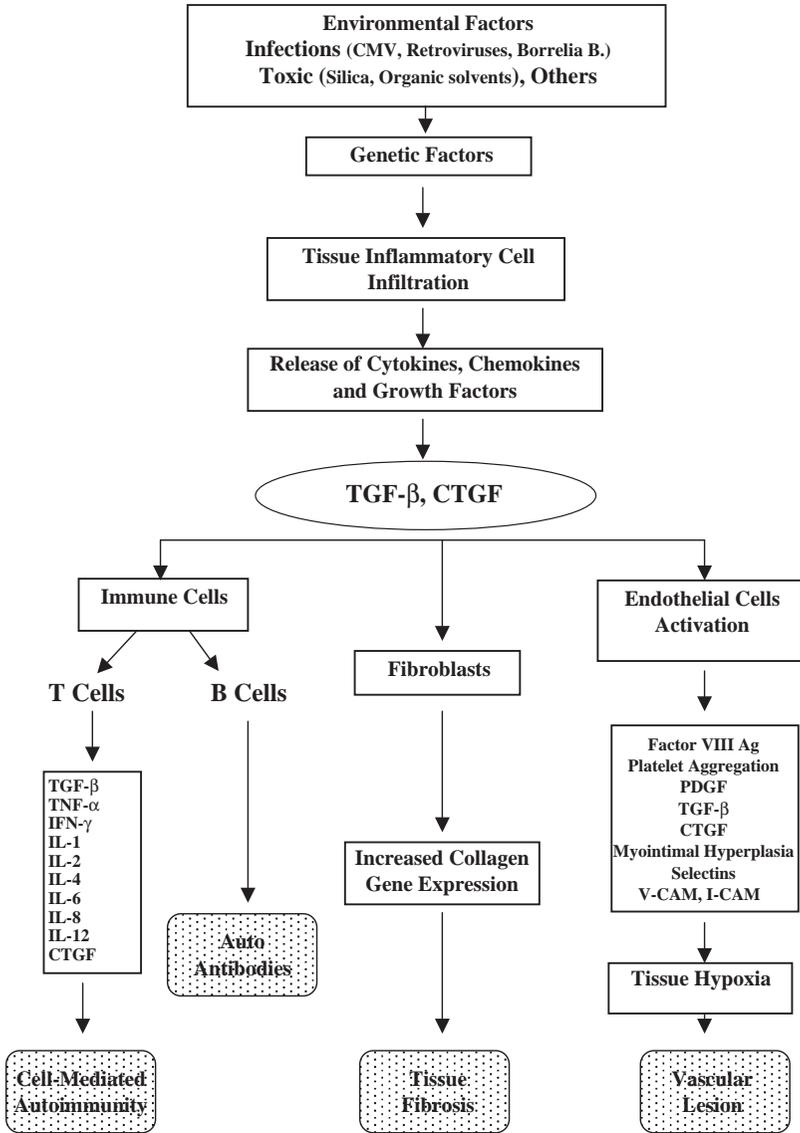


Fig. 1. Sequence of events involved in the onset of juvenile systemic sclerosis. CMV, human cytomegalovirus; CTGF, connective tissue growth factor; ICAM-1, intracellular adhesion molecule-1; IFN- γ , interferon- γ ; PDGF, platelet-derived growth factor; VCAM-1, vascular cell adhesion molecule-1. (Modified from Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann Intern Med 2004;160:37-50; with permission.)

(ACE) activity, and accelerated endothelial cell apoptosis [18–20]. The microvascular injury leads to arteriolar intimal fibrosis and narrowing of the vascular lumen, which results in ischemic damage.

Microchimerism, the presence in an individual of a very low level of cells derived from different individuals, was postulated as a possible cause of scleroderma. This hypothesis was considered because of the frequent occurrence of sclerodermatous skin involvement in patients with graft-versus-host disease. Although microchimerism can be identified in normal persons, chimeric cells are increased in number in patients with scleroderma and are more similar to the maternal cells than in normal persons [21,22]. These studies concluded that fetal antimaternal graft-versus-host reactions may play an important role in the pathogenesis of scleroderma [23].

Clinical features

Early signs and symptoms

The presenting signs and symptoms of juvenile systemic scleroderma are shown in Table 1. The onset is often characterized by the development of Raynaud's phenomenon and tightening, thinning, and atrophy of the skin of the hands and face [24–26]. There is often a diagnostic delay of years because of the subtle nature of this presentation and the insidious onset of cutaneous abnormalities [8,26–28].

Cutaneous changes characteristically evolve in a sequence beginning with edema, followed by induration and sclerosis resulting in marked tightening and contracture, and finally leading to atrophy. During the sclerotic phase, the skin becomes waxy in texture, tight, hard, and bound to subcutaneous structures. This phenomenon is particularly noticeable in skin of the digits and face; the characteristic expressionless appearance of the skin may be the first clue to diagnosis.

The long-term consequence of edema and sclerosis is atrophy of skin and adnexa accompanied by areas of hypopigmentation or hyperpigmentation and, often, by deposition of calcium salts in the subcutaneous tissues [29].

Table 1
Presenting signs and symptoms in children with systemic sclerosis

Signs and symptoms	% patients ^a (N = 164)
Skin tightening	84.4
Raynaud's phenomenon	72.4
Arthralgia	32.2
Muscle weakness and pain	17.1
Subcutaneous calcification	10.2
Dysphagia	15.5
Dyspnea	14.1

^a Percentage calculated only on those series in which detailed information was provided.

Telangiectases, characteristic signs of juvenile systemic sclerosis, are fine, macular dilatations of cutaneous or mucous-membrane blood vessels. The peri-ungual nailfold is often the most obvious early location and on examination with an ophthalmoscope demonstrates capillary dropout, tortuous dilated loops, and, occasionally, distorted capillary architecture [30]. Digital pitting, sometimes with ulceration, occurs in the pulp of the fingertips as a result of ischemia.

Raynaud's phenomenon occurs in 80% to 90% of children and is often the initial symptom of the disorder, in some instances preceding other manifestations by years [31]. Raynaud's phenomenon is much more common in the fingers than elsewhere, but it can be observed in toes and, occasionally, ears, tip of the nose, lips, or tongue.

Musculoskeletal symptoms are common in juvenile systemic sclerosis and characteristically occur at or near the onset of the disease. Among the 127 children with juvenile systemic sclerosis included in the Padua International database of PRES, 36% had musculoskeletal symptoms during the course of the disease [8]. Arthralgia is usually mild and transient; joint contractures are most common at the proximal interphalangeal joints and elbows, but other joints are also affected. Muscle inflammation can occur in up to 38% of children and seems to be the characteristic feature of the overlapping presentation of the disease in children [32].

Upper gastrointestinal involvement is present in almost 40% of the patients during the course of the disease, and dysphagia may be one of the presenting signs in 14% of children [8]. Typically, dysphagia is caused by esophageal dysmotility and gastroesophageal reflux. Small bowel involvement develops in up to 50% of children, usually in association with esophageal or colonic disease [33]. Radiologic and functional studies of the gastrointestinal tract often demonstrate characteristic abnormalities even in the absence of symptoms. Manometry and intra-esophageal 24-hour pH monitoring provide more sensitive indicators of diminished lower sphincter tone and presence of reflux [34].

Cardiopulmonary disease, although uncommon at presentation, is a primary cause of morbidity among children with juvenile systemic sclerosis [26,35]. Cardiac fibrosis causes conduction defects, arrhythmias, and impaired ventricular function. Pericardial effusions are quite common but usually are not hemodynamically significant. Severe cardiomyopathy, although rare, can be one of the causes of early death in these patients and requires prompt and aggressive immunosuppressive treatment [35]. Cardiorespiratory complications are probably the greatest cause of juvenile systemic sclerosis-related death. Pulmonary involvement, although frequently asymptomatic, can manifest as dry, hacking cough or dyspnea on exertion [36]. Interstitial pulmonary fibrosis is a devastating complication but, unlike in adults, is rarely reported in children [8]. Pulmonary vascular disease can occur secondary to pulmonary fibrosis, but it is the isolated form of this complication, typically occurring in the limited variety of juvenile systemic sclerosis, that seems to have a much worse prognosis. High-resolution CT (HRCT) may reveal pulmonary disease even in the presence of a normal chest radiograph. In children, the most frequent HRCT findings

are ground-glass opacification, subpleural micronodules, linear opacities, and honey combing [37,38]. Pulmonary diffusion (DLCO) and spirometry are sensitive measures of involvement of the respiratory tract. Echocardiography is important in confirming early pulmonary hypertension by documenting a dilated right ventricle and blood pressure in the pulmonary artery.

Few data on the prevalence of renal involvement in children are available, although children seem to have less kidney involvement than adults [25,26]. Among children included in the International Padua database, 9.4% had renal involvement, and only one developed renal crisis [6]. Although renal involvement can be indolent, the abrupt onset of accelerated hypertension with acute renal failure (scleroderma renal crisis) is the most feared complication.

The most frequently described central nervous system (CNS) abnormality is cranial nerve involvement. Peripheral neuropathies are uncommon ($\leq 1.6\%$). Clinical involvement of the CNS is usually secondary to renal or pulmonary disease [39].

Table 2 summarizes the prevalence of the involvement of organ systems during the course of the disease.

Laboratory findings

Anemia, although not common, is present in approximately one fourth of patients and is characteristic of the anemia of chronic disease. Less commonly, in case of chronic malabsorption, macrocytic anemia, reflecting vitamin B₁₂ or folate deficiency, may occur. Microangiopathic hemolysis or bleeding from mu-

Table 2
Organ system involvement during the course of disease in children with systemic sclerosis

Organ system	No. observed ^a	Percentage
Skin		
Subcutaneous calcification	28/135	21
Ulcerations	57/133	43
Raynaud's phenomenon	115/141	82
Musculoskeletal system		
Arthritis/arthralgia	46/127	36
Muscle weakness	34/137	25
Gastrointestinal tract		
Abnormal oesophageal motility	51/135	38
Lungs		
Abnormal diffusion	47/89	53
Abnormal vital capacity	66/109	61
Heart		
Electrocardiographic abnormalities	9/139	7
Congestive heart failure	10/139	7

^a Cumulative series from Martini G, Foeldvari I, Russo R, et al. Systematic scleroderma syndromes in children: clinical and immunological characteristics of 181 patients. *Arthritis Rheum* 2003;48(9):S512; and Cassidy JT, Sullivan DB, Dabich L, et al. Scleroderma in children. *Arthritis Rheum* 1977;20:351-4.

cosal telangiectases may also occur. Leukocytosis is not prominent but when present may correlate with advanced visceral or muscle disease. Synovial fluid contains increased protein content and polymorphonuclear leukocytosis. Pericardial fluid has the characteristics of an exudate.

Antinuclear antibodies (ANA) are frequently demonstrated in the sera of children with juvenile systemic sclerosis. The prevalence of ANA positivity in the Padua database was 80.8%, a frequency lower than reported in adults [8]. The prevalence of Scl-70 (anti-topoisomerase I) ranges from 20% to 30%, whereas anticentromere antibodies are much less common than in adults (approximately 7%) [8,32]. In adults, Scl-70 antibodies occur most frequently in patients with diffuse systemic sclerosis, in whom it is associated with peripheral vascular disease and pulmonary interstitial fibrosis [40]. Anticentromere antibodies occur almost exclusively in adult patients with limited systemic sclerosis in association with calcinosis, telangiectases, and the late development of pulmonary hypertension.

Management

The management of patients with juvenile systemic sclerosis presents one of the most difficult and frustrating challenges in pediatric rheumatology. None of the agents currently used as disease-modifying treatments for juvenile systemic sclerosis have undergone rigorous placebo-controlled evaluation.

Methotrexate, a proven effective drug for juvenile idiopathic arthritis, showed clinical benefit in adult systemic sclerosis as documented by skin score and pulmonary function [42]. Unfortunately, a substantially larger study from North America was negative [43]. Mycophenolate mofetil has recently been used for scleroderma. The apparent safety and tolerability of this drug makes it a potential choice as an immunodulatory drug for maintenance [44], but its role needs to be defined by controlled clinical trials.

Glucocorticoids are generally ineffective except during the early inflammatory stage of muscle involvement or in the edematous phase of the cutaneous disease [45]. Because higher doses seem to be associated with an increased frequency of renal crisis [46], their use should be accompanied by vigilant monitoring of the renal function.

Because TNF α antagonizes a number of profibrotic cytokines, including TGF- β 1, it was postulated that its blockade would be beneficial in systemic sclerosis. A pilot study treating 10 patients with early diffuse systemic sclerosis suggests that treatment with soluble TNF α receptor (etanercept) is well tolerated, although conclusions about efficacy would be premature [47].

Autologous hemopoietic stem cell transplantation (HSCT) represents one of the most aggressive recent approaches to therapy for juvenile systemic sclerosis [48]. The rationale for this therapy is that ablation of self-reactive lymphocyte clones responsible of 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, and halted pulmonary hy-

pertension. Disease progression occurred in 19% of patients, however, and 17% died of complications related to the procedure [49]. The European Bone Marrow Transplantation/European League Against Rheumatism (EBMT/EULAR) registry has recently reported similar results. In this study, a durable clinical response was observed in two thirds of the patients. Treatment-related mortality was 9% [50]. Because of this mortality rate, HSCT must be considered carefully for systemic sclerosis patients, especially children.

During the last few years, the use of D-penicillamine has decreased. Several studies examining its effect in systemic sclerosis were either retrospective [51,52] or poorly controlled [53]. A carefully executed, double-blind RCT showed no difference between high-dose (750–1000 mg daily) and low-dose (125 mg on alternate days) regimens, certainly providing no justification for using high doses [54]. Although there are no controlled studies on the use of D-penicillamine in juvenile systemic sclerosis, it is a well-known antifibrotic agent and may still have a place in the treatment of this disease in combination with other anti-inflammatory or immunosuppressive agents.

Therapy of specific complications

Raynaud's phenomenon is difficult complication to treat. The most widely used vasodilator agents are the calcium channel blockers. Nifedipine is most widely recommended, although this priority may change as new agents are developed. In several controlled trials, nifedipine has been well tolerated, has reduced the frequency and severity of Raynaud's phenomenon, and promoted healing of cutaneous ischemic ulcers [55–57]. Intermittent infusions of prostacyclin or its analogues have been reported to be safe and effective in treatment of Raynaud's phenomenon and ischemic digits of children with juvenile systemic sclerosis and other connective tissue diseases [58]. Orally active formulations of prostacyclin or its analogues are an attractive alternative, but unfortunately two large studies from Europe and North America have failed to demonstrate efficacy [59,60].

In the past, renal involvement was the leading cause of mortality in patients with systemic sclerosis. ACE inhibitors (eg, captopril, quinapril) are useful in preventing vascular damage, providing effective long-term control of blood pressure, and stabilizing renal function [61–63].

Cyclophosphamide is used in treatment of scleroderma-associated pulmonary fibrosis. A number of retrospective series have suggested its efficacy and have delineated factors associated with responsiveness [41]. As in other disorders, the toxic side effects of cyclophosphamide, such as premature ovarian failure, opportunistic infections, and the possibility of late secondary malignancies, should be carefully balanced against efficacy. Following the experience in adults, it is common practice to combine cyclophosphamide (monthly intravenous infusions of 500–750 mg/m²) with prednisone (0.3–0.5 mg/kg/day). Treatment is generally recommended for at least 6 to 9 months. Controlled trials comparing cyclophosphamide treatment with placebo are underway, and a recently reported open study was encouraging [64].

Continuous infusion of prostacyclin (or analogues such as epoprostenol) has been used with good results to treat pulmonary hypertension occurring in the context of established interstitial lung fibrosis or in limited systemic sclerosis [65,66]. Recently an endothelin-1 receptor antagonist, bosentan, was demonstrated to be safe and effective in the treatment of pulmonary hypertension [67]. The oral formulation and the potential use for other vascular complications are important factors for its use in juvenile systemic sclerosis.

Course of the disease and prognosis

Generally, the prognosis of juvenile systemic sclerosis is poor. Skin tightness and joint contractures inevitably lead to severe disability [68]. It has been reported that the skin may eventually soften years after onset of the disease. The most common causes of death in children are related to involvement of the cardiac, renal, and pulmonary systems. Arrhythmias may develop during the course of the disease secondary to myocardial fibrosis. Cardiomyopathy, although rare, can be one of the causes of early death, especially in children [35]. Interstitial lung disease and renal failure or acute hypertensive encephalopathy lead to potentially fatal outcomes in a few children and seem more likely to occur early in the course of the disease.

Survivorship has not been determined in any large series of children; because of the rarity of this disease, few retrospective data are available [6,69]. The mortality rate in adults, particularly under the age of 35 years, is significantly increased, and the extent of sclerosis of the skin seems to be an important determining factor in prognosis [70].

Juvenile localized scleroderma

Definition and classification

Juvenile localized scleroderma is a distinct entity from juvenile systemic sclerosis because of its almost exclusive cutaneous involvement and, with some exceptions, internal organs are not involved. The most widely used classification divides juvenile localized scleroderma into five general types: plaque morphea, generalized morphea, bullous morphea, linear scleroderma, and deep morphea (Box 2) [71]. Some conditions, such as atrophoderma of Pasini and Pierini, eosinophilic fasciitis, or lichen sclerosus and atrophicus, are classified among the subtypes of juvenile localized scleroderma, but their inclusion is still controversial. Indeed, this classification does not include the mixed forms of juvenile localized scleroderma in which different types of lesions occur in the same individual and which are probably more common than previously recognized. A multiphase project considering all these issues and sponsored by the PRES is developing new classification criteria for juvenile localized scleroderma [2].

Box 2. The Mayo Clinic classification of localized scleroderma*Plaque morphea*

Morphea en plaque

Guttate morphea

Atrophoderma of Pasini and Perini

Keloid morphea

[Lichen sclerosus et atrophicus]

*Generalized morphea**Bullous morphea**Linear scleroderma*

Linear morphea

En coup de sabre scleroderma

Progressive hemifacial atrophy

Deep morphea

Subcutaneous morphea

Eosinophilic fasciitis

Morphea profunda

Disabling pansclerotic morphea

Epidemiology

Although localized scleroderma is relatively uncommon, it is far more common than systemic sclerosis in childhood, by a ratio of at least 10:1 [72,73]. Few adequate studies have addressed the incidence or prevalence of this disorder, which is believed to occur only in up to 1 per 100,000 of the population [73]. It has been reported that in pediatric rheumatology practice around 2% of the patients have localized scleroderma, that is approximately one case of localized scleroderma for every 20 cases of juvenile rheumatoid arthritis [74]. Many patients seen by dermatologists are never referred to rheumatologists because of the mild nature of their disease, however.

Etiology and pathogenesis

The causes and pathogenesis of the localized sclerodermas are unknown. As in systemic sclerosis, the focus of much investigation is on abnormalities of regulation of fibroblasts, production of collagen, and immunologic abnormalities. Autoimmunity, environmental factors, infection, and trauma have all been associated with localized disease. It seems certain that autoimmunity is an important etiologic factor, given the presence of abnormal serum antibodies in patients with localized scleroderma.

A number of drugs and environmental toxins, including bleomycin, ergot, bromocriptine, pentazocine, carbidopa, and vitamin K₁, have resulted in scleroderma-like reactions [75]. Although some studies have documented evidence of *Borrelia Burgdorferi* infection in patients with morphea [76], serologic testing for Lyme disease is not likely to be helpful in the evaluation of patients with juvenile localized scleroderma unless they have been in an endemic area [77].

Trauma has been implicated in initiation of lesions in 2.6% to 12.7% of the patients [78,79,116]. The mechanism by which a physical trauma may contribute to the development of scleroderma is unclear. Some authors have suggested a role for cytokines and neuropeptides such as endothelin-1 that normally are involved in the process of wound healing [78,80], but further studies are needed to elucidate the pathogenetic process fully.

A positive family history for rheumatic or autoimmune diseases was reported in approximately 12% of patients in two series [78,81].

Clinical features and subtypes of localized scleroderma

Plaque morphea is characterized by oval or round circumscribed areas of induration with a central waxy, ivory area surrounded by a violaceous halo (Fig. 2). It is confined to the dermis with only occasional involvement of the superficial panniculus. Depending on the shape and size of the lesions, various subtypes of plaque morphea have been described (guttate, keloid morphea, atrophoderma of Pasini and Pierini). The plaques may be of different sizes and evolve from an erythematous inflammatory stage through a sclerotic indurated phase with surrounding inflammation and subsequently to softening and dermal atrophy with associated hypopigmentation or hyperpigmentation. Atrophoderma of Pasini and Pierini, characterized by hyperpigmented atrophic patches with well-demarcated borders, may coexist with other sclerotic lesions or represent the involutionary phase of plaque morphea.



Fig. 2. Plaque morphea.

When individual plaques become confluent or multiply and affect three or more anatomic sites, the condition is called generalized morphea.

In the rare subtype of bullous morphea, lesions are probably related to lymphatic obstruction secondary to the sclerodermatous process [82].

Linear scleroderma is the most common subtype in children and adolescents [73]. It is characterized by one or more linear streaks that typically involve an upper or lower extremity (Fig. 3). With time, the streaks can extend through the dermis, subcutaneous tissue, and muscle to the underlying bone causing significant deformities.

When a linear lesion involves the face or scalp, it is referred to as *en coup de sabre* scleroderma because the lesion is reminiscent of the depression caused by a dueling stroke from a sword (Fig. 4).

Parry–Romberg syndrome (PRS) is characterized by hemifacial atrophy of the skin and tissue below the forehead, with greater involvement of the lower face than in *en coup de sabre* scleroderma and relatively minor involvement of the superficial skin. PRS probably represents the severe end of the spectrum of *en coup de sabre* scleroderma, because some cases of PRS have definite localized scleroderma lesions on the face and in the other parts of the body [83]. Also, much like PRS, some typical localized scleroderma lesions present no evidence of inflammation and sclerosis preceding the severe atrophy on the limbs [84,85].



Fig. 3. Linear scleroderma.

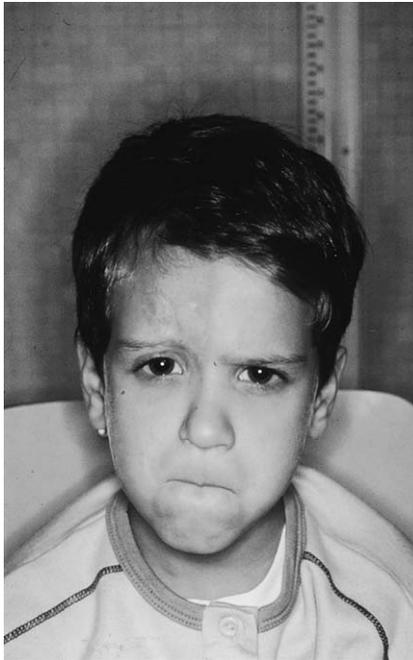


Fig. 4. En coup de sabre scleroderma.

A number of associated disorders, including seizures, uveitis, and dental and ocular abnormalities, have been reported in both conditions.

Deep morphea is the least common but most disabling variant and includes subcutaneous morphea, eosinophilic fasciitis, morphea profunda, and disabling pansclerotic morphea of children.

In subcutaneous morphea, the primary site of involvement is the panniculus or subcutaneous tissue [86]. The plaques are hyperpigmented, symmetric, and somewhat ill defined.

In morphea profunda, the entire skin feels thickened, taut, and bound down, sometimes with the appearance of a solitary, indurated plaque [87,88]. Disabling pansclerotic morphea, an extremely rare but severe disorder, is characterized by generalized full-thickness involvement of the skin of the trunk, extremities, face, and scalp with sparing of the fingertips and toes (Fig. 5) [89]. In eosinophilic fasciitis, lesions typically involve the extremities but spare the hands and feet and have a peau d'orange appearance [90,91]. Reports of combined syndrome of fasciitis and morphea and histologic changes similar to eosinophilic fasciitis found in some subtypes of localized scleroderma seem to strengthen the hypothesis that this disorder may be a subtype of juvenile localized scleroderma [92]. Conversely, the characteristic cutaneous features such as pitting edema, diffuse painful areas with peau d'orange appearance, increased serum acute-phase



Fig. 5. Pansclerotic morphea.

reactants, peripheral blood eosinophilia, and hypergammaglobulinemia may suggest a separate nosologic classification.

Extracutaneous involvement

During the last decade, the publication of some case reports on possible transition from localized to systemic scleroderma and of case series of patients with localized scleroderma and internal organ involvement [93,94] have raised suspicions that systemic sclerosis and localized scleroderma are not always clearly distinct.

Approximately one fourth of patients with juvenile localized scleroderma have been reported as having one or more extracutaneous manifestations during the course of the disease [93–95]. Articular involvement is the most frequently reported complication of juvenile localized scleroderma, accounting for almost one half of the reported extracutaneous manifestations especially in the linear subtype [95]. Sometimes arthritis is completely unrelated to the site of the skin lesion.

Epilepsy and recent-onset headache are the most frequent reported neurologic involvements [88–99], but behavioral changes and learning disabilities have also been described [100,101]. Other abnormalities on MRI such as cal-

cifications and white matter changes, vascular malformations, and even CNS vasculitis have been reported [102–105].

Ocular changes are almost exclusively reported in linear scleroderma involving the face. They include eyelid or eyelash abnormalities, inflammatory changes such as uveitis, episcleritis, keratitis, glaucoma, and xerophthalmia, and motility disorders [105–110].

Gastroesophageal reflux has been reported in adults and children with localized scleroderma [93,95,111,112]. Respiratory involvement, consisting of restrictive changes with mildly decreased respiratory volume and impaired DLCO, was reported [94,95,113].

Systemic manifestations are rarely observed in localized scleroderma, although internal organ involvement is frequently found when searched for systematically. These extracutaneous manifestations, usually mild, may suggest that localized scleroderma and systemic sclerosis represent two ends of a continuous spectrum of disease.

Single-case reports have reported a transition from localized scleroderma to systemic sclerosis in children [114,115]. In adults this evolution has been reported in 0.9% and 1.3% of the patients [94,116]; it is reported more rarely in children (0.13%) [95].

Considering this low prevalence of transition to systemic sclerosis and the lack of prospective follow-up studies, a practical suggestion could be to investigate for eye and CNS complications in patients with head involvement (en coup de saber scleroderma or PRS) and to look for internal organ involvement in other patients with juvenile localized scleroderma only if they are symptomatic.

Laboratory results

The diagnosis of localized scleroderma is established by the clinical picture, sometimes aided by biopsy of skin or subcutaneous tissues. The erythrocyte sedimentation rate may be increased in the subtypes of the disease with active inflammation, such as eosinophilic fasciitis. Eosinophilia and hypergammaglobulinemia are hallmarks of this disorder but also may occur in linear scleroderma and the other deep subtypes. Rheumatoid factor is present in 25% to 40% of patients [81,117,118], and higher titers are usually associated with more severe cutaneous and articular involvement [114].

ANA can be present in any of the morphea subtypes with a frequency ranging from 23% to 73% [81,119]. ANAs were found in 34% to 50% of patients with plaque morphea, 31% to 100% of those with generalized morphea, and 47% to 67% of those with linear scleroderma [81,120]. Anti-Scl70 antibodies, a marker of systemic sclerosis in adults, were positive in 2% to 3% patients. [81,121,122]

Anticardiolipin antibodies have recently been shown to be present in adults with localized scleroderma with an overall prevalence of 46% that increases to 70% in patients with generalized forms [123]. In children this prevalence falls

Table 3
Role of thermography in juvenile localized scleroderma

Advantages	Disadvantages
Noninvasive	Expensive to set up
Well tolerated	False positivity
Easy interpretation	Atrophy, old lesions, site (ie, scalp)
Possible computerized quantitation	
Rapid results, helpful in decision-making	
Prediction of progress (?)	

to 13%, and, in contrast to adults, the presence of anticardiolipin antibodies is not associated with thromboembolic events or clotting abnormalities [81].

Antihistone antibodies seem to be associated with more extensive localized disease [123]. Serum concentrations of soluble IL-2 receptor have been noted to be increased in localized scleroderma and may differentiate active from inactive disease [124], although this finding is not supported by all studies [78].

Thermography shows promise when associated with clinical examination in discriminating disease activity. Table 3 summarizes the advantages and disadvantages of this methodology. This technique has high reproducibility, but it remains to be seen whether it truly will predict outcome and subclinical areas likely to progress to serious disease [125,126].

The application of newer imaging techniques such as MRI and ultrasound also shows promise in supporting clinical management and greater understanding of disease characteristics. MRI is most useful when CNS or eye involvement is suspected but can demonstrate the true depth of soft tissue lesions and the degree to which different tissues are involved in other sites. In addition, early in lesion development MRI may provide supporting evidence that true inflammation is occurring in tissue thought to be undergoing spontaneous atrophy [127]. High-frequency ultrasound has shown similar promise [128,129]. Table 4 summarizes the advantages and disadvantages of the two different ultrasound modalities, 13- and 20-Mhz probes, used in the management of localized scleroderma.

Table 4
Comparison of 20- and 13-MHz ultrasound probes in the management of localized scleroderma

13-MHz ultrasound		20-MHz ultrasound	
Advantages	Disadvantages	Advantages	Disadvantages
Noninvasive	Difficult in overweight patients	Noninvasive	Penetration depth 7 mm
Good sensitivity and specificity	Worse image definition	Higher resolution = better quality images	
Cost-effective		Clear identification of pathological skin structures	
Penetration depth 60 mm		Useful to evaluate the evolution of sclerotic plaques	

Treatment

Therapy for juvenile localized scleroderma is as challenging as therapy for juvenile systemic sclerosis. The literature contains many case reports or case series, but few controlled trials have been published. Indeed, management decisions must be based on the understanding that these disorders are benign in the many patients and often spontaneously enter remission after 3 to 5 years [116,130].

Morphea en plaque generally is of cosmetic concern only, and therefore treatments with potentially significant toxicity are not justified. In general, these lesions remit spontaneously with residual pigmentation as the only abnormality. Therefore, treatment should be directed mainly at topical therapies such as moisturizing agents, topical glucocorticoids, or calcipotriene [131].

When there is a significant risk for disability, such as in linear scleroderma and the deep subtypes, systemic treatment should be considered. Methotrexate has been used successfully in children with localized scleroderma [132,133]. Unfortunately, these studies were not controlled trials, and the series of treated patients were very small. In adults, a recent well-conducted multicenter randomized, controlled trial in patients with early diffuse systemic sclerosis confirmed that methotrexate is effective in reducing the skin involvement, especially during the first 6 months of treatment [134].

During the last few years, the use of D-penicillamine, a proven antifibrotic agent [135,136], has decreased without clear evidence of lack of efficacy. D-penicillamine has been used successfully for the treatment of localized scleroderma in adults [137]. Although there are no controlled studies on the use of D-penicillamine in the treatment of children with localized scleroderma, it is a well-known antifibrotic agent and may still have a place in the treatment of this disease.

In a well-designed randomized, controlled drug trial, use of the intralesional cytokine interferon- γ proved no better than placebo for established lesions; however, it may prevent the appearance of new lesions [138]. The use of UV light therapy, with or without chemical agents such as psoralen, has been reported in a number of recent studies with suggestions of clinical benefit. It may be much more effective for localized or superficial lesions [139,140]. Extracorporeal photochemotherapy (with UVA and psoralen) has been reported in localized scleroderma, but the evidence to support its usefulness is still relatively weak [141–143]. Topical or systemic use of vitamin D or its analogue has been reported in several case series, again with encouraging results [144–146]; in the only controlled trial, however, it was no more effective than placebo [147].

It is clear that multicenter randomized, controlled trials are needed to evaluate the efficacy of these or other new agents for the treatment of juvenile localized scleroderma by using uniform diagnostic criteria and validated outcome measures.

Physical and occupational therapy usually have a major role in the management of juvenile localized scleroderma, particularly when joint structures

are involved. Surgical reconstruction may be considered, usually after the active phase of the disease has abated, and the child's growth is complete [148,149].

References

- [1] The American Rheumatism Association Diagnostic and Therapeutic Criteria Committee, Subcommittee for Scleroderma Criteria. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581–90.
- [2] Zulian F, Ruperto N, editors. Proceedings of the Second Workshop on Juvenile Scleroderma Syndrome. Padua, Italy, June 3–6, 2004.
- [3] Mayes MD. Scleroderma epidemiology. *Rheum Dis Clin North Am* 2003;29:239–54.
- [4] Tuffanelli DL, LaPerriere R. Connective tissue diseases. *Pediatr Clin North Am* 1971;18:925–51.
- [5] Komreich HK, King KK, Bernstein BH, et al. Scleroderma in childhood. *Arthritis Rheum* 1977;20:343–50.
- [6] Medsger Jr TA. Epidemiology of systemic sclerosis. *Clin Dermatol* 1994;12:207–16.
- [7] Black CM. Scleroderma in children. *Adv Exp Med Biol* 1999;455:35–48.
- [8] Martini G, Foeldvari I, Russo R, et al. Systemic scleroderma syndromes in children: clinical and immunological characteristics of 181 patients. *Arthritis Rheum* 2003;48(9):S512.
- [9] Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med* 2004;140:37–50.
- [10] Abraham DJ, Shiwen X, Black CM, et al. Tumor necrosis factor alpha suppresses the induction of connective tissue growth factor by transforming growth factor-beta in normal and scleroderma fibroblasts. *J Biol Chem* 2000;275:15220–5.
- [11] Varga J, Rosenbloom J, Jimenez SA. Transforming growth factor beta (TGF beta) causes a persistent increase in steady-state amounts of type I and type III collagen and fibronectin mRNAs in normal human dermal fibroblasts. *Biochem J* 1987;247:597–604.
- [12] Stratton R, Shiwen X, Martini G, et al. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. *J Clin Invest* 2001;108:241–50.
- [13] Gore-Hyer E, Pannu J, Smith EA, et al. Selective stimulation of collagen synthesis in the presence of costimulatory insulin signaling by connective tissue growth factor in scleroderma fibroblasts. *Arthritis Rheum* 2003;48:798–806.
- [14] Needleman BW, Wigley FM, Stair RW. Interleukin-1, interleukin-2, interleukin-4, interleukin-6, tumor necrosis factor alpha, and interferon-gamma levels in sera from patients with scleroderma. *Arthritis Rheum* 1992;35:67–72.
- [15] Hasegawa M, Sato S, Ihn H, et al. Enhanced production of interleukin-6 (IL-6), oncostatin M and soluble IL-6 receptor by cultured peripheral blood mononuclear cells from patients with systemic sclerosis. *Rheumatology (Oxford)* 1999;38:612–7.
- [16] Atamas SP, Yurovsky VV, Wise R, et al. Production of type 2 cytokines by CD8 + lung cells is associated with greater decline in pulmonary function in patients with systemic sclerosis. *Arthritis Rheum* 1999;42:1168–78.
- [17] Sato S, Hanakawa H, Hasegawa M, et al. Levels of interleukin 12, a cytokine of type 1 helper T cells, are elevated in sera from patients with systemic sclerosis. *J Rheumatol* 2000;27:2838–42.
- [18] Matucci-Cerinic M, Pignone A, Lotti T, et al. Reduced angiotensin converting enzyme plasma activity in scleroderma. A marker of endothelial injury? *J Rheumatol* 1990;17:328–30.
- [19] Kahaleh MB, Osborn I, LeRoy EC. Increased factor VIII/von Willebrand factor antigen and von Willebrand factor activity in scleroderma and in Raynaud's phenomenon. *Ann Intern Med* 1981;94:482–4.

- [20] Sgonc R, Gruschwitz MS, Dietrich H, et al. Endothelial cell apoptosis is a primary pathogenetic event underlying skin lesions in avian and human scleroderma. *J Clin Invest* 1996;98:785–92.
- [21] Ohtsuka T, Miyamoto Y, Yamakage A, et al. Quantitative analysis of microchimerism in systemic sclerosis skin tissue. *Arch Dermatol Res* 2001;293:387–91.
- [22] Nelson JL, Furst DE, Maloney S, et al. Microchimerism and HLA-compatible relationships of pregnancy in scleroderma. *Lancet* 1998;351:559–62.
- [23] Artlett CM, Smith JB, Jimenez SA. Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. *N Engl J Med* 1998;338:1186–91.
- [24] Goel KM, Shanks RA. Scleroderma in childhood. Report of 5 cases. *Arch Dis Child* 1974;49:861–6.
- [25] Jaffe MO, Winkelmann RK. Generalized scleroderma in children. Acrosclerotic type. *Arch Dermatol* 1961;83:402.
- [26] Cassidy JT, Sullivan DB, Dabich L, et al. Scleroderma in children. *Arthritis Rheum* 1977;20:351–4.
- [27] Suarez-Almazor ME, Catoggio LJ, Maldonado-Cocco JA, et al. Juvenile progressive systemic sclerosis: Clinical and serologic findings. *Arthritis Rheum* 1985;28:699–702.
- [28] Hanson V. Dermatomyositis, scleroderma, and polyarteritis nodosa. *Clin Rheumat Dis* 1976;2:445.
- [29] Lababidi HM, Nasr FW, Khatib Z. Juvenile progressive systemic sclerosis: report of five cases. *J Rheumatol* 1991;18:885–8.
- [30] Spencer-Green G, Schlesinger M, Bove KE, et al. Nailfold capillary abnormalities in childhood rheumatic diseases. *J Pediatr* 1983;102:341–6.
- [31] Duffy CM, Laxer RM, Lee P, et al. Raynaud syndrome in childhood. *J Pediatr* 1989;114:73–8.
- [32] Arkachaisri T, Scalapini T, Fertig N, et al. Comparison of clinical and serological findings in childhood and adult onset systemic sclerosis. *Arthritis Rheum* 2004;50(9):S686–7.
- [33] D'Angelo WA, Fries JF, Masi AT, et al. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med* 1969;46:428–40.
- [34] Weber P, Ganser G, Frosch M, et al. Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease. *J Rheumatol* 2000;27:2692–5.
- [35] Quartier P, Bonnet D, Fournet JC, et al. Severe cardiac involvement in children with systemic sclerosis and myositis. *J Rheumatol* 2002;29:1767–73.
- [36] Eid NS, Buchino JJ, Schikler KN. Pulmonary manifestations of rheumatic diseases. *Pediatr Pulmonol Suppl* 1999;18:91–2.
- [37] Koh DM, Hansell DM. Computed tomography of diffuse interstitial lung disease in children. *Clin Radiol* 2000;55:659–67.
- [38] Seely JM, Jones LT, Wallace C, et al. Systemic sclerosis: using high-resolution CT to detect lung disease in children. *Am J Roentgenol* 1998;170(3):691–7.
- [39] Lee P, Bruni J, Sukenik S. Neurological manifestations in systemic sclerosis (scleroderma). *J Rheumatol* 1984;11:480–3.
- [40] Sato S, Hamaguchi Y, Hasegawa M, et al. Clinical significance of anti-topoisomerase I antibody levels determined by ELISA in systemic sclerosis. *Rheumatology (Oxford)* 2001;40:1135–40.
- [41] Steen VD, Lanz Jr JK, Conte C, et al. Therapy for severe interstitial lung disease in systemic sclerosis. A retrospective study. *Arthritis Rheum* 1994;37:1290–6.
- [42] 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* 1996;35:364–72.
- [43] Pope JE, Bellamy N, Seibold JR, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001;44:1351–8.
- [44] Stratton RJ, Wilson H, Black CM. Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma. *Rheumatology (Oxford)* 2001;40:84–8.
- [45] Clements PJ, Furst DE, Campion DS, et al. Muscle disease in progressive systemic sclerosis: Diagnostic and therapeutic considerations. *Arthritis Rheum* 1978;21:62–71.

- [46] Steen VD, Medsger Jr TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998;41:1613–9.
- [47] Ellman MH, MacDonald PA, Hayes FA. Etanercept as treatment for diffuse scleroderma: a pilot study [abstract]. *Arthritis Rheum* 2000;43:S392.
- [48] Wulfraat NM, Sanders LA, Kuis W. Autologous hemopoietic stem-cell transplantation for children with refractory autoimmune disease. *Curr Rheumatol Rep* 2000;2:316–23.
- [49] 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* 2001;60:577–84.
- [50] Farge D, Passweg J, van Laar J, et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. *Ann Rheum Dis* 2004;63(8):974–81.
- [51] Jayson MIV, Lovell C, Black CM, et al. Penicillamine therapy in systemic sclerosis. *Proc R Soc Med* 1977;70(Suppl 3):82–8.
- [52] Steen VD, Medsger Jr TA, Rodnan GP. D-penicillamine therapy in progressive systemic sclerosis: a retrospective analysis. *Ann Intern Med* 1982;97:652–9.
- [53] Jimenez SA, Sigal SH. A 15-year prospective study of treatment of rapidly progressive systemic sclerosis with D-penicillamine. *J Rheumatol* 1991;18:1496–503.
- [54] 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* 1999;42:1194–203.
- [55] Smith CD, McKendry RJ. Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982;2:1299–301.
- [56] 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* 1983;308:880–3.
- [57] 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* 1984;11:362–4.
- [58] 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)* 2004;43:229–33.
- [59] Black CM, Halkier-Sorensen L, Belch JJ, et al. Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br J Rheumatol* 1998;37:952–60.
- [60] Wigley FM, Korn JH, Csuka ME, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis Rheum* 1998;41:670–7.
- [61] Beckett VL, Donadio Jr JV, Brennan Jr LA, et al. Use of captopril as early therapy for renal scleroderma: a prospective study. *Mayo Clin Proc* 1985;60:763–71.
- [62] 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* 1990;113:352–7.
- [63] Moddison P. Prevention of vascular damage in scleroderma with angiotensin-converting enzyme (ACE) inhibition. *Rheumatology (Oxford)* 2002;41:965–71.
- [64] 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* 2000;132:947–54.
- [65] 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* 2003;167:580–6.
- [66] 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* 2000;132:425–34.
- [67] Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.

- [68] 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* 2000;20:442–9.
- [69] 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)* 2000;39:556–9.
- [70] Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis. *Br J Rheumatol* 1998;37:750–5.
- [71] Peterson LS, Nelson AM, Su WPD. Subspecialty clinics: rheumatology and dermatology. Classification of morphea (localized scleroderma). *Mayo Clin Proc* 1995;70:1068–76.
- [72] Bodemer C, Belon M, et al. Scleroderma in children: a retrospective study of 70 cases. *Ann Dermatol Venereol* 1999;126:691–4.
- [73] Peterson LS, Nelson AM, Su WP, et al. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960–1993. *J Rheumatol* 1997;24:73–80.
- [74] Levinson JE, Bove KE. Scleroderma. In: Gershwin ME, Robbins DE, editors. *Musculoskeletal diseases of children*. Orlando (FL): Grune & Stratton; 1983. p. 195–208.
- [75] Hausteil UF, Haupt B. Drug-induced scleroderma and sclerodermiform conditions. *Clin Dermatol* 1998;16:353–66.
- [76] Aberer E, Neumann R, Stanek G. Is localised scleroderma a Borrelia infection? *Lancet* 1985; 2:278.
- [77] Fan W, Leonardi CL, Penneys NS. Absence of *Borrelia burgdorferi* in patients with localized scleroderma (morphea). *J Am Acad Dermatol* 1995;33:682–4.
- [78] Vancheeswaran R, Black CM, David J, et al. Childhood onset scleroderma: is it different from adult onset disease? *Arthritis Rheum* 1996;39:1041–9.
- [79] Falanga V, Medsger TA, Reichlin M, et al. Linear scleroderma: clinical spectrum, prognosis and laboratory abnormalities. *Ann Intern Med* 1986;104:849–57.
- [80] Kanzler MH, Gorsulowsky DC, Swanson NA. Basic mechanisms in the healing of cutaneous wound. *J Dermatol Surg Oncol* 1986;12:1156–64.
- [81] Zulian F, De Oliveira SKF, Lehman TH, et al. Juvenile localized scleroderma: clinical epidemiological features of 688 patients [abstract]. *Arthritis Rheum* 2003;48(9):512.
- [82] Daoud MS, Su WP, Leiferman KM, et al. Bullous morphea: clinical, pathologic, and immunopathologic evaluation of thirteen cases. *J Am Acad Dermatol* 1994;30:937–43.
- [83] Menni S, Marzano AV, Passoni E. Neurologic abnormalities in two patients with facial hemiatrophy and sclerosis coexisting with morphea. *Pediatr Dermatol* 1997;14:113–6.
- [84] Blaszczyk M, Jablonska S. Linear scleroderma en coup de sabre: relationship with progressive facial hemiatrophy. *Adv Exp Med Biol* 1999;455:101–4.
- [85] Lehman TJ. The Parry Romberg syndrome of progressive facial hemiatrophy and linear scleroderma en cop de sabre: mistaken diagnosis or overlapping conditions? *J Rheumatol* 1992; 19:844–5.
- [86] Person JR, Su WP. Subcutaneous morphoea: a clinical study of sixteen cases. *Br J Dermatol* 1979;100:371–80.
- [87] Su WP, Person JR. Morphea profunda: a new concept and a histopathologic study of 23 cases. *Am J Dermatopathol* 1981;3:251–60.
- [88] Whittaker SJ, Smith NP, Jones RR. Solitary morphoea profunda. *Br J Dermatol* 1989;120: 431–40.
- [89] Diaz-Perez JL, Connolly SM, Winkelmann RK. Disabling pansclerotic morphea in children. *Arch Dermatol* 1980;116:169–73.
- [90] Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? *Trans Assoc Am Physicians* 1975;88:70–86.
- [91] Rodnan GP, Di Bartolomeo A, Medsger Jr TA. Eosinophilic fasciitis. Report of six cases of a newly recognized scleroderma-like syndrome. *Arthritis Rheum* 1975;18:525.
- [92] Miller III JJ. The fasciitis-morphea complex in children. *Am J Dis Child* 1992;146:733–6.
- [93] Lunderschmidt C, König G, Leisner B, et al. Zirkumskripte sklerodermie: interne manifestationen und signifikante correlation zu HLA-DR1 und –DR5. *Hautarzt* 1985;36:516–21.
- [94] Dehen L, Roujeau JC, Cosnes A, et al. Internal involvement in localized scleroderma. *Medicine* 1994;73:241–5.

- [95] Zulian F, Russo R, Laxer R, et al. Is juvenile localized scleroderma really “localized”? [abstract]. *Arthritis Rheum* 2003;48(9):512.
- [96] Heron E, Hernigou A, Fornes P, et al. Central nervous system involvement in scleroderma. *Ann Med Interne (Paris)* 2002;153(3):179–82.
- [97] Blaszczyk M, Krolicki L, Krasu M, et al. Progressive facial hemiatrophy: central nervous system involvement and relationship with scleroderma *en coup de sabre*. *J Rheumatol* 2003;30:1997–2004.
- [98] Grosso S, Fioravanti A, Biasi G, et al. Linear scleroderma associated with progressive brain atrophy. *Brain Dev* 2003;25:57–61.
- [99] Woolfenden AR, Tong DC, Norbash AM, et al. Progressive facial hemiatrophy: abnormality of intracranial vasculature. *Neurology* 1998;50(6):1915–7.
- [100] David J, Wilson J, Woo P. Scleroderma “*en coup de sabre*”. *Ann Rheum Dis* 1991;50:260–2.
- [101] Goldberg-Stern H, deGrauw T, Passo M, et al. Parry-Romberg syndrome: follow-up imaging during suppressive therapy. *Neuroradiology* 1997;39(12):873–6.
- [102] Flores-Alvarado DE, Esquivel-Valerio JA, Garza-Elizondo M, et al. Linear scleroderma *en coup de sabre* and brain calcifications: is there a pathogenic relationship? *J Rheumatol* 2003;30:193–5.
- [103] Higashi Y, Kanekura T, Fukumaru K, et al. Scleroderma *en coup de sabre* with central nervous system involvement. *J Dermatol* 2000;27(7):486–8.
- [104] Luer W, Jockel D, Henze T, et al. Progressive inflammatory lesions of the brain parenchyma in localized scleroderma of the head. *J Neurol* 1990;237:379–81.
- [105] Miedziak AI, Stefanszyn M, Flamagan J, et al. Parry-Romberg syndrome associated with intracranial vascular malformations. *Arch Ophthalmol* 1998;116:1235–7.
- [106] Goldenstein-Schainberg C, Pereira RM, Gusukuma MC, et al. Childhood linear scleroderma “*en coup de sabre*” with uveitis. *J Pediatr* 1990;117:581–4.
- [107] Serup J, Alsbirk PH. Localized scleroderma “*en coup de sabre*” and iridopalpebral atrophy at the same line. *Acta Derm Venereol* 1983;63:75–7.
- [108] Campbell WW, Bajandas FJ. Restrictive ophthalmopathy associated with linear scleroderma. *J Neuroophthalmol* 1995;15:95–7.
- [109] Tang RA, Mewis-Christmann L, Wolf J, et al. Pseudo-oculomotor palsy as the presenting sign of linear scleroderma. *J Pediatr Ophthalmol Strabismus* 1986;23:236–8.
- [110] Suttorp-Schulten MS, Koornneef L. Linear scleroderma associated with ptosis and motility disorders. *Br J Ophthalmol* 1990;74:694–5.
- [111] Zaninotto G, Peserico A, Costantini M, et al. Oesophageal motility and lower oesophageal sphincter competence in progressive systemic sclerosis and localized scleroderma. *Scand J Gastroenterol* 1989;24:95–102.
- [112] Weber P, Ganser G, Frosh M, et al. Twenty-four hour intraesophageal pH monitoring in children and adolescents with scleroderma and mixed connective tissue disease. *J Rheumatol* 2000;27:2692–5.
- [113] Bourgeois-Droin C, Touraine R. Sclérodémie en plaque: Perturbations immunologique et viscérales. *Ann Med Interne (Paris)* 1978;129:107–12.
- [114] Birdi N, Laxer RM, Thomer P, et al. Localized scleroderma progressing to systemic disease. Case report and review of the literature. *Arthritis Rheum* 1993;36:410–5.
- [115] Mayorquin FJ, McCurley TL, Levernier JE, et al. Progression of childhood linear scleroderma to fatal systemic sclerosis. *J Rheumatol* 1994;21:1955–7.
- [116] Christianson HB, Dorsey CS, O’Leary PA, et al. Localized scleroderma. A clinical study of two hundred thirty-five cases. *Arch Dermatol* 1956;74:629–39.
- [117] Kornreich HK, King KK, Bernstein BH, et al. Scleroderma in childhood. *Arthritis Rheum* 1977;20(Suppl 2):343–50.
- [118] Torok E, Ablonczy E. Morphoea in children. *Clin Exp Dermatol* 1986;11:607–12.
- [119] Uziel Y, Krafchik BR, Silverman ED, et al. Localized scleroderma in childhood: a report of 30 cases. *Semin Arthritis Rheum* 1994;23:328–40.
- [120] Takehara K, Moroi Y, Nakabayashi Y, et al. Antinuclear antibodies in localized scleroderma. *Arthritis Rheum* 1983;26:612–6.

- [121] Blaszczyk M, Jarzabek-Chorleska M, Jablonska S. Relationship between cutaneous and systemic scleroderma. Are immunopathological studies helpful in evaluating transition of cutaneous to systemic scleroderma? *Przegl Dermatol* 2000;2:119–25.
- [122] Marzano AV, Menni S, et al. Localized scleroderma in adults and children. Clinical and laborator investigations on 239 cases. *Eur J Dermatol* 2003;13:171–6.
- [123] Sato S, Fujimoto M, Hasegawa M, et al. Antiphospholipid antibody in localized scleroderma. *Ann Rheum Dis* 2003;62:771–4.
- [124] Uziel Y, Krafchik BR, Feldman B, et al. Serum levels of soluble interleukin-2 receptor. A marker of disease activity in localized scleroderma. *Arthritis Rheum* 1994;37:898–901.
- [125] Martini G, Murray KJ, Howell KJ, et al. Juvenile-onset localized scleroderma activity detection by infrared thermography. *Rheumatology (Oxford)* 2002;41(10):1178–82.
- [126] Birdi N, Shore A, Rush P, et al. Childhood linear scleroderma: a possible role of thermography for evaluation. *J Rheumatol* 1992;19:968–73.
- [127] Liu P, Uziel Y, Chuang S, et al. Localized scleroderma: imaging features. *Pediatr Radiol* 1994;24:207–9.
- [128] Seidenari S, Conti A, Pepe P, et al. Quantitative description of echographic images of morphea plaques as assessed by computerized image analysis on 20 MHz B-scan recordings. *Acta Derm Venereol* 1995;75:442–5.
- [129] Cosnes A, Anglade MC, Revux J, et al. Thirteen-megahertz ultrasound probe: its role in diagnosing localized scleroderma. *Br J Dermatol* 2003;148:724–9.
- [130] Chazen EM, Cook CD, Cohen J. Focal scleroderma. *J Pediatr* 1962;60:385–93.
- [131] Cunningham BB, Landells ID, Langman C, et al. Topical calcipotriene for morphea/linear scleroderma. *J Am Acad Dermatol* 1998;39:211–5.
- [132] Uziel Y, Feldman BM, Krafchik BR, Yeung RS, Laxer RH. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000;136:91–5.
- [133] Walsh J, Martini G, Murray KJ, et al. Evaluation and treatment of childhood onset localized scleroderma [abstract]. *Arthritis Rheum* 1999;42(9):231.
- [134] Pope JE, Bellamy N, Seibold JR, et al. A randomized controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001;44(6):1351–8.
- [135] Herbert CM, Lindberg KA, Jayson MIV, et al. Biosynthesis and maturation of skin collagen in scleroderma and effect of D-penicillamine. *Lancet* 1974;1:187–92.
- [136] Uitto J, Helin P, Rasmussen O, et al. Skin collagen in patients with scleroderma: biosynthesis and maturation in vitro, and the effect of D-penicillamine. *Ann Clin Res* 1970;2:228–34.
- [137] Falanga V, Medsger Jr TA. D-penicillamine in the treatment of localised scleroderma. *Arch Dermatol* 1990;126:609–12.
- [138] Hunzelmann N, Anders S, Fierlbeck G, et al. Double-blind, placebo-controlled study of intra-lesional interferon gamma for the treatment of localized scleroderma. *J Am Acad Dermatol* 1997;36(3 Pt 1):433–5.
- [139] De Rie MA, Bos JD. Photochemotherapy for systemic and localized scleroderma. *J Am Acad Dermatol* 2000;43:725–6.
- [140] Kerscher M, Volkenandt M, Gruss C, et al. Low dose UVA phototherapy for treatment of localized scleroderma. *J Am Acad Dermatol* 1998;38:21–6.
- [141] Camacho NR, Sanchez JE, Martin RF, et al. Medium dose UVA phototherapy in localized scleroderma and its effect in CD34-positive dendritic cells. *J Am Acad Dermatol* 2001;45:697–9.
- [142] Cribier B, Faradj T, Le Coz C, et al. Extracorporeal photochemotherapy in systemic sclerosis and severe morphea. *Dermatology* 1995;191:25–31.
- [143] Grundmann-Kollmann M, Ochsendorf F, Zollner TM, et al. PUVA cream photochemotherapy for the treatment of localized scleroderma. *J Am Acad Dermatol* 2000;43:675–8.
- [144] Caca-Biljanovska NG, Vlckova-Laskoska MT, Dervendi DV, et al. Treatment of generalized morphea with oral 1,25-dihydroxyvitamin D3. *Adv Exp Med Biol* 1999;455:299–304.
- [145] Cunningham BB, Landells ID, Langman C, et al. Topical calcipotriene for morphea/linear scleroderma. *J Am Acad Dermatol* 1998;39(2 Pt 1):211–5.

- [146] Hulshof MM, Pavel S, Breedveld FC, et al. Oral calcitriol as a new therapeutic modality for generalized morphea. *Arch Dermatol* 1994;130:1290–3.
- [147] Hulshof MM, Bouwes BJN, Bergman W, et al. Double-blind, placebo-controlled study of oral calcitriol for the treatment of localized scleroderma and systemic scleroderma. *J Am Acad Dermatol* 2000;43:1017–23.
- [148] Sengezer M, Deveci M, Selmanpakoglu N. Repair of “coup de sabre,” a linear form of scleroderma. *Ann Plast Surg* 1996;37:428–32.
- [149] Lapiere J, Aasi S, Cook B, et al. Successful correction of depressed scars of the forehead secondary to trauma and morphea en coup do sabre by en bloc autologous dermal fat graft. *Dermatol Surg* 2000;26:793–7.