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Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study

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***Objective*. Juvenile localized scleroderma (JLS) includes a number of conditions often grouped together. With the long-term goal of developing uniform classification criteria, we studied the epidemiological, clinical and immunological features of children with JLS followed by paediatric rheumatology and dermatology centres.**

***Methods*. A large, multicentre, multinational study was conducted by collecting information on the demographics, family history, triggering environmental factors, clinical and laboratory features, and treatment of patients with JLS.**

***Results*. Seven hundred and fifty patients with JLS from 70 centres were enrolled into the study. The disease duration at diagnosis was 18 months. Linear scleroderma (LS) was the most frequent subtype (65%), followed by plaque morphea (PM) (26%), generalized morphea (GM) (7%) and deep morphea (DM) (2%). As many as 15% of patients had a mixed subtype. Ninety-one patients (12%) had a positive family history for rheumatic or autoimmune diseases; 100 (13.3%) reported environmental events as possible trigger. ANA was positive in 42.3% of the patients, with a higher prevalence in the LS-DM subtype than in the PM-GM subtype. Scl70 was detected in the sera of 3% of the patients, anticentromere antibody in 2%, anti-double-stranded DNA in 4%, anti-cardiolipin antibody in 13% and rheumatoid factor in 16%. Methotrexate was the drug most frequently used, especially during the last 5 yr.**

***Conclusion*. This study represents the largest collection of patients with JLS ever reported. The insidious onset of the disease, the delay in diagnosis, the recognition of mixed subtype and the better definition of the other subtypes should influence our efforts in educating trainees and practitioners and help in developing a comprehensive classification system for this syndrome.**

KEY WORDS: Scleroderma, Morphea, Scleroderma en coup de sabre, Progressive hemifacial atrophy, Parry–Romberg syndrome.

Significant familial and environmental factors may influence the development of juvenile localized scleroderma (JLS). The data collected represent the starting point for the development of a more comprehensive classification and a resource for further clinical research.

JLS, often termed 'morphea' in the dermatology literature, refers to a number of different conditions characterized by skin thickening with increased collagen deposition. JLS includes several subtypes, including plaque morphea (PM), linear scleroderma (LS) and the en coup de sabre (ECDS) type, which affects the face and head [1–4].

Superficial patches of morphea may be relatively benign. But LS tends to involve not only the skin but also subcutaneous tissue, muscle tissue and bone, resulting in functional disabilities and cosmetic problems. Many children develop severe atrophy of the extremities, deformities, contractures and limb length discrepancies. In the ECDS variety, involvement of the underlying

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structures may cause hemiatrophy of the face and facial deformity. In addition, involvement of the eye and brain may lead to more serious complications [5, 6].

Unfortunately, there is no accepted uniform terminology, as shown by the fact that dermatologists use the term 'morphea' and the paediatricians and rheumatologists use the term 'scleroderma' to refer to the same condition. There are no uniform criteria for classification of JLS subsets either. Indeed, practising physicians are not sufficiently aware of this condition, leading to a delay in diagnosis.

Up to now, the published series of children with JLS are few, with a limited number of patients and reflect, in many aspects, the specialty of the reporting authors [1–4, 7–9].

We now report data on the demographic, epidemiological, clinical and laboratory features of a large cohort of patients from several paediatric rheumatology and dermatology centres around the world. This is part of a multiphase project sponsored by the Pediatric Rheumatology European Society (PRES) with a view to developing new classification criteria for JLS.

Patients and methods

A data collection form was developed to gather information on demographic, epidemiological, clinical and laboratory features and the treatment of children with JLS, and this was distributed to 270 paediatric rheumatology and dermatology centres in Europe (166), North America (42), South America (28), Asia (30), Australia (2) and Africa (2). The centres that were addressed were based on the mailing lists of PRES and PRINTO (Paediatric Rheumatology International Trial Organization).

Each questionnaire consisted of a cover letter and a form focusing on information about the following items:

(i) Demographics (gender, age at first signs or symptoms of the disease, age at diagnosis, age at last evaluation).
(ii) Epidemiology (environmental factors considered by physicians and by the patients or their families significantly related to the disease onset, family history for connective tissue or autoimmune diseases in first- and second-degree relatives).
(iii) Clinical subtypes: investigators were requested to use the Mayo Clinic classification criteria [1]. This classification gathers the different variety of localized scleroderma into five groups: (a) PM; (b) generalized morphea (GM); (c) bullous morphea (BM); (d) LS, including the head–face subtypes ECDS and progressive hemifacial atrophy (PHA), also known as Parry–Romberg disease; and (e) deep morphea (DM), including four subtypes: subcutaneous morphea (SM), morphea profunda (MP), disabling pansclerotic morphea (DPM) and eosinophilic fasciitis (EF).
(iv) Clinical description of the lesions at onset and at the last evaluation, including the body site (symmetry, shape and maximum size), lesion depth evaluated clinically and, when possible, by ultrasound, MRI or biopsy.
(v) Abnormal laboratory parameters at diagnosis. They included haemoglobin, total white blood cell count (WBC), eosinophil count, platelet, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase (CK) and serum immunoglobulins (IgG, IgA, IgM).
(vi) Serum autoantibodies, ANA, anti-double-stranded DNA (dsDNA), anti-sclero-70 (Scl70), anticentromere and other extractable nuclear antigen (ENA) autoantibodies, anticardiolipin antibodies (aCL), lupus anticoagulant (LAC) and rheumatoid factor (RF). Abnormal values were referenced to the normal range of laboratory standards of each participating centre.
(vii) Type and duration of treatment.

Since all clinical information was collected anonymously from the patients' charts, approval was obtained from the institutional review board where necessary.

Statistical analysis

Descriptive statistics were used for reporting demographic, clinical and laboratory characteristics of the patients. Data analysis included the χ^2 test, Student's *t*-test and Fisher's exact test as appropriate.

Results

Demographics

During the period from January 2002 to December 2003, 138 centres participated in the survey, with a 51% response rate. Sixty-eight were interested in the study but did not have patients to include in the database. Seventy centres (38 European, 12 North American, 11 South American, eight Asian and one Australian) reported 750 patients.

The clinical characteristics of the patients are summarized in Table 1. There were 529 females (70.5%) and 221 males; the female:male ratio was 2.4:1. This proportion was higher in the GM and DM subtypes but the difference was not significant. In the group of patients aged >10 yr at onset, the female:male was 2.7:1; in those aged <10 yr the ratio was 1.5:1.

The mean age at disease onset was 7.3 yr (range 0–16). The mean time between the first manifestation of the disease and diagnosis was 1.6 yr (median 11 months, range 0–16.7 yr). Age of onset and

Table 1. Main demographic features of 750 patients with JLS

	Overall	Linear	Plaque	Generalized	Deep
Patients[a]	750	489 (65)	194 (26)	51 (7)	16 (2)
Gender (female:male)	2.4:1	2.1:1	2.8:1	3.6:1	4.3:1
Male	221	156	51	11	3
Female	529	333	143	40	13
Age at onset (yr, months)					
Mean	7.3	6.11	7.8	8.7	8
Median	6.10	6.3	7.7	8.11	7.5
Range	0–16	0–16	0.6–16	0.6–16	1.6–15.1
Disease duration at diagnosis (yr, months)					
Mean	1.6	1.6	1.6	1.7	1.2
Median	0.11	0.11	0.9	1	0.9
Range	0–16.7	0–12.3	0–13.8	0–16.7	0.1–5
Family history[a]	91 (12.1)	60 (12.3)	17 (8.8)	12 (23.5)	2 (12.5)
Environmental factors[a]	100 (13.3)	69 (14.1)	26 (13.5)	3 (5.9)	2 (12.5)

Data are number (%).
[a]Values are the number (%).

duration of delay in diagnosis were not significantly different in the various subtypes.

Clinical subtypes

Four hundred and eighty-nine patients (65%) were diagnosed as having LS, 192 (26%) PM, 51 (7%) GM and 16 (2%) DM.

Among patients with LS, 265 (54%) presented lesions on the trunk and/or limbs. Two hundred (41%) had unilateral involvement and 11% had bilateral involvement; only 2% had central lesions either on the abdomen or on the trunk.

One hundred and thirteen patients (23%) had a face–head localization (linear head), including 99 with ECDS, eight with PHA and six with both head (three with PHA) and limb involvement.

In this group of patients with face–head localization, neurological involvement was reported in 21 patients and included seizures (9), recent onset headache (5), vascular malformations (2), behavioural changes (2), neuroimaging abnormalities (e.g. white matter abnormalities, calcifications) and EEG alterations casually found in two and one asymptomatic patient, respectively. These alterations were equally present in the two conditions, being reported in 19/102 (18.6%) patients with ECDS and 2/11 (18.2%) with PHA. Ocular involvement was reported in 10 patients with ECDS-PHA and consisted of anterior uveitis (4), episcleritis (3), glaucoma (2) and keratitis (1). Again, the frequency of these complications was similar in the two conditions, being present in 8/102 (7.8%) patients with ECDS and in 2/11 (18.2%) of those with PHA.

One hundred and eleven patients (23%) had a mixed variety, consisting in a combination of LS-PM in 99 patients (20%), LS-GM in nine (2%) and LS-DM in three (1%). In particular, in the LS-PM subtype, 49 patients (44%) had linear lesions at first then plaque; vice versa in 40 (36%). In 7/9 patients with LS-GM and in 2/3 with LS-DM, linear lesions appeared at the same time as the plaques. For 13 patients (12%) we were unable to determine the time when the lesion appeared.

Most of the 192 patients with PM presented morphea en plaque (99%), followed by guttate and atrophoderma of Pasini–Pierini in one patient (0.5%).

GM was present in 51 children, representing 7% of all JLS patients. Thirty-two of them (63%) had limb–trunk involvement, 6 (12%) had lesions on the trunk alone, 3 (6%) only on the limbs, and 10 (19%) had limb, trunk and head involvement.

DM, reported in 16 patients, was mainly represented by EF in 10 patients (62.5%). These patients presented characteristic cutaneous features such as pitting oedema, diffuse painful areas with peau d'orange appearance mainly involving the extremities proximal to the hands and feet. Of interest, all these patients, at the onset of the disease, had increased ESR and peripheral blood eosinophilia; deep skin biopsy, performed in 9/10 children, revealed a significant eosinophilic infiltrate in the panniculus and deep fascia.

MP was reported in four patients (25%) and DPM in two (12.5%). Of interest, one of these two patients with DPM developed a severe skin–muscle atrophy of the right leg that resulted in autoamputation. The other patient developed a squamous cell carcinoma over a chronic ulcer of the leg and died.

Family history

Ninety-one patients (12.1%) reported a family history positive for rheumatic and/or autoimmune diseases in 129 relatives (Table 1). In 44 patients they were first-degree relatives; in the other 47 they were second-degree relatives. This positive family history was self-reported by 12.3% of patients/parents with LS, 8.8% of those with PM, and 12.5% of those with DM. In GM the prevalence was 23.5%, significantly higher than in the other three groups ($P < 0.05$).

As shown in Table 2, among the 129 relatives, 82 (63.6%) had various rheumatic diseases and 47 presented other autoimmune diseases involving either the skin (19.4%) or internal organs (17%). As for rheumatic diseases, rheumatoid arthritis was the most frequently reported, being present in 36.4% of the relatives, followed by scleroderma and systemic lupus erythematosus (SLE). Cutaneous autoimmune diseases, reported in 25 relatives, consisted of psoriasis, vitiligo and lichen sclerosus et atrophicus. Autoimmune diseases involving internal organs were essentially represented by thyroiditis, insulin-dependent diabetes mellitus, inflammatory bowel disease and, to a lesser extent, myasthenia gravis, multiple sclerosis and sarcoidosis.

Environmental factors

One hundred patients (13.3%) reported specific events that occurred very close to disease onset and were thus considered significant triggers by both parents and reporting physicians. Mechanical events accounted for 67% of these factors, followed by infections (25%), drugs (5%) and psychological distress (3%) (Table 3). These events were equally distributed among the various subtypes with a prevalence varying between 12.5 and 14.1%, except for GM, where they were reported with a significantly lower prevalence (5.9%). Local mechanical factors, including accidental trauma, insect bite and vaccination, were reported in approximately 10% of the patients. In particular, they were reported in 10.4 and 12.5% of the patients with LS and DM, respectively, 5.9% of those with GM and 5.7% of those with PM. Although quite variable, this prevalence in the four subtypes was not significantly different.

Laboratory variables

Laboratory characteristics of the patients at the time of diagnosis are summarized in Table 4. Acute-phase reactants (WBC, ESR, CRP) and other inflammatory parameters were elevated mainly in DM and particularly in EF. In the other groups laboratory signs of inflammation were present in less than 10% of the patients except for LS, where ESR was increased in 22.2% of the patients.

Table 2. Rheumatic and autoimmune diseases reported in 129 relatives of patients with JLS

Disease	No. relatives	%
Rheumatic diseases	82	63.6
Rheumatoid arthritis	47	36.4
Scleroderma	11	8.5
Systemic lupus erythematosus	10	7.8
Acute rheumatic fever	4	3.1
Raynaud's phenomenon	3	2.3
Polydermatomyositis	3	2.3
Undifferentiated connective tissue disease	3	2.3
Behçet's disease	1	0.8
Immune-mediated diseases	47	36.4
Cutaneous	25	19.4
Psoriasis	21	16.3
Vitiligo	3	2.3
Lichen sclerosus et athrophicus	1	0.8
Non-cutaneous	22	17.0
Thyroiditis	8	6.2
Insulin-dependent diabetes mellitus	6	4.6
Inflammatory bowel disease	4	3.1
Myasthenia gravis	2	1.6
Multiple sclerosis	1	0.8
Sarcoidosis	1	0.8
Overall	129	100

Table 3. Environmental factors reported very closely to disease onset in 100 patients with JLS

	Overall ($n=750$)	Linear ($n=489$)	Plaque ($n=194$)	Generalized ($n=51$)	Deep ($n=16$)
Mechanical factors	67 (8.9)	51 (10.4)	11 (5.7)	3 (5.9)	2 (12.5)
Trauma	53 (7.1)	40 (8.2)	8 (4.2)	3 (5.9)	2 (12.5)
Insect bite	11 (1.4)	8 (1.6)	3 (1.5)	–	–
Vaccination	3 (0.4)	3 (0.6)	–	–	–
Infections	25 (3.3)	12 (2.5)	13 (6.8)	–	–
Drug	5 (0.7)	3 (0.6)	2 (1.0)	–	–
Psychological distress	3 (0.4)	3 (0.6)	–	–	–
Overall	100 (13.3)	69 (14.1)	26 (13.5)	3 (5.9)*	2 (12.5)

Data are number (%). *$P<0.05$.

Table 4. Abnormal laboratory parameters in children with JLS at the time of diagnosis

	Linear	Plaque	Generalized	Deep
WBC	20/474 (4.2)	9/152 (5.9)	2/51 (3.9)	6/16 (**37.5**)
Eosinophil count	57/474 (**12**)	28/152 (**18.4**)	7/51 (**13.7**)	10/16 (**62.5**)
Haemoglobin	22/474 (4.6)	5/152 (3.3)	5/51 (9.8)	4/16 (**25**)
Platelet count	19/474 (4)	1/152 (0.7)	2/51 (3.9)	5/16 (**31.3**)
ESR	102/460 (**22.2**)	13/138 (9.4)	4/49 (8.2)	4/16 (**25**)
CRP	22/238 (9.2)	3/78 (3.8)	3/36 (8.3)	5/14 (**35.7**)
CK	7/231 (3)	6/74 (8.1)	0/34 (0)	2/16 (**12.5**)
IgG	52/249 (**20.9**)	11/74 (14.9)	5/42 (11.8)	9/16 (**56.3**)
IgA	31/249 (**12.4**)	10/74 (13.5)	5/42 (11.8)	3/16 (**18.8**)
IgM	40/249 (**16.1**)	6/74 (8.1)	4/42 (9.5)	1/16 (6.2)

Data are number abnormal/number tested (%). Bold type indicates that abnormal values were reported in more than 10% of the patients.

Table 5. Serum autoantibodies in JLS

Serum autoantibody	Overall	Linear	Plaque	Generalized	Deep morphea
ANA	284/671 (42.3)	211/446 (47.3)	56/163 (34.4)	15/48 (31.3)	6/14 (43)
Scl70	12/378 (3.2)	7/250 (2.8)	4/88 (4.5)	0/29 (0)	1/11 (9)
ACA	4/240 (1.7)	3/162 (1.9)	0/45 (0)	1/25 (4)	0/8 (0)
Anti-dsDNA	16/382 (4.2)	12/246 (4.9)	3/105 (2.9)	0/26 (0)	1/5 (20)
RF test	74/464 (15.9)	59/311 (19)	12/117 (10.3)	4/30 (13.3)	1/6 (17)
aCL	14/111 (12.6)	10/71 (14.1)	2/26 (7.7)	2/8 (25)	0/6 (0)

Data are number positive/number tested (%).

Peripheral blood eosinophilia was found with a prevalence ranging from 12 to 18.4% in LS, PM and GM. In DM it was reported in a higher percentage of the children (62.5%), all with EF. None of those with either MP or pansclerotic morphea had peripheral blood eosinophilia.

CK was elevated in a minority of the patients. However, it was increased in 2/16 DM patients (12.5%) who had myalgias and fatigue as presenting signs of the disease. These two patients had MP.

Serum IgG was particularly increased in LS and DM, IgA in DM, and IgM in 16.1% of patients with LS.

ANA, tested in 671 (89%) of the patients, were positive in 284 (42.3%) (Table 5). In LS they were present in 47.3% of the cases, in DM in 43%, and in PM and GM in 34.4 and 31.3%, respectively. Of interest, they were found to be present with similar frequency in ECDS and PHA subtypes (28.4 and 25%, respectively). Scl70 antibody was tested in 378 patients and was found to be positive in 12 (3.2%): seven had LS, four had PM and one had DM. Anticentromere autoantibodies (ACA) were found in four patients: three with LS and one with GM. None of these patients revealed any evolution towards systemic sclerosis after a mean follow-up of 3.4 yr (range 1.8–10 yr). None had a positive family history for scleroderma.

Anti-dsDNA antibodies were reported to be positive in 16 patients (4.2%): 12 had LS, three had PM and one had DM. Again, none of these patients developed signs or symptoms compatible with SLE during the long-term follow-up (mean 3.6 yr, range 1–8 yr). None had a positive family history for SLE.

Seventy-four patients (16%) were positive for RF. RF was found in almost one-fifth of the LS patients tested (19%), in 10% of those with PM, in 13% of those with GM and in only one with DM. A significant correlation between presence of RF and arthritis was found ($P<0.01$). Indeed, seven of 12 patients with both RF-positivity and a positive family history for rheumatic diseases had first-degree relatives with rheumatoid arthritis.

aCL antibodies were tested in only 14.8% of the patients and were found to be positive in 14/111 (12.6%). Ten had LS, one had PM and one had GM. These patients did not report either thromboembolic symptoms or alterations of the coagulation panel.

Treatment

During the course of the disease, 17% of the patients never received treatment (Table 6). This group essentially included patients with PM (25%), LS and GM (14%) and only 6% of those with DM. Among the immunosuppressors, methotrexate (MTX) was the drug most frequently used, being used in 44% of patients with LS or DM, in 31% of those with GM and in 21% of those with PM.

Interestingly, in the group of patients whose diagnosis was made after 1998, when MTX was first introduced for the treatment

Table 6. Drug treatment being used during the course of the disease

	Overall	Linear	Plaque	Generalized	Deep
None	128 (17)	14 (3)	49 (25)	7 (14)	1 (6)
Immunosuppressors					
Methotrexate	278 (37)	215 (44)	40 (21)	16 (31)	7 (44)
Cyclosporin A	15 (2)	12 (2)	4 (2)	2 (4)	0 (0)
Other	8 (1)	5 (1)	2 (1)	4 (8)	0 (0)
Steroids					
Topical	105 (14)	65 (13)	33 (17)	9 (18)	3 (19)
Oral	203 (27)	137 (28)	37 (19)	16 (31)	11 (69)
Parenteral	60 (8)	48 (10)	10 (5)	5 (10)	1 (6)
D-Penicillamine	195 (26)	148 (30)	34 (18)	12 (24)	3 (19)
PUVA	30 (4)	15 (3)	14 (7)	2 (4)	0 (0)
Vitamin D	75 (10)	42 (9)	28 (14)	4 (8)	0 (0)
NSAIDs	128 (17)	95 (19)	18 (9)	8 (16)	6 (38)
Symptomatics (prokinetics, H2 antagonists, anti-epileptics, emollients, ophthalmics etc.)	218 (29)	133 (27)	65 (34)	18 (35)	2 (13)

Data are number (%).

of morphea [35], more than 50% were treated with this drug *vs* only 12% of those whose diagnosis was made before 1998.

Cyclosporin A and other immunosuppressive treatments, such as azathioprine, cyclophosphamide and mofetil mycophenolate, were used in a minority of patients.

Steroids were used in 49% of children as topical, oral or parenteral treatments. While topical steroids were reported in the treatment of the various lesion groups with a similar prevalence, ranging from 13 to 19%, oral steroids were employed in two-thirds of patients with DM, one-third of those with LS and GM, and 19% of those with PM. Parenteral steroids were use in a minority of patients.

D-penicillamine was used in more than one-quarter of the patients. In the group of patients whose diagnosis was made before 1998, 39% had been treated with this drug *vs* only 13% of those diagnosed since 1998, representing a reverse trend after the introduction of MTX as the preferred treatment option.

Psoralen ultraviolet A treatment, employed mainly in adults during the last decade, was used rarely in children (4%). Vitamin D was the drug of choice in 10% of patients; there were no significant differences among the groups except for DM, in which it was never used. Non-steroidal anti-inflammatory drugs (NSAIDs) were reported in 17% of children, particularly in the subtypes with potential articular involvement, such as LS, GM and DM.

Supportive treatment with drugs such as H2 antagonists, anti-epileptics, emollients and ophthalmics, were used in almost one-third of the patients in each group, with the exception of DM.

Discussion

This study represents the largest collection of patients with JLS reported to date. The wide participation of centres from all over the world and the high response rate make this survey the most representative of the full spectrum of the disease in different countries.

Like many other connective tissue diseases, JLS mainly involves females and this is in agreement with other reported studies [2, 3, 4, 7–10]. This female preponderance is most marked after the age of 10 and is more evident in the GM and DM subtypes, where the F:M ratio reaches 4:1.

JLS affects children during the late infancy at a mean age of 7.3 yr, without difference among the various subtypes. This confirms previous studies [3, 4, 8].

LS, present in two-thirds of the patients, was the most frequently reported subtype, followed by PM (26%), GM (7%) and DM (2%). The high relative frequency of the more severe subtypes reflects, in part, the type of provider who evaluated and referred these patients. Among the 70 participating physicians, the vast majority (87%) was rheumatologists. This possible referral bias, a recognized limitation of retrospective studies, might also explain the high prevalence of immunosuppressive treatments reported in these patients.

Disease duration at diagnosis was often long and in 20% of the patients it took more than 2 yr to be diagnosed correctly. This finding, already reported by other authors [3, 4], suggests that more effort should be made to increase awareness of this condition among physicians and allied health professionals. In particular, paediatricians in training and practitioners should be taught to consider the diagnosis of JLS in any child who develops a circumscribed area of thickening of the skin with altered texture and colour, and encouraged to initiate appropriate studies, including skin biopsy and referral.

One of the most important observations in this study is the recognition of the mixed type of JLS. In this group, which made up 15% of the study population, linear lesions were associated with circumscribed lesions, superficial and deep. In a majority of patients (64%), linear lesions appeared before or at the same time as the plaque lesions. In the reminder of the patients linear lesions appeared after the appearance of the plaques. This evolution of a mixed type was known to clinicians but has never been identified as a separate entity and should probably be considered as a distinct subgroup in any new classifications system.

In trying to clarify the relationship between PHA and ECDS, we found that the percentage of patients with CNS and ocular involvement and ANA were similar in the two groups. This is in agreement with what has been reported in a long-term follow-up of patients with these two conditions [11] and from other studies showing similar prevalences of CNS and ocular involvement [6, 12–14] and autoantibodies [15–17]. Indeed, while some authors contend that it is possible to differentiate the two conditions histologically [18], others do not agree [19]. There are also reports of coexistence of ECDS and PHA and of PHA with LS of the trunk and extremities in the same patient [20]. All these observations suggest that ECDS and PHA are different manifestations of the same pathological process: the first involving mainly the superficial skin, the latter involving mainly subcutaneous tissue, muscle and bone [21].

Another significant finding in the study relates to EF. This condition exhibits clinical, laboratory and histological characteristics quite different from the other forms of JLS. In fact, these patients, at the time of diagnosis, present characteristic cutaneous features, such as pitting oedema, diffuse painful areas with peau d'orange appearance that usually involve the extremities proximal to the hands and feet. Laboratory studies show increased ESR, peripheral blood eosinophilia and

hypergammaglobulinaemia while deep skin biopsy reveals the unique histological picture of eosinophilic infiltrate in the panniculus and deep fascia.

Later during the disease course, the lesion become fibrotic and this has led some authors to include this condition in the DM subtype [1]. However, EF may have to be excluded from the DM subtype in any future classification of JLS.

A positive family history for rheumatic or autoimmune diseases was reported in 12% of patients. In two-thirds of the relatives they were mainly rheumatic conditions and, among these, scleroderma was the second most frequently reported disease after rheumatoid arthritis. There is very little information on this topic in the published literature. Vancheeswaran *et al*. [4] found a positive family history for autoimmune diseases in 12.7% of 47 patients with JLS but the type of disease was not specified. Other authors reported other cases of scleroderma in the families of five patients, with an overall prevalence of 2.6% [9]. Morphea was described in two generations of families [22] and in one parent and daughter [23, 24]. No cases of monozygotic twins were found in our series and we found only one in the literature [25]. Two cases of monozygotic twins discordant for JLS and two sisters with JLS were present in our series.

Additional support for the autoimmune basis of the disease is provided by the occurrence of SLE in family members of 10 patients with JLS. Indeed, anti-dsDNA antibodies were found in 4% of the patients but none of them developed SLE during the follow-up or had a positive family history for this disease. SLE has already been reported in family members of patients with JLS and even in combination with JLS in some patients [26–28].

A positive family history for various autoimmune conditions in one out of eight JLS patients could support the hypothesis that the genetic background contributes to susceptibility to clinically distinct autoimmune/inflammatory diseases. A non-random clustering of non-MHC candidate loci, already shown in other conditions such as multiple sclerosis, Crohn's disease, familial psoriasis, asthma and type-1 diabetes [29], may explain this overlapping susceptibility. On the other hand, the lack of similarity in disease expression within a family, the low incidence of multicase families and the data on twins seem to indicate that non-hereditary factors may play a major role in the pathogenesis of the disease.

Significant environmental factors, as possible triggers for disease onset, were reported in 13.8% of the patients in our series. Accidental trauma, reported in 7.3% of the patients, was the commonest, and this is in agreement with previous studies reporting the incidence of trauma in 2.6–12.7% of patients [4, 9, 30]. Unfortunately, the lack of a control population and possible recall bias, typical of a retrospective study, make it difficult to assign a causative role to trauma in the aetiology of JLS.

Autoantibodies have been found in many patients with JLS. ANA were found to be positive in 42.3% of the patients; this is comparable with the prevalence previously reported, which ranges from 32 to 76% [3, 4, 7, 15, 16, 31, 32]. Despite the fact that LM and DM were the subtypes associated with higher prevalence, there was no correlation between these antibodies and the various subtypes or the disease course.

Of interest, anti-Scl70 antibodies and ACA antibodies, markers of SSc in many adults, were found to be positive in 3.2 and 1.7% of patients, respectively. Other authors report similar findings in JLS, with a similar prevalence of 2–3% for anti-Scl70 [7, 31] and 0–12% for ACA [16, 33]. None of the Scl70- or ACA-positive patients in our series presented signs or symptoms of internal organ involvement after a mean follow-up of 3.4 yr. However, these patients require careful follow-up to look for possible systemic symptoms, which in previous studies appeared several years after disease onset [31, 34]. Whether these antibodies are markers that reflect the immunological component of the disease process or can have a prognostic significance is unclear. However, the reported relationship between their presence and a more aggressive disease course [30] was not confirmed in our study. In fact, both the prevalence of articular complications and the need for a more aggressive treatment were similar in ANA-positive and ANA-negative patients.

On the contrary, the only significant correlation that we found was between the presence of arthritis and positivity for RF. This finding, in 16% of the patients in our series, has already been reported, with a prevalence of 26–39% [3, 4, 30]. Although these antibodies may not be directly involved in the pathogenesis of the disease, they may be linked to its course, particularly to the articular involvement.

As for treatment, MTX was the drug most frequently used in our series, especially during the last 5 yr. Conversely, the use of D-penicillamine has decreased during the last few years. MTX has been successfully used both in adults [35] and in children with localized scleroderma [36, 37] while D-pencillamine has been reported to be effective only in adults [38]. Unfortunately, these studies were not randomized controlled trials and the series of treated patients was very small.

Several observations made in this study are likely to have a major impact on the classification and follow-up of children with localized scleroderma (JLS). The insidious onset of the disease and the delay in diagnosis, documented in this study, should influence our efforts in educating trainees and practitioners. The recognition of mixed subtype of JLS, the differences between EF and DM and the similarities between ECDS and PHA are important findings that should be addressed in developing a comprehensive classification system for this syndrome.

This study, which is the first step of an international project sponsored by PRES and involving rheumatologists, dermatologists and paediatricians, will help complete these tasks and hopefully will become a resource for future clinical research.

Rheumatology	Key messages
	• We describe the clinical and immunological features of 750 children with juvenile localized scleroderma. • The delay in diagnosis and the peculiar familial and environmental factors that are closely related to this disorder are analysed.

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