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ORIGINAL ARTICLE

Juvenile localized scleroderma: beyond our eyes can see

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Abstract

Introduction: Juvenile localized scleroderma (JLS) is the most common form of scleroderma in childhood and represents a group of distinct clinical entities with thickening of epidermis, dermis and adjacent subcutaneous tissue. There are few data described in the Brazilian population. Clinical presentation is variable, with five subtypes that may manifest with extracutaneous involvement. Immunosuppressive treatment is indicated in most cases, with favorable prognosis, but progression to functional limitation occurs in 25% of patients. **Objectives:** To describe and correlate with literature demographic, clinical and therapeutic data of a sample with JLS. **Methods:** A descriptive observational study was conducted involving patients diagnosed with JLS between 2015 and July 2022 under regular follow-up in a pediatric rheumatology unit of a childrens tertiary hospital. **Results:** Medical records of 23 patients were reviewed, 60% of them female, with a median age of onset of 6 years and diagnostic delay in of two years or more in 39%. Linear and mixed JLS were the most prevalent subtypes. Chronic skin manifestations were present in 74% cases at diagnosis and extracutaneous involvement in 78% during follow-up. Methotrexate and prednisone were used in 91% of patients and 36% of then required other medications. Disease complications were described in 43% of cases. **Conclusions:** There was higher percentage of patients with diagnostic delay in relation to literature, in addition to high presence of chronic manifestations at diagnosis and progression to complications. Dissemination of knowledge about JLS is important for early diagnosis and reduction in the functional impact related to the disease.

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INTRODUCTION

Scleroderma is a group of diseases in which excessive collagen production causes fibrosis of the skin and adjacent tissues, in addition to involving other organs. The condition manifests in two main forms: localized scleroderma (LS) and systemic scleroderma (SS), each with different subtypes [1]. SS occurs with multisystem involvement and diffuse skin changes. LS is characterized by localized skin involvement and less frequent extracutaneous involvement [2].

Most patients with juvenile scleroderma develop the disease before the age of 16 years, with patterns of involvement differing from those in adults. Juvenile localized scleroderma (JLS), or morphea, is the most common presentation in the pediatric age group, with 6 to 10 times more cases than systemic scleroderma [1]. Incidence has been estimated at 0.34 to 2.7 cases per 100,000 children annually. The disease preferentially affects females, with an average age of onset between 6.4 and 10.5 years [3]. There are five well-defined subtypes of morphea: linear, circumscribed (in plaques), generalized, pansclerotic, and mixed [1,2,3].

JLS has a wide range of clinical presentations, with skin lesions differing in shape, extent, and location between the various subtypes, although they generally occur unilaterally[3]. In the initial stage of the disease, lesions present an erythematous to violaceous color and a normal texture, and there may be edema and a sensation of warmth [4]. Once fibrosis sets in, the lesions develop a raised and hardened surface with a waxy center, surrounded by an erythematous or violaceous halo (lilac ring) [3]. In the later stages, there is depigmentation (hyper or hypopigmentation), atrophy of the dermis and adjacent subcutaneous tissue, and loss of skin appendages [3,4].

The average time between the onset of symptoms and the diagnosis of JLS is 13 months, and a fifth of pediatric patients are diagnosed after two years of disease [1]. Outcomes are good in adequately treated cases. However, about a quarter of patients develop functional impairments [5].

Although rare, this condition is relevant because it is the most common form of scleroderma in children. The difficulty recognizing cases of JLS often delays referral to a specialist. This article describes the signs and symptoms observed in children and adolescents with JLS and compares findings with the literature.

METHOD

This cross-sectional observational descriptive study included the medical records of patients seen at the outpatient clinic of the pediatric rheumatology unit of a tertiary pediatric hospital. The records of patients under 20 years of age diagnosed with JLS between 2015 and July 2022 and under regular follow-up for at least six months were included. Patients with other autoimmune rheumatological diseases in association with morphea were excluded.

A form was designed to collect demographic, clinical, laboratory, histopathological, therapeutic, and disease progression data. Data collection took place in January 2023.

The variables analyzed included sex, age at symptom onset (in years), interval between symptom onset and diagnosis (in years), length of follow-up (in years), JLS subtypes (linear, circumscribed, generalized, pansclerotic, or mixed), location of the lesions, presence of chronic cutaneous manifestations (atrophy or fibrosis) [3] at the time of diagnosis, current disease status (activity, described as increase and/or intensification of thickening of previous lesions, appearance of new lesions and/or edema, redness and/or sensation of warmth, stop of progression of lesions with or without medication, characterized by reduction in size and thickening of lesions and absence of worsening of the initial condition) [3,6], histopathology findings from skin biopsies, positive test results for autoantibodies [antinuclear factor (ANA), rheumatoid factor (RF), anti-single-stranded DNA (anti-ssDNA), anti-histone, and anti-topoisomerase I (anti-SCl 70)], systemic treatment prescribed (prednisone, methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, tocilizumab), [7,8] and disease complications (joint and muscle contracture, muscular hypotrophy, anisomelia, ophthalmological, dental, neurological, gastrointestinal, and pulmonary sequelae)[9].

The presence of musculoskeletal (arthralgia, arthritis, and/or myalgia), gastrointestinal (heartburn, epigastric pain, and/or dysphagia), ophthalmological (ocular hyperemia), dental (temporomandibular dysfunction and/or dental arch asymmetry), neurological (seizures and/or headache), pulmonary (dyspnea on exertion) and vascular (Raynaud's phenomenon) manifestations was also analyzed.

Statistical analysis included the calculation of medians for continuous variables and absolute numbers and proportions for categorical variables. The Institution's Research Ethics Committee approved the study under certificate no. 5.813.449

RESULTS

The medical records of 23 patients are summarized in Table 1. Females accounted for the majority of the patients (60%). Median patient ages at the onset of symptoms and diagnosis were six (2.1 – 15.9) and nine (3.1 – 16.9) years, respectively. The median time between the onset of symptoms and diagnosis was 1.4 (0.2 – 12) years. None of the patients had symptoms in the first year of life. In three, symptoms started in the second year of life. In three cases, possible triggers were reported before the appearance of skin symptoms (chickenpox in one and local trauma in two). Nine patients (39%) were diagnosed two years after the onset of symptoms and four more than five years after the onset of symptoms, the majority with facial involvement. Five patients (21%) had a family history of autoimmune disease (AID), including Hashimoto's thyroiditis, systemic lupus erythematosus, and JLS.

Table 1. Demographic, clinical, laboratory, treatment, and disease progression data of 23 patients with JLS.

Sex ratio (females : males)	1.5:1
Age at the onset of symptoms (years): median (min-max)	6 (2,1 – 15,9)
Age at diagnosis (years): median (min-max)	9 (3,1 – 16,9)
Time between onset of symptoms and diagnosis (years): median (min-max)	1,4 (0,2 – 12)
Length of follow-up (years): median (min-max)	3 (0,5 – 7,2)
JLS subtypes:	N (%)
Linear	10 (43)
Mixed	10 (43)
Circumscribed	2 (9)
Generalized	1 (5)
Pansclerotic *	0 (0)
Extracutaneous (EC) manifestations on follow-up:	N (%)
Patients with EC manifestations	18 (78)
Joint	11 (61)
Gastrointestinal	8 (44)
Neurological	3 (16)
Muscular	2 (11)
Vascular	2 (11)
Pulmonary	1 (5)
Ophthalmological	1 (5)
Dental	1 (5)
Skin biopsy findings:	N (%)
Inflammatory infiltrate	10 (62)
Collagen changes	9 (56)
Skin appendage changes	8 (50)
Positive autoantibody tests:	N (%)
Patients with positive autoantibody tests	10 (43)
ANA	9 (39)
RF	3 (13)
Anti-ssDNA	3 (13)
Anti-histone	0
Anti-SCl 70	1 (4)
Prescribed treatment:	N (%)
Prednisone + methotrexate	21 (91)
Mycophenolate mofetil	6 (26)
Cyclophosphamide	4 (17)
Tocilizumab	2 (8)
Azathioprine	1 (4)
Current disease status:	N (%)
Progression interrupted; using medication	14 (61)
Active disease	5 (21)
Progression interrupted; not using medication	4 (18)
Complications:	N (%)
Joint contracture	4 (17)
Muscle contracture	2 (8)
Muscle hypotrophy	5 (21)
Anisomelia	3 (13)
Temporomandibular disorder	2 (8)
Dental arch changes	2 (8)
Intellectual deficit	1 (4)
Difficulty memorizing and learning	1 (4)

JLS: juvenile localized scleroderma; ANA: antinuclear factor; RF: rheumatoid factor; Anti-ssDNA: Anti-single-stranded DNA antibody; Anti-SCl 70: anti-topoisomerase antibody 1.

* Two patients with pansclerotic morphea associated with other subtypes of JLS were diagnosed with mixed morphea.

Regarding the distribution by subtypes, 10 patients (43%) had linear scleroderma, with involvement of extremities in 60% of the cases. Four children had facial involvement (Figure 1), three with Parry-Romberg syndrome (PRS) and one with en coup de sabre lesion (ECDS). The mixed subtype was observed in 43% of the children, with the association between the linear and circumscribed forms being more common. Two patients presented symptoms consistent with circumscribed, linear, and pansclerotic morphea; one had involvement consistent with PRS (Figure 2). No cases of the pansclerotic subtype were detected in isolation. Two patients had circumscribed scleroderma, and one had generalized morphea (Figure 3).

Seventeen patients (74%) had chronic skin involvement (atrophy or fibrosis) at diagnosis. They were diagnosed after a median of 1.7 (0.2 – 12) years from the onset of disease, against 0.6 (0.5 – 1.4) years for patients without chronic skin involvement.

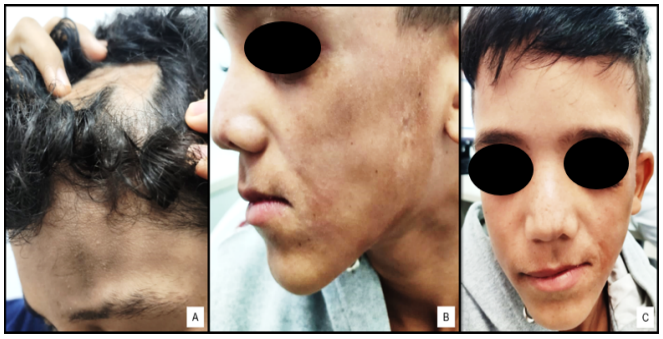


Figure 1. Linear scleroderma of the face. A) A 17-year-old with en coup de sabre lesions: an area of thickening with hyperpigmentation and a large thick plaque with atrophy and alopecia in the left frontal area of the head; B and C) A 12-year-old with Parry-Romberg syndrome: hyperpigmentation on the left hemiface without cutaneous fibrosis, but with atrophy of subcutaneous tissue generating accentuation of the ipsilateral nasolabial groove, oral fissure deviation, and nasal ala asymmetry.



Figure 2. Mixed juvenile localized scleroderma. A 5-year-old girl with extensive skin involvement of the left hemibody with linear lesions in the neck, trunk, abdomen, and left arm and a pansclerotic lesion in the left leg. Other signs include hypotrophy of the left arm and joint contractures of the third and fifth fingers. A significant circumferential lesion with atrophy and fibrosis affects the entire length of the left leg, causing muscle hypotrophy and anisomelia. Isolated morphea plaques can be seen on the right hemiabdomen and leg.



Figure 3. Generalized morphea. An 11-year-old with multiple plaque lesions (>4), some larger than 3 cm, in the neck, trunk, abdomen, pelvis, back, legs, and arms, with areas of confluence, depigmentation, and loss of skin appendages.

Extracutaneous manifestations were present in 17 children (74%) at diagnosis, and 65% had joint symptoms (arthralgia and/or arthritis), most in areas close to the skin lesions. Nine percent of the patients had myalgia. Gastrointestinal symptoms (heartburn, epigastric pain, and/or dysphagia) were reported in 47% of cases. However, few underwent complementary examination with upper digestive endoscopy, esophagram, and/or esophageal manometry. Three patients had seizures, and one teen complained of ocular redness, although without an ophthalmological evaluation, in addition to temporomandibular disorder and dental arch asymmetry. Two children had Raynaud's phenomenon at diagnosis. One underwent capillaroscopy and was diagnosed with a nonspecific microangiopathy.

During follow-up, extracutaneous manifestations were documented in 18 cases, mainly with musculoskeletal involvement, followed by gastrointestinal and neurological symptoms. An adolescent with linear scleroderma of the extremities developed dyspnea on exertion, restrictive lung disease verified on spirometry, mild diffuse thickening of the bronchial walls, and minor atelectatic streaks in the right lung on chest tomography without positive autoantibody tests or changes in capillaroscopy. All patients with neurological, dental, and/or ophthalmological disorders had facial lesions, which were more common in patients with PRS than with coup de sabre lesions.

Sixteen patients underwent skin biopsies, with findings of inflammatory infiltrate in 62%, collagen changes in 56%, and skin appendage alterations in 50%. Autoantibody tests were performed in all patients, and ten (43%) were positive. Nine patients were positive for ANA, three for RF, three for anti-ssDNA, and one for anti-SCl 70 (with PRS). Three children were positive for more than one antibody.

Regarding treatment, the combination of prednisone and methotrexate (MTX) was prescribed as first-choice therapy to 21 patients (91%), three of whom had to take it for more than three years. Progression of lesions was interrupted in 66% of cases, while 24$ showed a partial response.

Other drugs were prescribed to eight patients, with mycophenolate mofetil (MMF) topping the list, either due to refractoriness to standard treatment or an adverse reaction to MTX. Six children were on MMF, with disease progression interrupted in five and partial response in one case. Four patients were on cyclophosphamide in monthly pulse therapy, two due to neurological impairment (one with PRS and the other with a combination of PRS and ECDS) and two for severe skin disease. Progression was interrupted in two cases, one had a partial response, and one is still taking medication. One patient is currently on azathioprine due to the return of the lesions after treatment with cyclophosphamide (CFM), in addition to the lack of response to MTX and an adverse event to MMF. Monthly tocilizumab was prescribed in two cases, one a patient with mixed morphea with indication due to severe disease and refractoriness to previous treatments, in whom disease progression was interrupted, and the other a patient with mixed morphea with indication due to severe disease, who responded poorly to treatment.

The median follow-up time of the study population was three (0.5 – 7.2) years. Five children currently have active disease, disease progression was halted in 61% of the patients with medication, and 18% have stable disease after stopping medication, 75% of whom have linear and 25% circumscribed scleroderma. Among the patients with active lesions, four have mixed scleroderma, one has PRS and ECDS, and one has an en coup de sabre injury. Currently, 14 children (61%) are on immunosuppressants.

Ten patients had complications, 70% related to musculoskeletal conditions (joint and muscle contracture, muscular hypotrophy, and anisomelia). Two children had dental sequelae with TMD and oral fissure deviation. Two developed neurological disorders (intellectual disability and learning and memory deficits). The subtype with the highest rate of comorbidities was mixed scleroderma (60%).

DISCUSSION

JLS is a rare disease, with few reports describing its occurrence in the Brazilian population. That, coupled with the condition's wide array of clinical presentations, may explain the difficulty in making an early diagnosis. We found substantial delays in diagnosis in our population, with a significant proportion of patients diagnosed with JLS two years after the onset of symptoms, which is twice the time described in the literature[1].

The etiology of JLS remains unclear. An autoimmune nature is eminently suggested by the presence of autoantibodies and the family or personal history of other autoimmune diseases [10,11]. Previous studies have described cases of morphea after infection with the Epstein-Barr virus, Borrelia burgdorferi, and the varicella virus [10]. Mechanical events, such as trauma, vaccination, and surgery, have been described as potential triggers in 10 to 15% of patients with LS [3]. In our series, 21% of patients had a family history of autoimmune disease, and 13% were exposed to potential triggers for the disease.

The high rates of chronic skin manifestations found in our study reflect the longer diagnostic delays and the consequent delays in starting treatment. The difference in the median time until diagnosis between patients with and individuals without chronic signs and symptoms at initial assessment was 1.1 years. In line with the literature [1], children with facial lesions represented the majority of patients with delayed diagnosis (75%). However, the longest time until diagnosis was seen in the case of a patient with linear scleroderma of the extremities who had symptoms for 12 years at the time of diagnosis.

Linear is the most common subtype of scleroderma described in the literature, seen in 50-65% of cases [3]. Our population had a high prevalence of the mixed subtype, which occurred in equal proportion to linear scleroderma, with ten cases each. However, all patients with the mixed subtype had linear lesions associated with other subtypes. Linear morphea presents as indurated linear plaques that may follow the Blaschko lines. They may extend to muscle and bone tissue, causing atrophy, thinning, and shortening of the affected limb [6].

Linear scleroderma of the face presents in two forms: en coup de sabre lesion and Parry-Romberg syndrome [6]. The association of the two has been described in 28-42% of adult patients [12]. In our population, only one individual had it. ECDS manifests as a band of thickened skin that extends vertically over the forehead and/or scalp, sometimes accompanied by alopecia and thinning or depression of the skull [3]. PRS is characterized by progressive hemifacial atrophy, atrophy of subcutaneous tissue, muscles, and bone, without significant change to the overlying skin [13].

Only 9% of our patients had circumscribed scleroderma in isolation. Plaque morphea accounts for 25-40% of the cases described in the literature, presenting as oval or rounded lesions, preferentially affecting the trunk. Patients may develop one or multiple lesions with superficial or deep involvement [3]. Generalized morphea, an uncommon subtype in the pediatric population, is characterized by the presence of four or more plaques, larger than 3 cm each, involving two or more anatomical sites [2,3]. Only 5% of our patients had this subtype of the disease.

Pansclerotic morphea is the most severe and rarest form. It progresses rapidly and is characterized by circumferential involvement of one or more limbs, affecting the skin and deep tissues [13]. It may develop into squamous cell carcinoma, a rare and potentially fatal complication [3]. Two patients in our population had the mixed subtype, including pansclerotic involvement. Both had severe disease and required multiple therapeutic regimens. To date, none has developed carcinoma.

Extracutaneous involvement is reported in 22-75% of patients in the literature [4], as observed in our population (74%), with musculoskeletal involvement being the most common.

Linear is the subtype described as having greater involvement of other organs, associated with arthritis, muscle contracture, myositis, muscular atrophy, and anisomelia. About 25% of the cases of joint involvement occur in areas distant from skin lesions [1,4]. In our population, given the high prevalence of mixed morphea, extracutaneous involvement was found in equal proportions in the linear and mixed subtypes.

ECDS and PRS may be associated with neurological, ophthalmological, and dental symptoms. Up to 10% of patients may present symptoms such as seizures, headache, central nervous system vasculitis, and changes in neuroimaging scans, which may precede or occur years after the lesions appear [3,14]. One patient with PRS in our population started experiencing seizures one year before the onset of skin manifestations, and two others developed neurological conditions two and ten years after the appearance of skin lesions.

Involvement of other systems has been reported scantly in the literature. Vascular symptoms, such as Raynaud's phenomenon, were described in less than 10% of the patients, gastrointestinal in less than 5%, and pulmonary in less than 4%[14,15]. Gastrointestinal involvement was seen in large numbers in our population and ranked second in the list of affected systems after the musculoskeletal system, which accounted for almost half of extracutaneous symptoms. We found one patient with lung involvement (not associated with Raynaud's phenomenon) and two with Raynaud's phenomenon (not associated with pulmonary manifestations), which are more often described in cases of systemic scleroderma [2]. Only one of the patients with vascular involvement had a positive autoantibody test (ANA).

The diagnosis of JLS is clinical and can be based on histopathological evaluation in doubtful cases, which must be based on collecting specimens from the edge of an active lesion. There are no specific laboratory test findings[16]. Concerning laboratory test changes, 39% of our patients tested positive for ANA, against up to 50% described in the literature [6]. Although studies describe an association between anti-histone and anti-ssDNA with disease activity [17], only three of our patients were positive for anti-ssDNA and none for anti-histone. Anti-SCl 70 is present in less than 5% of cases, with no relation to progression to systemic disease [3]. Only one of our patients tested positive.

The combination of methotrexate and corticosteroids is the first-line therapy for patients with active disease [18] and was prescribed to 91% of the children included in our study. About 30% of patients require alternative medications, which include other synthetic disease-modifying antirheumatic drugs (DMARDs) and biologicals [19]. In line with these data, 36% of our patients did not respond well to standard therapy and were prescribed mycophenolate mofetil, azathioprine, cyclophosphamide, or tocilizumab.

On average, the disease persists for three to five years, although the linear subtype may take longer to treat [9]. Recurrence is seen in about 25% of patients and occurs up to two and a half years after treatment cessation [20]. Interruption of disease progression without medication was seen in only four patients in our series. All had symptoms for five or more years and had been prescribed immunosuppressants for more than two years. Scores from the LoSCAT (Localized Scleroderma Assessment Tool), an instrument for assessing disease activity and damage, were not included in our study on account of inter-examiner variability and the fact that the tool does not evaluate extracutaneous manifestations or deeper lesions [21].

Morbidity is generally associated with extracutaneous involvement and includes joint contractures, anisomelia, seizures, and visual impairment [5]. Complications were detected in 43% of our cases. The time from symptom onset to diagnosis was five months longer in patients with complications than in individuals without.

The limitations of our study were the small size of the patient population, although this is a rare disease, the absence of a control group, the lack of objective parameters to characterize and quantify extracutaneous manifestations, especially gastrointestinal ones, and not using the LoSCAT.

General pediatricians and dermatologists must be aware of the diagnostic signs of JLS, including persistent skin lesions in any topography, skin thickening associated or not with depigmentation, and loss of skin appendages. General pediatricians must first rule out latent infections (through the tuberculin skin test, chest X-rays, serology tests for hepatitis and human immunodeficiency virus) and then prescribe antiparasitic drugs since patients will likely be prescribed immunosuppression.

The proportion of patients in our population without a diagnosis two years after the onset of symptoms was more significant than the numbers reported in the literature, which tells of the need to disseminate knowledge about the disease in Brazil. This data was reflected in the high rates of chronic cutaneous manifestations at diagnosis and complications related to JLS, mainly musculoskeletal. The first-line therapy was effective and safe in most cases. Although rare, JLS may cause complications and deformities that result in significant functional and cosmetic impairments.

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