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Clinical characteristics of children with scleroderma in a referral hospital

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ABSTRACT

Introduction: Scleroderma is an autoimmune disease that involves the connective tissue characterized by skin fibrosis, classified as localized and systemic (participation of one or more internal organs). The primary objective of this study is to describe and analyze the clinical and laboratory findings in a group of children diagnosed with scleroderma at a referral hospital.

Material and methods: Extraction of data from clinical charts of children with scleroderma in the rheumatology department at the Hospital Infantil de México Federico Gómez, between January 2000 and December 2007.

Results: Sixty-two patients were included in the group. All of them completed the classification criteria for juvenile sclerodema, both systemic and localized. The mean age at diagnosis was 7.8 (1–14) years. The mean time from disease onset to diagnosis, based on clinical manifestations, was 23 months. The lesions found were: linear scleroderma (42%), mixed morphea (22%), circumscribed morphea (19%), generalized morphea (13%), and panclerotic morphea (4%). Involvement associated with systemic scleroderma was gastrointestinal 100% (18 patients), pulmonary 100% (18/18), Raynaud's phenomenon 89% (16/18), proximal sclerosis 89% (16/18), sclerodactilia 67% (12/18), joint pain 28% (5/18), calcinosis 56% (10/18). Positive antinuclear antibodies (ANA) were present in 14/62 (23%) patients (10 with systemic range and 4 localized), antiSCL 70 in 2/62 (4%) cases. The most common drug used was methotrexate.

Conclusion: The most common skin lesions found were linear morphea, followed by the mixed and circumscribed types. In systemic scleroderma the most involved systems are the gastrointestinal, respiratory, and vascular (associated with Raynaud's phenomenon). There is a special need for knowledge of this disease in first contact physicians for a faster and better diagnosis and treatment, in order to avoid complications. It is also necessary to improve resources in developing countries for complimentary studies, classification, treatment, and follow-up.

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Características clínicas de niños con esclerodermia en un hospital de referencia

RESUMEN

Palabras clave:

Esclerodermia sistémica

Esclerodermia localizada

Morfia

Fenómeno de Raynaud

Metotrexato

Introducción: La esclerodermia es una enfermedad del tejido conectivo, autoinmunitaria y caracterizada por fibrosis de la piel; además, puede ser localizada o sistémica (participación de uno o de más órganos internos). El objetivo del presente estudio es describir y analizar las características clínicas y de laboratorio observadas en un grupo de niños con esclerodermia en un hospital de referencia.

Material y métodos: Recopilación de datos de los expedientes clínicos de niños con diagnóstico de esclerodermia del Departamento de Reumatología del Hospital Infantil de México Federico Gómez durante el período comprendido entre los años 2000 y 2007.

Resultados: Se incluyó a 62 pacientes que cumplieron con los criterios de clasificación preliminar para esclerodermia juvenil, localizada y sistémica. La edad media al diagnóstico fue de 7,8 años (1–14). La duración media de la enfermedad al diagnóstico fue de 23 meses. Las lesiones encontradas fueron esclerodermia lineal (42%), morfia mixta (22%), morfia circunscripta (19%), morfia generalizada (13%) y morfia panesclerótica (4%). Los hallazgos asociados a esclerodermia sistémica (ES) fueron afección gastrointestinal en 18 de 18 pacientes (100%), afección pulmonar en 18 de 18 pacientes (100%), fenómeno de Raynaud en 16 de

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18 pacientes (89%), esclerosis proximal en 16 de 18 pacientes (89%), esclerodactilia en 12 de 18 pacientes (67%), calcinosis en 10 de 18 pacientes (56%) y afección articular en 5 de 18 pacientes (28%). Se hallaron anticuerpos antinucleares positivos en 14 de 62 pacientes (23%) (10 con ES y 4 con escleroderma localizada) y anticuerpos anti-Scl70 en 2 de 62 pacientes (4%). El medicamento más utilizado fue metotrexato.

Conclusión: Las lesiones en piel más frecuentes corresponden a morfea lineal seguida de morfea mixta y morfea circunscripta. En la ES los sistemas más frecuentemente afectados son el gastrointestinal, el respiratorio y el vascular (este último relacionado con el fenómeno de Raynaud). Se necesita de un mayor conocimiento de esta enfermedad en medicina de primer contacto para el diagnóstico rápido y tratamiento oportuno. Es importante superar la carencia de recursos en países en desarrollo para estudios auxiliares necesarios, tanto para la clasificación como para el seguimiento.

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Introduction

The first modern publication on scleroderma is generally attributed to the Italian researcher Curzio in 1753. Later, Alibert claimed to be the first to recognize the disease, calling it “*sclermia circumscripta*,” and described 2 cases of what later would be known as linear scleroderma.^{1,2}

Scleroderma can be classified into systemic, localized, and scleroderma-like syndromes. It is an autoimmune disease of unknown etiology characterized by fibrosis.

Systemic scleroderma (SS) affects organs such as the skin, digestive tract, lungs, heart, and kidneys. Recently, a classification criteria committee for systemic juvenile scleroderma, which included members of the European Society of Pediatric Rheumatology, the American College of Rheumatology, and the European League Against Rheumatism, developed new criteria to help normalize the performance of research into this rare pediatric disease.^{3,4}

Localized scleroderma (LS) has commonly been classified into 3 groups: morphea, generalized morphea, and linear scleroderma. In 2004, the European Society of Pediatric Rheumatology proposed new classification criteria for juvenile LS and included 5 subtypes: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and mixed scleroderma (when a combination of 2 or more of the abovementioned subtypes are present).⁵

The onset of scleroderma in children is rare, with less than 5% of cases presenting before 16 years of age, with a mean age at onset of 8.1 years and a peak between 10 and 16 years of age according to worldwide medical literature.^{5–7}

Scleroderma and its different subtypes present variability in its prevalence in different regions of the world, and genetic, racial, and environmental factors seem to be involved. The present study attempts to describe the clinical and laboratory characteristics in a group of 62 pediatric patients with scleroderma in a third level hospital center.

Material and methods

Clinical histories of children with a diagnosis of scleroderma at the Hospital Infantil de México Federico Gómez (third level reference hospital center) between 2000 and 2007 were reviewed. The diagnosis was established based on clinical data, skin biopsy, organ involvement, vascular abnormalities (Raynaud's phenomenon), and the presence of autoantibodies, such as antinuclear antibodies (ANA) anti-Scl70 and anticentromeric antibodies.

The present study used the new preliminary classification criteria for SS. Patients with other autoimmune diseases were excluded.

The following data was collected at the beginning and during follow-up: patient gender, age at onset of disease and at diagnosis, number of visits prior to diagnosis, nutritional status, skin alterations (edema, sclerosis, sclerodactyly, calcinosis, digital lesions, telangiectasias, and skin thickening), cardiovascular alterations (Raynaud's phenomenon, pericarditis, hypertension, heart failure,

arrhythmias, and lung hypertension), respiratory alterations (cough, pleuritis, fibrosis, spasmometric, and plethysmographic alterations), gastrointestinal alterations (dysphagia, diarrhea, constipation, and gastroesophageal reflux disease [GERD]), musculoskeletal alterations (arthritis and muscle affection), renal alterations (proteinuria) and others (weight loss, growth retardation, and convulsions). In addition, the presence of autoantibodies, such as ANA, anti-RNP, anti-Sm, anti-Scl70, and anti-centromere, and treatment received (steroids, immunosuppressants, and vasodilators) was documented.

Results

General characteristics

Sixty-two patients were included, between 2000 and 2007, with a diagnosis of scleroderma; 21 patients (34%) were male and 41 patients (66%) female/male ratio was 2:1. The diagnosis of scleroderma was more frequent in the 5 to 11 years of age group, with 39 patients (63%), with a mean age of 7.8 years (range, 1–14).

Regarding the number of visits prior to hospitalization, it is important to mention that 100% of the patients were seen by a physician prior to their diagnosis, and in 54 cases (87%) 2 or more visits occurred. Regarding non-medical personnel, 5 patients were seen (8%) once, and 13 patients (21%) in 2 or more occasions.

Regarding the clinical progression prior to diagnosis, 60% of patients presented skin lesions without a diagnosis for one or more years and 40% of patients remained without a diagnosis for months. Of these, only 3 patients were diagnosed one month after the lesions appeared. At the moment of diagnosis, the duration of disease, in general, had a mean of 1.9 years (range, 1 month–10 years). SS had a mean of 2.4 years (1 month–10 years) and LS a mean 1.6 years (1 month–16.7 years).

History prior to the disease: of the total number of patients, 11 (18%) had a history prior to the disease, with only 4 revealing infectious respiratory diseases prior to the disease, 3 with a history of malformation, and the remaining 4 patients had previous trauma (Table 1).

Nutritional status: most patients were eutrophic, adding a total of 51 patients (82%). Even then, there were an important number of malnourished patients: eleven patients (18%) in total, of which 6 (10%) were at nutritional risk, 4 (6%) had moderate malnutrition, and 1 (2%) had severe malnutrition and cachexia.

Clinical characteristics

Eighteen cases (29%) with SS and 44 cases (71%) with LS were found. Of the total, in turn, 7 patients (11%) had linear scleroderma of the Parry-Romberg type, 3 patients (4.5%) had coup de sabre variety, and 6 patients had both. (Figures 1 and 2).

The onset of the lesions was progressive in all patients. Among the signs and symptoms associated to patients with SS, fatigue, loss of appetite, pyrosis, epigastric pain, joint pain, cough, livedo reticularis,

telangiectasias, calcinosis Raynaud's phenomenon were the most common. Eleven patients (61%) presented dysphagia, pyrosis, and epigastric pain; only 2 patients presented cough during follow-up; 10 patients (56%) presented calcinosis (Figure 3); 16 patients (89%) presented Raynaud's phenomenon, 14 in the fingers of the hand and 2 on the hands and feet; 5 patients (28%) presented joint pain, only 1 with transitory oligoarthritis, and 11 patients (61%) presented livedo reticularis and telangiectasias. Convulsions were also seen in 3 patients, 2 with linear scleroderma of the coup de sabre variety. In some cases, muscle weakness, edema, and 1 case of renal affection were detected. No cardiac, endocrine or eye alterations were seen (Table 2).

Regarding the types of morphea, 16 patients (26%) had facial LS, 10 patients (16%) presented extrafacial LS, 12 patients (19%) circumscript morphea, 2 patients (4%) pansclerotic morphea, 8 patients (13%) generalized morphea, and 14 patients (22%) mixed morphea.

Study variables

With respect to laboratory studies, the complete blood count showed leukocytopenia in 5 patients (8%), 2 of them with

lymphopenia. Normocytic, normochromic anemia was seen in 10 patients. Regarding the acute phase reactants. Eleven patients (18%) presented elevated erythrosedimentation rate and the C-reactive protein CRP was performed in 12 patients (19%), with 4 of them (6%) having an elevated result.

Urinalysis was performed in all cases, with proteinuria present only in the patient that underwent a biopsy, with the finding of segmental glomerulosclerosis and vascular arteriolar lesions, compatible with scleroderma. Regarding renal function, all of the patients had normal urea and creatinine results. Three patients presented alterations in aminotransferases, with an elevation of these during treatment, meriting therapy adjustment.

Among the immunology tests performed, ANA was seen in 35 patients (56%), with 14 cases positive (10 for SS and 4 for LS); anti-Scl70 in 19 patients (31%), only 2 cases positive (both SS); anticentromere in only 1 case, negative result, and anti-RNP in 13 patients (21%), con all negative.

Other studies included an esophagogastroduodenal series (EGDS), ultrasounds, tomography, spiroometry, and plethysmography. Of the

Table 1
Main demographic characteristics of 62 patients with scleroderma

	All	Systemic scleroderma	Localized scleroderma
Patients	62	18	44
Gender (female/male)	2/1	2.6/1	1.75/1
Male	21	5	16
Female	41	13	28
Age at onset of symptoms, y/mo			
Mean	7/10	7/8	7/11
Median	7/0	7/6	6/6
Range	1–14 y	2–14 y	1–14 y
Duration of disease prior to diagnosis, y/mo			
Mean	1/11	3/2	0/7
Median	1/0	2/0	1/0
Range	1 mo–10 y	1 mo–10 y	1 mo–10 y
Environmental factors	8	2	6



Figure 2. Patient with linear scleroderma of the coup de sabre variety in the right frontoparietal region. Source: patients of the Immune-mediated Diseases Clinic.



Figure 1. Patient with systemic sclerosis and an extensive lesion. Source: patients of the Immune-mediated Diseases Clinic.



Figura 3. Calcinosis on the left elbow in a patient with systemic scleroderma. Source: patients of the Immune-mediated Diseases Clinic.

Table 2
Frequency of signs and symptoms of systemic sclerosis (n=18)

Symptom	Patients, No.	%
Proximal sclerosis	16	89
Sclerodactilia	12	67
Raynaud's phenomenon	16	89
Joint pain	4	22
Arthritis	1	6
Edema	6	33
Calcinosis	10	56
Dysphagia, pyrosis, and epigastric pain	11	61
Muscle weakness	2	11
Cough	2	11
Livedo reticularis	11	61

total of patients, EGDS was done in 56 (90%), with 12 presenting stage 1 GERD, 4 stage 2, and 2 stage 3 GERD. Spirometry was performed in 33 patients (53%), 15 with normal results, 10 with mild restriction, 4 with a mixed pattern, 3 with mild obstruction, and 1 with moderate restriction. Pletysmography was performed in 24 patients (39%), 8 normal, 6 with mild restriction, 5 mild obstruction, and 1 with a mixed pattern.

Twenty-nine patients underwent a biopsy, 27 skin biopsies, 1 renal biopsy, and 1 a rectal hemangioma. The most common skin findings were a lack of annexial tissue, atrophy, lymphocyte infiltrates, and collagen deposits.

Capillaroscopy was performed in only 1 patient with SS, finding dilated vessels.

Treatment

All patients received immunosuppressants, using one or a variety of drugs.

The most commonly used drug was methotrexate in 60 cases (96%) followed by D-penicillamine in 9 cases (14%), steroids in 7 cases (11.5%) and thalidomide, cloroquine, and cyclosporine A in 1 case each.

For the most, methotrexate alone was the treatment of choice from the onset (43 cases). In the rest of the cases, treatments were begun with D-penicillamine, steroids, thalidomide, cloroquine, or cyclosporine A which were associated to methotrexate during the progression of the disease up until its substitution, except in 2 cases who continued D-penicillamine with a favorable progression.

In the case of associated Raynaud's phenomenon, most of the patients received nifedipine (14 cases) without complications and in 2 cases no drug was employed.

Of the 62 patients with scleroderma, 13 (21%) underwent surgery, in 12 patients (19%) for autologous fat lipojunction, and in 1 case for a Nissen's funduplicature due to severe GERD.

Time under treatment was 6 months to 10 years according to the clinic follow up.

As for disease progression, clinical files show improvement in 40 patients (65%), 27 of them with LS, and 13 with SS. Patients discharged due to age (18 years): 8 patients (12.5%) in good health; 2 patients (3%) transferred to other hospitals, 10 patients (16%) abandoned treatment, and 5 patients (8%) are currently without treatment. Of the 62 cases, 3 patients (all with SS) had important general complications, with class 4 functional status.

Discussion

This study represents an important sample of children with scleroderma in Mexico. As with other autoimmune diseases it is more frequent in women, something seen in other studies.^{6,8,9}

It affects schoolchildren and adolescents mostly, with a mean age of 8 and a range that goes from 7 to 11 years of age, coinciding with other studies.^{8,9}

The most commonly encountered subtype was LS (71%) followed by SS (29%), in agreement with previous studies, although a difference of up to 1:10 has been seen between SS and LS; however, we found a difference of up to 1.8:4.4.⁷

At the moment of diagnosis, duration of disease is frequently longstanding, with a mean age of presentation between the first manifestation and the diagnosis of 1.9 years and a range that went from 0 and 10 years of age, without much difference with prior reports, both for SS, with a mean of 2.4 years (range, 0-10) as with LS with a mean of 1.6 years (range, 0-16.7). This finding, which has been informed by other authors, shows that a greater effort must be undertaken to increase awareness of this disease among physicians and health professionals.

The most common skin lesions were linear morphea followed by mixed morphea and circumscribed morphea, coinciding with other reports. The term linear morphea of the coup de sabre variety refers to a linear lesion that is generally found in the frontoparietal or paramedian frontal scalp, simulating the stroke of a sword and which can extend to the face. The Parry-Romberg syndrome or idiopathic hemifacial atrophy, can affect tissue under the forehead, generally with no skin affection.¹⁰ Interestingly, we found 6 cases of both.

In contrast with other studies,^{5,8,11} in SS we found more visceral involvement and Raynaud's phenomenon with a greater frequency, with respiratory and gastrointestinal affection in all of the patients and Raynaud's in 88% of cases.

In general, patients with SS developed progressive atrophy of the skin associated to its thinning and, therefore, had a lower score on the Rodnan test. However, this still needs to be validated in children who tend to have a higher score (even regarding health status), in accordance to the body mass index and the Tanner stage. This point cannot be discussed because it was not performed in any of the patients.

On the other part, Pavlov et al have shown that capillaroscopic changes reflect different stages of disease in patients with systemic sclerosis.¹² Unfortunately, measurements were only performed in 1 patient due to the lack of experienced personnel.

From what we found in the medical literature, the presence of ANA in children, is seen with a frequency of 81% to 97%, less than in adults.^{5,7,8} However, no comparison was performed in this study because, although 56% of cases presented it, as well as anti-Scl70 and anticentromere antibodies, only 19 patients an one child respectively had it documented, due mainly to economic reasons.

In accordance to the latest recommendations, treatment is directed against the predominant manifestation and, as in other studies, the skin was the most commonly affected followed by the presence of Raynaud's phenomenon, using mainly methotrexate and nifedipine for both affections with a good apparent response.^{5,7–11}

The 5-year survival rate in this group was 100%, coinciding with previously described survival rates^{7–9} and seems to be better than in previous decades. However, scleroderma can be a radical disease, with an unpredictable progression that requires early diagnosis and treatment, making it important to follow-up on these patients because all of the patients with SS have different degrees of affection in different organs and, with respect to children with LS, the possibility of it progressing to SS is unknown.

It is concluded that there are no variations in the clinical characteristics of scleroderma in children. However, it is important to emphasize the need for a greater knowledge of this disease by primary care attention for its rapid diagnosis and early treatment. In addition, it is important to overcome the lack of resources in developing countries to obtain adequate auxiliary studies needed for both its classification and follow-up.

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