Prevalence of localized scleroderma in a specialized dermatology center in the State of Ceará, Brazil

Prevalência da esclerodermia localizada em um serviço de referência em dermatologia do Estado do Ceará

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Vale TCB, Barros LCM, Lima MES, Maia MR, Aires MAP. *Prevalence of localized scleroderma in a specialized dermatology center in the State of Ceará, Brazil* / Prevalência da esclerodermia localizada em um serviço de referência em dermatologia do Estado do Ceará. Rev Med (São Paulo). 2020 Nov-Dec;99(6):568-72.

ABSTRACT: *Introduction:* Scleroderma encompasses a broad spectrum of clinical manifestations, being subdivided into localized and systemic forms. The localized form exclusively affects the skin and surrounding tissues and has a partially known physiopathology and epidemiology, with the majority of epidemiological studies focusing on the systemic form and extrapolating its results to the other one. This study aim to clarify the epidemiology of localized scleroderma in the state of Ceará, Brazil, in order to understand its risk factors in the Brazilian population. This is the first Brazilian epidemiological study of localized scleroderma. *Methods:* A quantitative retrospective study was conducted, in which all the records of the medical consultations performed at the Reference Center for Dermatology Dona Libânia (CDERM), Fortaleza, Ceará, Brazil, in 2015 were analysed using the variables: name, gender, date of consultation, medical record number, presumptive or confirmed diagnosis and the patient's frequency in CDERM. *Results:* Of the 19.576 patients analysed, 124 were diagnosed with scleroderma, representing an approximate incidence of 0.62% in the service. Among these patients, 96 (77.42%) were female and 28 (22.58%) were male. The mean age of the patients was 29.7 years. *Discussion:* Prevalence and distribution by sex obeyed the worldwide trends reported in other studies. However, there was a higher prevalence of diagnoses in females in the pediatric age group, which contrasts with data in the literature affirming that differences in gender distribution only begin in early adolescence. This difference may be due to cultural factors, underdiagnosis in the male population or a regional trend in the Brazilian epidemiology of localized scleroderma. *Conclusion:* More extensive and multicentric studies are needed to better understand the disease in our population and, thus, serve as a basis for healthcare in the future.

Keywords: Scleroderma, localized; Epidemiology; Dermatology; Rheumatology.

RESUMO: *Introdução:* A esclerodermia abrange amplo espectro de manifestações clínicas, sendo subdividida em forma localizada e sistêmica. A forma localizada, com acometimento exclusivamente cutâneo e de tecidos circunvizinhos, apresenta fisiopatologia e epidemiologia parcialmente conhecidas pela comunidade científica, com a maioria dos estudos epidemiológicos se concentrando na forma generalizada e extrapolando seus resultados para a outra forma. Este estudo tem o intuito de esclarecer a epidemiologia da esclerodermia localizada no estado do Ceará, visando compreender seus fatores de risco na população brasileira. Trata-se do primeiro estudo epidemiológico brasileiro acerca da esclerodermia localizada. *Metodologia:* Delineou-se um estudo retrospectivo quantitativo, no qual foram analisados todos os registros das consultas médicas realizadas no Centro de Referência em Dermatologia Dona Libânia (CDERM), Fortaleza, Ceará, em 2015, através das variáveis: nome, sexo, idade, data da consulta, número do prontuário, diagnóstico presuntivo ou confirmado e a frequência do paciente no CDERM. *Resultados:* Dos 19.576 pacientes analisados, 124 pacientes foram diagnosticados com esclerodermia localizada, representando uma incidência aproximada de 0,62% no serviço. Dentre estes pacientes, 96 (77,42%) eram do sexo feminino e 28 (22,58%) do sexo masculino. A idade média dos pacientes foi de 29,7 anos. *Discussão:* A prevalência e distribuição por sexo obedeceram às tendências mundiais relatadas em outros trabalhos. Entretanto, constatou-se elevada prevalência de diagnóstico no sexo feminino na faixa etária pediátrica, o que contrasta com dados na literatura que afirmam que as diferenças na distribuição de gênero começam a existir no início da adolescência. Esta diferença pode dever-se à fatores culturais, subdiagnóstico na população masculina ou uma tendência regional na epidemiologia da esclerodermia localizada. *Conclusão:* Este estudo corresponde ao primeiro estudo epidemiológico brasileiro acerca da esclerodermia localizada, sendo necessários estudos mais amplos e multicêntricos que permitam entender melhor a doença na nossa população e, assim, possam servir de base para futuras ações assistenciais

Palavras-chave: Esclerodermia localizada; Epidemiologia; Dermatologia; Reumatologia.

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INTRODUCTION

Scleroderma is a rare multisystemic disease, with morphological and functional impairment of small blood vessels, fibrosis of the skin and internal organs, activation of the immune system, and autoimmunity¹. The term scleroderma comprises various clinical entities, encompassing both localized and systemic forms. The localized form, also known as morphea, is restricted to skin and subcutaneous involvement, and may extend to bones and adjacent neurological structures. The systemic form is subdivided into limited and diffuse, and is characterized by involvement of internal organs, notably gastrointestinal tract, lung, and kidneys, in addition to skin involvement². Due to the scope of the term, the literature on scleroderma encounters difficulties in relation to the standardization of its terminology, notably in the term generalized scleroderma. In this article, generalized scleroderma refers to a variant of localized scleroderma.

Localized scleroderma has a wide spectrum of manifestations, ranging from small plaques to large aesthetic and functional deformities. Among the variants, the following can be mentioned: circumscribed, linear, generalized, pansclerotic, and mixed form³. The initial lesion is characterized by erythema, progressing to a yellow-white plaque limited by blue-violet erythema. As skin infiltration occurs, atrophy of hair follicles and hyper- or hypopigmentation are observed⁴.

The circumscribed variant, also called plaque scleroderma, preferentially affects the trunk and manifests itself as indurated, infiltrated, circumscribed plaques, with undefined borders, with a violet ring and absence of hair, as well as anhidrosis. In the linear subtype, there are linear bands of sclerosis that can advance to subcutaneous, muscle, and bone tissue, generating deformities. The generalized variant has four or more confluent sclerotic plaques larger than 3 cm. It differs from systemic forms in that it does not present Raynaud's phenomenon or capillaroscopic changes. The pansclerotic subtype leads to generalized and full-thickness skin involvement. The mixed form has manifestations of two or more of the variants described⁶.

The etiology and pathogenesis of localized scleroderma are still unknown, probably involving exposure to environmental factors in genetically predisposed individuals. No specific genetic changes were found in this form of scleroderma, although associations with other autoimmune diseases have been described^{5,6}. In contrast, different gene loci have already been associated with systemic scleroderma, including changes in the HLA, IRF5, CD247, BANK1, STAT4, TNFSF4, and BLK6 genes. Multiple environmental factors seem to be involved, such as radiation exposure, trauma, medications, Lyme disease, and viral infections⁵. Despite having similar pathophysiological aspects, localized scleroderma differs significantly from its systemic form, with only nine cases described in the

literature of patients with localized scleroderma that progressed to systemic sclerosis⁷.

Few studies have been conducted on the epidemiology of localized scleroderma, with a prevalence ranging from 0.4 to 2.7 per 100,000 people^{2,8,9}. The female sex is predominantly affected, and the peak incidence according to age depends on the clinical variant. In plaque scleroderma, the most common form, the mean age of presentation is in the fourth decade of life, while the linear and pansclerotic variants predominate in the pediatric age group¹⁰. The generalized variant, in turn, is typical of adults⁴.

Brazilian epidemiological data on localized scleroderma are scarce and most of them are restricted to systemic forms, making a detailed analysis of the risk factors related to the localized form in Brazil difficult. In our research, we did not find any epidemiological study carried out in Brazil regarding localized scleroderma. Thus, the relevance of an epidemiological study focusing on this form of scleroderma is justified, to clarify aspects related to the prevalence, risk factors, and pathogenesis of localized scleroderma.

METHODS

We carried out a retrospective quantitative study, in which all records of medical consultations held at Dona Libânia Dermatology Center (CDERM), Fortaleza, Ceará, from January to December 2015, were analyzed.

The handwritten records provided the following variables: name, sex, age, date of consultation, medical record number, presumptive or confirmed diagnosis, and patient's frequency at CDERM (first or follow-up consultation). Based on the variable name, 19,593 patients were treated in the stipulated period, excluding patients treated by non-medical health professionals. Of these, 17 patients whose identification was impaired by poor quality handwritten records were excluded. The number of follow-up consultations at CDERM was counted.

Of these 19,576 records, those whose diagnosis was localized scleroderma were selected, in order to know its incidence in this service and to analyze its variables in search of causal relationships. Patients with systemic forms of scleroderma were excluded.

Due to technical-operational limitations regarding patients with few consultations at the CDERM at the time of the research, with handwritten medical records available only to patients with multiple follow-up consultations, data related to the therapy used in the treatment of the selected patients were not available for most of the patients analyzed, as well as data related to the localized scleroderma subtype.

Data were collected from October 2016 to June 2017. The variables were entered into a Microsoft Office Excel ® spreadsheet, where they were subjected to

statistical analysis of absolute and relative frequencies.

With regard to the Introduction and Discussion, MedLine® and Google Scholar® databases were searched using the search terms “localized scleroderma”, “morphea”, “epidemiology”, and “Brazil”. Search terms and related articles were searched in English and Portuguese. Articles on systemic scleroderma were excluded. Thirteen articles published between 1993 and 2019 were selected. No articles were found on the epidemiology of localized scleroderma in Brazil in both databases.

The research project was sent to and approved by the CDERM Ethics Committee, according to the ethical

dictates of respect for patient confidentiality and autonomy. There is no conflict of interest in this work.

RESULTS

Of the 19,576 patients analyzed, 124 patients were diagnosed with localized scleroderma, representing an approximate incidence of 0.62% at the service. Of these patients, 96 (77.42%) were female and 28 (22.58%) were male. The mean age of the patients was 29.7 years. The detailed age is shown in Table 1.

Table 1. Age and sex of patients with localized scleroderma

Age	Absolute number	%	Male	Female
0-10	14	11.29%	2	12
11-20	33	26.61%	11	22
21-30	24	19.36%	5	19
31-40	22	17.74%	4	18
41-50	13	10.48%	3	10
51-60	11	8.87%	2	9
61-70	4	3.23%	0	4
>70	3	2.42%	1	2

The recurrence to the service varied, as can be seen in Table 2. A total of 299 consultations were carried out over the year with these patients. Most patients (62.1%) reconsulted at least once during the year. Of the 124 patients, 22 (17.74%) had another dermatological condition besides localized scleroderma. Among other dermatological comorbidities, we can highlight vitiligo (present in 6 of the patients), leprosy (present in 2 of the patients), and acne (present in 2 of the patients).

Table 2. Recurrence of consultations

Number of Consultations	Patients	%
1	47	37.90%
2	28	22.58%
3	23	18.55%
4	12	9.68%
5	7	5.64%
6	5	4.03%
7	2	1.61%

Regarding the clinical subtypes, two patients were classified as having scleroderma en coup de sabre, one patient as having generalized scleroderma and the others as having localized scleroderma.

DISCUSSION

Localized scleroderma is a rare disease, with previous studies showing a prevalence between 0.4 and 2.7 per 100,000 inhabitants². Based on data from the Brazilian Institute of Geography and Statistics (IBGE) regarding the population of Ceará in 2015, and assuming that a considerable majority of patients with localized scleroderma, or even approximately 100%, were referred to the center studied, as it is the most important dermatology center in Ceará, an estimated prevalence of 1.39 per 100,000 inhabitants was found in our population, in accordance with that described in the literature of other countries. This prevalence may be underestimated, considering the possible underdiagnosis of this condition - the mean time between the onset of symptoms and the diagnosis of juvenile localized scleroderma, for example, is 11 to 13 months¹¹. A study carried out with 750 children with localized scleroderma revealed that in about 20% there was a delay of more than 2 years to reach the diagnosis⁸, in addition to a minority of patients referred to smaller dermatology services.

The sex prevalence was also consistent with that found by other studies: the literature shows a female prevalence of 2.4 to 4.2: 1^{2,6}. Our study showed a ratio of 3.4: 1, with women being the most affected sex in all age groups (Table 1). Interestingly, the age group

that showed the highest female prevalence was that of patients under the age of 10, with a ratio of 6: 1, being inconsistent with the data in the literature that female prevalence is more significant after 10 years of age⁸. As there are no comparative data in Ceará or in Brazil, it is not possible to determine whether this would be a regional trend or be correlated with other factors, such as a greater underdiagnosis of males in this age group due to a lower diagnostic suspicion, for example.

Regarding the age group of the population studied, our study showed a prevalence of the adult population in relation to the pediatric population of approximately 1:6. Previous studies have shown a similar prevalence between the two populations². The study with the longest follow-up carried out to date, which evaluated the incidence of localized scleroderma over a 33-year period in Olmsted County, Minnesota, United States, considering all age groups, demonstrated that the incidence increased significantly after 33 years of age in the 82 patients analyzed between 1960 and 1993¹². Our study showed a mean age of 29.7 years. However, since this is a study of prevalence, not incidence, it is possible to hypothesize that the mean age of the initial diagnosis would be even lower, possibly demonstrating an earlier age of onset of the disease in the population studied in relation to the literature. An earlier age of onset of symptoms may have an implication in the prognosis: adult patients who started having symptoms earlier, in pediatric age, when they have active disease, tend to have less severe activity compared to those who started having symptoms later on¹³.

Association of localized scleroderma with other autoimmune diseases is already described in the literature. Concomitance with vitiligo has already been reported, but in most publications, in isolated cases. A study carried out with 245 patients with localized scleroderma showed that approximately 1.2% of them had vitiligo concomitantly⁶. In our study, the association was about 4 times greater, with 4.8% of patients having vitiligo. There was also a female predominance of 2:1. Association with Sjögren's syndrome, also described in the literature, was found in one patient. Associations with other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and multiple sclerosis are also well established in the literature⁶. However, they were not identified among the patients analyzed in this study.

CONCLUSIONS

Localized scleroderma is a rare disease whose pathogenesis is not yet completely clarified. There is a lack of studies on localized scleroderma in the Brazilian literature, thus making it more difficult to understand its prevalence, risk factors, and associations with other diseases. This is the first Brazilian epidemiological study on localized scleroderma, and there is a need for broader and multicenter studies that allow a better understanding of the disease in the Brazilian population and, thus, can serve as a basis for future care actions.

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Received: 2019, July 07

Accepted: 2020, December 15