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Familial autoimmunity and polyautoimmunity in 60 Brazilian Midwest patients with systemic sclerosis

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology, characterized by a triad of vascular injury, autoimmunity and tissue fibrosis. It is known that a positive family history is the greatest risk factor already identified for the development of SSc in a given individual. Preliminary observation of a high prevalence of polyautoimmunity and of familial autoimmunity in SSc patients support the idea that different autoimmune phenotypes may share common susceptibility variants.
Objectives: To describe the frequency of familial autoimmunity and polyautoimmunity in 60 SSc patients in the Midwest region of Brazil, as well as to report the main autoimmune diseases observed in this association of comorbidities.
Methods: A cross-sectional study with recruitment of 60 consecutive patients selected at the Rheumatology Department, University Hospital, Medicine School, Federal University of Mato Grosso do Sul (FMUFMS), as well as interviews of their relatives during the period from February 2013 to March 2014.
Results: A frequency of 43.3% of polyautoimmunity and of 51.7% of familial autoimmunity in SSc patients was found. Patients with the presence of polyautoimmunity and familial autoimmunity presented primarily the diffuse form of SSc, but this indicator did not reach statistical significance. The autoimmune diseases most frequently observed in polyautoimmunity patients were: Hashimoto's thyroiditis (53.8%), Sjögren's syndrome (38.5%), and inflammatory myopathy (11.5%). The main autoimmune diseases observed in SSc patients' relatives were: Hashimoto's thyroiditis (32.3%), rheumatoid arthritis (22.6%), and SLE (22.6%). The presence of more than one autoimmune disease in SSc patients did not correlate with disease severity or activity.

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Conclusions: From the high prevalence of coexisting autoimmune diseases found in SSc patients, we stress the importance of the concept of shared autoimmunity, in order to promote a continued vigilance and promptly diagnose other possible autoimmune disease in patients, or in their kin.

Autoimunidade familial e poliautoimunidade em 60 pacientes portadores de esclerose sistêmica da região Centro-Oeste do Brasil

Palavras-chave:
Autoanticorpos
Esclerose sistêmica
Doença autoimune
Poliautoimunidade
Autoimunidade familiar

RESUMO

Introdução: A esclerose sistêmica (ES) é uma enfermidade do tecido conjuntivo de etiologia desconhecida, caracterizada pela tríade de injúria vascular, autoimunidade e fibrose tecidual. Sabe-se que uma história familiar positiva representa o maior fator de risco já identificado para o desenvolvimento da ES em um determinado indivíduo. Observação prévia de alta prevalência de poliautoimunidade e de autoimunidade familiar em pacientes com ES, reforça a ideia de que fenótipos autoimunes distintos podem dividir variantes comuns de susceptibilidade.

Objetivos: Descrever a frequência de autoimunidade familiar e de poliautoimunidade em 60 pacientes com ES da região Centro Oeste do Brasil, bem como relatar as principais doenças autoimunes observadas nesta associação de comorbidades.

Métodos: Realizou-se um estudo transversal com recrutamento de 60 pacientes consecutivos, selecionados no Serviço de Reumatologia do Hospital Universitário da Faculdade de Medicina da Universidade Federal de Mato Grosso do Sul (FMUFMS), bem como entrevista de seus parentes, durante o período de fevereiro de 2013 a março de 2014.

Resultados: Foi encontrada uma frequência de 43,3% de poliautoimunidade e de 51,7% de autoimunidade familiar nos pacientes com ES. Os pacientes com presença de poliautoimunidade e de autoimunidade familiar eram principalmente da forma difusa de ES, porém este índice não atingiu significância estatística. As doenças autoimunes mais comumente observadas nos pacientes com poliautoimunidade foram: tireoidite de Hashimoto (53,8%), síndrome de Sjögren (38,5%) e miopatia inflamatória (11,5%). As principais doenças autoimunes observadas nos parentes dos pacientes com ES foram: tireoidite de Hashimoto (32,3%), artrite reumatóide (22,6%) e LES (22,6%). A presença de mais de uma enfermidade autoimune em pacientes com ES não se correlacionou com maior gravidade ou atividade da doença.

Conclusões: A partir da alta prevalência encontrada de doenças autoimunes coexistentes em pacientes com ES, salientamos a importância do conceito de autoimunidade compartilhada, de forma a promover uma vigilância constante e diagnosticar prontamente uma possível outra doença autoimune nos pacientes ou em seus familiares.

Introduction

Systemic sclerosis (SSc) is a disease of the connective tissue with an autoimmune character, and with extreme heterogeneity in its clinical presentation, with involvement of multiple systems and following a varied and unpredictable course.[1] Its etiology remains unknown, and a multifactorial cause is suggested; possibly SSc is triggered by environmental factors in a genetically predisposed individual.[2]

The hallmark of SSc is the occurrence of microvasculopathy, fibroblast activation and an excessive production of collagen.[3] This is a unique condition, because it displays features of three distinct pathophysiological processes, the so-called triad of vascular injury, autoimmunity (cellular and humoral), and tissue fibrosis, leading to cutaneous involvement, besides affecting multiple internal organs, for instance, lungs, heart and gastrointestinal tract, as well as musculoskeletal manifestations.[3,4]

The genetic component of autoimmune diseases is represented by the increased risk of developing SSc in twin brothers of affected individuals.[3,4] Basically, SSc is not a genetic disorder, but there is consensus that, actually, the disease has a genetic component based on reports of monozygotic twins with a propensity to SSc.[5]

In 1953, Rees and Bennett[6] described the first case of localized scleroderma in a father and his daughter. Later, several reports of familial scleroderma in different populations and family relationships were published.[2,5,7] Moreover, an association between HLA and SSc has been described.[5,8,9]

A positive family history is the greatest risk factor ever identified for the development of SSc in a given individual.[8,10]

However, the low frequency of concordance rate of autoimmune diseases among siblings *versus* monozygotic twins favors the presence of multiple genes contributing to a genetic predisposition, including SSc.[11]

Hudson et al. used the term "autoimmunity kaleidoscope" in reference to SSc patients to describe the fact that more than one different autoimmune disease may coexist in a single patient (polyautoimmunity) or in the same household (familial autoimmunity).[12] The high prevalence of polyautoimmunity (38%) as well as of familial autoimmunity (36%) in SSc patients reinforces the idea that clinically distinct autoimmune phenotypes may share common susceptibility variants.[12]

Objectives

In this study, we aim to describe the frequency of familial autoimmunity and polyautoimmunity in 60 SSc patients living in the Midwest region of Brazil, to report the main autoimmune diseases observed in this association of comorbidities, and also to evaluate if the presence of more than one autoimmune disease in SSc patients is associated with an increase of disease activity or severity.

Methods

This is an observational, cross-sectional study.

Sixty consecutive patients were seen and selected at the Rheumatology Department, University Hospital, Medicine School, Federal University of Mato Grosso do Sul (FMUFMS) during the period from February 2013 to March 2014.

To participate in this study, the patients should meet the following criteria:

- Comply with the new 2013 classification criteria for SSc[13];
- In the absence of skin thickening, the patients should comply with LeRoy and Medsger[14] criteria for early-onset SSc.
- All patients who had other associated infectious diseases or malignancies were excluded.

The study was approved by the Ethics Committee on Research of the Federal University of Mato Grosso do Sul (opinion CAAE: 31442614.3.0000.0021).

Polyautoimmunity was defined as the occurrence of any other autoimmune disease observed in patients with systemic sclerosis. Familial autoimmunity was defined as the occurrence of any other autoimmune disease affecting ancestors (grandparents, mother, father by blood) or blood descendant relatives (daughters, sons, granddaughters, grandsons) relatives, or second- (sisters, brothers) or third- (aunts, uncles, nieces and nephews) degree collateral SSc patients' relatives.

To confirm the illnesses associated with SSc patients or with their families, the following criteria were used:

- For systemic lupus erythematosus (SLE): compliance with the new SLE classification criteria (2012 of the Systemic Lupus International Collaborating Clinics (SLICC) for lupus derivation and validation.[15]
- Sjögren's syndrome (SS): the diagnosis was based on the American College of Rheumatology (ACR) criteria of 2012.[16]
- Rheumatoid arthritis (RA): RA classification criteria of ACR/EULAR 2010.[17]
- Psoriasis: diagnosis based on clinical criteria[18] and, when necessary, on a histopathological study.
- Pemphigus: clinical criteria were used[18] through cytological analysis, histopathological study and/or immunological tests for detection of antiepithelial antibodies.
- Vitiligo: clinical criteria were used:[18] history and physical examination, as well as Wood lamp technique.
- Spondyloarthritis: new classification criteria (2011) for axial and peripheral espondiloartritrites by ASAS (Assessment on Spondyloarthritis International Society) group were used.[19]
- Crohn's disease: criteria from the American College of Gastroenterology's Practice Parameter Committee 2001.[20]
- Antiphospholipid syndrome: criteria from the international consensus (2006) for updating antiphospholipid syndrome classification and definition.[21]
- Hashimoto's thyroiditis: the diagnosis was based on the presence of anti-thyroid peroxidase and/or anti-thyroglobulin antibodies in association with thyroid parenchyma ultrasonographic changes compatible with thyroiditis.[22]
- Diabetes mellitus type 1: criteria of the American Diabetes Association, based on glycated hemoglobin, fasting glucose, oral glucose tolerance test and classic symptoms of hyperglycemia, revised in 2010.[23]
- Mixed connective tissue disease (MCTD): criteria of Alarcon-Segovia, 1989.[24]
- Inflammatory myopathy: Bohan and Peter criteria, 1975.[25]
- Localized scleroderma: the diagnosis was based mainly on visual examination, taking into account the characteristics commonly observed in skin lesions, plus a skin biopsy consistent with increased collagen deposits.[18]

We obtained the information necessary for a sociodemographic and clinical characterization of the disease through an analysis of the medical records of each patient, with completion by patient interviews. At the first visit, demographic and clinical data were collected, including disease duration, year of diagnosis, Rodnan skin score (modified),[26] autoantibody tests, a full clinical examination, and current treatment. Subsequently, all patients were evaluated and interviewed with respect to all family members, in order to confirm the occurrence of other autoimmune diseases.

At the initial evaluation of the patient, we collected specific data on Medsger severity criteria,[27] Valentini criteria for disease activity[28] and Scleroderma Health Assessment Questionnaire (sHAQ).[29]

In our study, we used sera from patients previously selected. The samples were properly frozen to −50 °C and stored in the laboratory at the University Hospital of UFMS.

a. Antinuclear antibodies (ANA) – an indirect immunofluorescence technique was used for ANA test, and HEp2 cells were used as substrate (Faar technique). The II Brazilian Consensus on Antinuclear Factor in Hep-2 cells (2003) criteria[30] were used in the interpretation of our findings.

Sera were considered positive with a title ≥160 and diluted to obtain fluorescence negativity.
Sera were considered positive with a title ≥160 and diluted until a negative result of fluorescence has been obtained.

b. Anti-Sm, anti-RNP, anti-Jo1, anti-Ro (SSA) and anti-La (SSB) test – enzyme-linked immunosorbent assay (ELISA) technique was used, as previously described by McClain;[31] specific kits were used as substrate for each test, according to the manufacturer's specifications (Hemagen Diagnostics, Inc.). We considered a positive result for the sample when the value found was ≥3-fold greater than the cutoff point.
c. Rheumatoid Factor test – nephelometry technique was used; the sample was considered positive with a title >40 IU/ml.
d. Anti-thyroglobulin and anti-thyroid peroxidase tests – a chemiluminescent microparticle immunoassay technique was used according to the manufacturer's instructions (Abbott ARCHITECT anti-Tg and anti-TPO, chemiluminescent microparticle immunoassay for quantitative determination of autoantibodies of IgG class anti-thyroglobulin and thyroid peroxidase in human serum and plasma). For anti-thyroglobulin, the test was considered as non-reactive if <40.0 IU/ml, and as reactive if >40.0 IU/ml. For anti-thyroid peroxidase, the test was considered as non-reactive if <35.0 IU/ml, and as reactive if >35.0 IU/ml.
e. Anticentromere test – indirect immunofluorescence technique, with HEp2 cells as substrate, according to the II Brazilian Consensus on Antinuclear Factor in Hep-2 cells (2003) criteria[30] for interpretation of results.
f. Anti-DNA topoisomerase 1 (anti-Scl70) test – an enzymatic immunoassay technique[32] was used with the specific kit QUANTA Lite TM Scl-70 from INOVA Laboratory (INOVA Diagnostics, Inc., San Diego, CA, USA), according to the manufacturer's specifications. The test was considered as non-reactive if <20 units; weakly reactive if between 20 and 39 units; moderately reactive if between 40 and 80 units; and highly reactive (high values) if >80 units.
g. Anti-RNA polymerase III antibody – ELISA was used as previously described[33] with the specific kit QUANTA Lite RNA Pol III ELISA INOVA Laboratory (INOVA Diagnostics, Inc., San Diego, CA, USA), according to the manufacturer's specifications. The test was considered as non-reactive if <20 units; weakly reactive if between 20 and 39 units; moderately reactive if between 40 and 80 units; and highly reactive (high values) if >80 units.

Statistical analysis

The comparison between patients with and without polyautoimmunity and familial autoimmunity, with respect to the quantitative variables evaluated in this study, was carried out using Student's *t* test. The chi-squared test was used to assess the association between the presence or absence of polyautoimmunity and familial autoimmunity with the qualitative variables measured in this study. The results of the other variables assessed in this study were presented in the form of descriptive statistics, or in tables and graphs. Statistical analysis was performed using the software SPSS, version 20.0, and a 5% significance level was considered.

Results

Table 1 shows, in descending order, the diseases observed among polyautoimmunity patients, and among patients' relatives in whom familial autoimmunity was diagnosed. The most frequent illnesses among patients with polyautoimmunity were Hashimoto's thyroiditis (*n* = 14–53.8%), Sjögren's disease (*n* = 10–35.8%) and inflammatory myopathy (*n* = 3–11.5%). On the other hand, the most frequent autoimmune diseases observed in SSc patients' relatives were Hashimoto's thyroiditis (*n* = 10–32.3%), rheumatoid arthritis (*n* = 7–22.6%) and SLE (*n* = 7–22.6%).

Table 2 shows the number of concomitant autoimmune diseases in SSc patients. The vast majority (*n* = 19–73.08%) of patients had only one autoimmune disease associated with SSc. Among patients with two other autoimmune diseases concomitantly with SSc (*n* = 6–23.08%), one of these was always Hashimoto's thyroiditis, and the other autoimmune diseases were: 3 patients also with Sjögren's syndrome, one patient with polymyositis, 1 patient with psoriasis, and 1 patient with type 1diabetes. Only one (3.84%) patient (a woman) had more than three concomitant diseases (SSc, Sjögren's syndrome, Hashimoto's thyroiditis, and polymyositis).

The results regarding epidemiological data and monitoring index in patients with and without polyautoimmunity are shown in Table 3, while the results regarding epidemiological data and monitoring index in patients with and without familial autoimmunity are presented in Table 4.

The time elapsed after the diagnosis of the disease among polyautoimmunity patients (11.27 ± 1.27 years) was

Table 1 – Diseases most frequently observed among polyautoimmunity patients and among SSc patients' relatives and familial autoimmunity.

Variable	*n* (%)
Polyautoimmunity (*n* = 26)	
Hashimoto's thyroiditis	14 (53.8)
Sjögren's syndrome	10 (38.5)
Inflammatory myopathy	3 (11.5)
Type 1 Diabetes mellitus	3 (11.5)
APS	2 (7.7)
Rheumatoid arthritis	1 (3.8)
Crohn disease	1 (3.8)
Psoriasis	1 (3.8)
Familial autoimmunity (*n* = 31)	
Hashimoto's thyroiditis	10 (32.3)
Rheumatoid arthritis	7 (22.6)
SLE	7 (22.6)
Systemic sclerosis	5 (16.1)
Type 1 Diabetes mellitus	3 (9.7)
Scleroderma	2 (6.5)
Sjögren's syndrome	2 (6.5)
Vitiligo	2 (6.5)
Crohn's disease	1 (3.2)
MCTD	1 (3.2)
Pemphygus	1 (3.2)
Spondyloarthritis	1 (3.2)

MCTD, mixed connective tissue disease.
The results are presented in absolute frequency (relative frequency).

Table 2 – Number of concurrent autoimmune diseases in patients with a diagnosis of systemic sclerosis (*n* = 26).

Number of other concurrent diseases	*n* (%)
1	19 (73.08)
2	6 (23.08)
≥3	1 (3.84)

The results are presented in absolute frequency (relative frequency).

significantly greater than this time for patients without polyautoimmunity. On the other hand, we found no other significant difference between patients with and without polyautoimmunity, with respect to other quantitative and qualitative variables.

No significant difference between patients with and without familial autoimmunity was observed in relation to quantitative or qualitative variables.

Tables 5 and 6 present, respectively, distributions of patients with or without polyautoimmunity and with or without familial autoimmunity in relation to results of laboratory tests. It was observed that the percentage of polyautoimmunity patients positive for anti-Ro antibody (*n* = 6–23.1%) was significantly higher than that of those patients without polyautoimmunity (*n* = 1–2.9%; *p* = 0.016). No other statistical significance was found between the presence or absence of polyautoimmunity and familial autoimmunity.

In this study, the percentage of polyautoimmunity patients with a positive anticentromere antibody (*n* = 9–29.0%) was significantly lower *versus* patients without polyautoimmunity (*n* = 16–55.2%; *p* = 0.040). However, no association was found between the presence or absence of familial autoimmunity and the result for other autoantibodies.

Discussion

The coexistence of several autoimmune diseases in SSc patients (polyautoimmunity) is well established.[12,34–38] The aggregation of various autoimmune diseases in families of SSc patients is being also increasingly recognized.[12,36,37,39]

Many genetic factors that confer susceptibility to SSc were recently identified and are primarily related to genes coding for proteins responsible for transduction of signals that comprise autoimmunity pathways common to many diseases.[12,39–41] In this group, polymorphisms related to innate immunity pathways (IRF5), activation and differentiation of T lymphocytes (*STAT4*, *PTPN22*) and autoimmune intracellular signaling pathways (*BANK1*, *BLK*, *TNFAIP3*) are included.[12,39,40]

The fact that most of these susceptibility factors have been identified in other autoimmune diseases support the existence of genetic overlapping between SSc and other

Table 3 – Epidemiological data and monitoring index in patients with or without polyautoimmunity.

Variable	Polyautoimmunity		*p*-Value
	Yes (*n* = 26)	No (*n* = 34)	
Epidemiological data			
Age	52.50 ± 2.12	50.18 ± 2.24	0.466
Gender			
Male	0 (0.0)	1 (2.9)	0.378
Female	26 (100.0)	33 (97.1)	
Race			
Caucasian	14 (53.8)	16 (47.1)	0.295
Brown	12 (46.2)	15 (44.1)	
Afro-descendent	0 (0.0)	3 (8.8)	
Diagnosis time			
<5 years	6 (23.1)	10 (29.4)	0.053
5–10 years	9 (34.6)	19 (55.9)	
>10 years	11 (42.3)	5 (14.7)	
Pre-diagnosis FRy time	3.19 ± 1.20	4.12 ± 1.27	0.608
Disease time after diagnosis	11.27 ± 1.27	7.76 ± 0.93	0.026[a]
Clinical form			
Limited	9 (34.6)	17 (50.0)	0.634
Diffuse	10 (38.5)	10 (29.4)	
Recent onset	3 (11.5)	4 (11.8)	
Overlap	4 (15.4)	3 (8.8)	
Monitoring indexes			
sHAQ	0.68 ± 0.08	0.60 ± 0.07	0.492
Severity scale	5.31 ± 0.60	4.53 ± 0.47	0.307
Activity scale	2.31 ± 0.30	2.37 ± 0.22	0.868
Skin score	13.92 ± 1.39	12.44 ± 1.54	0.491

The results are presented as mean ± mean standard error, or as absolute frequency (relative frequency).

[a] *p*-Value in Student's *t* test or chi-squared test.

Table 4 – Epidemiological data and monitoring index in patients with or without familial autoimmunity.

Variable	Familial autoimmunity		*p*-Value
	Yes (*n* = 31)	No (*n* = 29)	
Epidemiological data			
Age	54.00 ± 2.02	48.17 ± 2.31	0.062[a]
Gender			
Male	1 (3.2)	0 (0.0)	0.329
Female	30 (96.8)	29 (100.0)	
Race			
Caucasian	15 (48.4)	15 (51.7)	0.741
Brown	15 (48.4)	12 (41.4)	
Afro-descendent	1 (3.2)	2 (6.9)	
Diagnosis time			
<5 years	9 (29.0)	7 (24.1)	0.912
5–10 years	14 (45.2)	14 (48.3)	
>10 years	8 (25.8)	8 (27.6)	
Pre-diagnosis FRy time	3.42 ± 0.99	4.03 ± 1.51	0.731
Disease time after diagnosis	9.16 ± 1.22	9.41 ± 1.00	0.874
Clinical form			
Limited	12 (38.7)	14 (48.3)	0.193
Diffuse	14 (45.2)	6 (20.7)	
Recent onset	3 (9.7)	4 (13.8)	
Overlap	2 (6.5)	5 (17.2)	
Monitoring indexes			
sHAQ	0.62 ± 0.07	0.66 ± 0.08	0.682
Severity scale	5.26 ± 0.54	4.45 ± 0.51	0.284
Activity scale	2.60 ± 0.27	2.07 ± 0.21	0.136
Skin score	14.06 ± 1.59	12.03 ± 1.37	0.341

The results are presented as mean ± mean standard error, or as absolute frequency (relative frequency).

[a] *p*-Value in Student's *t* test or chi-squared test.

autoimmune diseases, as well as the concept of shared autoimmunity.[39,40]

A shared autoimmunity seems to be a critical component of the genetic basis of autoimmune diseases.[39,42,43] Polymorphisms in major histocompatibility complex (HLA) have also been linked to numerous autoimmune diseases such as RA, spondyloarthritis, and SLE,[39,40,43] being of particular interest the high frequency of HLA-DQA1*0501 in men with SSc.[40]

At first, it was believed that scleroderma or systemic sclerosis familial grouping was an uncommon event.[44] However, subsequently it was demonstrated 1.6% of recurrence of systemic sclerosis in families of SSc patients *versus* an estimated risk of only 0.026% in the general population.[45] Currently, it is suggested that a positive family history is the greatest risk factor ever identified for development of SSc in a given individual.[8,12,40]

Likewise, it is well known the high incidence of overlap syndromes in SSc patients, represented by an association with inflammatory myopathies, Sjögren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus in these patients.[38,43,46–48]

This study confirms the high frequency of polyautoimmunity (43.3%) and familial autoimmunity (51.7%) in SSc patients living in the Brazilian Midwest region. Caramaschi et al.[35] found, among 118 SSc patients, 32.2% with one or two concomitant autoimmune diseases, with a total of 42 different diagnoses. In a larger sample, a study of 719 patients from Canada and Colombia, its authors found 38% of polyautoimmunity and 36% of autoimmunity in SSc patients,[12] but only first-degree relatives of these patients were evaluated, which could explain the divergence between the Canadian/Colombian study and ours.

A more recent study found, among 121 of 373 (32.4%) families of SSC patients, at least one autoimmune disease in one or more first-degree relatives.[39] It is likely that the percentage of familial autoimmunity, much higher on our population compared to other studies, is due to the fact that we decided to extend our search also for ancestors, descendants and collaterals to the third degree of kinship.

In our study, the main autoimmune diseases associated with SSc patients were in agreement with the literature, being mainly represented by autoimmune thyroiditis, Sjögren's syndrome, and inflammatory myopathies.[12,35,38,46–48] However, we found a lower prevalence of rheumatoid arthritis in our patients, compared to other studies. Probably this occurred because we have adopted a stricter criterion for the diagnosis of an actual overlap with rheumatoid arthritis with the use of ACR/EULAR[17] classification criteria for RA, plus the compulsory presence of anti-cyclic citrullinated peptide antibody (anti-CCP) and/or of typical radiological manifestations of the disease.

As to familial autoimmunity, our data were consistent with those published in the literature, represented by the observation of autoimmune thyroiditis, RA, and SLE in SSc patients'

Table 5 – Autoantibodies in patients with or without polyautoimmunity.

Variable	Polyautoimmunity		*p*-Value
	Yes (*n* = 26)	No (*n* = 34)	
Familial autoimmunity			
Yes	15 (57.7)	16 (47.1)	0.414
No	11 (42.3)	18 (52.9)	
Anti-Ro			
Positive	6 (23.1)	1 (2.9)	0.016[a]
Anti-La			
Positive	1 (3.8)	0 (0.0)	0.249
Anti-Sm			
Positive	0 (0.0)	1 (2.9)	0.378
Anti-RNP			
Positive	5 (19.2)	5 (14.7)	0.641
Anti-Jo 1			
Positive	0 (0.0)	2 (5.9)	0.208
Anti-SCL 70			
Positive	10 (38.5)	6 (17.6)	0.071
Anti-centromere			
Positive	9 (34.6)	16 (47.1)	0.333
Anti-RNA Pol 3			
Positive	4 (15.4)	3 (8.8)	0.433

The results are presented as absolute frequency (relative frequency).
[a] *p*-Value in chi-squared test.

Table 6 – Autoantibodies in patients with or without familial autoimmunity.

Variable	Familial autoimmunity		*p*-Value
	Yes (*n* = 31)	No (*n* = 29)	
Anti-Ro			
Positive	4 (12.9)	3 (10.3)	0.758
Anti-La			
Positive	1 (3.2)	0 (0.0)	0.329
Anti-Sm			
Positive	0 (0.0)	1 (3.4)	0.297
Anti-RNP			
Positive	6 (19.4)	4 (13.8)	0.563
Anti-Jo 1			
Positive	1 (3.2)	1 (3.4)	0.962
Anti-SCL 70			
Positive	9 (29.0)	7 (24.1)	0.668
Anti-centromere			
Positive	9 (29.0)	16 (55.2)	0.040[a]
Anti-RNA Pol 3			
Positive	4 (12.9)	3 (10.3)	0.758

The results are presented as absolute frequency (relative frequency).
[a] *p*-Value in chi-squared test.

relatives.[36,39,42,43] Koumakis et al. found that thyroid autoimmune disease and connective tissue diseases (SSc, SLE, SS, RA) were more common in families of SSc patients than in families in the control group.[39]

With regard to epidemiological data, the only difference found in the group of polyautoimmunity patients was a longer duration of the disease after diagnosis. The most plausible explanation for this finding would be a diagnosis that occurred earlier in these carriers with more than an autoimmune disease, contributing to their development and survival. Recently, another Brazilian study conducted by Skare[49] stressed that the knowledge of the coexistence of autoimmune diseases is vitally important for the correct diagnosis of other autoimmune diseases in SSc patients.

We would expect to find a lower quality of life, or a greater severity/disease activity in polyautoimmunity patients, but this result did not come true. Actually, the literature describes the inverse. Avouac et al.,[50] for instance, found a milder form of the disease in patients with the limited form of SSc, and an association with polyautoimmunity. Caramaschi et al.[35] emphasize that the severity of SSc appears to be a risk factor for development of an additional autoimmune disease.

However, we point out that, in SSc patients and polyautoimmunity, there is a likelihood of clinically significant differences when one set apart a particular subgroup of associated comorbidities. For example, a recent Brazilian Southern regional study found a higher frequency of pulmonary hypertension (PH) and a trend of interstitial lung disease in a group of SSc patients in association with Hashimoto's thyroiditis (HT), when compared to patients without HT.[49] Taking into account the 6 cases of PH observed in our SSc patients, we also found a higher prevalence of PH in those showing an association with HT (*n* = 4–66.67%) *versus* patients without HT (unpublished data).

These patients were predominantly affected by the limited form of the disease (57.0% *versus* 34.6%) and exhibited significant features of vascular disease, such as the increased occurrence of an objective Raynaud's phenomenon (92.6% *versus* 66.7%) and telangiectasia (85.7% *versus* 68.3%). Our patients with SSc and HT had a higher incidence of pulmonary fibrosis, but this finding did not reach statistical significance (57.1% *versus* 45.0%).

Moreover, a large study of 24,728 patients and 55,632 controls found a positive association between history of personal and familial autoimmune disease with risk of non-Hodgkin's lymphoma development, and its authors suggested that the shared susceptibility can only explain a small fraction of this increase.[37]

In this study, the observation of an increased frequency of anti-Ro in patients with SSc and polyautoimmunity is easily explained, because the positivity to this antibody was associated with Sjögren's syndrome, a very prevalent condition in this group of patients. On the other hand, the observation of a lower frequency of anticentromere in patients with familial autoimmunity was due to the fact that this group of patients was primarily presenting the diffuse form of the disease, once again without reaching statistical significance. The patients showing polyautoimmunity and familial autoimmunity were primarily carriers of the diffuse form of SSc, but this indicator did not reach statistical significance.

A peculiarity of the city of Campo Grande–MS is that its population is basically composed of national and foreign immigrants, who came predominantly from the states of Minas Gerais, Rio Grande do Sul, Parana and Sao Paulo; and from countries like Germany, Spain, Italy, Japan, Paraguay, Portugal, Syria and Lebanon.

The main limitation of this study was the small sample of SSc patients; but with this strategy, we seek to eliminate the main bias observed in large studies of coexistence of autoimmune diseases, in which the familial autoimmunity history was provided by the patient, without an independent confirmation, or a medical record review. All our SSc patients are accompanied by the same physician, some of them for almost 10 years; and all their family and a large number of SSc patients' relatives are followed in other outpatient clinics at FMUFMS.

It is worth emphasizing the importance of the shared autoimmunity concept, in order to promote a continuous surveillance of SSc patients; it is expected that in this scenario the doctor is able to establish a timely diagnosis of possible second or third associated autoimmune disease, or even an autoimmune disease that is affecting the patient's relatives.

Conclusions

Our SSc patients had a frequency of 43.3% of polyautoimmunity and 51.7% of familiar autoimmunity.

The autoimmune diseases most frequently observed in polyautoimmunity patients were: Hashimoto's thyroiditis (53.8%), Sjögren's syndrome (38.5%), and inflammatory myopathy (11.5%). The main autoimmune diseases observed in of SSc patients' relatives were: Hashimoto's thyroiditis (32.3%), rheumatoid arthritis (22.6%), and SLE (22.6%). The presence of more than one autoimmune disease in SSc patients did not correlate with disease severity or activity.

Conflict of interests

The authors declare no conflict of interests.

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