Autoantibodies in scleroderma and their association with the clinical profile of the disease. A study of 66 patients from southern Brazil *

Autoanticorpos em esclerodermia e sua associação ao perfil clínico da doença. Estudo em 66 pacientes do sul do Brasil

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Abstract: BACKGROUND: Scleroderma is a fairly rare connective tissue disease whose autoantibody profile is associated with different clinical manifestations. The prevalence of autoantibodies in scleroderma is influenced by race and genetics.
OBJECTIVE: To study the prevalence of anti-Scl-70, anti-centromere (ACA) and anti-U1-RNP antibodies in patients with scleroderma in southern Brazil and verify their association with clinical manifestations of the disease.
METHODS: A retrospective study involving 66 patients with scleroderma for the presence of anti-Scl-70, anti-centromere and anti-U1-RNP and of clinical manifestations such as Raynaud's phenomenon, digital micro scars, digital necrosis, telangiectasias, calcinosis, pulmonary fibrosis, pleuritis, pericarditis, cardiomyopathy, arthralgia and arthritis, skin sclerosis, joint contractures, tendon friction rubs, pulmonary hypertension, esophageal disorders and renal crisis.
RESULTS: The prevalence of anti-Scl-70 was 17.8% , that of ACA was 33.3% and the prevalence of U1 RNP was 11.8%. Anti-Scl-70 was associated with the diffuse form of the disease (p = 0.015), presence of cardiomyopathies (p = 0.016) and digital micro scars (p = 0.05). Anti-centromere was more common in the limited form, although it was not statistically significant, and had a protective role associated with cardiomyopathies (p = 0.005). Anti-U1-RNP was more common in the overlap forms (p = 0.0004).
CONCLUSION: The prevalence and profile of clinical associations of autoantibodies in Brazilian patients with scleroderma are similar to those found in the literature.
Keywords: Antibodies, antinuclear; Scleroderma, diffuse; Scleroderma, limited

Resumo: FUNDAMENTOS: A esclerodermia é uma colagenose relativamente rara, cujo perfil de autoanticorpos está associado a diferentes manifestações clínicas. A prevalência de autoanticorpos na esclerodermia sofre influência racial e genética.
OBJETIVO: Estudar a prevalência dos anticorpos anti-Scl-70, anticentrômero e anti-U1-RNP em pacientes com esclerodermia do sul do Brasil e verificar suas associações às manifestações clínicas.
MÉTODOS: Estudo retrospectivo de análise de 66 pacientes com esclerodermia para presença de anti-Scl-70, anticentrômero (ACA) e anti-U1-RNP e de manifestações clínicas como: Raynaud, cicatrizes estelares, necrose digital, telangiectasias, calcinose, fibrose pulmonar, pleurites, pericardites, miocardiopatias, artralgias e artrites, grau de esclerose da pele, contraturas articulares e atritos de tendão, hipertensão pulmonar, manifestações esofágicas e crise renal.
RESULTADOS: A prevalência do anti-Scl-70 foi de 17,8%, a do ACA, de 33,3%, e a do U1 RNP foi de 11,8 %. O anti-Scl-70 estava associado à forma difusa da doença (p=0,015), presença de miocardiopatias (p=0,016) e de cicatrizes estelares (p=0,05); o anticentrômero foi mais comum na forma limitada, embora sem significância estatística e mostrou-se protetor para as miocardiopatias (p=0,005). O anti-U1-RNP foi mais comum nas formas de superposição (p=0,0004).
CONCLUSÃO: A prevalência e o perfil de associações clínicas dos autoanticorpos em esclerodermia de pacientes brasileiros assemelham-se aos da literatura mundial.
Palavras-chave: Anticorpos antinucleares; Esclerodermia difusa; Esclerodermia limitada

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INTRODUCTION

Scleroderma (SSc) is a relatively rare connective tissue disease characterized by dysfunction in fibroblasts, endothelial cells and the immune system. [1] In 75 to 95% of the cases, autoantibodies directed against nuclear antigens and which are associated with different forms of clinical presentation are found. [2] These autoantibodies are useful in determining the patient's prognosis. [1] These autoantibodies include anti-topoisomerase 1 (anti-Scl-70 or anti-topo1), anti-centromere antibodies (ACA) and anti-U1-RNP. [1,3]

It has been described that the presence of ACA is associated with manifestations of limited cutaneous forms and with a low frequency of involvement of internal organs. [1] Anti-Scl-70, in turn, has been linked to the diffuse forms of cutaneous involvement, severity of interstitial lung disease and increased prevalence of right heart failure secondary to pulmonary disease. [1]

Race and genetic *background* influence the clinical presentation and frequency of autoantibodies in SSc.[4] Very little is know about this influence on the Brazilian population, which has a peculiar ethnic profile, given the high degree of racial miscegenation. In this study, we studied the profile of autoantibodies and their association with clinical findings in a population of 66 patients with SSc in southern Brazil.

METHOD

This is a retrospective study of the medical records of 66 patients with a diagnosis of scleroderma. These medical records were filled out in accordance with the preliminary classification criteria of the American College of Rheumatology for this disease. [5] In this study, we collected demographic data, data on the profile of autoantibodies and clinical manifestations. This sample represents the total number of patients followed up at the rheumatology outpatient clinic of our institution in the last 5 years.

Diffuse scleroderma (dSSc) was defined by the presence of skin thickening near elbows and knees at any time of the disease course. Overlap forms were defined as those with evidence of inflammatory myopathy or aspects of systemic lupus erythematosus (SLE) according to classification criteria of the American College of Rheumatology for SLE. [6]

The visceral involvements studied were:

a) Peripheral Vessels: we focused on the presence of Raynaud's phenomenon, telangiectasias, digital pitting scars and digital gangrene.

b) Skin: involvement was measured by modified Rodnan skin score (MRSS). [7] Microstomia was considered when the oral aperture was less than the width of the patient's three middle fingers.

c) Joints: Presence of arthritis (when presence of inflammatory phenomena in the joints was detected) and arthralgia were characterized.

d) Involvement of tendons: presence of tendon friction rub and contracture of fingers with a distance between the palm and finger tip larger than 1.9 cm when the fingers were at maximum flexion.

e) Myositis: it was considered present when there was muscle weakness on physical examination plus one of the following findings: increase in CPK (creatine phosphokinase), myopathic changes on electromyography or biopsy revealing myositis.

f) Esophageal involvement: when there was distal esophageal hypomotility documented by manometry or barium swallow.

g) Pulmonary fibrosis: when restrictive disease was evidenced by spirometry (forced vital capacity – FVC – in 1 second < 70% of predicted plus forced expiratory volume in 1 second/FVC > 80% of predicted) or pulmonary fibrosis was revealed by computed CT or X-ray.

h) Pulmonary hypertension: it was considered present when right heart catheterization yielded values above 30 mm or echocardiography revealed values above 40 mm.

i) Cardiomyopathy: when left heart failure was revealed by clinical examination, echocardiography showed ejection fraction <45%, arrhythmia requiring treatment, complete heart block.

j) Pericarditis: revealed by clinical examination or by echocardiography.

k) Pleuritis: revealed by clinical examination or imaging findings (CT or X-ray)

l) Scleroderma renal crisis: characterized by abrupt onset of hypertension or renal failure.

m) Peripheral neuropathy: when there were clinical symptoms characterizing it or suggestive electromyography findings.

n) Calcinosis: when there were clinical, radiographic and anatomopathological findings documenting it.

Data on the following autoantibodies were collected: ANA (antinuclear antibody), anti-Scl-70, ACA and anti-U1-RNP.

The data were analyzed statistically with grouping in frequency and contingency tables. For studies of association, we used the Fisher's exact test and the Chi-square test when the data were nominal and the Mann-Whitney test and Kruskal Wallis test when they were numerical. The calculations were made using the *GraphPad Prism* software version 4.0 and the level of significance adopted was 5%.

RESULTS

Description of the population studied: Of the 66 patients studied, 61 (92.4%) were women and

5 (7.6%) were men aged 17 to 79 years (mean 51.35 ± 13.72 years) and with time of diagnosis between 1 and 40 years (mean 11.08 ± 8.56 years). In this population, there were 41 (62.1%) limited forms (lSSc), 14 (21.2%) dSSc forms, 9/66 (13.6%) overlap forms and 2 (3%) *sine*-scleroderma forms. The profile of autoantibodies and clinical findings in this population are summarized in Table 1.

b) Analysis of associations with anti-Scl-70 antibody: A study of the presence of anti-Scl-70 in the various forms of scleroderma revealed the following regarding the 10/66 patients with this antibody: 6/10 (60%) had the diffuse form of the disease and 4 (40%) had the limited form. Among the 56 who were Scl-70 negative, there were 37/56 (66.07%) patients with the limited from, 8/56 (14.2%) with the diffuse form, 2/56 (3.57%) with the *sine* scleroderma form and 9/56 (16.07%) with the overlap form (p = 0.0151, Graph 1).

The analysis of the association between presence of anti-Scl-70 and the different clinical manifestations are summarized in Table 2.

c) Study of the anticentromere antibody: This antibody was studied in 48 patients and was positive in 15/48 (33.3%). Of these 15 patients, 1 (6.6%) had the diffuse form, 1 had the overlap form (6.6 %) and 13/15 (86.6%) had the limited form. Among those without ACA, 8/33 (24.4%) had the diffuse form, 19/33 (57.5%) had the limited form, 5/33 (15.2%) had the overlap form and 1 (3.03%) had the *sine* scleroderma form (p = 0.16).

A study of the association between presence of ACA and the different clinical manifestations revealed the data found in Table 3.

d) Study of anti-U1-RNP antibody: The anti-U1-RNP antibody was studied in 55 patients and was positive in 7/55 (12.7%). Among these patients, 2/7 (28.5%) had the limited form and 5/7 (71.4%) had the overlap form. Among the 48/55 (87.3%) patients who did not present this antibody, there were 7/48 (14.5%) with the diffuse form, 32/48 (66.6%) with the limited form, 4/48 (8.3%) with the overlap form and 2 (4.16%) with the *sine* scleroderma form (p = 0.0004, Graph 1).

Table 1: Profile of clinical findings and autoantibodies in 66 patients with scleroderma

Clinical manifestation	N	Percent (%)
Raynaud's Phenomenon	62/63	98.4
Digital pitting scars	19/62	30.6
Calcinosis	18/62	29.03
Microstomia	16/63	15.87
Telangiectasia	29/63	46.03
Tendon contractures	15/63	23.80
Mean MRSS	15.63 ± 10.38	
Arthritis	28/63	44.4
Arthralgia	51/63	80.9
Tendon Friction	16/62	25.8
Myositis	12/63	19.04
Esophageal disorders	37/63	58.73
Pulmonary hypertension	19/63	58.7
Pulmonary fibrosis	26/63	41.2
Pleuritic disease	2/63	3.1
Pericardial disease	3/63	4.7
Myocarditis	17/63	26.98
Renal crisis	1/63	1.58
Peripheral neuropathy	7/63	11.13
Antinuclear antibody	61/66	92.4
Anti-U1-RNP	7/54	11.8
Anti-topoisomerase 1 (Scl70)	10/56	17.8
Anti-centromere	15/48	33.3

MRSS = modified Rodnan skin score
N = number of sample

Table 2: Study of the association of the anti-scl-70 antibody with clinical manifestations in 66 patients with scleroderma

Clinical manifestation	Anti-Scl-70 present (N = 10)	Anti-Scl-70 absent (N = 56)	p
Raynaud's Phenomenon	10/10 (100%)	55/56 (982%)	1.00
Digital pitting scars	4/10 (40%)	7/56 (12.5%)	0.05
Microstomia	0/7 (0%)	7/56 (12.5%)	1.00
Telangiectasia	4/10 (40%)	26/56 (46.4%)	0.74
Mean MRSS	23.13 ± 7.643	14.67 ± 10.40	0.026 (*)
Arthritis	4/10 (40%)	25/56 (44.6%)	1.00
Arthralgia	7/10 (70%)	45/56 (80.3%)	0.43
Contracture	2/10 (20%)	14/56 (25%)	1.00
Calcinosis	2/9 (22.2%)	16/56 (28.5%)	1.00
Esophageal disorders	7/9 (77.7%)	32/56 (57.1%)	0.29
Tendon friction	3/10 (30%)	13/55 (23.6%)	0.69
Myositis	2/10 (20%)	12/56 (21.4%)	1.00
Pulmonary hypertension	2/10 (20%)	16/55 (29.09%)	0.71
Pulmonary fibrosis	7/10 (70%)	21/56 (37.5%)	0.29
Pleuritic disease	0	2/56 (3.57%)	1.00
Pericardial disease	0	3/54 (5.5%)	1.00
Cardiomyopathy	6/10 (60%)	11/54 (20.34%)	0.016
Renal crisis	0	1/56 (0.17%)	1.00
Peripheral neuropathy	0	7/56 (12.5%)	0.58

(*) Mann Whitney; others - Fisher.
MRSS = modified Rodnan skin score
N = number of sample

The study of the presence of anti-U1-RNP in relation to the clinical manifestations is presented in Table 4.

DISCUSSION

The prevalence of the major autoantibodies studied in this sample, ANA (92.4%), Anti-Scl-70 (17.8%), ACA (33.3%) and anti-U1-RNP (11.6%) is in accordance with what has already been found in other populations. According to a review by Walker et al., anti-Scl-70 is found in 9-20%, ACA is found in 20-30% and anti-U1-RNP is found in 8% of the patients with scleroderma.[8]

Anti-Scl-70 and ACA are considered mutually exclusive antibodies and anti-Scl-70 is the most frequently found in the diffuse form of scleroderma, as seen in our population. [1,9] Its presence in patients with pulmonary fibrosis reaches 45% and appears to be associated with a more severe pulmonary disease. [1] In this sample, were were not able to demonstrate a higher prevalence of pulmonary fibrosis in those with positive anti-Scl-70. However, considering only the population of patients with pulmonary fibrosis, we observed that this antibody was present in 7/26 (27%) of the patients with this manifestation compared with 3/37 (8.1%) patients without it (data not shown). It is possible that the number of patients included in this sample did not allow for demonstration of this association. This is an antibody that apparently does not suffer much ethnic variation. [1] Hamaguchi et al. observed an association between anti-Scl-70 and the presence of digital pitting scars in the Japanese population, which was also found in this study. [10]

HLA-DB1*11 is associated with anti-Scl-70 in all ethnic groups. [1] HLA-DPB1 is also associated with the anti-Scl-70 response in scleroderma, especially in Caucasians and the Japanese. [11]

The variability of ACA according to ethnicity has also been well studied and it is higher in Caucasians and lower in Hispanic, African American and Thai patients. [1,12,13] Its presence has been associated with HLA-DRB1*01, HLA-DRB1*04 and HLA-DRB1*05 and its production appears to be influenced by both HLA-DRB1 and HLA-DQB1 alleles.[13,14] From the clinical point of view, this antibody has been linked to the CREST (limited) form and to less visceral involvement. [1] In our sample, a greater percentage of patients with the lSSc form was present in the ACA positive population (however, without statistical significance). We could not find an association between presence of ACA and calcinosis and digital ischemia in our sample, as described in other populations.[1]

Anti-U1-RNP has been associated with a variety of connective tissue diseases including lupus, polymyositis, scleroderma and overlap syndromes. [8] Its presence in scleroderma tends to indicate a disease of better prognosis, more responsive to corticosteroids and with characteristics of mixed disease, as observed

Table 3: Study of clinical manifestations in 48 patients with scleroderma according to presence of anti-centromere antibody (ACA)

Clinical Manifestations	ACA present (N = 15)	ACA absent (N = 33)	P
Raynaud's Phenomenon	15/15 - 100%	32/33 - 96.6%	1.00
Digital pitting scars	4/15 - 26.6%	12/33 -36.3%	0.74
Microstomia	4/15 - 26.6%	8/31 - 25.8%	1.00
Telangiectasia	9/15 -60%	13/33 -39.39%	0.22
Contracture	4/15 -26.2%	8/33 -24.4%	1.00
Calcinosis	3/15 - 20%	10/33 -30.3%	0.72
Myositis	2/15 -13.3%	5/33 -15.15%	1.00
Tendon friction	1/15 -6.6%	11/33 -33.3%	0.07
Mean MRSS	16.67 ± 9.64	15.85 ± 10.39	0.84(*)
Arthritis	5/15 - 33.3%	16/33 -48.4%	0.36
Arthralgia	12/15 -80%	28/33 -84.8%	0.66
Esophageal disorders	10/15 - 55.5%	18/32 -56.25%	0.53
Pulmonary hypertension	5 / 15 - 33.3%	7/33 -21.21%	0.47
Pulmonary fibrosis	2/15 - 13.3%	14/33 -42.42%	0.053
Pleuritic disease	0	0	-
Pericardial disease	0	2/33 - 6.06%	1.00
Cardiomyopathy	1/15 - 6.6%	12/33 -36.3%	0.005
Renal crisis	0	0	0
Peripheral neuropathy	4/15 - 26.2%	2/32 - 6.25%	0.072

(*) Mann Whitney; others – Fisher
N = number of sample

Table 4: Study of clinical manifestations in 55 patients with scleroderma according to presence of anti-U1-RNP antibody

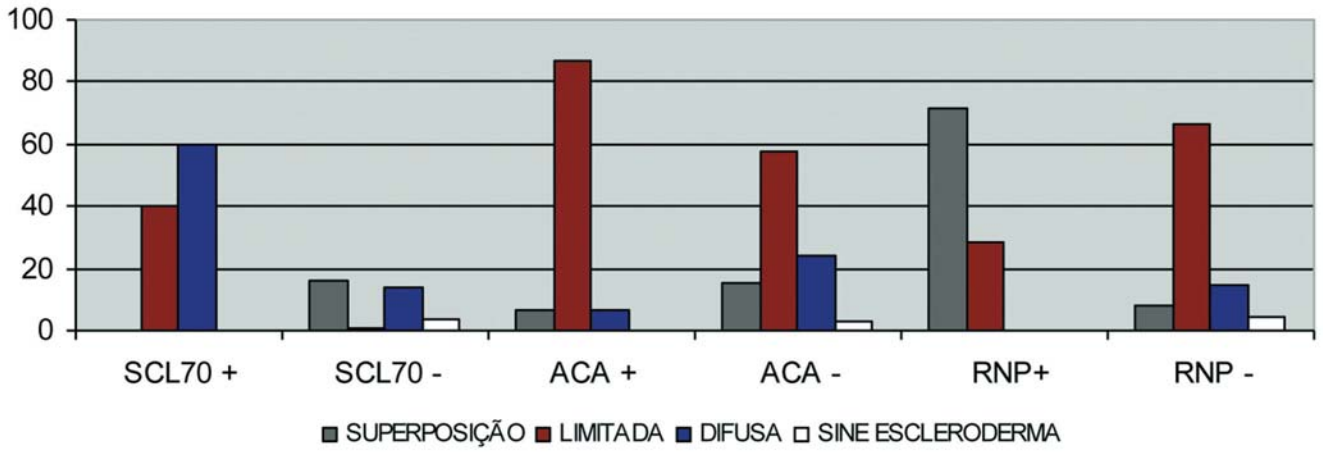
Clinical Manifestations	With anti-U1 RNP (N = 7)	Without anti-U1-RNP (N = 48)	p
Raynaud's Phenomenon	7/7 100%	48/48 - 100%	1.0
Digital pitting scars	1/7 -14.28%	15/48 - 31.2%	0.65
Microstomia	1/7 -14.28%	12/47 -25.53%	1.00
Contracture	1/7 -14.28%	12/48 - 25%	1.00
Telangiectasia	2/7 -28.57%	21/48 - 43.7%	0.68
Mean MRSS	10.60 ± 6.148	15.68 ± 10.99	0.28 (*)
Arthritis	4/7 - 57.14%	22/48 -45.8%	0.69
Arthralgia	7/7 - 100%	39/48 - 81.2%	0.58
Esophageal disorders	3/7 - 42.8%	29/47 - 61.7%	0.42
Pulmonary hypertension	2/7 - 28.57%	14/47 -29.78%	1.00
Pulmonary fibrosis	4/7 -57.14%	20/48 -41.66%	0.68
Pleuritic disease	1/7 -14.28%	1/48 -2.08%	0.28
Pericardial disease	0/6 -0%	2/48 -4.16%	1.00
Cardiomyopathy	1/6 - 16.6%	13/48 - 27.08%	1.00
Renal crisis	0 -0%	1/48 - 2.08%	1.00
Calcinosis	2/7 28.57%	13/48 -27.08%	1.00
Tendon friction	3/6 - 50%	10/48 -20.8%	0.14
Myositis	1/7 -14.28%	9/48 -18.7%	1.00
Peripheral neuropathy	1/7 -14.28%	4/47 -8.51%	0.51

(*) Mann Whitney; others - Fisher
N = number of sample

in our study. Except for the presence of the latter finding, this autoantibody did not seem to interfere with the clinical findings studied. [1,15] The anti RNP antibody is associated with the presence of HLA-DR2 and DR4. [1]

A finding of particular importance was the positive association between anti-Scl-70 and cardiomyopathy and a protective association of ACA and this type of lesion. The association of anti-Scl-70 and diffuse forms of scleroderma with heart damage has already been described by Perera et al., who noted that it was

Graph 1: Prevalence (%) of SCL-70, anti-centromere and anti-RNP antibodies in the various forms of scleroderma



Anti-Scl-70 antibody
Diffuse X limited p = 0.02
Diffuse X overlap p = 0.05
Limited X overlap p = 1.0

Anti-centromere antibodies
Diffuse X limited p = 0.22
Diffuse X overlap p = 0.53
Limited X overlap p = 0.39

Anti-RNP antibody
Limited X overlap p = 0.002
Overlap X diffuse p = 0.03
Diffuse X limited p = 1.0

particularly common in patients with rapid establishment of skin thickening. Cardiac involvement in SSc is responsible for a high percentage of deaths among these patients, having reached 65% in a Hungarian study.[16,17] In the early stages, it tends to be relatively silent, becoming symptomatic in advanced situations.[18,19] Thus, the presence of anti-Scl-70 should alert the clinician to an active search and early treatment of this severe form of the disease.

CONCLUSION

In conclusion, it can be stated that the prevalence of anti-Scl-70, ACA and anti-U1-RNP antibodies in this sample of scleroderma patients from southern Brazil is similar to that among the world population. Also, it is possible to state that anti-Scl -70 is more common in patients with the diffuse form of the disease, ACA is more common in the limited form and anti-U1-RNP is more frequent in the overlap forms. In this sample, the anti-Scl-70 antibody has shown to be linked to cardiomyopathies, while ACA has demonstrated to play a protective role concerning them. ❑

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