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Prevalencia de anticuerpos anti-Ro en la esclerosis sistémica y su influencia en el cuadro clínico del paciente

Prevalence of anti-Ro antibody in systemic sclerosis and its influence on the patient's clinical profile

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RESUMEN

Introducción: los anticuerpos anti-Ro/SSA son de los más comunes en la práctica diaria y se encuentran en varias enfermedades autoinmunes.

Objetivos: determinar la prevalencia del anticuerpo anti-Ro en pacientes brasileños con esclerosis sistémica (ES) y su influencia en el perfil clínico y epidemiológico.

Materiales y métodos: estudio retrospectivo de revisión de historias clínicas que incluyó pacientes con ≥9 puntos según los criterios ACR/EULAR 2013 para ES, inicio de la enfermedad después de los 16 años y resultado de anticuerpos anti-Ro.

Resultados: se incluyeron 142 pacientes, con prevalencia del sexo femenino (relación 11:1), 65,6% caucásicos, con una edad media de 55 años y una duración mediana de la enfermedad de 11 años. La forma limitada fue la más frecuente. La mediana de la puntuación Rodnan modificada fue de 8. El fenómeno de Raynaud se observó en 97,1%, los síntomas articulares en 53,1%, las molestias gastrointestinales en 66,6%, la dismotilidad esofágica en 69,5% y la enfermedad pulmonar intersticial en 63,5%. El anticuerpo anti-Ro fue positivo en el 24,1%. Los pacientes con anti-Ro presentaron mayor frecuencia de miositis (p=0,005), xeroftalmía (p=0,002) y síndrome de Sjögren secundario (p<0,0001), además de menor engrosamiento cutáneo (p=0,002). Anti-La (p<0,0001) y anti-RNP (p<0,0001) fueron más comunes en pacientes con anti-Ro positivos, mientras que el anticentrómero fue menos frecuente (p=0,02).

Conclusiones: el anti-Ro se asoció a mayor prevalencia de miositis, xeroftalmía, síndrome de Sjögren secundario y menor afectación cutánea.

ABSTRACT

Introduction: *anti-Ro/SSA antibodies are some of the most commonly encountered antinuclear antibodies in daily clinical practice and are closely associated with several autoimmune diseases.*

Objectives: *to determine the prevalence of anti-Ro antibody in Brazilian patients with systemic sclerosis (SSc) and its influence on clinical and epidemiological features.*

Materials and methods: *retrospective chart review including patients with ≥9 points in the 2013 ACR/EULAR criteria for SSc, age of onset >16 years, and anti-Ro results.*

Results: *142 patients were included, predominantly female (11:1 ratio), 65.6% Caucasian, with median age 55 and median disease duration of 11 years. Limited SSc was the most common subtype. Median modified Rodnan score was 8. Raynaud's phenomenon was observed in 97.1%, joint symptoms in 53.1%, gastrointestinal complaints in 66.6%, esophageal dysmotility in 69.5%, and interstitial lung disease in 63.5%. Anti-Ro antibody was detected in 24.1% of patients. Those with anti-Ro had more myositis (p=0.005), xerophthalmia (p=0.002), and secondary Sjögren's syndrome (p<0.0001), with lower skin thickening (p=0.002). Anti-La (p<0.0001) and anti-RNP (p<0.0001) were more frequent in anti-Ro positive patients, while anti-centromere was less frequent (p=0.02).*

Conclusions: *anti-Ro antibodies were present in about one-fourth of SSc patients and associated with higher frequency of myositis, xerophthalmia, secondary Sjögren's syndrome, and less skin involvement. Their presence also predicted positivity for anti-La and anti-RNP, and absence of anti-centromere.*

INTRODUCTION

Systemic sclerosis (SSc) may represent a diagnostic and treatment challenge, offering clinical difficulties that may rank highest among all rheumatologic diseases[1]. It is a chronic disease that affects multiple organ systems, characterized by structural and functional abnormalities of small blood vessels, fibrosis of the skin and internal organs, and autoimmune dysregulation[2,3].

Although SSc may appear in all age groups, the age of onset peaks between 55 and 69 years, with women being more commonly affected than men. (3:1 to 8:1)[3]. This disease may affect the skin, muscles, joints, blood vessels, lungs, kidneys, heart and other organs[2,4].

SSc etiology remains elusive and may be multifactorial; possibly it is triggered by environmental factors in a genetically predisposed individual[4]. Autoimmunity, suggested by the presence of several autoantibodies against nuclear and nucleolar components, is one of the players[5]. In SSc, autoantibodies do not appear to be just an epiphenomenon, but rather to be involved in the disease pathogenesis. SSc-specific autoantibodies are believed to be responsible for both amplifying the immune response and targeting cell types that are relevant in the pathophysiology of the disease[4]. Subsets of autoantibodies may characterize subsets of SSc. Some of them have important value in diagnosing and predicting clinical outcomes[6].

Anti-Ro/SSA antibodies are some of the most commonly encountered antinuclear antibodies in daily clinical practice and are closely associated with Sjögren's syndrome (SjS), systemic lupus erythematosus, neonatal lupus, and SSc[7]. It is directed against cytoplasmic proteins in a complex with several small RNA antibodies. At least two polypeptides have been identified: 52-kDa Ro and 60-kDa Ro. The presence of this antibody is of clinical importance, since it is associated with photosensitivity, thrombocytopenia, lymphopenia, nephritis, complement deficiency (C2) and vasculitis in lupus. However, although anti-Ro is also found in SSc, there is a paucity of literature that associates this antibody with these patients ' clinical profile[7].

Herein, this study aimed to analyze the prevalence of anti-Ro antibody in a sample of SSc patients and its association with clinical profile, SSc subtype, and demographic features.

MATERIALS AND METHODS

This is a retrospective analytical study, in which the medical records of patients with SSc who attended the rheumatology outpatient clinic of the Hospital Universitário Evangélico Mackenzie, who attended the outpatient clinic for the last 30 years, were reviewed. The project was approved by the local Committee of Ethics in Research.

Participants who met at least 9 points of the ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria for 2013 were included[8]. Patients with disease onset below 16 years of age and those with medical records with incomplete data were excluded.

The following data were extracted from the medical records: a) demographics: age (years); gender; ethnic background, weight, and height to calculate the body mass index (BMI); use of tobacco and alcohol; b) clinical data: SSc subtype (limited, diffuse, sine sclerosis, and overlap)[9], age at disease onset, presence of microstomy,

Raynaud phenomena, digital ulcers; telangiectasias; pitting scars, digital necrosis; synovitis, arthritis; arthralgias; tendon friction rubs, calcinosis; myositis; esophageal complaints (dysphagia, reflux, distal esophageal hypomotility); gastric complaints (early satiety, vomiting, heartburn); intestinal complaints (diarrhea, flatulence, constipation); systemic arterial hypertension, renal crisis; interstitial lung disease (evidence of restrictive disease on spirometry or pulmonary fibrosis on X-ray orCT); pulmonary hypertension; pleuritis; myocarditis; pericarditis; peripheral neuropathy. The presence of organ involvement was classified according to ACR definition[10]. The degree of skin involvement was measured using the modified Rodnan score (Rodnan-m). The Rodnan-m score is an assessment tool that graduates skin thickness of 17 body surface areas giving each one of them a value from 0–3 where 0 is normal skin, 1=skin with mild thickness; 2=with moderate thickness and 3=is given for severe thickness. The maximum value is 51[11]; c) autoantibodies data: Antinuclear antibodies (ANA), Anti-Ro, Anti-La, Anti-RNP, Anti-centromere, Anti-Scl70.

Data were collected and stored in a Microsoft Excel spreadsheet. Results were expressed as means, medians, minimum values, maximum values and standard deviations (quantitative variables) or as frequencies and percentages (qualitative variables). The comparison between data from anti-Ro positive and anti-Ro negative individuals was performed using Chi-Square, Fisher's Exact Test when the data was nominal and Student's T Test or Mann Whitney test when data was numerical. P values less than 0, 05 were considered significant. Data analysis was performed using the SPSS v.22.0 computer program.

RESULTS

About 200 patients with SSc were identified; 142 met the inclusion criteria. The population found was predominantly female (n=130; 91.5%), in a proportion of about 11:1 in relation to males. According to Table 1, the patients were predominantly Caucasian and did not have alcohol or smoking habits.

Table 2 shows that the most prevalent clinical findings were Raynaud phenomenon, joint complaints, esophageal dysmotility, gastric complaints, and interstitial lung disease. The limited and diffuse subsets included most of individuals; the median Rodnan-m score was of 8[2-16]. Regarding the laboratory profile, almost all patients had a positive ANA test, predominantly with a fine speckled nuclear pattern; anti-centromere autoantibody was the most prevalent, and anti-Ro was found in 24.1% of the sample, as shown in Table 3.

The comparison of the Rodnan-m scores according to the presence of anti-Ro showed that anti-Ro-negative patients had more skin thickening (Figure). Table 4 displays that there was a higher prevalence of myositis, xerophthalmia, and secondary SjS in the anti-Ro positive group than in the negative. As for autoantibodies, anti-La and anti-RNP were associated with the presence of anti-Ro, while the anti-centromere was associated with its absence.

Table 1: Characterization of the studied sample. 142 patients with systemic sclerosis.

Mean (±SD) age-years		**55 years ±15.3**	
Median (IQR) disease duration -years		**11 (8-14)**	
Tobacco exposure (n)			
	Yes	14/142	9.86%
	Ex	36/142	25.35%
Alcohol exposure (n)			
	Yes	10/142	7.04%
	Ex	4/142	2.82%
Ethnic group (n)	Caucasian	88/134	65.67
	Afrodescendant	43/134	32.0%
	Asian	2/134	1.49

N: number; SD: standard deviation; IQR: interquartile range.

Table 2: Clinical characterization of the studied series. 142 patients with systemic sclerosis.

Parameter (n)		Frequency/total	%
SSc subtype	Difuse	58/130	44.6
	Limited	59/130	45.3
	Sine scleroderma	5/130	3.8
	Overlap	8/130	6.1
Microstomy		56/141	39.7
Raynaud'sphenomenon		138/142	97.1
Digital ulcers		22/141	15.6
Telangiectasia		60/141	42.5
Pitting scars		55/142	38.7
Digital necrosis		10/142	7.0
Joint complaints		76/143	53.1
Tendon friction		7/140	5.0
Calcinosis		27/141	19.1
Myositis		21/142	14.7
Esophageal dysmotility		98/141	69.5
Gastric complaints		94/141	66.6
Intestinal complaints		45/141	31.9
Arterial hypertension		62/140	44.2
Renal crisis		6/141	4.2
Interstitial lung disease		89/140	63.5
Pulmonary hypertension		55/141	39.0
Pleural effusion		12/141	8.5
Myocarditis		3/141	2.1
Pericarditis		6/141	4.2
Peripheralneuropathy		14/141	9.9
Dry eye		45/142	31.6
Dry mouth		43/142	30.2
Sjogren		28/140	20.0

SSc: systemic scleroderma; n: number.

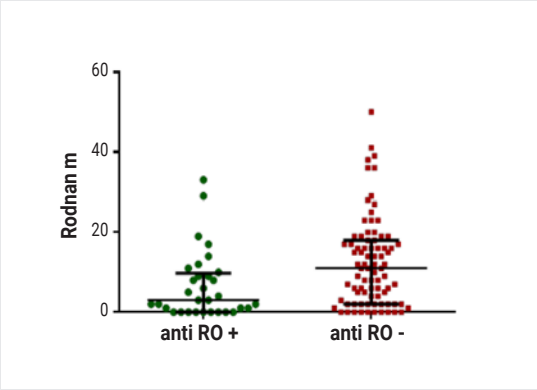
Table 3: Laboratory characterization of autoantibodies in the series studied: 142 patients with systemic sclerosis.

	Number	%
ANA	131/140	93.5
Anti-Ro	34/141	24.1
Anti-La	19/138	13.7
Anti-RNP	23/127	18.1
Anti- centromere	31/83	37.3
Anti-Scl70	23/133	17.2

Table 4: Comparison of systemic scleroderma patients according to the presence of anti-Ro.				
		Anti-Ro + N=	**Anti-Ro – N=**	**P**
Demographic data				
Male (n)		2/34 - 5.8%	10/108 – 9.2%	0.73
Mean (±SD) age -years		54.4±12.7	56.3±16.1	0.51
Median (IQR) age at diagnosis – years		44 (37-50)	47 (38-56)	0.18
Ethnic background (n)				
	Caucasian	22 – 73.3%	66 – 63.4%	0.50
	Afrodescendant	8 – 26.6%	36 – 34.6%	
	Asian	0	2 – 1.9%	
Clinical data				
SSc Subtype (n)				0.11
	Difuse	12	46	
	Limited	14	45	
	Sine scleroderma	1	4	
	Overlap	5	3	
Median (IQR) Rodnan-m		3 (0-9.7)	11 (2-18)	**0.002**
Microstomy (n)		14/34-41.1%	42/107 – 39.2%	0.84
Digital ulcers (n)		3/33-9.0%	19/108 – 17.5%	0.28
Raynaud's phenomenon (n)		32/24-94.1%	106/108 –98.1%	0.24
Telangiectasia (n)		13/34-38.2%	47/107 – 43.9%	0.55
Pitting scars (n)		12/34-35.2%	43/108 – 39.8%	0.63
Digital necrosis (n)		2/34-5.8%	8/108 – 7.4%	1.00
Joint complaints (n)		19/34-55.8%	57/108 – 52.7%	0.75
Tendon friction (n)		1/34-2.9%	6/106 – 5.6%	1.00
Calcinosis (n)		9/34-26.4%	18/107 – 16.8%	0.21
Myositis (n)		10/34-29.4%	11/108 – 10.1%	**0.005 (*)**
Esophageal dysmotility (n)		24/34-70.5%	74/107 – 69.1%	0.87
Gastric complaints (n)		24/34-70.5%	70/107 – 65.4%	0.57
Intestinal complaints (n)		12/34-35.2%	33/107 – 30.8%	0.62
Arterial hypertension (n)		14/34-41.1%	48/106 – 45.2%	0.67
Renal crisis (n)		2/34-5.8%	4/107 – 3.7%	0.63
Interstitial lung disease (n)		24/34-70.5%	65/106 – 61.3%	0.32
Pulmonary hypertension (n)		10/34-29.4%	45/107 – 42.0%	0.22
Pleural effusion (n)		4/34-11.7%	8/107 – 7.4%	0.48
Myocarditis (n)		2/34-5.8%	1/107 – 0.9%	0.14
Pericarditis (n)		2/34-5.8%	4/107 – 3.7%	0.63
Peripheral neuropathy (n)		3/34-8.8%	11/107 – 10.2%	1.00
Dry eye (n)		18/34-52.9%	27/108 – 25%	**0.002 (**)**
Dry mouth (n)		17/34-50%	36/108 – 33.3%	0.07
Sjogren (n)		16/34-47.0%	12/106 – 11.3%	**< 0.0001 (***)**
Auto-antibodies				
Anti-La (n)		17/34-50%	2/104 – 1.9%	**< 0.0001** (§)
Anti-RNP (n)		15/32-46.8%	8/95 – 8.4%	**< 0.0001** (§§)
Anti-centromere (n)		3/19-15.7%	28/64 – 43.7%	**0.02** (§§§)
Anti Scl-70 (n)		4/31-12.9%	19/102 – 18.6%	0.59

N: number; SD: standard deviation; IQR: interquartile range.
**OR= OR=3.6 (95% CI=1.3 - 9.6); **OR=3.3 (95% CI= 1.5 -7.5); ***OR= 6.9; (95% CI=2.8 -17.1)*
§OR=51.0 (95% CI=10.7 -241.0); §§ - OR=9.4 (95% CI=3.4 a 25.8); §§§ -OR=0.24 (95% CI=0.06 a 0.91).

Figure: Comparison of the Rodnan-m scores in systemic scleroderma patients according to the presence of anti-Ro antibody.



Median Rodnam-m in anti-Ro positive patients of 3 (0-9.7); median Rodnan-m in anti-Ro negativeof 11 (2-18); p=0.002.

DISCUSSION

This study evaluated the prevalence of anti-Ro antibody in a Brazilian sample of SSc patients and its influence on the patients' clinical-epidemiological profile. Anti-Ro presence was associated with a higher prevalence of myositis, xerophthalmia, secondary SjS, and less skin involvement. As for autoantibodies, anti-La and anti-RNP were associated with anti-Ro; whereas anticentromere was associated with its absence.

SSc is a rare but serious disease, characterized by a high level of clinical heterogeneity and unpredictable evolution, representing one of the greatest challenges in the management of autoimmune rheumatic diseases. Therefore, a better knowledge of the patients' individual characteristics is important to improve diagnostic and treatment strategies[12].

The sample presently studied has some peculiarities. Although the female predominance is already well known in the literature, Fuschiotti[13] found a 4:1 female-to-male ratio, which was lower than the 11:1 ratio detected presently. In addition, ethnicity also disagreed with prior studies, as it has been shown presently that Caucasian individuals are more likely to develop the disease than African Americans[13]. These findings highlight the need for specific knowledge of disease behavior in populations of different ethnic backgrounds. Brazilians are a highly mixed population, which gives them a unique genetic profile.

The prevalence of anti-Ro in SSc and its relationship with the clinical manifestations of the disease are not very well established in the literature. Bell et al.[15] detected anti Ro/SSA in 36.8% of their 114 German patients, a higher value than presently found (24.1%). These same authors[14] pointed out that, regarding the clinical manifestations, there was no difference in major organ involvement (esophagus, lungs, heart, kidneys and joints)between positive and negative anti-Ro/SSA patientsbut they found that SjS and myositis were more frequent in patients with the anti-Ro/SSA antibody than in the negative group, findings corroborated by the present study. Furthermore, in the present study, the Rodnan-m score presented a statistically significant value, showing that the group with negative anti-Ro has more skin thickening when compared to the positive anti-Ro autoantibody.

In relation to autoantibodies, the present study showed that there was a statistically significant difference regarding anti-La and anti-RNP, associated with the presence of anti-Ro, while anti-centromere was associated with the absence of this antibody, replicating the results shown by Bell et al.[14].

Autoantibodies in SSc are associated with significant clinical manifestations and should be considered for patient monitoring, treatment, and prognosis[12]. Studies related to anti-Ro antibody in SSc are scarce, although it has a close relationship with some clinical manifestations of SSc as observed presently.

As a limitation of this study, it should be mentioned that there was no differentiation as to the subtypes of anti-Ro autoantibodies, as it was a retrospective study and this investigation was not carried out in the service.

CONCLUSIONS

The results of the study show that the anti-Ro antibody can be detected in 24.1% of a sample of Brazilian patients with SSc. It is associated with a lower degree of skin involvement, presence of myositis, xerophthalmia, and secondary SjS. Anti-La and anti-RNP antibodies were more common, while the anti-centromere was less common in anti-Ro-positive than in anti-Ro-negative SSc patients.

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