Anti-Ro Antibodies in Rheumatoid Arthritis

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ABSTRACT

Background: Some autoantibodies are associated with peculiar clinical findings. Patients with rheumatoid arthritis (RA) may have anti-Ro antibodies.
Objective: To study prevalence and clinical associations of anti-Ro antibodies in RA patients.
Methods: We studied 385 patients with RA for anti-Ro by Elisa testing and for clinical profile, functional assessment, DAS-28 4v. (ESR), extra-articular manifestations, thyroid function, autoantibodies and treatment.
Results: The prevalence of anti-Ro was 8.31%. There was no significant difference in sex distribution, HAQ, DAS-28 or functional classification in patients with positive anti-Ro (p=ns). Patients with anti-Ro were younger at diagnosis (p=0.02). Analyzing extra-articular disorders we found a greater prevalence of cardiac valvular lesions (p<0.001) in patients with anti-Ro antibodies. No differences were found in other extra-articular manifestations, associated hypothyroidism, amyloidosis, treatment requirements, presence of rheumatoid factor (RF) or anti citrullinated protein antibodies (ACPA).
Conclusions: We conclude that in RA patients with anti-Ro have disease onset at an earlier age. Anti-Ro may be a risk factor for the development of cardiac valvular lesions. There was no association between this antibody and thyroid disease, amyloidosis and treatment needs.

Keywords: Rheumatoid arthritis; Anti-Ro; Sjogren's syndrome; Cardiac valvular lesions.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic rheumatic disease that can present itself with a wide range of clinical findings and severity[1]. Extra articular features such as nodules, vasculitis, eye disease, lung and cardiac involvement are some of the clinical findings responsible for this diversity as well as the antibody profile, including rheumatoid factor (RF), anti citrullinated protein antibodies (ACPA), antinuclear antibodies (ANA), anti-Ro and anti La[2].

Some auto antibodies are associated with particular clinical manifestations and their presence can help the clinician predict which of these events will be present[3,4]. Anti-Ro, typically seen in primary Sjögren's syndrome, has been linked to symptoms of oral and eye dryness and secondary Sjögren syndrome in RA[4,5] systemic lupus erythematosus[3,4] (SLE), scleroderma[4] and primary biliary cirrhosis[4]. Photosensitivity is also related to its presence both in patients with SLE and in neonatal lupus or in sub acute cutaneous lupus[4].

Anti-Ro is present in 3 to 15% of RA patients[1,4,5], and in this context it has been associated with more extra articular features (such as nodules[5], sicca symptoms, skin vasculitis and leukopenia[1,5]) and also with a wide range of immunological activation markers (such as hypergammaglobulinemia, high titer RF and ANA and complement activation[1,6]). Tisher et al[7] have found an association of anti-Ro and HLA DR4 in RA patients, although not confirmed by others[5]].

In this paper, we study the prevalence of anti-Ro in a population of RA patients from Southern Brazil searching for associations between clinical and serological profile, as well as treatment requirements.

METHODS

This study was approved by the local Committee of Ethics in Research and all participants signed consent. All included patients fulfilled at least 4 classification criteria of the American College of Rheumatology (1987)[8] and were seen at a single university center. This sample represents all RA patients seen during one year at our service that agreed to participate in the study. Charts were reviewed for demographic data, clinical profile (presence of extra articular manifestations), HAQ[9], Steinbrocker functional index[10] and DAS 28 4v

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using ESR[11,12], associated diseases, presence of auto antibodies (RF, ANA, ACPA) and medication use.

Extra articular manifestations considered were: a) Secondary Sjogren's syndrome- when the patient fullfilled the American-European criteria for this syndrome[13]; b) nodules - detected by physical examination; c) episcleritis, scleritis and *scleromalacia perforans* confirmed by ophthalmologic examination; d) interstitial lung disease - when ground glass, fibrosis and honey combing images were present at high resolution CT scan; e) leg ulcers - when present at physical examination and not attributable to other disease; f) cardiac valvular lesions - when present at transthoracic echocardiography; g) serositis (pleuritis and pericarditis) when clinically detected or detected by image exams such as chest X Rays, chest CT scan and echocardiography.

Associated diseases considered where: a) amyloid deposition – when positive by subcutaneous fat aspiration; b) hypothyroidism - when serum levels of TSH were above 4,5 µg/ml[14] at least twice.

Anti-Ro was searched by ELISA using the commercial *ELISA kit* (*Orgentec* Diagnostika GmbH, Germany); values were considered positive when above 25 U/ml according to the manufacturer's instructions.

All collected data were analyzed through frequency and contigency tables. Used tests for association studies were Fisher and chi-squared (nominal data) and unpaired t test and Mann Whitney (numeric data). Variable with $p<0.05$ in the univariate analysis, were submitted to analysis through a model of logistic regression to determinate the odds ratio and 95% confidence interval. Calculations were done with help of the software Graph Pad Prism version 4.0 and Medcalc version 12.1.3.0. The adopted significance was 5%.

RESULTS

CHARACTERIZATION OF THE STUDIED SAMPLE

The studied sample had 385 patients: 87.8% (n=338) were females and 12.2% (n=47) males. The mean age was 53.18 ±12.16 (from 22 to 89 years) and the age at diagnosis was 43.41 ±12.91 years (from 16 to 83 years). Tobacco exposure was seen in 49.7% (181/362); 24.3% (88/362) were current smokers and 25.7% (93/362) former smokers. Functional class was available in 351 patients and 4.8% were class 4; 10.2% were class 3; 35.9% were class 2 and 49.0% were class 1. DAS 28 4v was available in 271 patients and the mean value was 3.66±1.57 (values from 0 to 9.19); HAQ was obtained in 283 patients and had a median value of 1 (from 0 to 3).

The clinical and autoantibody profile seen in these patients are shown in Table I.

In this sample, 47.3% were using antimalarials; 63.3% were on methotrexate; 23.8% were using leflunomide; 8.05% on sulphasalazine; 6.4% on anti-TNF alfa drugs and 74.5% were on prednisone.

In this population anti-Ro was positive in 8.3% (32/385).

COMPARISON OF RA PATIENTS ACCORDING TO ANTI-RO PRESENCE

Comparing demographic data on anti-Ro positivity in RA patients no differences could be found in gender distribution (p=0.78). Patients with anti-Ro had disease onset earlier than anti-Ro negative (p=0.02; mean age at diagnosis of anti-Ro positive patients of 38.38±13.54 years *versus* 43.87 ±12.77 years in anti-Ro negatives). Exposure to tobacco was more com-

TABLE I. CLINICAL AND SEROLOGICAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS PATIENTS (N=385)

	N	%
Subjective dry eye	141/375	37.6%
Subjective dry mouth	161/375	42.93%
Positive Schirmer	102/341	29.91%
Positive glandular biopsy	136/343	39.65%
Secondary Sjögren's syndrome	52/321	16.19%
Pleuritis	10/356	2.88%
Interstitial lung disease	59/358	16.48%
Scleral disease	9/359	2.50%
Pericarditis	3/356	0.84%
Valvular lesions at echocardiography	33/360	9.16%
Reumatoid nodules	53/377	14.05%
Leg ulcers	1/356	0.28%
Felty syndrome	2/356	0.56%
Skin vasculitis	9/356	2.52%
Positive rheumatoid factor (RF)	261/365	71.50%
Anti citrullinated protein antibodies (ACPA)	109/144	75.69%
Positive antinuclear antibody (ANA)	109/378	28.83%
Hypothyroidism	70/359	19.49%
Positive amyloid deposition	21/142	14.79%

TABLE II. CLINICAL PROFILE OF 385 RHEUMATOID ARTHRITIS PATIENTS ACCORDING TO PRESENCE OF ANTI-RO

	Positive anti-Ro N=32		Negative anti-Ro N=353		P
Secondary Sjögren sindrome	9/30	30%	43/291	14.77%	0.03
Pleuritis	1/30	3.33%	9/326	2.76%	0.59
Interstitial lung disease	5/30	16.66%	53/328	16.15%	0.94
Scleral disease	0/30	0	9/328	2.74%	1.00
Pericarditis	1/30	3.33%	2/326	0.84%	0.23
Cardiac valvular lesions	8/30 (*)	26.6%	25/330	7.57%	<0.001
Rheumatoid nodules	6/31	9.35%	49/346	14.16%	0.43
Skin vasculitis	2/30	6.66%	7/326	2.14%	0.17
Hypothyroidism	6/31	19.35%	65/328	19.82%	0.95
Amyloid deposition	3/14	21.42%	18/128	14.06%	0.43

* the cardiac valvular lesions were: aortic insufficiency n=3; mitral insufficiency n=3; double aortic lesion n=1; mitral insufficiency and aortic insufficiency=1

mon in anti-Ro negative patients (49.4%) than in anti--Ro positive (29.0%), with p= 0.029.

No differences were detected in HAQ (p=0.73), DAS-28 (p=0.57) or Steinbrocker functional index (p=0.50).

Comparison of clinical data can be seen in Table II, which shows a higher prevalence of secondary Sjögren's syndrome and cardiac valvular lesions in the anti-Ro positive population.

Studying the presence of autoantibodies according to presence of anti-Ro we found no relationship with RF (p=0.54) or ACPA (p=1.0) but a positive association was found with ANA (p<0.0001), as expected.

No association could be found with any drug requirement: antimalarial (p=0.24), methotrexate (p=0.78), corticosteroid (p=0.95), leflunomide (p=0.87), sulphasalazine (p=0.31) and anti TNF alfa (p=1.0).

When Secondary Sjögren syndrome, cardiac valvular lesions and positive ANA and early age at onset were studied through logistic regression only ANA (OR 5.96; 95% CI=2.57 to 13.86), cardiac valvular lesion (OR 4.53; 95%CI=1.65 to 12.33) and age at disease onset (OR=0.95; 95%CI=0.91 to 0.84) maintained an association with anti-Ro.

DISCUSSION

Anti-Ro antibody has been found in several autoimmune diseases and has kept in each of them an association with certain clinical findings[4,5,6]. In SLE, it has been associated with the presence of HLA DR3, later disease onset, photosensitivity, deforming arthropathy like Jaccoud and a lower prevalence of kidney disease[4,15]. In scleroderma, where it occurs in 3-11% of cases[4,16,17], it is associated with symptoms of dry mucous membranes, photosensitivity and severe pulmonary involvement[17-20]. In RA, it has been described in association with symptoms of dry mucous membranes, photosensitivity, reduced complement and a higher prevalence of side effects to gold and d-penicillamine use[1,4,5].

In our study, which focused the clinical findings in anti-Ro positive RA patients, three associations were present. The first one was with an earlier disease onset although, it was not possible to verify that these patients had a worse outcome in observed functional indices, HAQ and DAS and even use of drugs. The second and already expected association was with the presence of ANA.

The third and most interesting association was with valvular heart lesions. Anti-Ro has been linked to several cardiac manifestations mainly of conduction disorders in infants who develop neonatal lupus[21]. In the same context, cases of cardiomyopathy and endomyocardial fibrosis have been found showing a tropism of anti-Ro for cardiac tissues[4,22]. In childhood systemic lupus anti-Ro has been linked with cardiac involvement (myocarditis and pericarditis)[23]. However these findings in adults are still controversial. Studies in anti-Ro positive lupus patients showed no change in PR interval[24] but conduction disturbances with in-

creased QTc were detected[25]. A group of researchers[26] found a positive association of anti-Ro with the presence of valvular lesions in 62 patients with SLE implying a causal relationship between the auto antibody and cardiac injury. With the present findings we suggest that maybe RA patients with anti-Ro should undergo a careful screening for cardiac valvular defects.

We conclude that the population of RA in the present study demonstrated a prevalence of anti-Ro of 8.3% and that this auto antibody was more common in patients with early disease onset and injuries of heart valve. No association could be established with other auto antibodies such as RF and ACPA or treatment needs.

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