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# CLINICAL SIGNIFICANCE OF ANTI-SSA/RO ANTIBODIES

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## ABSTRACT

**Introduction:** Anti-SSA / Ro antibodies are frequently encountered during systemic lupus erythematosus (LES) and Gougerot-Sjögren syndrome (SGS), they can however be associated with other autoimmune or non-auto-immune, which raises the question of their specificity and their interest in clinical practice. The aim of our study was to determine the clinical significance of anti-SSA antibodies's positivity. **Patients and Methods:** Our study focused on 87 patients with anti SSA / Ro antibodies positives, collected from cases of anti-ENA (Extractible nuclear antigens) antibodies, identified by an immuno-dot technique (D-teck, Bluediver, Aesku), after an AAN screening step (anti-nuclear antibodies) by indirect immunofluorescence (Hep-2, kallestad, Bio-rad). The identification of anti-ENA antibodies consisted in the characterization of the SSA Ro52 and Ro 60 subtypes as well as other autoantibody specificities (SSB, DNA, nucleosomes, histones, Sm, Sm/RNP, RNP, Jo-1, Scl70, PM/Scl) and anti-CCP detected by ELISA technique (EIA, Bio-rad). The result of these different autoantibodies was compared with the clinical and biological data of the patients. **Results:** The mean age of our patients was 46,64 ± 13,38 years (range: 21-76), with a female predominance (Sex-ratio M/F = 0,2). Among the 87 cases of anti-SSA / Ro positive selected, 35 (40%) of them had a SLE, 14 (16%) had rheumatoid arthritis, 12 (13,8%) a systemic scleroderma, 11 (12,6%) SGS including 8 cases (9,2%) of primary SGS and 3 cases (3.4%) of secondary SGS, 4 (5%) mixed connectivitis, 2 cases (2,3%) dermatomyositis and 1 case (1,15%) a polymyositis. In 9.2% of cases (n=8), anti-SSA antibodies were found in non-autoimmune diseases. Anti-SSA / Ro 60 were significantly associated with SLE (p=0,01), RA (p=0,04), mixed connectivitis (p=0,002) and dermatomyositis (p=0,04). No significant difference was noted between these antibodies or their subtypes, neither with the primary or secondary SGS. **Conclusion:** The presence of anti-SSA antibodies was more frequently encountered during SLE, RA, ScS and SGS, but were also found in non-autoimmune pathologies. These results underline the importance of a careful interpretation of these autoantibodies in order to establish with precision their real clinical significance and to help better therapeutic management of patients.

**KEYWORDS:** Anti-SSA antibodies, Ro52 / Ro60, autoimmune diseases, non autoimmune diseases.

## INTRODUCTION

Anti-SSA / Ro antibodies are among the most frequently prescribed autoantibodies in medical practice when systemic autoimmune diseases suspected.[1] They can be directed against several antigenic epitopes made up of proteins and small RNA (ribonucleic acid). According to their molecular weight, two types of anti-SSA / Ro antibodies have been identified; they are specific for two different SSA / Ro antigens of 60 kDa and 52 kDa derived from the RNP complex.[2,3] Anti-SSA / Ro 60 antibodies are generally associated with pathologies such as SGS, SLE, neonatal lupus and congenital atrioventricular block.[3-6] The specificity of these autoantibodies is however controversial since they have been described in various autoimmune or even non-autoimmune diseases,[1,7-12] and this varies according to the series in the literature.

The objective of this study was to determine the frequency and significance of anti- SSA antibodies in clinical practice.

## MATERIELS AND METHODS

This is a descriptive and analytical cross-sectional study, which involved a sample of 87 adult patients with anti-SSA / Ro antibodies, selected from a sample of 1,873 patients who have benefited from ANA and anti-SSA / Ro research collected from clinical departments (Internal Medicine, Rheumatology, Dermatology, Gastroenterology, Cardiology, Nephrology and Endocrinology).

The result of these different autoantibodies was compared with the demographic, clinical and biological data of the patients.

After a screening step for ANA (anti-nuclear antibodies) by indirect immunofluorescence (IFI, Hep-2, kallestad, Bio-rad), the identification of anti-ENA antibodies was carried out by immuno-dot technique (D-teck, Bluediver, Aesku), specifying the SSA sub-types Ro52 and Ro 60 as well as the other autoantibody specificities (SSB, DNA, nucleosomes, histones, Sm, Sm / RNP, RNP, Jo-1, Scl70, PM / Scl). The search for anti-CCP antibodies was carried out by ELISA technique (EIA- CCP, Bio-rad).

Statistical analysis consisted of a descriptive and analytical method with calculation of percentages, means and deviations using Graphpad Prism 7.00 software. The significance of association between the different parameters and the type of anti-SSA / Ro was evaluated by the chi2 test, considered significant in the face of a p-value <0,05.

## RESULTS

The average age of the patients in our series was 46,64 ± 13,38 years with extremes ranging from 21 to 76 years and a sex ratio of 0,2.

Clinical data collected from patient files made it possible to distinguish 35 cases of SLE (systemic lupus erythematosus), 14 cases of RA (rheumatoid arthritis), 12 cases of ScS (systemic scleroderma), 11 cases of GSS (Gougerot syndrome Sjögren), 4 cases of MC (mixed connectivity), 2 cases of DM (dermatomyositis), 1 case of PM (Polymyositis), and 8 cases of non-autoimmune diseases (NAID).

The overall result of the ANA and the different autoantibody specificities identified in our patients, translated into number and percentage is reported in Table-1.

**Table I: Frequency and specificities of autoantibodies found in our series.**

| Auto-antibody type | Numbre (%) |
|---|---|
| Anti-SSA | 87 (100%) |
| ANA | 73 (84,31%) |
| anti-DNA | 22 (25,49%) |
| anti-nucleosomes | 19 (21,57%) |
| anti-SSB | 17 (19,6%) |
| anti-Sm/RnP | 14 (13,72%) |
| anti-Sm | 13 (15,68%) |
| anti-histones | 10 (11,76%) |
| anti-CCP | 10 (11,76%) |
| anti-RNP | 5 (5,88%) |
| anti-Scl70 | 3 (3,92%) |
| anti-Jo-1 | 3 (3,92%) |
| anti-PM-Scl | 3 (3,92%) |

Among the 87 cases of anti-SSA / Ro positive, 35 (40%) of them had an SLE, 14 (16%) had a RA, 12 (13,8%) a ScS, 11 (12,6%) a GSS including 8 cases (9,2%) of primary GSS and 3 cases (3,4%) of secondary GSS, 4 cases (5%) of MC, 2 cases (2,3%) of DM and 1 case (1,15%) of PM. In 9,2% of cases (n = 8), anti-SSA antibodies were found during NAID.

The anti-SSA antibody type Ro60 was significantly associated with SLE (p = 0,01), RA (p = 0,04), MC (p = 0,002) and DM (p = 0.04), and Ro52 was rather significantly associated with ScS (p = 0.002). However, we did not observe any significant difference between the specificities Ro60 and Ro52 in the cases of SGS and the cases of PNAI (table-2).

**Table II: Profile of anti-SSA antibodies Ro60 and Ro52 and associated pathologies.**

| Associated pathologie | anti-SSA/Ro60 n (%) | anti-SSA/Ro52 (%) | anti-SSA/Ro60 et Ro52 n (%) | p-value |
|---|---|---|---|---|
| **SLE** (n=35) | 18 (52,63%) | 7 (21,05%) | 10 (26,31%) | **0,01** |
| **RA** (n=14) | 8 (55,55%) | 2 (11,11%) | 4 (33,33%) | **0,04** |
| **GSS (n=11):** | 5 (45,45%) | 2 (18,18%) | 4 (36,36%) | 0,41 |
| **Primitive GSS** (n=8) | 3 (37,50%) | 2 (25%) | 3 (37,50%) | 0,82 |
| **secondary GSS** (n=3)<br>- GSS/RA (n=2)<br>- GSS/ScS (n=1) | 2 (66,66%) | - | 1 (33,33%) | 0,22 |
| **ScS** (n=12) | 4 (33,33%) | - | 8 (66,66%) | **0,002** |

| | | | | |
|---|---|---|---|---|
| **Mixed Connectivity** (n=4) | 4 (100%) | - | - | **0,002** |
| **Dermatomyositis** (n=2) | 2 (100%) | - | - | **0,04** |
| **Polymyositis** (n=1) | - | - | 1 (100%) | - |
| **Non AI Diseases** (n=8) : | 3 (37,50%) | 2 (25%) | 3 (37,50%) | 0,82 |
| **Peripheral venous thrombosis** | - | - | 1 (1,15%) | - |
| **Ischemic heart disease** | - | 1 (1,15%) | - | - |
| **Pulmonary embolism** | 1(1,15%) | - | - | - |
| **Gout** | - | 1 (1,15%) | - | - |
| **Polyarthrosis** | - | - | 1 (1,15%) | - |
| **Cirrhosis** | 1 (1,15%) | - | - | - |
| **Pancreatitis** | 1 (1,15%) | - | - | - |
| **Tuberculous spondylitis** | - | - | 1 (1,15%) | - |

Reported to the different types of clinical and biological manifestations observed in the patients in our series (table-3), the cutaneous-mucous, articular and respiratory signs dominated the cases of anti-SSA positive antibodies with 78.4% (n = 69 ), 54.9% (n = 48) and 35.29% (n = 30) respectively.

A significant association was found between the positivity of anti-SSA / Ro and joint manifestations.
We did not find a significant association of clinical signs with a specific type of anti- SSA.

No significance was found between anti-SSA / RO and the various biological abnormalities.

**Table III: Association of anti-SSA antibodies with their isoforms and clinical- biological manifestations in patients of our series.**

| Clinical signs | Association anti-SSA positive Ro60 et/ou Ro52 n (%) | Anti-SSA/Ro 60 n (%) | Anti-SSA/Ro 52 n (%) | p-value |
|---|---|---|---|---|
| **Cutaneous-mucous** | 69 (78,43) | 26 (29,4) | 15 (17,65) | 0,07 |
| **Articular** | 48 (54,90) | 21 (23,53) | 10 (11,76) | **0,04** |
| **Respiratory** | 30 (35,29) | 8 (9,80) | 10 (11,76) | 0,8 |
| **Digestive** | 15 (17,65) | 5 (5,88) | 3 (3,92) | 0,7 |
| **neuropsychiatric** | 15 (17,65) | 5 (5,88) | 1 (1,96) | 0,2 |
| **cardiovascular** | 13 (15,69) | 3 (3,92) | 3 (3,92) | 0,99 |
| **Muscle** | 10 (11,76) | 5 (5,88) | - | 0,06 |
| **Urinary** | 9 (9,80) | 3 (3,92) | 2 (1,96) | 0,99 |
| **haematological** | 2 (2,29) | 1 (1,15) | - | 0,99 |
| **Ocular** | 2 (2.29) | 1 (1,15) | - | 0,99 |
| **high 24h proteinuria** | 12 (15,68) | 17 (20,75) | 8 (10,14) | 0,08 |
| **Anemia** | 12 (15,68) | 12 (15,68) | 10 (11,76) | 0,8 |
| **Lymphopenia** | 4 (5,07) | 7 (8,99) | 6 (7,84) | 0,99 |
| **Thrombocytopenia** | 2 (2,29) | 3 (3,92) | - | 0,2 |
| **Leukopenia** | 4 (5,07) | 3 (3,92) | 1 (1,15) | 0,6 |
| **Neutropenia** | 3 (3,92) | 2 (2,29) | 3 (3,92) | 0,99 |
| **High sedimentation rate** | 11 (14,53) | 10 (11,76) | 10 (11,76) | 0,99 |
| **High CRP** | 9 (11,29) | 7 (8,99) | 4 (5,07) | 0,5 |
| **Renal failure** | 6 (7,84) | 11 (14,53) | 5 (6,22) | 0,1 |
| **Hypoalbuminemia** | 9 (11,29) | 4 (5,07) | 6 (7,84) | 0,7 |
| **Hepatic cytolysis** | 4 (5,07) | 2 (2,29) | 2 (2,29) | 0,99 |
| **Hypercalcemia** | 1 (1,15) | - | 1 (1,15) | 0,99 |

## DISCUSSION

In this study, we compared a variety of clinical and biological manifestations in 87 patients with positive anti-SSA/RO. We have tried to establish a relationship between the anti-SSA/Ro subtype with the associated pathologies.

Anti-SSA antibodies are associated with autoimmune diseases at variable frequencies depending on the populations studied and the techniques used: They have been described in around 80% of cases during Gougerot-Sjögren syndrome and 50% of lupus cases,[13-16] 20% of scleroderma,[13] and around 10% of rheumatoid arthritis and polymyositis.[17,19] These figures have tended to increase in recent years as the sensitivity of techniques has increased.

Unlike our series; anti-SSA were associated mainly with SLE, RA, and ScS in 40%, 16% and 13.8% respectively. However, they were only found in 12.6% of GSS cases.

Anti-SSA/Ro patients in PM / DM have frequently shown specific reactivity to 52 kDa Ro without anti-60 kDa Ro,[20–22] but the significance of these results remains to be determined.

In the context of SLE, anti-Ro/SSA antibodies are also associated with non-erosive deforming arthropathy, Jaccoud arthropathy, due to inflammation of the soft tissue elements.[23,24]

Other authors suggest a strong association between anti-SSA/Ro antibodies and the late onset of SLE, defined as a disease with symptoms that appear after the age of 50. This particular subgroup of lupus is characterized by an increased prevalence of neurological features, interstitial lung disease, anti-Ro and anti-La antibodies and a lower frequency of signs of renal failure.[25–27]

Interstitial lung disease has been closely associated with anti-Ro antibodies in SLE, according to various authors,[26,29] but there is no evidence of direct involvement of these antibodies in the pathogenesis of pulmonary disease.

Menéndez and al.,[30] analyzed associations of anti-SSA / Ro reactivities with clinical and immunological manifestations in 141 SLE patients. Photosensitivity and dry syndrome were positively associated with anti-SSA/Ro60 (p=0,024 and p=0,019, respectively) and anti-SSA/Ro52 (p=0,026 and p=0,022, respectively) antibodies. On the other hand, a negative association was detected concerning anti-phospholipid antibodies, anti-SSA/Ro60 having a stronger effect (p=0,014) than anti-SSA/Ro52. Anti-SSA / Ro60 antibodies had a specific positive association with hypocomplementemia (p=0.041), mainly with low levels of C4 (p=0,008), while anti-SSA/Ro52 was found to be positively associated with Raynaud's phenomenon (p=0,026) and cytopenia (p=0,048) and negatively associated with anti-DNAs (p=0,013).

**1- AntiSSA52 + / antiSSA60 +association**

The first studies on anti-SSA antibodies 60 and 52 kDa noted a frequent association of the two antigenic specificities in lupus and GSS, but with a significant link between the diagnosis of Gougerot-Sjögren and the presence of anti- SSA 52 kDa isolated on the one hand and the diagnosis of lupus and the presence of anti-SSA antibodies 60 kDa isolated on the other hand,[13,31,32] then it appeared that, depending on the techniques used, and depending on the populations studied, the results needed to be nuanced.[33–37]

The association of antibodies directed against the two specific anti-SSA 52 and 60 kDa was found mainly in patients with Systemic Scleroderma and polymyositis in our study population.

**2- AntiSSA52+/antiSSA60**

Our results concerning the positivity of anti-SSA 52 kDa antibodies are slightly different from those of the authors cited above.[33–37] Some authors have investigated the significance of anti-SSA antibodies of the 52 kDa type.[37-43] The presence of this autoantibody was noted in certain cases either associated with other markers of connectivitis, or isolated and allowing to support the diagnosis of Gougerot-Sjögren.

Peene,[44] performed several different techniques to identify the isolated anti- SSA/52 kDa and found some positive results in non-autoimmune pathologies such as hepatitis C and some neoplasias. The expression of anti-SSA 52 antibodies is mainly associated with connective tissue diseases, although their precise clinical significance is still unknown.

Autoantibodies to the 52 kDa Ro protein are variably laboratory specific and may exist without the concomitant presence of 60 kDa anti-SSA/Ro antibodies in autoimmune diseases.[45] They were also found in 2.7% of the roughly 2,000 asymptomatic residents of a small Japanese town.[46]

Another study,[47] found that the prevalence of isolated anti-SSA/52 kDa antibodies was around 0,5%, and this detection had no significant clinical benefit because it was never the only explanation for the symptoms.

In a recent study,[48] the frequency of anti-SSA/52kDa antibodies was similar to the frequency of anti-SSA/60kDa in all groups except myositis (35,4% vs 0,0%, p=0,001) and systemic scleroderma cohorts (19% versus 6%, b=0,005) using the consensus of three different laboratory methods. In the same study, the percentages of anti-Ro52 antibodies that occur without anti-Ro60 antibodies also ranged from 5,4% in childhood SLE to 35,4% in the myositis group. In the GSS group, 63,2% of anti-Ro52 sera also had anti-Ro60 autoantibodies.

Anti-Ro52 antibodies appear as a specific marker independent of myositis, Rutjes and al, in 1997,[49] found anti-Ro52 reactivity in 58% of myositis sera positive for Jo-1, observation confirmed by Rozman et al, Brouwer et al, and Koenig et al.[50– 52]

**Table V: Prevalence of anti-Ro52 antibodies in various.**

| Authors | Pathology | Prevalence of anti-SSA / Ro52 |
|---|---|---|
| Peene and al.[44] 2002 | systemic lupus erythematosus | 53% |
| Schulte-Pelkum and al.[48] 2009 | polymyositis | 35,40% |
| | systemic scleroderma | 19% |
| | systemic lupus erythematosus | 5,40% |
| | Gougerot Sjögren syndrome | 63,20% |
| Rutjes and al.[49] 1997 | polymyositis+anti-Jo-1 | 58% |
| Rozman and al.[50] 2000 | | |
| Brouwer and al.[51] 2001 | | |
| Koenig and al.[52] 2007 | | |
| Granito and al.[53] 2007 | primary biliary cirrhosis | 28% |
| Defendenti and al.[54] 2008 | autoimmune hepatitis | 17% |
| Cavazzana and al.[55] 2006 | rheumatoid arthritis | 6% |
| Brucato and al.[56] 2001 | complete congenital atrioventricular block. | 1–5% |
| Jaeggi and al.[57] 2010 | complete congenital atrioventricular block. | 5% |

Autoimmune diseases according to literature.

**3- AntiSSA52-/antiSSA60**

As previously noted, we find a greater association of the anti-SSA antibody type 60 kDa with lupus, in agreement with the publications of Tsuzaka,[33] Saint Clair,[34] Lopez-Longo,[35] Bozic,[36] Belfiore,[37] and Gal,[58] as well as an important association with rheumatoid arthritis in our study population.

Some limitations inherent in this study are the retrospective clinical evaluations and the possible diagnostic biases in treating physicians requesting specialized laboratory tests. In addition, our study is based on a selected population of patients treated in a university hospital center (mainly in the rheumatology and internal medicine departments), we do not know if the prevalence of antiSSA / Ro is similar in the general population, these results should therefore not be extended to the general population. A prospective study, including a larger control group, should be performed to validate these results.

## CONCLUSION

Anti-SSA / Ro antibodies show a close association with various autoimmune diseases (mainly SLE, RA, and GSS) as well as with specific clinical manifestations such as cutaneous-mucous, articular and respiratory. This obviously requires a careful interpretation of these anti-SSA / Ro in order to establish with precision their real clinical significance and to help better therapeutic management of patients.

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