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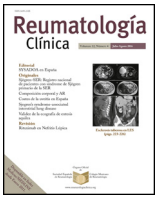

Original Article

Association of anti-Ro52, anti-Ro60 and anti-La antibodies with diagnostic, clinical and laboratory features in a referral hospital in Jerez, Spain

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ABSTRACT

Objective: Several antibodies have proven to be useful in autoimmune diseases, as markers for diagnosis, prognosis or clinical manifestations. Our objective was to evaluate the diagnosis and manifestations associated for antibodies anti-Ro52, anti-Ro60 and anti-La at a referral hospital in Spain.
Methods: We retrospectively analyzed the antigenic specificities of the consecutive samples submitted to the Immunology Unit for antinuclear antibody screening between 2002 and 2012. We included patients with more than one positive sample for some of the autoantibodies anti-Ro52, anti-Ro60 or anti-La. We also reviewed diagnosis, clinical and laboratory features. As dependent variable we evaluated possible combinations of anti-Ro52, anti-Ro60 and anti-La.
Results: 322 patients, 91% females, were studied (age 44.3 ± 15.51 years). The most frequent diagnosis was Sjögren's syndrome (40.06%) and systemic lupus erythematosus (SLE) (36.6%). The most prevalent pattern by indirect immunofluorescence was the fine speckled (69.9%). Anti-Ro52+/anti-Ro60+/anti-La+ combination was positively associated with fine speckled pattern (p: 0.001) and negatively with homogeneous (p: 0.016) and cytoplasmic pattern (p: 0.002). Isolated anti-Ro52+ was negatively associated with fine speckled pattern ($p < 0.001$) and positively with the cytoplasmic one ($p < 0.001$). The main positive associations with clinical symptoms were xerostomia and xerophthalmia with anti-Ro52+/anti-Ro60+/anti-La+ ($p < 0.001$), oral ulcers with anti-Ro52+/anti-Ro60+/anti-La− (p: 0.002) and alopecia with anti-Ro52−/anti-Ro60+/anti-La− (p: 0.003). Negative associations were xerophthalmia and photosensitivity with anti-Ro52+/anti-Ro60−/anti-La− (p: 0.003). Laboratory positive associations were hypergammaglobulinemia with anti-Ro52+/anti-Ro60+/anti-La+ (p: 0.003), and hypocomplementemia with anti-Ro52−/anti-Ro60+/anti-La− (p: 0.003). Leucopenia was negatively associated with anti-Ro52+/anti-Ro60−/anti-La− (p: 0.003).
Conclusion: Our study found significant relationships between clinical and laboratory manifestations with different patterns of antibodies to anti-Ro52, anti-Ro60 and anti-La. The combination of antibodies might be clinically useful due to prognostic and therapeutic implications.

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Asociación de los anticuerpos anti-Ro52, anti-Ro60 y anti-La con las características diagnósticas, clínicas y de laboratorio en un hospital de referencia en Jerez, España

Palabras clave:
Anticuerpo anti-Ro/SSA
Anticuerpo anti-La/SSB
Enfermedades autoinmunes
Patrones de inmunofluorescencia indirecta

R E S U M E N

Objetivo: Varios anticuerpos han demostrado ser útiles en enfermedades autoinmunes, como marcadores de diagnóstico, pronóstico o manifestaciones clínicas. Nuestro objetivo fue evaluar el diagnóstico y las manifestaciones asociadas a anticuerpos anti-Ro52, anti-Ro60 y anti-La en un hospital de referencia en España.

Métodos: Se analizaron retrospectivamente las especificidades antigénicas de todas las muestras consecutivas solicitadas a la Unidad de Inmunología para la detección de anticuerpos antinucleares entre 2002 y 2012. Se incluyeron pacientes con más de una muestra positiva para algunos de los autoanticuerpos anti-Ro52, anti-Ro60 o anti-La, y se revisaron sus características diagnósticas, clínicas y de laboratorio. Como variable dependiente se evaluaron las combinaciones de anti-Ro52, anti-Ro60 y anti-La.

Resultados: 322 pacientes, 91% mujeres, fueron estudiados (edad 44.3 ± 15.51 años). El diagnóstico más frecuente fue el síndrome de Sjögren (40.06%), y el lupus eritematoso sistémico (LES) (36.6%). El patrón por inmunofluorescencia indirecta más prevalente fue el moteado fino (69.9%). La combinación Anti-Ro52+/anti-Ro60+/anti-La+ se asoció positivamente con el patrón moteado fino (p: 0.001) y negativamente con el homogéneo (p: 0.016) y el citoplasmático (p: 0.002). Anti-Ro52+ aislado se asoció negativamente con el patrón moteado fino ($p < 0.001$) y positivamente con el citoplasmático ($p < 0.001$). La principal asociación con síntomas clínicos fue de xerostomía y xeroftalmia con anti-Ro52+/anti-Ro60+/anti-La+ ($p < 0.001$), úlceras orales con anti-Ro52+/anti-Ro60+/anti-La− (p: 0.002) y alopecia con anti-Ro52−/anti-Ro60+/anti-La−. Asociaciones negativas fueron xeroftalmia y fotosensibilidad con anti-Ro52+/anti-Ro60−/anti-La− (p: 0.003). Asociaciones positivas de laboratorio fueron hipergammaglobulinemia con anti-Ro52+/anti-Ro60+/anti-La+ (p: 0.003) e hipocomplementemia con anti-Ro52−/anti-Ro60+/anti-La− (p: 0.003). Leucopenia se asoció negativamente con anti-Ro52+/anti-Ro60−/anti-La− (p: 0.003).

Conclusión: Nuestro estudio encontró una relación significativa entre las manifestaciones clínicas y de laboratorio con diferentes patrones de anticuerpos anti-Ro52, anti-Ro60 y anti-La. La combinación de anticuerpos podría ser clínicamente útil, debido a implicaciones pronósticas y terapéuticas.

Introduction

Autoimmune diseases represent a wide variety of clinical problems affecting multiple organs and systems, and affect as least 5% of the population.[1] A great diversity of antibodies has been associated with different clinical manifestations and clinicians have relied on them guiding clinical diagnosis, prognostic implications, and in some cases therapeutic decisions.[2,3] Current knowledge on pathogenesis of autoimmune diseases agrees that a complex interaction of genes and environmental features are needed for them to appear.[4]

Combination of line immunoblot ENA assay (INNOLIA-ANA) and indirect immunofluorescence techniques to detect antinuclear antibodies in HEp-2 cells as substrate are good screening methods in patients with a clinical suspicion of an autoimmune disease, mainly systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Although false positive results can occur, titers >1:80 suggest the possibility of an autoimmune disorder and should prompt ordering more specific evaluations to determine specific reactivities of the antinuclear antibodies (ANA) such as anti-double stranded DNA and extractable nuclear antigens (ENA).[5]

Ro/SSA and La/SSB are heterogeneous antigenic complexes formed by three different proteins (Ro-52, Ro-60 and La) and four YRNA particles. The Ro60 protein acts as a quality check point for RNA misfolded with molecular chaperones for defective RNAs. The misfolded RNAs are recognized and then tagged by Ro60 for degradation. Ro52 interacts with different molecules, among them calreticulin and the immunoglobulin heavy chain-binding protein. Ro52 is thought to modify the role or stability of its substrates through ubiquitination, and this modification might result in the Ro52 mediated biological events.[6]

Anti-Ro/SSA and anti-La/SSB antibodies have been described in various autoimmune diseases. In primary Sjögren's syndrome (pSS) circulating antibodies are detected in approximately 60–70% of patients, and higher levels have been associated with early disease onset and systemic manifestations.[7,8] GEMESS Study Group, which included 12 reference centers in Spain, confirmed these clinical and laboratory features in a cohort of patients with pSS, and observed decreased levels of C4 in patients with early disease onset.[9]

Anti-Ro/SSA are detected in 30% of patients with SLE diagnosis, particularly (90%) those subtypes with late onset, subacute cutaneous lupus erythematosus, drug induced lupus and congenital deficiencies of C2, C4 and C1q, also in patients with SS/SLE overlap syndrome and undifferentiated connective tissue disease.[10] In contrast, anti-La/SSB is more commonly associated with SS,[11] and strongly correlated in anti-La/SSB positive with anti-Ro/SSA negative to organ dysfunction (kidney, lung, liver).[12]

Since the eighties, development of congenital heart blockade has been described in autoimmune diseases, such as SS and SLE. However cardiac involvement is more related to circulating antibodies from the mother rather than the diagnosis of autoimmune disease. Although the immune profile is variable among different studies the anti-Ro52 antibody is more common in mothers of children with congenital cardiac blockade, neonatal lupus, and neonates with prolonged QT without congenital cardiac blockade.[10,13,14]

Prevalence and clinical associations of anti-Ro/SSA and anti-La/SSB antibodies may vary in different ethnic groups. In addition to studies conducted in the Spanish population on immune expression of SS, other studies have been developed in recent years on the immune profile of patients with anti-Ro52, anti-Ro60 and anti-La antibodies. Most of them have been performed on specific