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Study Protocol:

Systemic Lupus Erythematous and Heart Conduction Disorders

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BACKGROUND

The incidence of sudden death and cardiac rhythm disorders is higher in patients with autoimmune diseases than in the general population.[1] Congenital atrioventricular block (AVB) in neonates has been classically associated with the transplacental passage of maternal anti-Ro antibodies.[2]

Complete AVB in adult patients with connective diseases is extremely rare, although not absent. From 1986 to 2015, 21 cases have been described in the medical literature of complete AVB in patients with connective diseases, 42% of whom were patients diagnosed with systemic lupus erythematosus. Of the total, 76% were positive for anti-Ro / SSA.1 antibodies, (PubMed® 1989-2015, keywords: atrioventricular block, autoimmune disease, systemic lupus erythematosus, SSA / anti-Ro antibodies).

Anti-Ro antibodies can be positive in several systemic diseases such as systemic lupus erythematosus, Sjögren's syndrome, polymyositis, dermatomyositis, systemic sclerosis and in 3% of the general population.[1] The pathogenesis of conductive defects in connective diseases in adults has been classically associated with infiltration of the conduction tissue by fibrosis or granulation tissue in some cases, with occlusion of the artery of the atrioventricular nodule by vasculitis in others, and with sequelae of myocarditis in others.[1,3,4]

The pathogenesis of cardiac conduction disorders in patients positive for anti-Ro / SSA antibodies is not clearly elucidated and there are conflicting data in this regard.[3,4] Recent experimental studies have allowed to elaborate a new theory in which there would be a unique pathogenic sequence based on the interaction of anti-Ro/SSA antibodies with the calcium channels of the cardiomyocyte surface. Anti-Ro antibodies would interact with calcium channels by molecular mimicry causing reversible inhibition of calcium currents at first and, at a later stage, internalization of these channels which would induce apoptosis and cell death. This would lead to a process of local inflammation that would sustainably create fibrosis of the conductive tissue. A possible explanation of the infrequent involvement of the adult heart compared to the neonate would be the greater dependence of the transarcolemmic calcium passage, through L-calcium channels, due to the underdevelopment of the neonatal sarcoplasmic reticulum.[1,5]

In June 2013, our group described the first case of complete BAV in a young patient with anti-Ro/SSA positive antibodies in whom an electrophysiological study is available and therefore the level of conduction block could be located, being this distal to the atrio-ventricular node. Together

with the presence of the left bundle branch block, these data suggested a specific involvement of Purkinje fibers.[6]

The only information available on this subject is based on isolated cases like ours. There are no publications on the subsequent follow-up of these patients, nor recommendations on the therapeutic attitude or cardiologic check-up in patients with connective diseases and anti-Ro/SSA antibodies. And there is not established indication for anti-Ro/SSA antibodies testing in young patients without known autoimmune pathology who have been diagnosed with an AVB.

Therefore, we carried out a first retrospective observational study in which the data of all patients implanted with a pacemaker in our center from 1987 to 2011 were reviewed. The study group included young adults between 18 and 50 years of age at the time of pacemaker implantation due to AVB of unknown origin and without structural heart disease. A total of 19 patients, with a mean implant age of 36 ± 10 years, was studied with clinical evaluation and an immunological study including antinuclear antibodies (ANA), extractable nuclear antigens (ENA) and anti-Ro/SSA. Six patients (31.6%) presented markers of immune disease, of whom 2 patients (10.5%) showed antibodies against specificities SS-A / Ro.[14]

The next step is to conduct a prospective analysis study of adult patients with autoimmune disease and presence of anti-SS-A/Ro antibodies and compare them with negative anti-SS-A/Ro patients to determine the existence of conduction disorders or other disorders by electrocardiographic non-invasive methods.

Currently available data on the effect of these autoantibodies on adult cardiac tissue are controversial. Logar and collaborators conducted a cohort study of 36 patients with SLE and 31 healthy controls and found that anti-Ro/SSA antibodies were associated with myocarditis and conduction defects in adults with SLE.[8] In patients with polymyositis, Behan and colleagues reported an association between the presence of anti-Ro antibodies and heart damage.[7] In addition, Lazzerini et al. described a high prevalence of the prolonged QTc interval in patients with connective tissue diseases that were anti-Ro/SSA positive.[13] On the other hand, Gordon et al., studied 19 mothers of children with neonatal lupus and 111 patients with SLE, but a relationship between the presence of anti-Ro/SSA and cardiac conduction defects could not be stablished.[15]

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HYPOTHESIS

- Patients with SLE positive for the antiRo/SSA autoantibody have a higher incidence of cardiac conduction disorders than those with negativity.
- Patients with SLE and antiRo/SSA have a higher incidence of syncopal episodes than patients with negativity.
- Patients with SLE and anti-Ro/SSA positive autoantibody have a longer QT and higher incidence of ventricular tachyarrhythmias than patients with SLE and negative test.

OBJECTIVES

- To describe the incidence of cardiac conduction disorders in patients with SLE based on their serological profile.
- If the association is confirmed, determine if the higher incidence of conduction disorders is clinically translated into a greater number of clinical events.
- To confirm that the presence of the anti-RO/SSA autoantibody in circulating blood in patients with SLE is associated with a lengthening of the QT interval with respect to subjects with negativity for the autoantibody.

SECONDARY OBJECTIVES

- To determine if the positivity for subunit 60 of the Ro autoantibody is associated with cardiac conduction disorders or alteration of cardiac repolarization by lengthening the QT interval.

METHODOLOGY

Design

- It is a cross-sectional study of which an observational analysis will be carried out.

Subjects

- Target population: Patients with SLE visited in the Rheumatology service of an hospital in Catalonia.
- Accessible population: Patients with SLE visited in the Rheumatology service of the Germans Trias i Pujol University Hospital in Badalona.

Criteria for selecting subjects:

- Inclusion criteria:
    - Diagnosis of SLE according to the 1997 diagnostic criteria (see annex 2).
- Exclusion criteria:
    - Presence of cardiac structural disease:
        - Ischemic heart disease
        - Congenital or acquired structural heart disease (hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, valvular heart disease).
        - History of cardiac surgery or cardiac ablation procedures.
        - History of other pathological processes that could affect cardiac conduction:
            - Steinert's disease
            - Lyme disease
            - Chagas disease
            - Hypothyroidism

Recruitment

The selection of patients and controls will be carried out by a consecutive sampling of the patients visited in the Rheumatology office.

MEASUREMENTS

Main variables:

- Study of cardiac conduction disorders by analyzing the resting electrocardiogram and 24-hour Holter.

Descriptive variables:

- Collection of the general pathological history of the patients, with targeted interrogation of the rheumatic and cardiac involvement and registration of the usual medication.
- Weight and height and physical examination.
- ECG at rest: analysis of the base rhythm, PR duration, QRS and QT intervals. Presence of intraventricular conduction disorders. Presence of ectopic beats.
- 24-hour Holter recordings: presence and number of ventricular ectopic beats, classification of episodes according to Lown's criteria. Presence of significant pauses (RR intervals> 2000 msec). QTc interval measurement. Autonomic dysfunction parameters: time domain parameters, such as the average of the RR intervals, the standard deviation of all normal RR intervals (SDNN), the root of the difference of successive means between the normal adjacent RR intervals (RMSSD), and the percentage of adjacent intervals with more than 50 ms (PNN50).
- Basic transthoracic echocardiogram: with analysis of ventricular diameters, systolic and diastolic function, valvular morphology and functionalism, determination of systolic pulmonary pressure, study of pericardial involvement and screening of acquired or congenital structural heart disease.
- Serological analysis: immunological profile, organic involvement by lupus, activity indices and chronic lupus damage. (see annex 3)

Confusion factors:

- Concomitant mediation with effect on AV conduction function.
- Immune profile.

STATISTICAL PLAN

With the hypothesis of demonstrating a correlation greater than 0.5 or greater difference in the control to 20%, a sample size has been calculated around 57 patients and 29 controls (for statistical power of 0.8, confidence interval and a ratio of 0.95 cases / controls 0.5). Since the aim of the study was to perform an analysis adjusted for confounders, and there are at least four factors (taking concomitant medication with effect on AV conduction, advanced age, sex and immunological profile) it has decided to predetermine the sample size of 100 cases and 50 controls.

First there will be a description of the sample, obtaining the average and standard deviation positive and negative for each of the variables in the group of 52 Ro-positive and the negative Ro52 as well as the percentage of the same. We will calculate the differences concerning the distribution of variables between groups using the Student t test and chi square. The analysis of association between these variables is made by linear regression analysis in the presence or absence of other factors, from which it obtained the odds ratio (odds ratio

- The obtained variables will be compared using Student's t-test for quantitative data and Fisher's and chi-square tests for qualitative data.
- Pearson correlation coefficient will be used to analyze the correlation between two variables.
- Calculations will be made using SPSS statistics software.
- The significance level adopted will be 5%.

INFORMED CONSENT FORM

CARDIC CONDUCTION DISORDERS
IN PATIENTS WITH SYSTEMIC LUPUS ERITEMATOSUS

INFORMED CONSENT FOR PATIENTS

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Mr/Ms

……., with

NIC…….., I manifest that I have been informed by

Dr.

. …… about

the nature of the study for which a series of tests and complementary tests will be carried out to determine:

The cardic conduction disorders in patients with systemic lupus eritematosus

I understand that the purpose of the tests is to help my doctor in the diagnosis of the disease and investigate the electrocardiographic alterations that it produces. Some of these complementary tests are not part of the usual clinical practice in patients with systemic lupus erythematosus (SLE).

I consider that the information has been given to me in an understandable way and my questions have been answered, so I have voluntarily decided to give my authorization. I understand that participation is voluntary, and that refusal to participate will not negatively influence the medical care received. Likewise, I have been informed as a patient that participation in this study includes additional visits.

I further understand that the data obtained may also be used for research in the knowledge of these diseases and that, although this information may not provide useful information for me at this time, it may be in the future.

For its side, the medical team undertakes to keep the anonymity of the data obtained, in compliance with Spanish Organic Law 15/99 on the Protection of Personal Data.

In Badalona at……. Of ……. Of …….

Signature of the investigator Signature of the patient