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Review

Prevalence and predictors of valvular heart disease in patients with systemic lupus erythematosus

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ABSTRACT

Objectives: We aimed to study the frequency, severity and predictors of valvular heart disease (VHD) in our lupus cohort.
Material and Methods: 211 patients were included. A transthoracic echocardiogram was used for this study. Significant valvular lesions were classified into two groups: valvular thickening and valvular dysfunction. Univariate logistic regression was performed in order to find associations with valvular thickening and dysfunction. Those variables with a p value ≤0.1 in the univariate analysis were subsequently included in multiple logistic regression models.
Results: Significant valve lesions were found in 53 patients (25%). The independent predictors of valvular thickening were the age at the time of the echocardiogram (OR 1.05, 95% CI 1.02–1.7), lymphopenia (OR 3.6, 95%CI 1.4–9.5), thrombocytopenia (OR 2.65, 95%CI 1.24–5.72), and anti-Sm antibodies (OR 3.28, 95%CI 1.44–7.33). The independent predictors of valvular dysfunction were age at the time of the echocardiogram (OR 1.045, 95%CI 1.009–1.083), thrombocytopenia (OR 5, 95%CI 1.66–14.86), hypertension (OR 6.2, 95%CI 2.1–18.4) and aPL (OR 6.2, 95%CI 2.1–18.4). Regarding the latter, the independent relation with valvular dysfunction was only seen for the double positivity aCL/LA, (OR 13.2, 95%CI 3.8–45.2, $p < 0.0001$).
Conclusions: Our study confirms the high prevalence of significant VHD in SLE patients. Clinical variables related with persistent inflammatory activity were associated with VHD. The association between VHD and aPL positivity was confirmed. Double-positive aCL/LA patients were most likely to suffer from valvular dysfunction.

Contents

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1. Introduction

Many studies have reported a high prevalence of valvular heart disease (VHD) in patients with systemic erythematosus lupus (SLE) compared with the general population [1–4]. Indeed, although it is frequently asymptomatic, VHD is the most frequent cardiac manifestation of lupus [2,3]. A wide spectrum of valvular lesions has been described: thickening, regurgitation, stenosis and vegetations. Transthoracic echocardiogram is the usual method of detection for VHD.

Since the first post-mortem studies reporting a 40% of Libman–Sacks endocarditis in lupus patients [5], the clinical course and survival of SLE have significantly improved, due to a number of factors such as the early diagnosis, the more accurate use of immunomodulatory drugs and the advent of new therapies. Therefore, the frequency and characteristics of several SLE manifestations are changing [6–8]. Taking this into account, we aimed to study the frequency, severity and predictors of VHD in a large monocentric observational cohort of SLE patients.

2. Patients and methods

2.1. Study design and objectives

This cross-sectional study has the main objective of analysing the prevalence, the severity and the clinical and immunological predictors of VHD in patients with SLE.

2.2. Study population

The Lupus–Cruces cohort is a longitudinal observational cohort joining SLE patients who fulfil the 1997 classification criteria of the American College of Rheumatology [9]. Between 2004 and 2009, we conducted a screening program focused on the prevalence and predictors of pulmonary hypertension in our cohort [10]. At least one transthoracic echocardiogram was performed to 245 patients. The local institutional review board approved the study and all the patients signed an informed consent authorizing the use of their clinical data for clinical research studies. Data describing the characteristics of cardiac valves were available for 214 patients of the cohort. Patients older than 80 years at the time of the echocardiogram were excluded ($n = 3$), thus, the study group consisted of 211 patients.

A number of clinical and immunological variables were retrieved from our database: demographic characteristics (gender, ethnicity, age at SLE diagnosis, follow-up time, age at the time of the echocardiogram), clinical manifestations of SLE, autoantibody profile (anti DNA, anti-ENA, antiphospholipid antibodies [aPL]), treatment received (glucocorticoids, antimalarials, immunosuppressive drugs), cumulative damage measured by the SLICC damage index (SDI) [11] and comorbidities (smoking, hypertension).

2.3. Echocardiographic study

A Philip SONOS 7500 echocardiography, 3-MHz probe, including two-dimensional anatomical image, M mode echocardiography and Doppler were used for this study. All the studies were performed by the same two cardiologists specialized in echocardiography. Valvular lesions were defined as thickening, regurgitation, stenosis and/or vegetations on the mitral and aortic valves. Thickening was considered in the presence of a mitral valve more than 3 mm or an aortic valve more than 2 mm thick. Vegetations were defined as non-mobile masses adhered to the leaflets. Regurgitation was classified as mild, moderate or severe according to the standard parameters of the regurgitant jet by Doppler mode [12].

For the purposes of this study, valvular lesions were classified into two groups: 1) valvular thickening and 2) valvular dysfunction, defined as moderate or severe regurgitation or stenosis.

2.4. Laboratory studies

Antinuclear antibodies were tested by indirect immunofluorescence performed on Hep-2 cells. Anti-DNA antibodies were tested by ELISA. Extractable nuclear antigens (anti-ENA, including anti-Ro, anti-La, anti-U_1RNP and anti-Sm) were tested using immunoblot. All patients were tested for anticardiolipin antibodies (aCL) IgG and IgM, and lupus anticoagulant (LA). aCL were measured using a commercial ß2-GPI-dependent standardized kit (Cheshire Diagnostics, Chaser Diagnostics Ltd., England). Titres below 13 G phospholipid units (GPL) and 11 M phospholipid units (MPL) were reported negative. LA was detected according to the recommendations of the International Society of Thrombosis and Hemostasis, using the Diluted Russell Viper Venom Time and the Silica Clotting Test [13]. Normalized ratios ≥1.2 were considered positive. All patients were repeatedly tested. In order to fulfil current classification criteria, only patients testing positive twice 12 weeks apart, with positive LA and/or IgG and/or IgM aCL at medium/high titres (≥ 40 GPL or MPL) were classified as aPL-positive [14]. We sub-classified these patients into three groups according to the immunological profile: (1) only aCL-positive, (2) only LA-positive and (3) positive for both aCL and LA simultaneously. Antiphospholipid syndrome (APS) was classified according to the 2006 classification criteria of the International Consensus Statement held in Sidney [14].

2.5. Statistical analysis

Descriptive data were generated, using percentages, means and standard deviations (SD). Univariate comparisons were made using Chi-square test, Fisher's exact test or non-paired Student's t-test, as appropriate. Univariate logistic regression was performed in order to find associations with valvular thickening and dysfunction. Those variables with a p value ≤0.1 in the univariate analysis were subsequently included in multiple logistic regression models (with both valvular thickening and valvular dysfunction as dependent variables) in order to identify independent associations. The software SPSS 22 (IBM Corp, Armonk, NY) was used for the statistical analysis.

The literature search was done by PubMed, using the following key words: “valvular heart disease AND systemic lupus erythematosus”, “valvulopathy AND systemic lupus erythematosus”, “valvular heart disease AND antiphospholipid antibodies”, “valvulopathy AND antiphospholipid antibodies”.

3. Results

3.1. Demographic, clinical and immunological characteristics

The demographic, clinical and immunological characteristics of the 211 patients included in the study are summarized in Table 1. One hundred and eighty seven patients (88%) were women. Most patients were Caucasians, with only two Hispanics, two Afro-Caribbeans, one