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Heart valve calcification in young patients with systemic lupus erythematosus: A window to premature atherosclerotic vascular morbidity and a risk factor for all-cause mortality

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Abstract

The objective of the study was to evaluate the association between heart valve calcification and atherosclerosis and outcome in systemic lupus erythematosus (SLE). One-hundred and seven patients with SLE (mean age 45.9 ± 14.7 years) were studied by 2D transthoracic echocardiography. Mitral annulus calcification (MAC) was detected in 24 patients (22.6%) and aortic valve calcification (AVC) in 22 (20.1%). Both MAC and AVC were associated with older age ($r = 0.2$, $p = 0.02$; $r = 0.40$, $p \leq 0.001$, respectively), high SLE damage index ($r = 0.3$, $p = 0.005$; $r = 0.40$, $p = 0.001$, respectively), diabetes mellitus ($r = 0.2$, $p = 0.05$; $r = 0.3$, $p = 0.003$, respectively), hyperlipidemia ($r = 0.03$, $p = 0.01$; $r = 0.03$, $p = 0.001$, respectively), hypertension ($r = 0.20$, $p = 0.07$; $r = 0.20$, $p = 0.08$, respectively), serum IgA isotype of anticardiolipin antibody ($r = 0.03$, $p = 0.03$; $r = 0.04$, $p = 0.02$, respectively), increased serum creatinine ($r = 0.03$, $p = 0.0005$; $r = 0.12$, $p = 0.02$, respectively), and stroke ($r = 0.3$, $p = 0.0008$; $r = 0.35$, $p = 0.0002$, respectively). In addition, MAC was associated with coronary artery disease ($r = 0.2$, $p = 0.05$). Both MAC and AVC were significantly associated with death during the follow-up period ($n = 9$, 8.6%) ($r = 0.20$, $p = 0.05$; $r = 0.20$, $p = 0.03$, respectively). On stepwise logistic regression analysis, MAC and AVC are independently associated with hyperlipidemia and antiphospholipid antibodies.

In conclusion, MAC and AVC are prevalent among young SLE patients, positively correlate with premature diffuse atherosclerosis, and are a risk factor for subsequent all-cause mortality.

Keywords: Atherosclerosis; Mitral annular calcification; Aortic valve calcification; Mortality; Systemic lupus erythematosus; SLICC/ACR damage index; Hydroxychloroquine

1. Introduction

Premature atherosclerotic cardiovascular and cerebrovascular diseases are leading causes of morbidity and mortality in patients with SLE compared to age- and sex-matched individuals in the general population. Reported rate of coronary artery disease (CAD) in lupus ranges from 6 to 54% [1], and epidemiological as well as autopsy studies have provided evidence of an increased incidence of CAD in this patient population. The Toronto Lupus Clinic group reported a 30% death rate due to CAD and showed that mortality and morbidity follow a bimodal pattern in which late death is due to myocardial infarction (MI) and strongly correlates with corticosteroid therapy [2,3].

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Risk factors for CAD in SLE include older age at diagnosis, longer disease duration, longer duration of use and higher cumulative dose of corticosteroids, hypercholesterolemia, postmenopausal status, obesity, and diabetes mellitus [4]. SLE poses a higher risk for CAD than the traditional Framingham risk factors. The incidence of MI in women with SLE aged 35–44 years is over 50 times greater than in sex- and age-matched non-lupus populations [3], and the risk of CAD or stroke is over seven-fold higher in lupus than in non-lupus individuals [5,6]. Accordingly, in a SLE cohort studied by our group, the incidence rates of CAD and stroke were 5.4 and 6.7%, respectively [7].

Mitral annulus calcification (MAC) and aortic valve calcification (AVC) are chronic degenerative processes associated with vascular atherosclerosis [8,9]. The incidence of MAC and AVC in the general population increases with advanced age, especially after age 65 years, and is strongly associated with coronary as well as peripheral arterial atherosclerosis in the general population [8–10].

In this study, using transthoracic echocardiography (TTE), we analyzed the prevalence and risk factors of MAC and AVC in a cohort of patients with SLE.

2. Patients and methods

2.1. Study subjects

The study group comprised 107 patients with SLE who were routinely followed between January 1995 and December 2002 in a Lupus Clinic of a university-affiliated primary community hospital and referral center. All patients met the revised criteria for the classification of SLE [11]. Patients were routinely evaluated for disease-related manifestations and co-morbidity every 3–4 months. Clinical and laboratory information was obtained at each routine clinic visit, and immediately converted into 25 history and 29 physical examination variables rated on a scale of 0–3 (none, mild, moderate, severe) [7]. At each visit, laboratory work-up included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood cell count (CBC), kidney and liver function tests, serum anti-double-stranded (ds) DNA antibody (by Farr assay), and complement level (C3, C4, CH100). Serum antibodies to Smith (Sm), Ro, La, ribonucleoprotein (RNP) were determined by enzyme-linked immunosorbent assay (ELISA, Inova Diagnostics, USA), antiphospholipid antibodies (APLA) [anticardiolipin and β_2-glycoprotein I (ELISA, Pharmacia, Germany), and lupus anticoagulant (LAC)] were assayed at least once during the study period. Lupus-related end-organ irreversible damage was scored using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index [12] for each patient at the time of echocardiography. All patients were evaluated for the presence of hypertension, diabetes mellitus, smoking, hypercholesterolemia, ischemic heart disease, congestive heart failure (CHF) and stroke. Hypertension was defined as either systolic or diastolic elevation of blood pressure (>140/90 mmHg) or ongoing antihypertensive pharmacologic therapy. Diabetes mellitus was defined as hyperglycemia requiring previous or ongoing pharmacologic therapy. Hypercholesterolemia was defined as a total cholesterol level of >200 mg/dl or ongoing statin therapy. Significant smoking history was defined as $\geq$10 pack-years of cigarette use. CAD was determined on the basis of history of MI, coronary artery bypass surgery, or angina pectoris with angiographic or scintigraphic evidence of coronary artery stenosis; left ventricular systolic and diastolic dysfunction, according to echocardiography; CHF, according to a history of pulmonary congestion; stroke, according to brain computed tomography or magnetic resonance imaging findings or history of hemiparesis/hemiplegia or aphasia.

2.2. Echocardiographic study

In order to be included in the study, patients underwent transthoracic echocardiography (TTE) either because of the presence of clinical indications of cardiovascular disorders or randomly, regardless of the presence or absence of clinically suspected cardiovascular disorders. Complete two-dimensional (2D) and Doppler color flow examinations were performed with the Hewlett-Packard-phased assay sector scanner (Sonos 5500) equipped with a Harmonic 53 transducer. MAC was defined as an intense echo-producing structure located at the junction of the atrioventricular groove and posterior mitral valve leaflet on the parasternal long-axis, apical 4-chamber view, or the parasternal short-axis view (10). AVC was defined as focal areas of increased echogenicity and thickening of the aortic valve leaflet [9]. The echocardiographic study also included the assessment of left- and right-side atrial and ventricular size and contractility, as well as the detection of valvular stenosis or regurgitation by color Doppler. All studies were recorded on super-HVS tape and evaluated by experts in echocardiography (M.V.M., A.S.A.). The observers who evaluated the echocardiographic studies were blinded to the presence or absence of cardiovascular disease in the study patients.

2.3. Statistical analysis

Continuous variables are shown as mean $\pm$ standard deviation. Pearson and Spearman correlation coefficients (r) and the significance for them (p) were calculated between the variables. χ^2-Test was used to analyze the statistical significant relationships between categorical variables. In order to predict valvular calcification, a multivariate stepwise logistic model was fitted to the data. Odds ratios (OR) and 95% CI were calculated from the model. A p-value less than or equal to 0.05 was considered statistically significant.