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RESEARCH ARTICLE

MULTIMODAL IMAGING FINDINGS OF SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS EVALUATED AT THE NAVAL GENERAL HOSPITAL OF HIGH SPECIALTY

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ABSTRACT

Introduction: Patients with systemic lupus erythematosus (SLE) have a high mortality due to cardiovascular disease (CV) associated with the presence of accelerated subclinical atherosclerosis, this atherosclerosis is one of the main factors for CV mortality.
Material and methods: Cross-sectional study, included patients diagnosed with SLE from December 2016 to July 2017. Patients were classified into 2 groups: active and non-active SLE. All patients had measurements of lipid profile, inflammatory reactants, blood chemistry, ego and creatinine clearance in 24 hrs, as well as the accomplishment of calcium score by tomography and bilateral carotid Doppler ultrasound. We performed bivariate association with Chi-square and logistic regression.
Results: A total of 41 patients were included, of which 3 were men (7.3%) and 38 were women (92.7%). The average ages were men 26.33 + - 5.03 years and women 41.52 + -13.87 years. Our model only identified 3 statistically significant variables: C3 ($p = 0.041$) and the variables that are obtained by ultrasound such as the presence of atherosclerosis plaque by ultrasound ($p = 0.043$) and the intima average thickness ($p = 0.027$). However, the calcium score taken by tomography did not show significant participation for this predictive model ($p = 0.683$). The largest OR was represented by the thickness of the left carotid intima.
Discussion: There is an association between the activity of the disease and the presence of hypertension, dyslipidemia within the classic factors, presence of atherosclerosis plaques observed by Doppler ultrasound, thickening of the intima media of the left carotid. A multivariate model allows early and timely detection of patients who are in non-active conditions of the disease and have a close follow-up with them to avoid the presence of subclinical atherosclerosis and thus have a better prognosis for patients.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease that is associated with the deposition of immune complexes, autoantibody production and various laboratory abnormalities and clinical manifestations. It has been observed that patients with systemic lupus erythematosus (SLE) present high mortality due to cardiovascular disease (CV) associated to the presence of subclinical atherosclerosis. Accelerated atherosclerosis that occurs in patients with SLE is one of the main factors for CV mortality. Factors contributing to the accelerated atherosclerosis process include classic CV risk factors, inflammatory factors, and systemic disease specific. This is why it is necessary to identify subclinical atherosclerosis and to develop measures to modify and / or

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prevent it. An increased risk of cardiovascular events in women with SLE up to 5 times greater than in the general population has been demonstrated as well as an increase in the prevalence of subclinical atherosclerosis. Although traditional coronary risk factors occur in patients with SLE do not fully explain the increase in cardiovascular risk. Today we do not have radiological indices to quantify the RCV in the population with SLE; for this reason, the traditional CVR factors (smoking, blood pressure, diabetes, body mass index, lipid profile) have been assessed; but the use of methods that allow an estimation of subclinical atherosclerosis can be implemented, in recent years the use of non-invasive imaging methods has been introduced to assess subclinical atherosclerosis in patients with systemic diseases, such as carotid ultrasound for the detection of atheromatous plaques and the measurement of the intima-media thickness, and obtaining more information with the SCORE of calcium. These methods allow to a certain extent to stratify the presence of subclinical atherosclerosis in an individualized way and to use a suitable therapeutic strategy to try to reduce the cardiovascular mortality that these patients suffer, thus benefiting the population and institution in general.

Carotid ultrasound is an accurate, non-invasive and validated method that allows the assessment of the IMC of the arterial wall and the presence of plaques, both of which are indicative of atherosclerosis. In addition, it has proven to be a reproducible technique to quantify "the burden of atherosclerotic disease" and to assist in the management of CVD. In relation to patients with SLE, there are a large number of studies that have assessed CVR using this technique and have demonstrated an accelerated progression in the evolution of atherosclerotic plaques. In addition, the presence of plaques has been related to the disease itself after controlling for traditional CVR factors and for this reason some authors consider that carotid ultrasound should be used in our daily clinic to assess and manage CVR in patients with SLE, proposing this technique as an indirect evaluation criterion for RCV in clinical trials with these patients. Atherosclerosis of the coronary arteries can be detected by the Calcium Score. This technique is a variant of CT scan that performs a capture of the heart in approximately one tenth of a second, avoiding blurred images caused by heart beats, and can detect calcium accumulation in the coronary arteries, with a predictive role for the development of future cardiac events.

MATERIALS AND METHODS

The present study is a cross-sectional study, carried out at the Naval General Hospital of High Specialty, in the Radiology service from December 2016 to July 2017, with the target population being patients diagnosed with systemic lupus erythematosus (SLE).

Inclusion Criteria: Patients older than 18 years with diagnosis of SLE, who agree to participate in the study and sign informed consent. Exclusion Criteria: Patients with infectious processes, patients with a history of cardiovascular disease and previous diagnosis of atherosclerotic disease, patients who do not complete the data required in the collection sheet, patients who withdraw or withdraw from participating in the study. We captured the patients with SLE in the outpatient rheumatology clinic, adhering to the criteria of inclusion, exclusion, explained the purpose of the study and the methodology, providing a letter of consent under information that specifies the taking of laboratory blood sample for lipid profile, inflammation reactants, blood chemistry, ego and creatinine clearance in 24 hrs, as well as the accomplishment of a bilateral carotid Doppler tomography and calcium score in order to measure the relationship intima-media and the presence or absence of atherosclerosis plaques and a direct interrogation that was registered in a data collection sheet (BMI, smoking, alcoholism, sedentarism). With the laboratory results, patients were classified into 2 groups: active and non-active SLE and comparisons were made with the data obtained by carotid Doppler ultrasound and the values of the Calcium Score. At the end of each of the studies the results obtained in a database, used for the analysis of the same, were emptied using the SPSS system.

Statistic Analysis

Descriptive statistics were used: arithmetic mean and standard deviation for continuous variables, and frequencies (percentage) for categorical variables. The comparison between groups for continuous variables used the Student's T test for independent variables when normal distribution of the data was demonstrated. If the distribution was not normal, the non-parametric "U-Mann-Whitney" test was used. The comparison between categorical variables was performed using contingency tables and the chi-square test (χ^2). In addition, we performed a binary logistic regression test, which allowed us to present a predictive model for the presence of "active lupus versus non-active lupus" using biochemical markers; and ultrasound and tomography markers. The odds ratios for each of the variables that participated in the predictive model, and their 95% confidence intervals, were also calculated. Finally, we calculated for this predictive model the diagnostic performance tests: sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios as well as the prevalence of Lupic activity goes from the calculation in the diagnostic tests.

RESULTS

A total of 41 patients were evaluated, of which 3 were men (7.3%) and 38 were women (92.7%). The average ages were men 26.33 + - 5.03 years and women 41.52 + -13.87 years.
The frequency of patients with atherosclerosis by ultrasound reported 12 positive cases (29.3%) vs 29 without plaques (70.7%). In relation to their lupus activity, 15 (36.6%) were active and 26 (63.4%) were non-active. The relationship between patients with active Les, not active with the Calcium Score is shown in Table 1. We found a non-significant association between LES activity (active vs non-active) and the calcium score (cardiovascular risk) x^2 (1) = 1789, p = 0.181. The comparison of intima media thickness in right and left carotid arteries did not show a significant difference, the right carotid artery showed an average of .64 mm + - .28 mm and left carotid artery an average of .58 + -.21. The value of the p is .564. The correlation (using the Spearman's coefficient) between the numerical variables thickness of the intima media and the Score of calcium showed statistical significance Rs = 0.244 and p = 0.027. In relation to age we found no difference in the ages of patients with active SLE (37 years) vs non-active lupus (42 years) and p = 0.240.

Table 1. Summary of the main variables studied comparing them with the presence fo lupus activity

Variable	LES Activo	LES No activo	p
Edad (años)	37±10.92	42.38±15.32	0.240
IMC categórica			
Normal	21.85±2.69	23.44±1.38	.110
Sobrepeso	25.85±.73	27.00±1.57	.112
Obesidad	33.52 ± 1.31	33.80±1.18	.796
Tiempo de enfermedad (meses)	6.9 ± 4.64	10.69±10.23	1.87
Grosor intima-media	.664 ± .247	.581±.253	.152
PCR (g/dl)	.733 ± .346	.846±.1.375	.758
VSG (mm/hr)	32.07 ± 27.93	15.81±15.31	.051 *
C3 (mg/dl)	83.88 ± 33.65	114.24±20.61	.005 **
C4 (mg/dl)	16.97±6.22	24.94 ± 18.04	.108
Genero			
Fem	14(36.84%)	24(63.15%)	0.105
Masc	1(33.33%)	2(66.67%)	0.564
Hipertensión Arterial			
Si	5(50%)	5(50%)	1
No	10(32.25%)	21(67.74%)	0.048 **
Tabaquismo			
Si	4(36.36%)	7(63.63%)	.366
No	11(36.66%)	19(63.33%)	1.44
Alcoholismo			
Si	6(42.85%)	8(57.14%)	.593
No	9(32.14%)	18(67.85%)	.083 *
IRC*			
Si	5(45.45%)	6(54.54%)	.763
No	10(33.33%)	20(66.66%)	.068 *
Sedentarismo			
Si	6(37.5%)	10(62.5%)	.317
No	9(36%)	16(64%)	.162
DM2			
Si	2(50%)	2(50%)	1
No	13(35.13%)	24(64.86%)	.071 *
Dislipidemia			
Si	7(53.84%)	6(46.15%)	.782
No	8(28.57%)	20(71.42%)	.023 **
Presencia de placa			
Si	5(41.66%)	7(58.33%)	.564
No	10(34.48%)	19(65.51%)	.095 *
Score de calcio			
Bajo	10(31.25%)	22(68.75%)	.034 **
Moderado	5(55.55%)	4(44.44%)	.739

* Likely to be statistically significant
** Statistically significant

Table 2. Correlation between patients with lupus activity and cardiovascular risk assessed by Calcium score

	Lupus activo		
Score de Calcio	No	Si	Total
Bajo	22	10	32
Moderado	4	5	9
Total	26	15	41

Table 3. Association between lupus activity and categorized body mass index

IMC Categórico	Lupus activo	Total	Media	Std. Desciación	Std.Error Media
Normal	No	12	23.44	1.38	.40
	Si	6	21.85	2.69	1.10
Sorepeso	No	11	27.00	1.57	.47
	Si	6	25.85	.73	.30
Obesidad	No	3	33.80	1.18	.68
	Si	3	35.52		.75

There was also no significant difference between male and female VS non active active lupus activity, males with p = 0.564 and female p = 0.105. In relation to the activity of lupus and the presence of atheroma plaque, we did not find a significant association between the number of patients x^2 (1) = .189, p = 0.664.

In the calcium score 32 (78%) patients with low score and 9 (22%) with moderate score. We found no significant difference between active non-active SLE activity for each of the categories studied based on BMI. For the normal group p = 0.110 for overweight p = .112 and for obesity p = 0.796.

In relation to the association between activity and hypertension, we initially compared the association between the two groups of these variables with a contingency table and did not find a significant association p = 0.260. From the previous finding, we analyzed separately the groups with and without hypertension to evaluate the number of patients with active lupus in each group. We only found a significant difference in the number of patients with active vs non-active patients in the group of patients who were not hypertensive x^2 (1) = 3,903, p = 0.048.*

We found no significant association between SLE activity and smoking at p = 0.641, nor was there a significant association between SLE activity and alcoholism P = 0.395. This same comparison with the LES activity did not show statistical significance with the diagnosis of Diabetes Mellitus p = 0.467 and the habit of sedentarism p = 0.590; and similarly for renal failure p> 0.050. In a similar way to that found in hypertension, we did not find a significant difference in the comparison of SLE and dyslipidemia, so we evaluated SLE activity separately for each group (with and without dyslipidemia). If we found a significant difference in the number of patients with active and non-active SLE with the group of patients without dyslipidemia x^2 (1) = 5,143, p = 0.023.*

As for the calcium score, only patients with a low calcium score showed a significant difference in the number of patients with or without lupus activity x^2 (1) = 4,500, p = 0.034.

For biochemical markers of acute phase reactants (VSG and CRP), we observed that CRP values were not significant when comparing groups of patients with active and non-active SLE; the VSG showed a significant trend to the statistical significance p = 0.051 and for the lupic activity (complement C3 and C4), the complement C3 was one of the results with the highest statistical significance of all variables studied p = 0.005 and C4 only a weak trend at the statistical significance p = 0.108.

Based on all the previous results in the last part of our analysis we performed a binary logistic regression analysis with the purpose of simultaneously evaluating those variables that were significant in their independent analysis and demonstrating their contribution percentage for a model that allows us to predict which patients have lupus activity. The following table shows the variables that were included in the model, their statistical significance and the odds ratio (Exp (B)) of each variable, as well as their confidence intervals.

The predictive capacity of the model in the initial evaluation (only the observed activity of the VS predicted model was 63.4% and after the inclusion of the variables presented in the table its performance rose to 87.8%. explains the variability for the activity of les in a range of 42.3 to 57.9%. From the last table that represents our model we only identified 3 statistically significant variables: C3 (p = 0.041) and the variables that are obtained by ultrasound such as the presence of atherosclerotic plaque by ultrasound (p = 0.043) and the average intima thickness (p = 0.027). However, the calcium score taken by tomography showed no significant participation for this predictive model (p = 0.683). The major OR is represented by the thickness of the intima media of the left carotid artery. The binomial regression model allowed us to construct a classification table of predicted lupus activity. With this table we evaluate the diagnostic performance of the model, obtaining the values shown below:

DISCUSSION

In relation to the main objective, which is to identify early factors that are associated with SLE and subclinical atherosclerosis, we consider it important to mention the significant finding of a smaller number of patients with lupus activity in the subgroups of patients without hypertension and without dyslipidemia. Although this finding seems obvious we consider it a quantitative evidence that indicates the groups of patients in which we can act to prevent the active disease or in whom we could put more attention in indicating studies of image more frequently for a better control and follow-up.

Table 4. Main variables of interest in the study model with its statistical significance and confidence intervals

							95% C.I. for Exp (B)	
	B	S.E.	Wald	df	Sig.	Exp (B)	Lower	Upper
Score de Calcio	-.617	1.512	.167	1	.683	.539	.028	10.443
Disli								
Dislipidemia	-2.321	1.326	3.062	1	.080	.098	.007	1.322
Hipertensión	1.593	1.373	1.347	1	.246	4.920	.334	72.575
C3	-.062	.030	4.195	1	.041	.940	.886	.997
C4	-.082	.061	1.797	1	.180	.921	.816	1.039
Aterosclerosis (US)	3.756	1.852	4.111	1	.043	42.785	1.134	1614.800
Grosor intima-media izq.	9.808	4.442	4.875	1	.027	18186.490	3.009	109912401.104
Constant	-2.71	3.709	.005	1	.942	.762		

Table 5. Diagnostic performance of the established model

		%
Sensitivity	0.733	73.33
Specificity	0.962	96.15
Positive predictive value	0.917	91.67
Negative predictive value	0.862	86.21
Accuracy	0.878	87.80
Prevalence	0.366	36.59

Maksimowicz-McKinnon *et al* studied 605 patients with SLE and reported a strong association of the prevalence of carotid atherosclerosis with age, with values ranging from 1% in the under 30s to 61% in those over 60 years.

I also reported association with traditional cardiovascular risk factors and elevated serum C3 levels. There was no evidence of association with disease activity (SLEDAI) nor with time of disease evolution. And in our study we demonstrated the association of the presence of active disease with the presence of atherosclerosis by ultrasound, as well as in hypertensive patients and with dyslipidemia. In another study, Telles *et al* reported a prevalence of carotid atherosclerosis of 9.3% in 172 patients with lupus. The presence of carotid atherosclerosis was associated with traditional cardiovascular risk factors. In our study we observed the presence of atherosclerosis plaques, as well as the thickness of the intima media of predominance in the left carotid as data associated with the activity of the disease. It was also found that in relation to lupus activity and the presence of atheroma plaque, there was no significant association between the number of patients $x^2 = .189$, $p = 0.664$.

Today, atherosclerosis is considered a systemic disease with an important inflammatory component. In its development intervenes a complex interaction of immunological mediators and cytokines that lead to the appearance of foam cells in the vascular wall with the subsequent formation of streaks of fat and plaques. This systemic inflammatory response responsible for atherosclerosis has been proposed as one of the possible links between atherosclerosis and SLE, since it seems evident that the systemic inflammatory response in lupus patients contributes to the development of atherosclerosis. This pathophysiological relationship between atherosclerosis and SLE has been suggested by several authors. Some studies have shown that higher serum levels of C-reactive protein (CRP) are predictors of cardiovascular events, increased carotid intima-media thickness (IMCT), and the presence of calcification in coronary arteries. The work published by Rho *et al*. is particularly interesting in demonstrating that markers or mediators of inflammation associated with atherosclerosis or cardiovascular risk in the general population, such as levels of endothelial adhesion molecules (VCAM, ICAM and E-selectin) and TNF-Î ±, are associated with atherosclerosis in SLE, and are also independent of classic cardiovascular risk factors. TNF-γ and other proinflammatory cytokines such as IL-6 and monocyte protein 1 (MCP-1) would intervene in the development of atherosclerosis by increasing hepatic CR synthesis and assisting in the onset of the 'lupus dyslipoproteinemia pattern'.

In LES, complement activation plays a role in atherosclerosis, and has been suggested by the Spanish group of Rua-Figueroa *et al*. by finding in SLE patients an association between high serum C5 concentrations and early atherosclerosis, as well as between elevated serum C3 levels and progression of CIMG in a 2-year prospective study. Risk factors related to systemic lupus erythematosus. In the increase of the CV risk of the patients with lupus, besides the classic cardiovascular risk factors and the inflammatory ones, the own disease intervenes, that behaves as an independent cardiovascular risk factor.

Conclusion

The study found an association between disease activity and the presence of hypertension, dyslipidemia within classic factors and the presence of atherosclerosis plaques observed by Doppler ultrasound, thickening of the left carotid intima-media, and in less statistical significance with the assessment of the calcium score and obtaining with the data a model that helps us in the sensitivity and specificity of the image studies to correlate with the activity of the disease, and with this to be able to detect in an early and timely way to patients who are in non-active conditions of the disease and to have a close follow-up with them to avoid the presence of subclinical atherosclerosis and with this to have a better prognosis for the patients. It was not possible to demonstrate a relation of carotid atherosclerosis in patients with SLE with the time of evolution of the disease, which has been reported in other studies with larger samples.

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