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Original Investigation

Cardiovascular Manifestations in Patients With Systemic Lupus Erythematosus During a One-year Period in an Institution in Cundinamarca, Colombia☆

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ABSTRACT

Introduction: Cardiovascular disease is a poorly recognized problem in systemic lupus erythematosus (SLE) patients, who may have their disease activity associated with cardiac disease at the time of diagnosis or at a later stage of the course of disease. Manifestations are variable, as all structures of the heart can be affected, and can cause significant morbidity and mortality.
Objective: The presentation may vary from subclinical form to advanced stages, which require aggressive immunosuppressive therapy. A description is presented of the frequency of these manifestations in patients with systemic lupus erythematosus attending a reference institution of Cundinamarca, Colombia.
Methods: A retrospective study was conducted with the recording of clinical aspects, laboratory tests, and cardiovascular manifestations over a period of one year.
Results: The study included a total of 45 patients with confirmed diagnosis of SLE, with a mean age of 35 years. Deterioration in functional class and dyspnea occurred more frequently. A positive anti-DNA was more frequent in patients with dyspnea (p=.037) and impaired functional class (p=.023). The lupus anticoagulant is also present in patients with deep venous thrombosis (60 vs. 15%; p=.018), and in patients with heart failure (66 vs. 16%: p=.036).
Conclusion: Cardiovascular symptoms are present in a high percentage of patients with SLE, thus these should be questioned to in order to detect them earlier and avoid cardiovascular complications. It is suggested that some autoantibodies, as anti-DNA, lupus anticoagulant, low plasma complement, and anti-C1q, could also be useful for detecting new cardiovascular events in patients with SLE.

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Manifestaciones cardiovasculares en pacientes con lupus eritematoso sistémico en una institución de referencia en Cundinamarca, Colombia, durante un periodo de un año

Palabras clave:
Lupus eritematoso sistémico
Enfermedades cardiovasculares
Sistema cardiovascular

RESUMEN

Introducción: El compromiso cardiovascular es un problema insuficientemente reconocido en pacientes con lupus eritematoso sistémico (LES). Este se puede presentar en cualquier momento de la evolución. Las manifestaciones son variables y puede comprometer todas las estructuras del corazón. Está asociado a morbimortalidad importante y su presentación puede ser subclínica o comprometer la vida del paciente, requiriendo tratamiento inmunosupresor agresivo.

Objetivo: Este trabajo pretende establecer cuál es la frecuencia de estas manifestaciones en los pacientes con LES, que asistieron a una institución de referencia en Cundinamarca, durante un año.

Métodos: Se realizó con la recolección retrospectiva de aspectos clínicos, paraclínicos y manifestaciones cardiovasculares en el periodo de un año.

Resultados: Se encontraron 45 pacientes con diagnóstico confirmado de LES, de edad promedio 35 años. El deterioro de la clase funcional y la disnea se presentaron con mayor frecuencia. El anti-DNA positivo fue más frecuente en los pacientes con disnea (p = 0,037) y deterioro de la clase funcional (p = 0,023). El anticoagulante lúpico, además de estar presente en pacientes con trombosis venosa profunda 60 vs. 15% (p = 0,018), también se encontró en pacientes con falla cardiaca, 66 vs. 16% (p = 0,036).

Conclusión: Se encontró que los síntomas cardiovasculares están presentes en un alto porcentaje de los pacientes con LES, por lo cual se deberían interrogar y detectar tempranamente para así evitar complicaciones cardiovasculares. Se sugiere que algunos autoanticuerpos, como los anti-DNA, anticoagulante lúpico y anti-C1q con hipocomplementemia, también podrían ser útiles para detectar nuevos eventos cardiovasculares en los pacientes con LES.

Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease associated with deposition of immune complexes and production of autoantibodies, affecting 0.1% or the world population. Cardiac involvement is frequent and is a major cause of morbidity and mortality. Its prevalence has been estimated at more than 50% of patients. However, the reported prevalence shows significant differences in relation to the definition of the disease and in determining whether or not to include the asymptomatic involvement.[1] It has been established previously that cardiovascular involvement is the leading cause of death in the non-initial phase of the disease.[2,3] In the study of Molina et al., it was found that Latin men with SLE exhibited more vascular thrombosis and cardiovascular involvement[4]; in the study of Peña et al., cardiac involvement was found in 27 patients with SLE, being pericardial effusion, diastolic and systolic dysfunction and left ventricular hypertrophy the most common manifestations.[5]

In large series, clinical or echocardiographic manifestations of pericarditis have been observed in 20-50% of patients and the series of autopsies have shown pericardial affection in more than 60% of patients.[6] Pericarditis is often associated with chest pain, however, patients may have asymptomatic pericardial effusions, since the effusions are usually mild and, even though they can become large, cardiac tamponade is infrequent in patients without renal insufficiency. The characteristics of the pericardial fluid are usually of neutrophilic exudative type, with high concentration of proteins and normal glucose, and therefore, infection must always be ruled out since it should be taken into account that due to the immunosuppression, patients with lupus can develop infectious pericarditis, mainly caused by *Salmonella*, *Candida* and mycobacteria.

Myocarditis is infrequent in SLE, the subclinical affection with detection of myocardial dysfunction in the echocardiogram is much more common than the clinical signs and symptoms.[7] Myocardial dysfunction in lupus may be of multifactorial origin since it can be a combination of ischemic heart disease, arterial hypertension, renal failure and valvulopathy. It has been described that there may be a relationship between skeletal muscle myositis and myocarditis, and for that reason the levels of creatine phosphokinase (CPK) should always be evaluated in these patients. The endomyocardial biopsy for the diagnosis of cardiomyopathy in SLE shows small foci of myocardial fibrosis, interstitial mononuclear cells infiltrates and occasional myocyte necrosis, with deposition of immune complexes and complement.

Regarding the valvular involvement in SLE, endocarditis is much more frequent in autopsy studies than in the clinical practice. In the autopsy studies, the presence of nonbacterial

vegetations is described in 15-60% of patients.[8] With the use of transesophageal echocardiography, valvular abnormalities have been observed in more than 50% of patients, with alterations ranging from mild and nonspecific valve thickening to the formation of large vegetations and nodules which can cause a severe valvular disfunction.[9] Vegetations are more frequent in the mitral valve, but they can affect any valve. They are usually located on the atrial side of the mitral valve and in the arterial side of the aortic valve. Complications of endocarditis are infrequent and the vegetations exceptionally cause embolic events. Valvular lesions may develop, resolve, persist or worsen independently of the disease activity; the fibrosis can lead to a valvular insufficiency[10] and even valve fenestrations can occur. As for the management of these lesions, there are no formal guidelines for antibiotic prophylaxis, specifically, in patients with SLE. There are studies that have associated the presence of antiphospholipid antibodies and valvular disease, such as the one of Khamashta et al., in which valvular disease was found in one fourth of 132 patients with SLE from different centers, showing a tendency to thrombosis and endocardial lesions with the presence of such antibodies.[11,12]

Concerning the conduction disorders, arrhythmias occur frequently, often sinus tachycardia, accompanying the myocarditis or pericarditis. In patients who have arrhythmias or conduction defects, a possible myocarditis must be evaluated. In patients with active SLE, sinus tachycardia can be observed without having heart disease and it usually resolves with the treatment of SLE. Other causes of tachycardia that must be taken into account are pulmonary embolism and infections. Although isolated conduction defects are very rare in adult patients with SLE, the newborns of mothers with positive anti-Ro or anti-La antibodies, regardless of the diagnosis of SLE, show an increased incidence of congenital complete atrioventricular block. The transplacental passage of these autoantibodies to the fetus can cause myocardial inflammation and fibrosis of the conduction system.[13] In addition, autonomic disorders (dysautonomia), which produce variability in cardiac rhythm, have been reported in patients with SLE.[14]

In relation to coronary disease, it has been recognized as the leading cause of morbidity and mortality in patients with SLE. Its incidence is 9 times higher compared with the general population, with an attributable mortality between 3 and 36%,[15] some factors have been implicated in the pathophysiology in the early development of arterial hypertension, dyslipidemia, renal disease and chronic use of steroids; in addition, it has been demonstrated that when there is lupus activity, there is an increase in triglycerides and VLDL (very low density lipoprotein), with significant reduction of HDL (high density lipoprotein) and apolipoprotein A1,[16] There are also recent studies on the role of the inflammatory process and accelerated atherosclerosis, since the endothelial cells infiltrated by leucocytes produce a variety of inflammatory mediators in the atherosclerotic plaque, such as serum amyloid A and phospholipase A2. Other metabolic and immunologic factors implied are the high levels of lipoprotein A, homocysteine, anticardiolipin antibodies, and anti-oxidized LDL (low density lipoprotein) antibodies. Finally, the procoagulant state in patients with SLE is determined not only by the APL antibodies, but also by high levels of fibrinogen and plasminogen activator inhibitor-1, promoting the development of acute coronary events.[3,17]

Taking into account all the aspects described above, cardiovascular disease is an under-recognized problem in patients with SLE, which can be present at any stage of the disease, with variable manifestations that contribute to higher morbidity and mortality in these patients, and therefore we aim to describe the prevalence of these manifestations in an institution in Cundinamarca, Colombia. Given the extent of the commitment at cardiovascular level in patients with SLE, it is important to have local studies that allow us to know the concurrent prevalence of these diseases, and this is the first study of this type in a reference institution in the Country.

Methodology

Cross-sectional analytic study with retrospective collection of clinical and paraclinical aspects and cardiovascular manifestations according to the criteria of the American College of Rheumatology, in patients with SLE, who attended a tertiary care level hospital of departmental reference in the city of Bogota, during the period between January 2011 and December 2012, having as a reference a population in the Department of Cundinamarca of 2,477,063 (DANE, 2010), from which were taken the patients with diagnoses of lupus, who were referred for evaluation by a specialist of III level, being this the only permanent availability of the specialty of Rheumatology. In this population it was documented the clinical and paraclinical information related with the disease and associated complications. Likewise, it was established the frequency of cardiovascular diseases or disorders related with cardiovascular risk, as well as electrocardiographic and echocardiographic measurements, in order to determine the presence of structural or functional cardiac alterations. The immunological profile given by measurement of antibodies was available, as well as the type of treatment received.

Results

45 patients with an average age of 35 years, 86.7% women, consulted within the period of one year; renal commitment occurred most frequently (66%), followed by hematological involvement (44%). The predominant treatment was with steroids (Table 1).

In this population, the most frequent non-cardiovascular clinical manifestations during the consultation were: arthritis, pleural effusion and ascites (Fig. 1). Fever was another important symptom, being associated with infections in 12 patients, and the urinary tract infection was the most frequent cause of these infections (Fig. 2). Regarding cardiovascular symptoms, dyspnea and functional class deterioration were present in almost half of the patients, with a compromised functional class, New York Heart Association stages III and IV in 26 and 20%, respectively (Table 2).

Table 1 – General Characteristics of Patients.

Variable	Estimate
Age	
Average-years	35.8 ±14.6
Gender	
Female-n (%)	39 (86.7)
Blood pressure	
Systolic blood pressure SBP - mmHg (SD)	136.9 (21.2)
Diastolic blood pressure DBP- mmHg (SD)	85.9 (13.6)
Weight	
Average-kilograms	61.1 ±11.2
Average body mass index - kg/m^2	23.6 ± 4.0
Renal involvement	
Presence of proteinuria - n/n total (%)	30/43 (66.7)
Proteinuria – average grams	2.4 ± 1.2
Nephrotic syndrome - n (%)	9 (20)
Glomerular filtration rate - average ml/kg	61.6 ± s40.08
Presence of urinary sediment - n (%)	22 (48.9)
Hematologic involvement	
Leukopenia - n (%)	11 (24.4)
Anemia - n (%)	20 (44.4)
Thrombocytopenia - n (%)	8 (17.8)
Positive Coombs test - n/n total (%)	3/42 (7.1)
Treatment	
Corticoid	32 (71.1)
Immunosuppressant	12 (26.7)

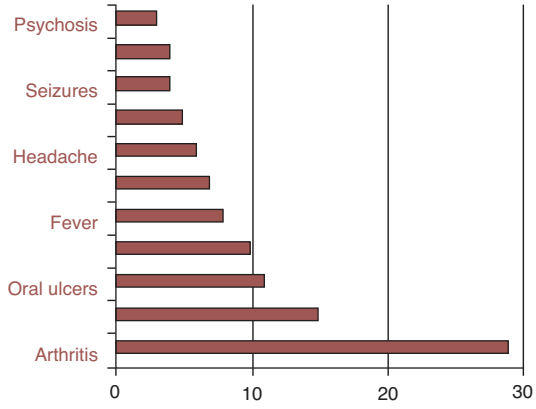

Figure 1 – Symptoms at the time of consultation.

A transthoracic echocardiogram was performed in 62% of patients, finding valvular heart disease, pericardial effusion and pulmonary hypertension. The pressures of the majority of patients with estimation of the systolic pulmonary artery pressure were higher than 35 mmHg (Table 2).

The previous cardiovascular entities found were arterial hypertension, chronic renal insufficiency and peripheral arterial disease. Other important incident events were deep venous thrombosis and arterial hypertension (Table 3).

As for the immunological profile, the majority of patients were ANA positive, being the speckle pattern the most frequent. Nearly one third of patients had positive anti-DNA and hypocomplementemia, and less frequently, but in more than a half, consumed C3 and C4 were found (Table 4).

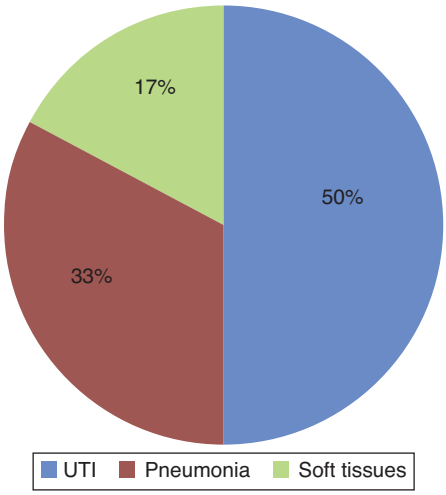

Figure 2 – Infections.

Table 2 – Cardiovascular Involvement in Patients.

Variable	Estimate
Functional class	
I - n (%)	21 (46.7)
II - n (%)	3 (6.7)
III - n (%)	12 (26.7)
IV - n (%)	9 (20.0)
Symptoms	
Chest pain - n (%)	11 (24.4)
Dyspnea - n (%)	20 (44.4)
Functional class deterioration - n (%)	21 (46.7)
Syncope - n (%)	0 (0)
New heart murmur - n (%)	2 (4.4)
Electrocardiographic findings	
Heart rate - beats/min	83.4 ± 21.1
Arrhythmias - n (%)	5 (11.1)
Left ventricular hypertrophy - n (%)	3 (6.7)
Electrocardiographic findings - n/n total (%)	
Ejection fraction - %	60.2 ± 4.2
Pericardial effusion - n (%)	6 (13.3)
PASP–mmHg	40.2 (10.8)
Dilatation of cavities - n (%)	2 (4.4)
Valvulopathies - n (%)	15 (33.3)
Radiological findings	6/99 (6.1)
Cardiomegaly - n (%)	6 (13.3)
Pleural effusion - n (%)	15 (33.3)

Table 3 – Risk Factors and Cardiovascular Events.

Characteristics	Previous	New
Coronary disease - n (%)	0 (0)	2 (4.4)
Arterial hypertension - n (%)	24 (53.3)	6 (13.3)
Dyslipidemia - n (%)	8 (17.8)	0 (0)
Stroke - n (%)	0 (0)	3 (6.7)
Chronic renal insufficiency- n (%)	19 (42.2)	9 (20)
Diabetes mellitus - n (%)	0 (0)	1 (2.2)
Heart failure - n (%)	1 (2.2)	3 (6.7)
Endocarditis - n (%)	0 (0)	1 (2.2)
Pericarditis - n (%)	1 (2.2)	0 (0)
Pulmonary hypertension - n (%)	2 (4.4)	5 (11.1)
Pulmonary thromboembolism - n (%)	0 (0)	2 (4.4)
Deep venous thrombosis - n (%)	1 (2.2)	5 (11.1)
Peripheral arterial disease - n (%)	4 (8.9)	0 (0)

Table 4 – Immunologic Profile of Patients.

Antibody	Estimate
Positive antinuclear ANA - n (%)	44/45 (97.8)
ANA homogeneous pattern	33 (73.3)
ANA speckled pattern	8 (17.8)
ANA cytoplasmic pattern	3 (6.7)
Anti-DNA	31 (68.9)
Hypocomplementemia	29 (64.4)
IgG anticardiolipin	4 (8.9)
IgM anticardiolipin	7 (15.6)
Antiphospholipid	1 (2.2)
Beta2–glycoprotein	3 (6.7)
Lupus anticoagulant	9 (20)
Anti-Ro	7 (15.6)
Anti-LA	2 (4.4)
Anti-C1q	6 (13.3)
Anti-RNP	1 (2.2)
ANCA	2 (4.4)
Anti-ScL	2 (4.4)

No significant differences were found when comparing hypocomplementemia and presence of anti-Ro antibodies with the symptoms or the cardiovascular outcomes. A positive anti-DNA was found more frequently in patients with dyspnea ($p = 0.037$) and functional class deterioration ($p = 0.023$). The lupus anticoagulant, besides being present in patient with deep venous thrombosis, 60 vs. 15% in patients without this event ($p = 0.018$), was also found in patients with heart failure (66 vs. 16% $p = 0.036$). Antiocardiolipin antibodies were present in a higher percentage ($p < 0.001$) in patients with deep venous thrombosis. Finally, the anti-C1q antibodies, besides being present more frequently in patients with chronic renal insufficiency ($p = 0.002$), were found in patients with valvulopathies ($p = 0.041$). Corticosteroid therapy was more frequent in the patients who did not develop CRI ($p = 0.048$). As for the symptoms, the use of steroids was greater in patients without dyspnea ($p = 0.005$) and without functional class deterioration ($p = 0.01$). Regarding the immunosuppressive treatment there was no significant difference in terms of the comparison variables.

Discussion and Conclusions

In this group of patients it was found that cardiovascular symptoms are present in a high percentage and even the non-classical symptoms described for SLE by other authors, such as chest pain, dyspnea and functional class deterioration. According to a study conducted in Sweden, at the Karolina Hospital, after 8.3 years of follow-up, 13% of patients experienced a cardiovascular event, which was linked to the presence of antiphospholipid antibodies, elevation or the Von Willebrand factor and of adhesion molecules type VCAM 1 and fibrinogen; in our study no measurements of this type of adhesion molecules were taken, however, the presence of lupus anticoagulant was significantly related to the presence of thrombotic events and heart failure. In the study described, the arthritis, pleuritis and venous thrombotic events were associated with future cardiovascular events, whereas thrombocytopenia was associated in a protective manner.[18]

In another study conducted in the University of Maryland, with a cohort of 1,874 patients with SLE, 134 cardiovascular events were observed, with an incidence of 14.1/1,000 patients per year, being the risk of cardiovascular events 2.66 times higher than in the general population and it was found the direct association with the levels of anti-DNA antibodies as it was also demonstrated in our study, with a significant relationship with dyspnea and functional class deterioration; in addition, they found that the use of corticosteroids in doses higher than 20 mg/day increased the cardiovascular risk, which is consistent with several publications that have linked the use of corticosteroids with increased cardiovascular risk, however, this is not demonstrated in our study, which may be secondary to the size of the sample.[19]

In New York, at Cornell University, a carotid ultrasonography and an echocardiogram were performed to 197 patients with SLE and 197 controls, and it was found that carotid atherosclerosis was more prevalent in patients with SLE than in controls (37.1 vs. 15.2% $p < 0.001$), with presence of 17.2% of valvular lesions, being consistent with our study in which 15% of these lesions were found; the lesions were significantly linked to higher levels of anti-C1q antibodies, which is a not often found relationship and may be subject to further studies.[20] In other study conducted at Tulane University in New Orleans, a coronary tomography was performed to 65 patients with SLE, finding calcification of the coronary arteries more frequently in patients with SLE (20 of 65 patients) than in control patients ($p < 0.001$)[21] demonstrating that patients with SLE, regardless of having other cardiovascular risk factors, exhibit atherosclerosis more frequently than the general population, and therefore is important to interrogate and perform an active search of cardiovascular symptoms in these patients in order to detect complications early.

The limitations of the present study, according with the design, were that there was not a calculation of the sample size that allow to establish measures of statistical association, since the data of incidence of this type of diseases in Colombia are not known with precision; likewise, in the files of the medical records there were not measurements of other variables such as glycemia, lipids, abdominal circumference, among others; that allow to establish more accurately cardiovascular risk profiles in these patients. However, taking into account that this is the first study carried out in our environment about the presence of cardiovascular diseases and alterations, it gives us an approach to this problem for patients with SLE and, therefore, are proposed future prospective studies with a longer follow-up period, even from the early stages of the initial diagnostic of lupus, that allow to make inferences on the local population.

In conclusion, this is an initial study in which important frequencies of cardiovascular diseases were observed in a group of Colombian patients with SLE, who were referred to a departmental reference rheumatology care center. In addition, it is suggested that there may be an association of some cardiovascular symptoms and cardiac diseases such as heart failure and valvulopathies with some autoantibodies, such as the anti-DNA, lupus anticoagulant and anti-C1q antibodies with hypocomplementemia, which might also be useful for detecting new cardiovascular events in patients with SLE.

Ethical Disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance to the ethical standards of the responsible committee on human experimentation and according with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors state that they have followed the protocols of their workplace regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent from patients and/or subjects referred in the article. This document is held in the posesión of the corresponding author.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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