DETECTION OF CAROTID ATHEROSCLEROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS RELATION TO RISK FACTORS

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KEY WORDS: CAROTID ATHEROSCLEROSIS, SYSTEMIC LUPUS ERYTHEMATOSUS

ABSTRACT

Objective: to detect early atherosclerotic changes in SLE patients and to evaluate its relation to traditional cardiovascular risk factors and lupus-related factors.

Methodology: Forty female SLE patients were included in this study. Their age ranged from 20 to 63 years. All of them were subjected to full history taking, thorough clinical examination, laboratory investigations, disease activity assessment using SLE Disease Activity Index (SLEDAI) and assessment of SLE-related disease damage according to the Systemic Lupus International Collaborating Clinics (SLICC) damage index. Intima-media thickness (IMT) and carotid plaques were measured with carotid B-mode ultrasound. Risk factors associated with carotid plaques and IMT were determined. They included traditional cardiovascular risk factors, SLE-related disease factors and inflammation markers.

Results: Eighteen patients out of the 40 (45%) had plaques. Those patients were statistically significantly (p<0.05) older and had higher systolic and diastolic blood pressure, greater body mass index, higher levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, fibrinogen and C-reactive protein (CRP) than patients without plaques. The patients with plaques had a statistically significant (p<0.05) longer disease duration, higher SLICC damage score and longer duration of prednisone use than those without plaques.

The mean level of IMT of the CCA showed a statistically significant increase (P < 0.05) in SLE patients as compared to controls. The IMT was statistically highly significantly (p<0.001) as correlated with the age, CRP, and SLICC damage index.

Conclusions: The prevalence of the plaques in the studied SLE patients was 45%. There were statistically significant differences between the patients with and those without plaques regarding disease-related factors (disease duration, SLICC damage score and duration of prednisone use) and inflammation markers (fibrinogen and C-reactive protein). IMT of the CCA showed a statistically significant increase (P < 0.05) in SLE patients as compared to controls. The IMT was statistically highly significantly correlated with SLICC damage index. These findings show that SLE-related disease factors
and inflammation markers are associated with carotid atherosclerosis in the SLE patients. SLE patients at risk of atherosclerosis should be examined by high resolution ultrasonography for identification of early stage atherosclerosis. Also, dampening of the inflammatory activity has a favorable impact on the progression of atherosclerosis in SLE patients.

INTRODUCTION

Women with SLE have a high frequency of coronary artery disease (CAD) and exhibit rates of myocardial infarction that are up to 50 fold higher than in women without SLE (Ames et al., 2002). In an autopsy study of 22 young women with SLE, Asanuma et al., (2003) found that 45% had at least one major significantly narrowed coronary artery by atherosclerotic plaques.

Roman et al. (2003) stated that the main findings of their study were that the prevalence of atherosclerosis is significantly increased among patients with lupus and that this increase is not attributable to traditional risk factors for cardiovascular disease.

The mechanism of accelerated atherosclerosis in SLE is not clear. Several factors have been implicated for the high prevalence of premature (CAD) including increased prevalence of conventional risk factors, corticosteroid therapy and factors related to lupus itself (Manzi et al., 1997). Rahman et al., (2000) on studying 15 lupus patients who developed premature CAD concluded that accelerated atherosclerosis in SLE may result from an ongoing inflammatory process accompanying multiple immunological and procoagulant abnormalities. They suggested the possibility that premature CAD may be a result of an underlying genetic susceptibility to develop accelerated atherosclerosis in patients with SLE.

Salzer et al., (2004) found a significant relation between asymptomatic carotid atherosclerosis and coronary artery disease. Also, Roman et al., (1995) found that higher left ventricular mass as detected by echocardiography was associated with the presence of carotid plaques while Manzi et al., (1999) found an independent and strong association between previous coronary events and the presence and severity of focal carotid plaques and increased intimal medial thickness (IMT).

Measurement of the intima-media thickness (IMT) of the far wall of the common carotid artery and the presence of carotid plaques by high-resolution ultrasonography have been established as a clinically useful index for identifying early-stage atherosclerosis. Common carotid artery IMT is strongly correlated with the presence of coronary artery diseases (Kumeda et al., 2002).

Aim of work:

The aim of this study was to detect early atherosclerotic changes in SLE patients and to evaluate its relation to traditional cardiovascular risk factors and lupus-related factors.

PATIENTS AND METHODS

This study included forty SLE female patients who attended the outpatient clinic of Rheumatology and Rehabilitation Department of Banha Hospitals. They were diagnosed according to the 1982 American College of Rheumatology revised criteria for the classification of SLE (Tan et al., 1982). Twenty normal controls with matched age and sex were also included for comparison.

Patients with previous myocardial affection and those with previous stroke were excluded from the study.

All patients were subjected to the following:

- Full medical history with special attention to steroid intake and history of
vascular affection.

Thorough clinical examination with special attention to the measures of systolic and diastolic blood pressure.

Laboratory investigations including:

- Complete blood count (CBC).
- Erythrocyte sedimentation rate (ESR) using Westergren method.
- C-reactive protein, serum albumin and fibrinogen
- Anti-nuclear antibody (ANA) using Kaalstad kits.
- Anti-double stranded DNA by indirect immunofluorescence technique.
- Lipid profile including total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol and atherosclerotic risk ratio (total cholesterol/HDL-cholesterol).
- Determination of C3 and C4 levels.
- Lupus anticoagulant using Russell’s viper venom time with mix.
- Anticardiolipin antibodies using enzyme linked immunosorbent assay.
- Complete urine analysis and protein in 24 hours urine collection in gm/dl.

The SLE Disease Activity Index (SLEDAI) was assessed according to Bombardier et al. (1992) (SLEDAI).

Assessment of SLE-related disease damage: according to the Systemic Lupus International Collaborating Clinics (SLICC) damage index (Gladman et al., 1996).

**Doppler ultrasound examination:**

Carotid ultrasound was performed at the Radiodiagnosis Department of Benha University Hospitals using TOSHIBA 526 – DEVICE equipped with 7.5 MHz imaging transducer. All the patients were examined in supine position with slight hyperextension of the neck. Right and left carotid arteries, carotid bulb, carotid bifurcation and the proximal portions of internal and external carotid arteries were imaged in multiple projections and then focused on the interfaces required to measure the intima media thickness (IMT) and also on any areas of focal plaques.

Plaques were defined as a distinct area protruding into the vessel lumen with at least 50% greater thickness than the surrounding areas. The degree of plaque was graded as follows: (Roman et al., 1995).

0=no plaque.

1=one small plaque (<30% of vessel diameter).

2=one medium plaque (between 30% to 50% of vessel diameter) or multiple small plaques.

3=one large plaque (>50% of vessel diameter) or multiple plaques with at least one medium plaque.

Several risk factors were ascertained. They included:

- **Traditional cardiovascular risk factors:** age, smoking habits, menopausal status, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides levels, diabetes mellitus, body mass index (BMI) [calculated by dividing body weight (kilograms) by the square of height (square meters)], family history of cardiovascular disease (myocardial infarction (MI), stroke or sudden death in a first-degree relative before the age of 60 years). Current hypertensive status was determined using an average of 2 consecutive-sitting blood pressure readings.

- **SLE-related disease factors:** SLEDAI, SLICC damage index, duration of prednisone use and current prednisone use and laboratory studies included ANA, anti-ds-DNA antibodies, C3 and C4 levels, lupus anticoagulant and anticardiolipin antibodies.

- **Inflammation markers:** serum albumin, C-reactive protein and fibrinogen.
**Statistical Analysis:**

Statistical analysis was done by using SPSS statistical package for social science. The data were parametric by using Kolmogrov-Smirnov test. The qualitative data presented in the form of number and percentage. The qualitative data presented in the form of mean, standard deviation and range. Students- t- test was used to compare two groups. Chi-square was used for qualitative data. Pearson correlation coefficient was done to study the relation between variables. Values of P < 0.05 were considered significant, but insignificance was considered when P-value > 0.05.

**RESULTS**

This study included forty women with SLE. Their age ranged from 20 to 63 years (mean±SD= 46.34±10.93 years). Their disease duration ranged from 13 to 230 months (mean ± SD = 114.40±56.93 months).

The results of this study showed that 18 patients (45%) out of the 40 patients had plaques (Fig. 1).

On comparison, the mean age of the patients with plaques was statistically significantly (p<0.05) higher than that of the patients without plaques. Although higher percentage of the patients with plaques was postmenopausal, this higher percentage was statistically non-significant (p>0.05) (Table 1).

The patients with plaques had statistically significant (p<0.05) higher systolic and diastolic blood pressure, greater body mass index, higher levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, fibrinogen and C-reactive protein than the patients without plaques (Table 1). The patients with plaques had statistically significant (p<0.05) longer disease duration, higher SLICC damage score and longer duration of prednisone use than the patients without plaques (Table 1).

The results of this study showed that there were statistically non-significant (p>0.05) differences between the patients with and those without plaques regarding SLEDAI, hypertension status, diabetes mellitus and high-density lipoprotein (HDL) cholesterol, triglycerides and serum albumin levels, current prednisone use, anti-ds-DNA antibodies, C3 and C4 levels, lupus anticoagulant and anticardiolipin antibodies (Table 1).
Table (1): Comparison between patients with plaques and those without plaques regarding traditional cardiovascular risk factors, SLE-related disease factors and inflammation markers.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients With plaques (Mean + SD)</th>
<th>Patients Without plaques (Mean + SD)</th>
<th>t or X²</th>
<th>p</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.00±7.29</td>
<td>39.91±12.09</td>
<td>2.93</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>148.68±54.59</td>
<td>90.64±44.71</td>
<td>2.45</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>55.55%</td>
<td>27.27%</td>
<td>1.65</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>138.11±6.98</td>
<td>124.00±8.06</td>
<td>3.35</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>89.33±7.50</td>
<td>78.55±6.40</td>
<td>2.83</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>44.44%</td>
<td>27.27%</td>
<td>0.64</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>222.67±25.09</td>
<td>178.00±24.53</td>
<td>2.88</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>147.49±20.01</td>
<td>104.98±18.22</td>
<td>2.57</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>61.44±13.10</td>
<td>60.00±14.85</td>
<td>0.06</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>133.67±37.88</td>
<td>120.09±24.16</td>
<td>0.98</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>28.62±4.56</td>
<td>24.40±3.65</td>
<td>2.30</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>11.11%</td>
<td>9.09%</td>
<td>0.02</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>C3 mg/dl</td>
<td>98.33±17.19</td>
<td>95.36±17.87</td>
<td>0.39</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>C4 mg/dl</td>
<td>21.57±6.91</td>
<td>19.44±4.74</td>
<td>0.80</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Anticardiolipin antibodies (% positive)</td>
<td>33.33%</td>
<td>27.27%</td>
<td>0.05</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Lupus anticoagulant (% positive)</td>
<td>33.33%</td>
<td>27.27%</td>
<td>0.05</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-dsDNA (% positive)</td>
<td>44.44%</td>
<td>36.36%</td>
<td>0.14</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>333.33±43.29</td>
<td>293.64±30.26</td>
<td>2.41</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>29.00±25.23</td>
<td>10.91±2.85</td>
<td>2.31</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>14.11±7.37</td>
<td>15.36±6.63</td>
<td>0.33</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>SLICC damage score</td>
<td>2.98±2.33</td>
<td>1.00±1.27</td>
<td>2.37</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Current prednisone use (%)</td>
<td>77.77%</td>
<td>72.72%</td>
<td>0.02</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of prednisone use (months)</td>
<td>84.43±38.86</td>
<td>52.26±26.22</td>
<td>2.29</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

Table (2): Carotid intima-media thickness in SLE patients and in healthy controls.

<table>
<thead>
<tr>
<th>Carotid IMT</th>
<th>SLE patients</th>
<th>Healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.73 to 1.44</td>
<td>0.5 to 1.22</td>
</tr>
<tr>
<td>Mean</td>
<td>0.89</td>
<td>0.79</td>
</tr>
<tr>
<td>± SD</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>t</td>
<td>1.99</td>
<td></td>
</tr>
<tr>
<td>P- value</td>
<td>0.042</td>
<td>Significant</td>
</tr>
</tbody>
</table>

DISCUSSION

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease that mainly affects women. Although treatment has improved during recent decades, patients with SLE appear to have increased morbidity and mortality from The results of this study showed that the mean level of IMT of the CCA showed a statistically significant increase (P<0.05) in SLE patients as compared to controls (Table 2 and Fig.2). The IMT was statistically highly significantly (p<0.0001) correlated with the age, CRP and SLICC damage index (r= 0.79, 0.84, and 0.86, respectively).
Connective tissue diseases such as rheumatoid arthritis (RA) and SLE appear to be associated with accelerated atherosclerosis. The mechanisms involved are not clear, but may include endothelial dysfunction mediated by systemic inflammation (Van Doornum et al., 2003).

A significant association was found between laboratory markers of systemic inflammation and the carotid artery intima-media thickness (IMT) and carotid plaques formation, both of which are non-invasive measures of atherosclerosis. This observation is important because of its implication regarding the pathogenesis of atherosclerosis in RA and other rheumatic diseases (Del Rincón et al., 2003).

Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Current evidence supports a central role for inflammation in all phases of the atherosclerotic process. Substantial biological data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in the thrombotic complications of this disease (Libby et al., 2002).

The aim of this study was to detect early atherosclerotic changes in SLE patients and to evaluate its relation to traditional cardiovascular risk factors and lupus-related factors.

The results of this study showed that 18 patients (45%) out of the 40 patients had carotid plaques. This result was in agreement with that of Manzi et al. (1999) where 40% of their SLE patients had carotid plaques and that of Roman et al. (2003) where 37.1% of their SLE patients had carotid plaques.

The results of this study showed that the SLE patients with plaques were significantly (p<0.05) older than those without plaques. Also, there was a statistically highly significant (p<0.001) correlation between IMT and the age in the SLE patients. These results were in agreement with the results of Asanuma et
al., (2003). Also, in a study done by Doria et al. (2003) on 78 patients with SLE without overt atherosclerotic disease, patients with carotid abnormalities were significantly older than those without any lesions and age was correlated with higher IMT.

The results of this study showed that the patients with plaques had statistically significant (p<0.05) higher systolic and diastolic blood pressure, greater body mass index and higher levels of total cholesterol and low-density lipoprotein (LDL) cholesterol than the patients without plaques. These results were in agreement with Hansoon. (2005) who stated that the presence of atherosclerosis as detected by carotid B-mode ultrasound has been positively associated with traditional cardiovascular risk factors.

The results of this study showed that the patients with plaques had statistically significant (p<0.05) higher levels of C-reactive protein and fibrinogen than the patients without plaques. These results were in agreement with El Magadmi et al. (2004) who stated that the pathogenesis of cardiovascular disease in lupus is likely multifactorial, involving an interaction between inflammation induced and antiphospholipid antibody-mediated vascular injury/thrombosis from the underlying disease and traditional risk factors. Recent studies indicated that, among various markers of inflammation, the CRP level was a particularly powerful predictor of cardiovascular disease independently of serum lipid levels (Abou-Raya & Abou-Raya, 2006). CRP is also hypothesized to be causally involved in the pathophysiology of atherosclerosis and its complications through its localization in the atheromatous plaques and stimulation of macrophages to produce tissue factor, an important procoagulant found in atheromatous plaques (Del Rincon et al., 2003).

The results of this study showed that the patients with plaques had statistically significant (p<0.05) longer disease duration and higher SLICC damage score than the patients without plaques. These results were in agreement with (Roman et al., 2003). Also, The IMT was statistically highly significantly (p<0.001) correlated with SLICC damage index. This result was in agreement with Manzi et al. (1999).

Roman et al. (2003) stated that the independent association of atherosclerosis with the duration of disease and extent of disease-induced damage is noteworthy, because the damage index is a marker of the cumulative severity of disease.

On the other hand, the results of this study showed that there was a statistically non-significant (p>0.05) difference in the SLEDAI and antiphospholipid antibodies between the patients with and those without plaques.

Roman et al. (2003) stated that the SLE is a chronic disease characterized by exacerbations and remissions; thus, measures of disease activity, laboratory assays, and therapy vary with time. However, scores for the disease-activity index, measured at the time of study, did not differ significantly between patients with plaques and those without plaques, whereas the damage-index score, a summation of the cumulative effects of disease, was greater in patients with plaques, associating chronic tissue damage with atherogenesis.

In the study of Manzi et al. (1999), the presence of antiphospholipid antibodies was not associated with either plaque or increased IMT which may be due to the fact that antiphospholipid antibodies were measured at one point in time not taking
into account the possible changing titers of the auto antibodies overtime.

The results of this study showed that the SLE patients with plaques had a statistically significant \((p<0.05)\) longer duration of prednisone use than those without plaques. Svenungsson et al. (2001) stated that steroid treatment is often believed to be atherogenic, due to effects on plasma lipoproteins. Manzi et al. (1999) found that women currently receiving prednisone tended to have higher total cholesterol and triglyceride levels. Similarly, women currently taking prednisone or those with higher cumulative prednisone use and longer duration of prednisone use had a higher systolic blood pressure.

Conclusions:

SLE patients exhibited greater thickness of the common carotid artery than healthy controls so SLE patients have an ultrasonic marker of early atherosclerosis. 18 patients (45%) out of the 40 patients had plaques there were statistically significant differences between the patients with and those without plaques regarding disease-related factors and inflammation markers. The IMT was statistically highly significantly correlated with SLICC damage index. These findings show that SLE-related disease factors and inflammation markers are associated with carotid atherosclerosis in the SLE patients.

We recommend: Early recognition of these findings before occurrence of atherosclerotic complications may reduce cardiovascular events in SLE patients. Because of the non-invasive character and easy applicability, SLE patients at risk of atherosclerosis should be examined by high resolution ultrasonography for identification of early stage atherosclerosis. Also, dampening of the inflammatory activity has a favorable impact on the progression of atherosclerosis in SLE.

REFERENCES


دراسة انتشار تصلب الشريان السباتي وعلاجته بعوامل الخطر في مرض الذنبة الحمراء

رفعت مصطفى الطناوي ، أمل فتحي سليمان ، شيرين عبدالفتاح الجرجاوي ،
وتهامي حليم عبدجليل *

قسم الروماتيزم والتأهيل والأنشطة التشخيصية - كلية الطب بينها - جامعة بها

الهدف من هذه الدراسة: هو دراسة انتشار تصلب الشريان السباتي في مرض الذنبة الحمراء وتقييم علاجاته بعوامل الخطر القلبية الوعائية التقليدية وعوامل متعلقة بمرض الذنبة الحمراء.

وقد استمرت هذه الدراسة على أربعين مريضًا مرض الذنبة الحمراء تراوحت أعمارهم من بين 20 و 63 عامًا، وقد تم أخذ تاريخ المرض كاملاً، وعمل فحص كلينيكي شامل وعمل تحاليل طبية وتقدير مستويات التلف المتعلق بمرض الذنبة الحمراء في جميع المرضى، وقد تم قياس سمك الجدار المبطن للشريان السباتي واللوحة السباتية بواسطة المجهر فوق الحوائية وتم تحديث عدلة الخطر المرتبطة بهما، وقد استمرت عمليات الخطر على عمولة الخطر القلبية الوقائية التقليدية وعوامل متعلقة بمرض الذنبة الحمراء والعلامات والأعراض

وأظهرت النتائج أن (45%) من الأربعة مريضات كان لديهم لوحة، وأن المريضات الثلاثي كان لديهم لوحة كافيةً لتصسب تصلب الشريان السباتي في مرض الذنبة الحمراء.

وتمثلت من هذا البحث: وجود تصلب الشريان دون الإكلينكي في مرض الذنبة الحمراء وبيئة التأديرة أن استخدام المكملات فوق الحميات تكون كليًا للتشخيص في الشريان السباتي كما أن الدراسة بعلاج الفعل للأمثلة المماثلة للذين تصلب الشرايين. كافل وسلبة لمنع حدوث تصلب الشرايين.