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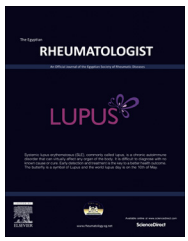

ORIGINAL ARTICLE

The neuropeptide adrenomedullin, could it be linked to renal involvement and disease activity in systemic lupus erythematosus?

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KEYWORDS

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SLE;
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Abstract *Aim of the work:* The aim of this study was to assess adrenomedullin level in systemic lupus erythematosus (SLE) patients with nephritis compared with those without and healthy controls and to correlate adrenomedullin level with SLE disease activity.

Patients and methods: Serum adrenomedullin was evaluated in 60 SLE patients (mean age 27.7 ± 8.25 years) and in 20 matched controls. The SLE patients were divided into two groups: Group I (with nephritis) and Group II (without) (30 patients each). The SLE disease activity index (SLEDAI) was assessed.

Results: The median serum adrenomedullin levels were significantly higher in SLE patients (7.4 ng/ml) compared to healthy controls (3.1 ng/ml) ($p < 0.001$). It showed a statistically significant difference between group I (8.8 ng/ml) and II (6.1 ng/ml) ($p < 0.01$). A significant relation was observed between the level of serum adrenomedullin with the neuropsychiatric manifestations ($p = 0.006$) and vasculitic lesions ($p = 0.014$) in group II patients and with pulmonary hypertension ($p = 0.04$), oral ulcers ($p = 0.03$), and serositis ($p = 0.02$) in group I. A significant negative correlation was found in group I patients between adrenomedullin and 24 h protein/day ($r = -0.38$, $p < 0.05$), as well as platelets & C4, and with C3 in group II as well as a highly significant correlation between SLEDAI and adrenomedullin level in SLE patients ($r = 0.76$, $p < 0.001$) and steroid dose ($p < 0.001$).

Conclusion: Serum AM is elevated in SLE especially in lupus nephritis patients & correlates with lupus disease activity. It is negatively associated with urine protein excretion per 24 h in the group of lupus nephritis patients. Serum AM may be considered among biological markers in SLE.

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1. Introduction

Lupus nephritis is one of the most severe forms of organ involvement in systemic lupus erythematosus (SLE) and occurs in at least 50% of patients [1]. Key factors play a considerable role in the pathogenesis of SLE as oxidative stress [2], apoptosis [3] and cytokine overproduction [4–7]. Current evidence suggests that dysregulated expression of cytokines plays a crucial role in the immunopathogenesis of SLE with a predominantly type 1 T-helper cell (Th1) activation in patients with active lupus nephritis [1].

A number of biochemical markers are currently used to clinically assess SLE renal disease activity, such as anti-double stranded deoxyribonucleic acid (ds-DNA) antibodies and complement component levels. Nevertheless, the correlation between these markers and lupus nephritis is imperfect, and their utility in reflecting disease activity remains controversial [8].

The importance of measuring vascular biomarkers as Adrenomedullin reflects the fact that the molecule is released by endothelial cells injury [9]. Adrenomedullin (AM) is a 52 amino acid peptide originally isolated from extracts of human pheochromocytoma tissue and it belongs to the calcitonin/calcitonin gene-related peptide (CGRP) family [10]. Pro-inflammatory cytokines especially interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α), which are pivotal in mediating the inflammatory process of SLE, appear to stimulate the production of AM in various cell types in SLE [11]. In lupus nephritis, the presence of IL-1, IL-6 and TNF-α in diseased kidney appears to mediate local pathogenic effects such as mesangial proliferation [12]. It has been shown that AM suppresses the secretion of pro-inflammatory cytokines such as TNF-α in macrophage cell line so that they can suppress mesangial cell mitogenesis [13]. Neuropeptides as AM can exhibit potent anti-inflammatory activities. They can regulate different critical levels of innate immunity [14]. The capacity of these neuropeptides to regulate adaptive immunity has been reported. They can impair activation/differentiation of Th1 cells [15].

The aim of this study was to assess adrenomedullin level in SLE patients with nephritis compared with those without and healthy controls, and to correlate its level with disease activity.

2. Patients and methods

Sixty SLE patients were recruited from the outpatient and inpatient units of Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals, and were diagnosed according to American College of Rheumatology (ACR) revised criteria [16]. Twenty healthy subjects, matched for age and sex included in the study served as a control group. The patients were classified according to renal SLEDAI score into 2 groups; Group I comprised 30 SLE patients with lupus nephritis (having a renal SLEDAI of $\geqslant 8$; at least 2 abnormal results for renal parameters on at least two occasions) [17] and group II comprised 30 SLE patients without nephritis. The following conditions which may affect adrenomedullin levels were excluded; uncontrolled systemic hypertension: systolic blood pressure (SBP) > 140 mmHg ± diastolic blood pressure (DBP) > 90 mmHg, coronary heart disease or congestive heart failure, end-stage renal failure, pregnancy, chronic respiratory diseases, diabetes mellitus, chronic liver diseases. Informed consents were taken from the patients and the study was approved by the local ethics committee.

All the patients were subjected to full history taking, clinical examination and Disease activity assessment using the SLE disease activity index (SLEDAI) [18]; Mild activity (SLEDAI; 1–10), Moderate activity (SLEDAI; 11–20), High activity (SLEDAI; 21–45). Patients were subjected to laboratory investigations as follows: complete blood count (CBC), erythrocyte sedimentation rate (ESR), Liver and kidney functions, urine analysis, antinuclear antibodies (ANA), anti ds-DNA, complement C3 (normal value: 90–180 mg/dl) and C4 (normal value: 10–40 mg/dl) tests. Adrenomedullin level was tested in the sera of patients and controls using Enzyme Linked Immunosorbent Assay (ELISA).

2.1. Serum adrenomedullin measurement

Blood samples from patients and controls were centrifuged and stored at -80° C until assay of adrenomedullin. Sera were analyzed by ELISA according to the manufacturer's protocols (ELISA kit, Cat No: EIA-3418, Lot: 601777, DRG International Inc., USA).

Renal biopsy was performed in those patients with lupus nephritis and classified according to the world health organization (WHO) criteria [19].

Statistical analysis: Data obtained from the study were coded and entered using the software SPSS (Statistical package for social science) version 16.0. Quantitative parametric data were described in mean and standard deviation (SD), while non parametric data in median and percentiles. Percentages were used when appropriate. Comparison between groups was done using Chi square test for qualitative variables. For quantitative data, comparison between 2 groups was done by Mann–Whitney test for nonparametric data and among 3 groups by Kruskal Wallis test. The correlation between serum adrenomedullin level and other biochemical data and SLEDAI was assessed by Spearman coefficient of correlation. ROC curve was done to get the best cutoff to discriminate between SLE nephritis versus non-nephritis and control and also to get the best cutoff to discriminate between SLE patients with activity $\leqslant 10$ according to SLEDAI versus SLE patients with more active disease > 10. Interpretation of the area under the curve (AUC): 0.50–0.75 = fair, 0.75–0.92 = good, 0.92–0.97 = very good and 0.97–1.00 = excellent [20]. The p-value is considered significant if < 0.05.

3. Results

The SLE patients were 54 females (90%) and 6 males (10%), their ages ranged from 13 to 51 years with mean age of 27.75 ± 8.25 years. The disease duration in all patients ranged from 0.33 to 20 years with mean of 5.5 ± 4.5 years. The 20 matched control ages ranged from 16 to 40 years with a mean of 29 ± 6.13 years.

On comparing between group I and II SLE patients as regards the various demographic and clinical parameters, no significant difference was found apart from the SLEDAI score that was significantly higher in group I compared to group II