The Egyptian Rheumatologist (2016) 38, 183–187

Egyptian Society of Rheumatic Diseases

The Egyptian Rheumatologist

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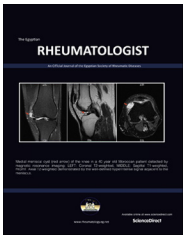

SHORT COMMUNICATION

The alternative complement pathway activity may depend on plasma malondialdehyde level in systemic lupus erythematosus patients: Preliminary results

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Received 1 February 2016; accepted 21 February 2016
Available online 21 March 2016

KEYWORDS

Malondialdehyde;
Oxidative stress;
Alternative complement pathway;
AH_{50};
Systemic lupus erythematosus

Abstract *Background:* Malondialdehyde (MDA) is a marker of oxidative stress (OS) and one of the major alternative complement pathway (ACP) activators associated with systemic lupus erythematosus (SLE) activity. ACP is the principal mediator of SLE inflammation and progression.

Aim of the work: To investigate the association between the ACP functional activity and plasma MDA in SLE patients.

Patients and methods: Sixteen consecutive SLE patients were analyzed for their complement profile and oxidative stress measurement. 60 healthy subjects were included as a control group. The Complement components C3, C4 and properdin-factor B (PfB) were assessed, ACP activity was assayed according to alternative hemolytic 50 (AH_{50}). Plasma total lipid peroxide quantification was performed by assessing the plasma MDA. Total antioxidant capacity was measured with oxygen radical absorbance capacity (ORAC). OS ratio was calculated by dividing the total antioxidant capacity by MDA.

Results: Sixteen patients (13 females and 3 males) with a mean age of 27.86 ± 6.26 years and a disease duration 69.65 ± 54.65 months were included. There was a significant increase of MDA in the patients (MFI = 613 ± 56.21) compared to the control (MFI = 460 ± 37.85) ($p = 0.003$). C3 was significantly consumed and MDA increased in the low AH50 compared to the normal AH50 patients ($p = 0.02$ and $p = 0.01$ respectively). AH50 significantly negatively correlated with the C3 ($p = 0.02$) and MDA ($p = 0.048$). There was lack of any association between ORAC and ACP. Properdin factor B significantly negatively correlated with C3 ($p = 0.007$).

Conclusions: These initial results encourage future in-depth studies on the association of OS–ACP in SLE pathogenesis.

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Peer review under responsibility of Egyptian Society of Rheumatic Diseases.

http://dx.doi.org/10.1016/j.ejr.2016.02.003

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by microvascular inflammation and development of autoantibodies [1]. The exact cause of SLE is unknown; multiple factors including genetic and environmental [2] and various key players as cytokines [3,4] oxidative stress [5] and apoptosis [6] are implicated in the pathogenesis of the disease. Dysfunction of the T lymphocytes, B lymphocytes and dendritic cells, production of antinuclear autoantibodies and the loss of self-tolerance reveal the defective immune regulatory mechanisms [7] and increased oxidative damage [8,9].

The past decade has known intensive research efforts concerning the two major damage factors in SLE: oxidative stress (OS) and the alternative complement pathway (ACP) [10,11]. Complement was found to bind to malondialdehyde (MDA) epitopes and protects from oxidative stress [12]. Complement plays a dual role in the progression of SLE since it has important protective functions, such as the clearance of immune complexes and apoptotic cells, but is also a mediator of renal inflammation. However, selectively inhibiting the ACP is beneficial, presumably because of protective contributions from the classical and/or lectin pathways [13].

Oxidative stress contributes to immunomodulation which may lead to autoimmune diseases as SLE, antiphospholipid syndrome, rheumatoid arthritis (RA) [14–16], scleroderma [17] and Behcet's disease [18]. Reactive oxygen species are implicated in SLE and oxidative stress has the potential to elicit an autoimmune response, to contribute to the pathogenesis and could be useful when determining a prognosis [19]. Oxidative imbalance with an increase in MDA and a decrease in antioxidants plays a pathogenic role in the progression of SLE disease [20,21] and a possible cause of disease activity [22]. Inhibition of oxidative stress may represent newly discovered molecular and cellular targets for the treatment of SLE [7]. Antioxidants may protect against development of RA or SLE by combating oxidative stress [23,24].

Oxidative stress plays an important role in many aging diseases, including cardiovascular disease and age-related macular degeneration (AMD). Complement factor H risk allele confers higher complement activation and cell lysis activity in AMD by modulating oxidative stress and interacting with oxidized phospholipids [25]. However, these two lesional factors have not been analyzed simultaneously in this SLE.

The current study aimed to describe some evidence for OS–ACP association with a hope to initiate further studies to fill this gap in such a complex inflammatory disorder.

2. Patients and methods

This pilot study involved 16 consecutive SLE patients attending different wards of the Military University Hospital of Oran, Algeria fulfilling the 1997 American college of Rheumatology criteria [26]. Sixty healthy subjects (30 females and 30 males) of matched age served as a control. The study protocol was fully approved by the ethics committee of the Regional Military University Hospital of Oran (Oran, Algeria). All patients gave written informed consent. Other diseases such as diabetes mellitus, rheumatoid arthritis and antiphospholipid syndrome that may cause oxidative stress were excluded.

The plasma was separated and stored at −80 °C until analysis. The Complement components C3, C4 and properdin-factor B (PfB) were assessed in all samples by nephelometry laser (Image 800, Beckman Coulter, USA). ACP activity was assayed according to previously described method AH_{50} [27]. Plasma total lipid peroxide quantification was performed by malondialdehyde (MDA) level measurement using thiobarbituric acid reactive substance (TBARS) method and the results were given as mean fluorescence intensity (MFI) [28,29]. Total antioxidant capacity was measured with oxygen radical absorbance capacity (ORAC) with a 1:150 plasma dilution. The results were given as area under curve (AUC) [30]. OS ratio was calculated by dividing the total antioxidant capacity by MDA [31].

Statistical analysis was done by using SPSS (IBM software version 20.0 Chicago-USA). Student's *t*-test was performed for means comparison. In order to investigate whether or not OS parameters and plasma ACP activity were correlated, two tailed Pearson correlation was carried out. Significance was defined as $p \leqslant 0.05$.

3. Results

Sixteen patients (13 females and 3 males) with a mean age of 27.86 ± 6.26 years and a disease duration of 69.65 ± 54.65 months were included. The antinuclear antibody (ANA) positivity, disease activity and medications received of the active and inactive SLE patients are presented in Table 1. The 60 control (30 females and 30 males) had a mean age of 27.88 ± 8.28 years.

There was a significant increase of MDA in the patients (MFI = 613 ± 56.21) compared to the control (MFI = 460 ± 37.85) ($p = 0.003$). When SLE patients were divided into two groups according to their ACP activity AH_{50} (<80% and ⩾80%), both groups showed higher plasma MDA adducts than controls, but the levels were much greater in the low AH_{50} group. Interestingly, only C3 and MDA changed when the ACP was consumed (Table 2). The lack of any association between antioxidant defense capacity (ORAC) and ACP (Table 3) was unexpected.

The MDA level significantly correlated with AH_{50}, indicating that increased complement ACP activity parallels with lipid peroxidation endproduct levels (Table 3). Furthermore, the estimation curve by linear regression shows that MDA may explain ACP function by nearly 26% ($R^2 = 0.27$, $p = 0.048$) (Fig. 1).

Table 1 Characteristics of the active and inactive SLE patients.

Characteristic mean ± SD or *n* (%)	SLE patients (*n* = 16)	
	Inactive (*n* = 5)	Active (*n* = 11)
Age (years)	31.67 ± 7.2	24.1 ± 5.3
Disease duration (months)	95.3 ± 59.1	44 ± 50.2
SLEDAI	–	10 ± 2.3
ANA positivity	5 (100)	10
Prednisone intake	3 (60)	11
Chloroquine intake	4 (80)	9

SLEDAI: systemic lupus erythematosus disease activity index, ANA: antinuclear antibodies.