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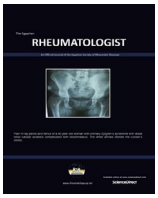

Original Article

Anti-nucleosome antibodies in systemic lupus erythematosus patients: Relation to anti-double stranded deoxyribonucleic acid and disease activity

Mayada Ali Abdalla [a,*], Shereen Ali Elmofty [a], Ahmed Amin Elmaghraby [a], Rania Hassan Khalifa [b]

[a] Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University, Egypt
[b] Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Egypt

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ABSTRACT

Aim of the work: To measure the level of anti-nucleosome (anti-NCS) antibodies in systemic lupus erythematosus (SLE) patients and to evaluate their relation with anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies and SLE disease activity.

Patients and methods: 66 Egyptian SLE patients were investigated for the detection of anti-NCS antibodies and anti-dsDNA antibodies. Disease activity was assessed using the SLE disease activity index (SLEDAI) and the European consensus lupus activity measurement (ECLAM).

Results: The median age of the patients was 25.5 years (12–48 years) and disease duration 3 years (1 month to 26 years). anti-NCS antibody was found in 48 (72.7%) patients. Non-significant difference was found between both those positive or negative anti-NCS antibodies regarding the clinical features apart from fever ($p = 0.019$). Lupus nephritis was present in 35/48(72.9%) of those with positive and in 11/18 (61.1%) of those with negative anti-NCS ($p = 0.35$) A significant correlation was found between anti-NCS antibodies with SLEDAI ($r = 0.36$, $p = 0.003$) and ECLAM ($r = 0.29$, $p = 0.019$). No significant relation was found between anti-NCS antibodies and clinical features of SLE, apart from fatigue ($r = 0.3$, $p = 0.015$). A significant correlation with hypocomplementemia (C3 $r = -0.37$, $p = 0.002$ and C4 $r = -0.32$, $p = 0.018$) and anaemia ($r = -0.32$, $p = 0.009$). anti-dsDNA antibodies were detected in 35 (53%) SLE patients; 70.8% of those with positive and 5.6% of those with negative anti-NCS antibodies.

Conclusion: Anti-NCS antibodies could play a role in the pathogenesis of SLE and is related to disease activity. Its association with anti-dsDNA antibodies and its presence in those with negative anti-ds DNA may aid in the diagnosis of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a common complex disease characterized by chronic generalized inflammation which may involve several tissues and organs [1]. It is a multisystem autoimmune disorder, characterized by the presence of circulating antinuclear antibodies (ANAs). One of the immunological hallmarks of SLE is the loss of tolerance to self-chromatin, manifesting as circulating auto-antibodies directed against three of its major subunits, namely, double-stranded deoxyribonucleic acids (ds-DNA), histones and nucleosomes [2].

Nucleosomes are basic elements of chromatin and are considered to be the major antigens in the pathogenesis of SLE [3]. The nucleosome is a fundamental chromatin unit, it consists of a core particle, composed of an octomer of two copies each of histone H2A, H2B, H3, H4 around which two superhelical turns of approximately 146 base pairs of helical DNA are wrapped. Its molecular weight is 262 KD, and its crystal structure has been identified [4]. Nucleosomes are generated during cell apoptosis by chromatin cleavage carried out by endonucleases [5]. They may become immunogenic during apoptosis when cellular debris containing chromatin are not cleared adequately [6]. It was proposed that the nucleosome is the principal antigen in the pathophysiology of SLE, and that anti-nucleosome (anti-NCS) antibodies are associated with organ damage [7]. Nucleosomes have been shown to be more strongly immunogenic than native DNA or histones and

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* Corresponding author.
E-mail address: mayada_ali.abdalla@hotmail.com (M.A. Abdalla).

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induce a strong T-helper cell response [8]. anti-NCS antibodies have been successively detected in different connective tissue diseases as SLE, scleroderma and mixed connective tissue disease [7] however, with high sensitivity and specificity in the diagnosis of SLE [9,10]. In Egyptian SLE patients, anti-NCS antibodies were elevated and related to the degree of renal affection [11].

A close relationship between anti-NCS antibody positivity and SLE disease activity evaluated by SLE disease activity index (SLEDAI) has been shown [7], particularly with renal flares [12]. Among the anti-chromatin antibodies, the strongest association with renal involvement was identified with anti-NCS antibodies, which presumably have a pivotal role in the pathogenesis of lupus nephritis [13] by mediating nucleosome-specific antibody binding to basement membrane and deposition in glomeruli [14].

The aim of the present work is to measure the level of anti-NCS antibodies in SLE patients and to evaluate their relation with anti-dsDNA antibodies and SLE disease activity.

2. Patients and methods

The study included 66 adult SLE patients; 62 females and 4 males. Patients were classified according to the American College of Rheumatology (ACR) revised classification criteria for SLE [15]. Patients were selected from the inpatient section of the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospital. Their age ranged from 21–48 years with a median of 25.5 years. Disease duration ranged from 1 month to 26 years with a median of 3 years. Patients were divided into two groups after screening for anti-nucleosome (NCS) antibodies: 48 SLE patients with positive anti-NCS antibodies (Group A) and 18 SLE patients with negative anti-NCS antibodies (Group B). The study conforms to the 1995 Helsinki declaration and all patients gave their informed consent prior to their inclusion. Disease activity was assessed for all patients using the SLE disease activity index (SLEDAI) [16] and the European Consensus Lupus Activity Measure (ECLAM) [17].

Laboratory investigations were carried out including the erythrocyte sedimentation rate (ESR), complete blood count (CBC), serum aspartate (AST) and alanine (ALT) transaminases, serum albumin, creatine phosphokinase (CPK), alkaline phosphatase (ALP), blood urea, serum creatinine, quantitative determination of serum complement level (C3and C4), complete urine analysis and 24 h-urinary proteins. Antinuclear antibody (ANA) was assessed by immunofluorescence technique (indirect fluorescent antibody kit ANAFAST™, No's1670, 6670,1680) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody by enzyme linked immunosorbent assay (ELISA) (using anti-dsDNA ELISA kit No. 7100). Quantitative measurement of anti-nucleosome antibodies was performed by ELISA (QUANTA Lite™ Chromatin ELISA) [18].

Abdominal ultrasound was performed to assess the presence of hepatomegaly, splenomegaly, ascites or renal involvement and determine the degree of nephropathy.

Renal biopsies were done in those with lupus nephritis. The specimens were processed for light microscopy and classified according to the 1982 modified world health organization (WHO) morphologic classification of lupus nephritis [19].

2.1. Statistical analysis

Data were statistically described in terms of mean (±SD) and range or frequencies and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann-Whitney *U* for independent samples. Chi-square test was performed for comparing categorical data. Correlation between various variables was done using Spearman rank correlation equation. All statistical calculations were done using SPSS version 15 for Microsoft Windows. Significant values are set at $p < 0.05$

3. Results

The 66 patients' age ranged from 21–48 years with a median of 25.5 years. Disease duration ranged from 1 month to 26 years with a median of 3 years. anti-NCS antibody was found in 48 (72.7%) patients. The clinical manifestations and disease activity of the studied SLE patients according to anti-NCS positivity are presented in table 1.

Anti-NCS antibody was found positive in 48 (72.7%) SLE patients: 45 females and 3 males. Their age ranged from 21–48 years with a median of 25.5 years. Disease duration ranged from 1 m-26 years with a median of 3 years. Anti-NCS antibody was not detected in 18 (27.3%) patients: 17 females and 1 male, with no significant statistical difference between both group A and group B SLE patients as regards demographic data ($p > 0.05$). Non-significant difference was found between both groups regarding the clinical features apart from fever ($p = 0.019$). Lupus nephritis

Table 1
The clinical manifestations and disease activity of the systemic lupus erythematosus patients according to anti-nucleosome antibody positivity.

Parameter n (%) or median (range)	SLE patients						p
	All (n = 66)		Group A (n = 48)		Group B (n = 18)		
Manifestations							
General	52	(78.8)	40	(83.3)	12	(66.7)	0.14
Mucocutaneous	55	(83.3)	38	(79.2)	17	(94.4)	0.14
Musculoskeletal	56	(84.8)	43	(89.6)	13	(72.2)	0.08
Renal	46	(69.7)	35	(72.9)	11	(61.1)	0.35
Haematological	44	(66.7)	32	(66.7)	12	(66.7)	0.49
Vascular	34	(51.5)	24	(50)	10	(55.6)	0.26
Pulmonary	20	(30.3)	16	(33.3)	4	(22.2)	0.38
Cardiac	17	(25.8)	12	(25)	5	(27.8)	0.82
Neuropsychiatric	16	(24.2)	11	(22.9)	5	(27.8)	0.68
Intestinal	1	(1.5)	0	(0)	1	(5.6)	0.1
Lymphadenopathy	2	(3)	1	(2.1)	1	(5.6)	0.46
Ocular	3	(4.5)	2	(4.2)	1	(5.6)	0.81
Disease activity							
SLEDAI	11	(0–39)	12.5	(0–39)	4	(0–10)	0.19
ECLAM	4	(0–10)	6.5	(0–27)	2.5	(1–10)	0.5

Group A: antinucelosome positive antibodies, Group B: antinucleosome negative antibodies. Significant $p < 0.05$.

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