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Antinucleosomal Antibodies and Its Correlation to SLE Manifestations

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Abstract

Subject: SLE is an autoimmune disease with skin, joint, renal, cardiovascular, and nervous manifestations. The disease is classified as an immune complex-mediated disease and is characterized by the production of various autoantibodies. Until now, more than 100 autoantibodies have been identified. **Patients and methods:** This study was performed on 200 SLE patients. All of them were females and their ages ranged from 20 to 49 years. All participants in this study were subjected to physical examination, thorough history taking including age, sex, age of onset, duration of SLE disease, family history, and SLEDAI. Laboratory investigations included: CBC, ESR, liver function tests, renal function tests, ANA, Anti-dsDNA, CRP, Complements C3, C4, and Anti-NCS. **Results:** There was a highly significant inverse correlation between anti-NCS antibodies and Hb level, a significant direct correlation between anti-NCS antibodies and 24hr proteinuria, a significant inverse correlation between anti-NCS antibodies and complements (C3 and C4), a significant correlation between anti-NCS antibodies and anti dsDNA antibodies, a significant correlation between anti-NCS and disease activity, SLEDAI, and renal affection. **Conclusion:** Anti-NCS antibody can be a useful tool in the diagnosis of SLE especially in patients who are negative for anti-ds DNA antibodies.

Keywords

SLE, Autoantibodies, Anti-NCS

1. Introduction

Systemic lupus erythematosus (SLE) is a non-organ specific autoimmune disease characterized by widespread inflammation, affecting virtually every organ and/or

system in the body, and by the production of various autoantibodies, in particular antinuclear autoantibodies (ANAs) [1].

Lupus nephritis (LN) refers to a spectrum of glomerulopathies that range from minor focal scarring to diffuse proliferative destruction of glomeruli with active inflammation and immune complex deposition [2]. It is one of the most serious manifestations of SLE and is associated with considerable morbidity and even mortality [3].

ANAs are autoantibodies directed against chromatin and its individual components including double-stranded deoxyribonucleic acid (ds-DNA), histones and some ribonucleoproteins (RNPs) [1]. Chromatin represents the main autoantigen-immunogen in SLE and its specific antibodies are an important marker of the disease [4]. Anti-chromatin antibodies appear to be a useful addition to the laboratory tests that can help in the diagnosis and treatment of SLE. These antibodies are both sensitive and specific for SLE, and are useful markers for an increased risk of lupus nephritis [5].

Nucleosomes are the basic elements of chromatin. During cell death, particularly during apoptosis, activated endonucleases cleave the chromatin into nucleosomes. The nucleosomes released into the circulation are rapidly and effectively removed by hepatic metabolization or immunological elimination under physiological conditions [6].

Anti-NCS antibody could be an early and sensitive tool in the diagnosis and assessment of disease activity in SLE patients who are negative for anti-dsDNA antibodies [1]. Both anti-NCS and anti-dsDNA antibodies, are related to disease activity, whereas only anti-dsDNA antibodies are related to renal disorders. It was also found that there is a better relationship of anti-dsDNA antibodies with nephropathy than with anti-NCS antibodies [7] [8] [9], while another study found a positive correlation between anti-NCS antibodies and nephritis in active SLE and in non-active SLE [10].

In murine models of lupus, anti-NCS antibodies arise before the development of other anti-chromatin antibodies and they have the highest prevalence from the early stages of life. It was hypothesized that anti-NCS antibodies could be useful in the diagnosis and assessment of disease activity in SLE patients [11] [12].

This study was carried out to assess the value of anti-NCS antibodies in diagnosing SLE; especially in anti-ds-DNA negative patients and to determine the association of these antibodies with disease activity in SLE patients.

2. Subjects and Methods

The present study was a cross-sectional study that was conducted on 200 SLE patients attended Rheumatology clinics of Al-Azhar University faculty of Medicine, Cairo, Egypt. All patients were females. Their ages ranged from 20 - 49 years (34.3 ± 7.1 years). Disease duration ranged from 6 - 240 months (44.4 ± 27.1 months).

Inclusion Criteria: All women at the start of the study fulfilled the SLICC criteria for classification of SLE [13].

Exclusion criteria: patients with overlap syndromes, and patients on dialysis were excluded from this study.

Control group comprised 100 normal healthy females of matching age to the patient group. Their ages ranged from 20 - 54 years (35.45 ± 12.5 years).

All patients subjected to careful history taking, thorough physical examination, and assessment of disease activity using The SLE disease activity index (SLEDAI) which has been shown to be reliable and reproducible [13] [14] [15].

Plain x-ray was done for the affected joints. Plain chest x-ray was done to detect enlargement of cardiac chambers, pleural and pericardial effusion or pneumonitis. Laboratory investigations included CBC, ESR, liver function tests, renal function tests, complete urine analysis, quantitative 24 hours urine examination for albumin, CRP, (C3 and C4), ANA, anti-ds-DNA antibodies, and serum level of anti-NCS antibodies detected by ELISA [10].

Lupus nephritis was diagnosed if patients had a biopsy consistent with the WHO classification, or if there were very strong supporting data implicating renal involvement attributable to SLE, when combinations of two or more of the following were present: diastolic blood pressure > 90 mmHg requiring diuretic therapy; hypertension; proteinuria > 0.5 g/24h; creatinine clearance < 60 ml/min; serum creatinine > 124 μmol/l [5], in the absence of any other relevant disease. [11].

Statistical analysis was performed using SPSS version 17 under the platform of Microsoft Windows XP, Professional edition.

3. Results

This study included 200 female patients suffering from SLE. Their age ranged from 20 - 49 years (34.3 ± 7.1 years), with disease duration of 44.4 ± 27.1 months, and family history was positive in only 30 patients. ANAs, anti-dsDNA and anti-NCS antibodies had a sensitivity of 95.0%, 75.0% and 76.7% respectively; specificity of 95.0%, 100% and 100% respectively; PPV of 98.3%, 100% and 100% respectively; NPV of 86.4%, 57.1% and 58.8% respectively for the diagnosis of SLE.

Anti-dsDNA and anti-NCS antibodies had a sensitivity of 75.0% and 87.5% respectively; specificity of 25.0% and 27.3% respectively; PPV of 26.7% and 30.4% respectively; NPV of disease onset.

Anti-dsDNA and anti-NCS antibodies had a sensitivity of 80.6% and 86.1% respectively; specificity of 33.3% and 37.5% respectively; PPV of 64.4% and 67.4% respectively; NPV of 53.3% and 64.3% respectively for the diagnosis of SLE with active disease.

Anti-dsDNA and anti-NCS antibodies had a sensitivity of 80.0% and 85.0% respectively; specificity of 27.5% for both of them; PPV of 35.6% and 37.0% respectively; NPV of 73.3% and 78.6% respectively for the diagnosis of SLE with renal affection.

Mild significant correlation was observed between the anti-NCS antibodies and anti-dsDNA as regarding SLEDAI ($P < 0.05$), while a high significant association was observed between the level of anti-NCS titer and renal affection ($P < 0.001$).

Significant correlations were observed between the anti-NCS antibodies and anti-dsDNA ($P < 0.01$), SLEDAI ($P < 0.01$), Hb ($P < 0.001$), C3 ($P < 0.005$), 24h proteinuria and C4 ($P < 0.05$) (Tables 1-4).

Table 1. Autoantibody profile in the studied group.

		Patients (n = 200)
ANA titre	Positive	95.0%
Anti-dsDNA titre	Mean ± SD	187.2 ± 81.0
	Positive	75.0%
Anti NCS titre	Mean ± SD	217.2 ± 148.9
	Positive	76.7%

Table 2. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ANA, Anti dsDNA and Anti NCS in the studied patients (n = 200).

	Sensitivity	Specificity	PPV	NPV
ANA	95.0%	95.0%	98.3%	86.4%
Anti dsDNA	75.0%	100.0%	100.0%	57.1%
Anti NCS	76.7%	100.0%	100.0%	58.8%

Table 3. Comparison between patients with positive and negative Anti NCS as regarding the clinical findings.

	+ve Anti NCS (n=153)	−ve Anti NCS (n = 47)	Chi-square test	
			X^2	p
Fatigue	46.7%	16.7%	0.52	0.47
Alopecia	46.7%	15.0%	0.053	0.82
Photosensitivity	41.7%	15.0%	0.43	0.51
Malar rash	41.7%	15.0%	0.43	0.51
Arthralgia	33.3%	6.7%	0.99	0.32
Arthritis	23.3%	10.0%	0.75	0.39
Fever	21.7%	5.0%	0.26	0.61
Pulmonary disease	20.0%	8.3%	0.49	0.48
Renal disease	38.3%	5.0%	1.17	0.28
Weight loss	21.7%	3.3%	1.1	0.29
Oral ulcer	21.7%	3.3%	1.1	0.29
Vasculitis	20.0%	5.0%	0.12	0.72
CNS affection	18.3%	1.7%	1.89	0.17
Discoid lesions	13.3%	5.0%	0.12	0.37
Cardiac affection	10.0%	3.3%	0.014	0.91
GIT affection	11.7%	1.7%	0.61	0.44
Decreased Appetite	6.7%	1.7%	0.034	0.85
Sore throat	5.0%	-	0.96	0.33

Table 4. Correlations between anti NCS and the laboratory findings (Spearman rank correlation coefficient).

	Anti NCS titer	
	R	p
Hb (gm/dl)	**−0.43**	**0.0001**
WBCs (×10³/ml)	−0.026	0.85
Platelets (×10³/ml)	−0.077	0.56
ESR 1st h. (mm/h)	−0.024	0.75
Serum creatinine (mg/dl)	0.19	0.15
24 h. proteinuia (mg/dl)	**0.3**	**0.021**
Bilirubin (mg/dl)	−0.11	0.41
AST (IU/L)	−0.22	0.1
ALT (IU/L)	0.068	0.6
C3 (mg/dl)	**−0.37**	**0.003**
C4 (mg/dl)	**−0.27**	**0.038**

4. Discusion

In this study we found that anti-NCS antibodies had a higher sensitivity in early SLE patients than Anti-dsDNA, and in active disease. Of special interest, the correlation of anti-NCS antibodies with lupus nephritis more than Anti-dsDNA

Although anti-dsDNA antibodies are considered the main diagnostic tool for SLE and may be a useful marker of disease activity, they are found only in 50% of SLE patients and do not always correlate with disease activity [16]. On the other hand, ANAs, the most prevalent antibodies, have low specificity for the diagnosis of SLE because they are found in most systemic autoimmune diseases and even in healthy individuals. Thus, it is important to look for other autoantibodies that may be useful in the diagnosis and assessment of the disease activity in SLE patients [12].

There are various reports on the presence of anti-NCS antibodies in active SLE and their role in the evolution of disease activity in patients with SLE suggesting that the determination of circulating anti-NCS antibodies could be a useful parameter for early diagnosis and follow-up of SLE patients [17] [18].

Furthermore, several studies have demonstrated the correlation of anti-NCS antibodies with renal disease in SLE patients. Most of these studies have suggested the increasing diagnostic importance of anti-NCS antibodies, in addition to antibodies directed against dsDNA [19] [20]. Also, anti-NCS antibodies are specifically induced by and react with only nucleosomes but not with its constituents' DNA, and histones [21].

In addition, anti-NCS antibodies occur before the development of anti-dsDNA and anti-HST antibodies. Studies have shown that anti-NCS possess high specificity for the disease and could be positively detected in SLE patients lacking anti-dsDNA antibodies [22] [23].

In the current study, anti-NCS as a diagnostic tool for SLE showed a specificity of 76.7%, a sensitivity of 100.0%. The corresponding values for ANAs were 95.0%, 95.0%, and for Anti-dsDNA were 75.0%, 100.0% respectively. These results were nearly the same as in many studies [19] [22] [24] [25] [26].

However, another study [27] reported that the anti-NCS assay does not offer additional information compared to conventionally used anti-dsDNA tests in the differential diagnosis of SLE.

In our study, anti-NCS had a sensitivity and specificity higher than that of anti-dsDNA, in early onset disease, and renal affection, which agrees earlier studies [12] [28]. Even in patients who were negative for anti-dsDNA, we found that anti-NCS showed sensitivity of 46.7%, and specificity of 100.0%%, which was concordant with an earlier study [24].

Comparative and correlative statistical analysis showed significant associations between anti-NCS and disease activity SLEDAI score in the studied group. This is in harmony with other studies [29] [30] [31].

Moreover, we found a significant elevation in anti-NCS levels in patients with renal affection as in earlier studies [18] [23] [31] [32]. However, other studies did not find such a relation [33] [34] [35].

Furthermore, we noted that patients positive for anti-NCS had significantly higher frequency of anemia with significantly lower Hb level as noted in a previous study [29].

Our findings provide evidence that anti-NCS are a sensitive and specific diagnostic biomarker in SLE. Moreover, we found that anti-NCS reactivity in SLE patients was correlated significantly with disease activity and nephritis. Thus, the anti-NCS antibody test may be particularly useful in the diagnosis of SLE when anti-dsDNA antibodies are not present.

However, there is clearly a need for further longitudinal studies to better define the clinical utility of anti-NCS, both in relation to disease activity and outcome.

5. Conclusion

Anti-NCS antibody could be a useful tool in the diagnosis of SLE especially in patients who are negative for anti-ds DNA antibodies. Determination of anti-NCS antibodies could be a useful parameter for early diagnosis of SLE patients as well as may be a promising marker, which is useful in assessment of disease activity in SLE patients. This study proved that Anti-nucleosome antibodies are more sensitive marker for diagnosis of SLE than anti-dsDNA. The increased titer of anti-NCS antibodies appears to be a sensitive marker for identifying patients at increased risk of LN.

6. Recommendations

- Longitudinal studies are needed to further establish whether high levels of circulating anti-nucleosomes may predict the occurrence of an SLE flare.

- Anti-NCS antibody has proved to be useful in diagnosing patients with SLE, perhaps a positive anti-NCS antibody test should be included as one of the criteria for diagnosing SLE
- Nucleosomes appear to be the prime auto antigen that is generated through apoptosis. Further understanding the processes involved in the pathogenesis could guide development of new therapeutic interventions.

Conflicts of Interest

All authors confirm that there are no any potential conflicts of interest of each of them. In addition, we confirm hereby that no part of this paper has been published before or is currently being considered for publication elsewhere.

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