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Antinucleosome Antibody in Children and Adolescents with Systemic Lupus Erythematosus

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Abstract

Background: SLE is an autoimmune disease of unknown etiology characterized by the production of abroad and heterogeneous group of autoantibodies. These autoantibodies are directed to nuclear, cytoplasmic, and cellular membrane antigens. Recently, it was proposed that the nucleosome is the principal antigen in the pathophysiology of SLE, and that anti-Nuc antibodies are associated with organic damage.

Aim of the Study: The aim of this work was to study the potential utility of serum levels of anti- nucleosome antibodies as a diagnostic tool and a disease activity marker in children and adolescents with systemic lupus erythematosus.

Patients and Methods: The study was carried out on forty five patients with SLE who attended to the outpatient clinic and inpatient of Pediatric Nephrology matched age and sex served as a control group. All studied children were subjected to full history, complete physical examination, SLEDAI score, routine laboratory investigations and anti-dsDNA and anti-nucleosome antibody IgG assay. Data was analyzed by using SPSS.

Results: The mean serum level of anti-Nuc antibody was significantly higher in patients than controls (p-value <0.001). But there was no significant difference between patients' subgroups. There was a weak correlation between serum anti-Nuc antibody and SLEDAI score (r: 0.213) but strong correlation between anti-dsDNA antibody and SLEDAI score (r: 0.711). Anti-Nuc antibody showed higher sensitivity but equal specificity to anti-dsDNA antibody for the diagnosis of SLE.

Conclusion: Anti-nucleosome antibodies are superior to anti-dsDNA antibodies in the diagnosis of SLE especially in anti-dsDNA negative patients as they have higher sensitivity but as regard to disease activity antidsDNA antibody is more accurate.

Key Words: *Systemic lupus erythematosus – Antinucleosome antibody IgG assay by ELISA.*

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Introduction

SYSTEMIC lupus erythematosus (SLE) is a heterogeneous, chronic, episodic and multisystem autoimmune disease associated with severe organ damage. SLE etiopathogenesis is a vicious cycle of autoantigen exposure, autoantibody production, chronic inflammation and tissue damage **[1]**.

Recently, it was proposed that the nucleosome is the principal antigen in the pathophysiology of SLE, and that anti-nucleosome antibodies (anti-Nuc) are associated with organic damage **[2,3]**.

Anti-nucleosome antibodies are a large family of autoantibodies directed against histone epitopes exposed in chromatin, against dsDNA and against conformational epitopes created by the interaction between dsDNA and core histones **[4,5]**.

Anti-dsDNA and anti-histone antibodies belong to the nucleosome family as do anti-Nuc specific antibodies, since nucleosomes share several common epitopes with dsDNA and histones. Nucleosome specific antibodies do not react with the individual components of the nucleosome, that is, DNA and histones, but recognize conformational epitopes resulting from interactions between the DNA and histone **[6]**.

Anti-Nuc antibodies have been recently shown to be a good diagnostic marker for SLE and, indeed, they represent the first serological marker described in association with this disease **[7]**.

In SLE patients and murine lupus the apoptosis is abnormal, chromatin components appear at the surface of apoptotic cells, the removal of apoptotic debris is defective and the release of apoptosis modified nucleosomes in the circulation is massive,

inducing the recognition by the immune system (T and B cells) and the production of autoantibodies. Nucleosomes play a pivotal role in the development of kidney lesions by mediating binding of autoantibodies to basal membranes [8,9].

There are various reports on the presence of anti-Nuc antibodies in active SLE and their role in the evolution of disease activity in patients with SLE, suggesting that the determination of circulating anti-Nuc antibodies could be a useful parameter for early diagnosis and follow-up of SLE patients [9-11].

Aim of the study:

Tha aim of this study was to study the potential utility of serum levels of anti- nucleosome antibodies as a diagnostic tool and disease activity marker in children and adolescents with systemic lupus erythematosus.

Patients and Methods

This was a prospective case-control study carried out in the Pediatric Nephrology Unit, Tanta University Hospital in the period from November 2015 to November 2016. Forty five patients were included in the study fulfilling the revised criteria of American College of Rheumatology (ACR) of SLE, thirty age and sex matched healthy subjects were taken as a control group.

SLE patients were categorized into 3 groups: group A1=fifteen newly diagnosed cases, group A2=fifteen known cases of SLE during disease activity and group A3=fifteen known cases of SLE with inactive SLE.

All subjects were subjected to: Complete history taking, through clinical examination, disease activity was evaluated according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, routine laboratory investigations: complete blood count, erythrocyte sedimentation rate, complete urine analysis, renal function tests, serum C3 and C4 levels and anti-dsDNA and antinuclear antibody and Anti-nucleosome antibody IgG assay for patients and controls was done by enzyme-linked immunosorbent assay (ELISA) [12] using Human anti-nucleosome antibody IgG (AnuA-IgG) ELISA Kit, supplied by SunRed Shanghai Biological Technology Company.

Statistical analysis

The SPSS version 11.0 was used for data entry and statistical analysis. Descriptive statistics was expressed by mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Non-parametric tests were used because of non-normal distribution of the variables in this study. The Mann-Whitney test was used to compare the median differences between the two groups. Non-parametric Spearman rank correlation coefficient was assessed to find the correlation between two continuous variables. Pearson chi-square test was applied to investigate the association between categorical variables. The level of significance was set at p-value <0.05 accepted as significant. Receiver operating curve (ROC) characteristic was used to determine cutoff value of antinucleosome antibody.

Results

Total number of patients was 45, 5 (11.11%) males and 40 (88.89%) females and total number of controls was 30,5 (16.67%) males and 25 (83.33%) females. Prevalence of the disease is higher in females with female: Male ratio 8:1. The age in studied patients ranged between (6-18) years with a mean±SD of 13.022±2.840 while in controls, age range was (7-17) years with a mean±SD of 12.633±2.580. There was insignificant difference between studied patients and controls as regard age and sex (p-value >0.05) as shown in Table (1).

Clinical manifestations of SLE were significantly higher in active (A1 & A2) than in inactive patients (A3) (p-value <0.05) except for CNS manifestations which were present only in active patients but didn't show statistically significant difference (p-value >0.05) as shown in Table (2).

There was significant difference between patients' subgroups regarding their SLEDAI score (p-value <0.05). SLEDAI score was highest in newly diagnosed SLE patients and lowest in old inactive SLE patients.

Patients had significantly higher levels of serum Anti-dsDNA & Anti-nucleosome antibodies than controls p-value $^{<0.001*}$. Anti-dsDNA antibody had a range of (10-863) U/ml in patients with a median of 255 and IQR of 282.5 while controls had a range of (15-45) U/ml with a median of 25 and IQR of 10. Anti-nucleosome antibody had a range of (30-120) U/ml in patients with a median of 52 and IQR of 34 while controls had a range of (10-55) U/ml with a median of 18 and IQR of 7.75.

In this study, results showed non-significant difference in serum anti-nucleosome antibody level among studied patients' subgroups (newly diagnosed, old active and old inactive patients) but there was significant difference between studied

subgroups regarding anti-dsDNA antibody as shown in Figs. (1,2).

This study showed that there was a weak correlation between serum anti-nucleosome antibody and SLEDAI score (r=0.213) but there was a strong correlation between serum anti-dsDNA antibody and SLEDAI score (r=0.711).

This study revealed that at cutoff point of >30, Anti-Nuc antibody has a sensitivity of 97.78% and a specificity of 93.33%for the diagnosis of SLE and at cutoff point of >40, Anti-dsDNA antibody has a sensitivity of 84.44% and a specificity of 93.33% for the diagnosis of SLE as shown in Table (6) and Figs. (3,4).

Anti-nucleosome antibody was positive in 44 patients (97.77%) and Anti-dsDNA antibody was positive in 38 patients (84.44%). Anti-Nuc antibody was positive in 7 patients who were negative for Anti-dsDNA antibody.

Table (1): Demographic data of studied subgroups.

	Groups											
	Patients						Controls (30)		Total		Chi-Square	
	Group A1 (15)		Group A2 (15)		Group A3 (15)							
	No.	%	No.	%	No.	%	No.	%	No.	%	X2	*p*-value
Sex:												
Male	2	13.33	1	6.67	2	13.33	5	16.67	10	13.33	0.86	0.834
Female	13	86.67	14	93.33	13	86.67	25	83.33	65	86.67	5	
Total	15	100.00	15	100.00	15	100.00	30	100.00	75	100.00		
Age Years:											ANOVA	
Range	6-18		10-18		10-17		7-17				F	*p*-value
Mean-}SD	12.267-}3.634		13.800-}2.597		13.000-}2.035		12.633-}2.580				0.909	0.441
Duration (Month):											*t*-test	
Range	–		12-120 month		6-72 month						*t*	*p*-value
Mean-}SD	–		42.400-}38.182		33.200-}20.393						0.823	0.417

Table (2): Clinical manifestations of SLE in studied patients.

At time of Examination	Subgroups						Total		Chi-Square	
	Group A1 (15)		Group A2 (15)		Group A3 (15)					
	No.	%	No.	%	No.	%	No.	%	X2	*p*-value
Hematological manifestations:										
No	4	26.67	5	33.33	15	100.00	24	53.33	19.821	<0.001*
Yes	11	73.33	10	66.67	0	0.00	21	46.67		
Renal manifestations:										
No	2	13.33	5	33.33	11	73.33	18	40.00	11.667	0.003*
Yes	13	86.67	10	66.67	4	26.67	27	60.00		
Musculoskeletal manifestations:										
No	4	26.67	4	26.67	12	80.00	20	44.44	11.520	0.003*
Yes	11	73.33	11	73.33	3	20.00	25	55.56		
Skin/MM manifestations:										
No	8	53.33	3	20.00	12	80.00	23	51.11	10.850	0.004*
Yes	7	46.67	12	80.00	3	20.00	22	48.89		
Constitutional manifestations:										
No	1	6.67	1	6.67	11	73.33	13	28.89	21.635	<0.001*
Yes	14	93.33	14	93.33	4	26.67	32	71.11		
CNS manifestations:										
No	13	86.67	13	86.67	15	100.00	41	91.11	2.195	0.334
Yes	2	13.33	2	13.33	0	0.00	4	8.89		

Subgroups	SLEDAI		ANOVA	
	Range	Mean±SD	F	*p*-value

	Range	Median	IQR	Mean Rank	Mann-Whitney Test	
					Z	*p*-value
Anti-dsDNA Antibody (U/ml):						
Patients (45)	10–863	255.00	282.50	48.40	5.065	<0.001*
Controls (30)	15–45	25.00	10.00	22.40		
Anti-Nuc Antibody (U/ml):						
Patients (45)	30–120	52.00	34.00	52.31	6.977	<0.001*
Controls (30)	10–55	18.00	7.75	16.53		

Table (5): Correlation between serum anti-Nuc and anti-dsDNA antibodies and SLEDAI score of patients.

Correlations		
Spearman's rho	SLEDAI	
	r	*p*-value
Anti-Nuc Antibody (U/ml)	0.213	0.159
Anti-dsDNA Antibody (U/mL)	0.711	<0.001*

Table (6): Diagnostic efficacy of anti-Nuc and anti-dsDNAantibodies for SLE.

	ROC curve between Patients and Control					
	Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
Anti-Nuc Antibody	>30	97.78	93.33	95.7	96.6	97.7%
AntidsDNA antibody	>40	84.44	93.33	95.0	80.0	88%

Table (7): The overall anti-dsDNA antibody and anti-Nuc antibody positivity.

	Anti-nucleosome Ab+ve	Anti-nucleosome Ab–ve	Total
Anti-dsDNA Ab +ve	37	1	38
Anti-dsDNA Ab-ve	7	zero	7
Total	44	1	45 (100%)

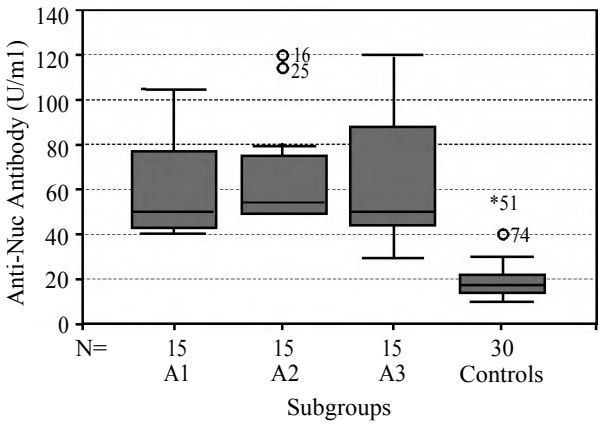

Fig. (1): Comparison between studied subgroups regarding serum anti-Nuc Ab.

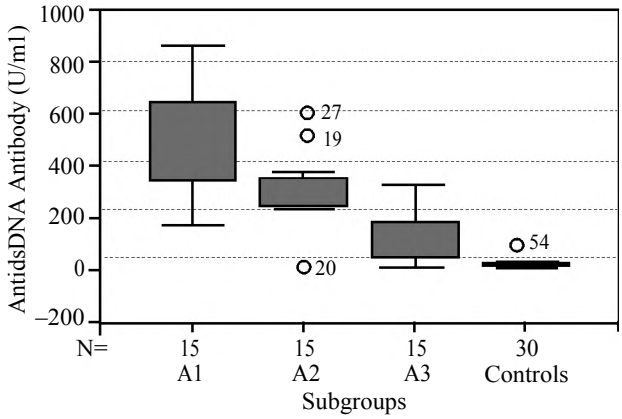

Fig. (2):Comparison between studied subgroups regarding serum Anti-dsDNA Ab.

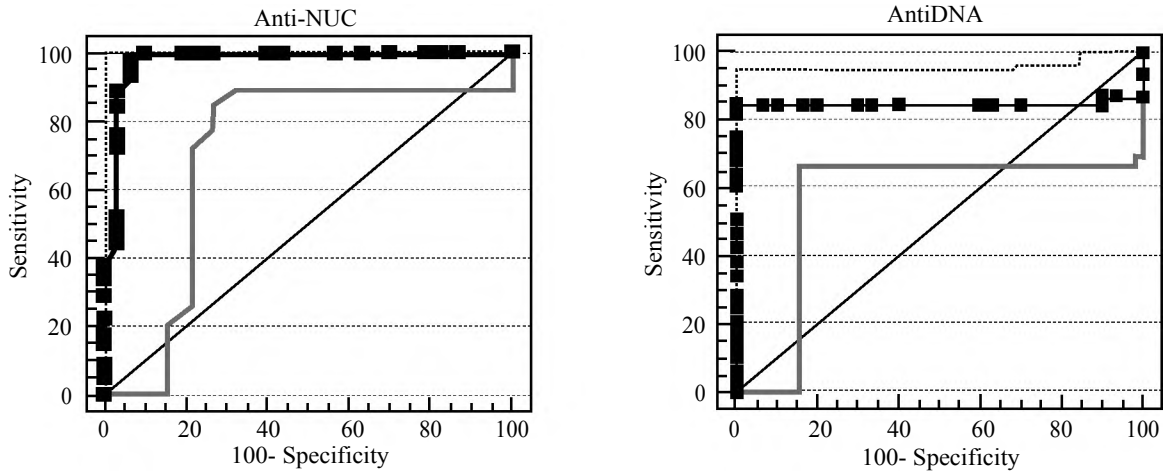

Fig. (3,4): Diagnostic efficacy of anti-Nuc and antidsDNA antibody for SLE.

Discussion

SLE has no single diagnostic marker, which makes it difficult to detect unless clinicians identify it through a combination of clinical manifestations and some laboratory findings [13].

In the present study, anti-nucleosome antibody showed high sensitivity (97.77%) for the diagnosis of SLE which is similar to results found by Simon JA, et al., [14] who reported that the prevalence of anti-nucleosome antibodies in SLE patients was 100% whereas in healthy controls it was 3%.

On the other hand Ghirardello A, et al., [15] demonstrated less sensitivity of anti-nucleosome antibodies (86.1%) for the diagnosis of SLE probably because they compared SLE patients with disease controls as other rheumatologic disorders or patients with systemic infections. A low sensitivity and specificity of anti-Nuc antibodies for the diagnosis of SLE was also reported by different studies; DÜzgÜn N, et al., [2] reported a lower sensitivity and specificity of anti-nucleosome antibodies, they were 83.6% and 70% respectively, Tikly M, et al., [16] reported the overall sensitivity of anti-nucleosome antibody was 45.3%, Suleiman S, et al., [13] reported that anti-nucleosome antibodies had a lower sensitivity of 52% but specificity was 98% and Saigal R, et al., [17] reported a low sensitivity of anti-nucleosome antibody 47.50%.

In the present study anti-dsDNA antibody showed a sensitivity of 84.44% and a specificity of 93.33% for the diagnosis of SLE. Specificity of anti-nucleosome antibody and anti-dsDNA antibody were equal but sensitivity of anti-nucleosome antibody was higher.

In the literature, the results are conflicting, Ant-Nuc antibodies were found to be more sensitive than anti-dsDNA antibodies in the diagnosis of SLE in the following studies; Simon JA, et al., [14] , Quattrocchi P, et al., [18] and Suleiman S. et al., [13] Pradhan VD, et al., [11] Bizzaro N, et al., [5] and Saigal R, et al., [17] . Equal sensitivity of both ant-Nuc and anti-dsDNA antibodies in the

diagnosis of SLE was reported by the following studies; Min, et al., **[19]** and Wu, et al., **[20]**. Anti-Nuc antibodies were found to be less sensitive than anti-dsDNA antibodies in the diagnosis of SLE in the following studies; Campos, et al., **[21]**.

The method used, patient types and number may contribute to such results. In the present study we classified patients into 3 groups to better detect the diagnostic utility of such serology. We found equal sensitivity of anti-Nuc and ant-dsDNA antibodies in the diagnosis of new cases of SLE, while in patients on treatment, anti-dsDNA antibody levels declined and became negative in some patients while not in anti-Nuc antibodies and this contributes to the better overall sensitivity of anti-Nuc antibodies in the diagnosis of SLE in the present study.

In the present study, anti-nucleosome antibodies were positive in all active SLE patients 100%. On the other hand, anti-dsDNA antibodies were found to be positive only in 90% of active-SLE patients while in inactive SLE patients, anti-Nuc antibodies were positive in 93.3% and anti-dsDNA antibodies were positive in 73.3%.

This study showed no statistically significant difference between studied patients' subgroups regarding serum anti-nucleosome antibody level so anti-nucleosome antibody couldn't differentiate between newly diagnosed, old active and old inactive SLE patients, while anti-dsDNA antibody showed statistically significant difference between patients' subgroups.

The results of longitudinal studies have, however, been less convincing on the relationship between anti-Nuc antibody levels and disease activity. Horak P, et al., **[22]** in a 6-month follow-up study found higher anti-Nuc antibody levels in patients with active disease compared to those with inactive disease but again found little variation in anti-Nuc antibody levels at three time points in the study. Ghirardello A, et al., **[15]** in a 2-year follow-up study reported that there was no strong relationship between anti-nucleosome or anti-dsDNA antibodies and disease activity or damage. Quattrocchi et al., **[18]** did not support a clear correlation between anti-nucleosome antibody and disease activity. DÜzgÜn N, et al., **[2]** reported that anti-nucleosome antibody levels were strongly associated with high disease activity compared to the other groups but there was no significant difference between mild-to-moderate disease activity and inactive group.

On the other side, Suleiman, et al., **[13]** reported that anti-nucleosome and anti-dsDNA antibodies were found to have a significant correlation with SLEDAI score, but the correlation coefficient for anti-nucleosome antibodies with SLEDAI score was found to be better than anti-dsDNA antibodies. Similar results were reported by several investigators such as: Simon JA, et al., **[14]**, Campos, et al., **[21]** and Wu, et al., **[20]**.

This discrepancy in the results between studies can be explained by many factors, First the clinical characteristics of the patients included in the study and the method of evaluation of the disease activity which was done by using different disease activity indices or following therapeutic management (only few studies recorded medical treatment and clearly defined their cut-offs) which may affect the level of antibody titers. Second, technical issues (different antigen preparations used in different studies; whether they used quantitative or qualitative kits). Third, because anti-dsDNA Ab and complement are important components of SLEDAI score, the association of anti-Nuc Ab with SLEDAI score might be a consequence of the strong correlation between anti-Nuc Ab, anti-dsDNA Ab and complement. Therefore it is better to use a modified SLEDAI score, in which anti-dsDNA Ab and complement were excluded to avoid overestimation of the correlation.

Interestingly anti-nucleosome antibody was positive in 7 (15.5%) patients who were negative for anti-dsDNA and only one patient was negative for anti-nucleosome but positive for anti-dsDNA antibody in the present study. Similar results were reported by Suleiman et al., **[13]** Campos et al., **[21]** and DÜzgÜn, et al., **[2]**.

Cut off value for positive anti- Nuc antibody was different between studies ranging from 10 – 55u/ml; Simon JA, et al., **[14]** used a cut off 55u/ml, Ghirardello, et al., **[15]** used a cut off 10u/ml, Wu, et al., **[20]** used a cut off 38.1u/ml, with a mean of 9.5 and S.D. of 5.7u/ml, Campos, et al., **[21]** used a cut off 20 u/ml and Suleiman, et al., **[13]** used a cut off 15u/ml.

The cut-off was taken as by the manufacture suggestion by Campos, et al., **[21]** or±2SD above normal controls by Simon, et al., **[14]** or above 5 SD of normal controls by Wu, et al., **[20]** or by ROC curve analysis by Ghirardello, et al., **[15]**.

This variation in the cut-off of anti-Nuc antibodies may explain – in part – the discrepancy of the utility of it as a marker for diagnosis or disease activity marker.

Conclusion:

Anti-nucleosome antibodies are superior to anti-dsDNA antibodies in the diagnosis of SLE especially in anti-dsDNA negative patients as they have higher sensitivity but as regard to disease activity, anti-dsDNA antibody is more accurate.

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Conflicts of interest:

No conflicts of interest declared.

Authors' contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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دراسة الأجسام المضادة للنيوكليوسوم في الأطفال والمراهقين المصابين بالذئبة الحمراء

الذئبة الحمراء هى مرض مناعى ذاتى معقد ، المسببات المرضية لهذا المرض غير معروفة. تتميز الذئبة الحمراء بعدم التجانس فى الاعراض ومسار المرض، وتتميز بمجموعة واسعة من الأجسام المضادة الذاتية، وبترسبات مناعية معقدة وتلف نهائى بأجهزة الجسم المختلفة.

الهدف من الدراسة : هو دراسة الفائدة المحتملة للأجسام المضادة للنيوكليوسوم كأداة تشخيصية وعلامة على نشاط المرض فى الأطفال والمراهقين المصابين بالذئبة الحمراء.

طرق البحث:اجريت الدراسة على خمسة وأربعون حالة يعانون من الذئبة الحمراء ويتابعون فى العيادة الخارجية ووحدة الكلي ،بقسم طب الأطفال، جامعة طنطا. وايضا على ثلاثين من الأطفال الأصحاء من نفس العمر والجنس كمجموعة تحكم. خضع جميع الأطفال إلى :التاريخ المرضى الكامل، الفحص الاكلينيكى الشامل، مؤشر نشاط مرض الذئبة الحمراء، التحاليل المعملية الروتينية و شملت صورة دم كاملة–وظايف كلى–كومبليمنت ٣و٤ –سرعة ترسيب –تحليل بول كامل والأجسام المضادة لشريط الحمض النووى والأجسام المضادة للنيوكليوسوم.

النتائج : أظهرت نتائج هذه الدراسة ان متوسط مستوى الاجسام المضادة للنيوكليوسوم في الاطفال والمراهقين الذين يعانون من مرض الذئبة الحمراء أعلى من ذويهم ممن لا يعانون من المرض وان هناك علاقة ضعيفة بين الاجسام المضادة للنيوكليوسوم ومؤشر نشاط مرض الذئبة الحمراء بينما العلاقة قوية بين الأجسام المضادة لشريط الحمض النووى المزدوج ومؤشر نشاط المرض.

الاستنتاج :من الممكن استخدام الاجسام المضادة للنيوكليوسوم فى تشخيص مرض الذئبة الحمراء ولكن العلاقة بين الاجسام المضادة للنيوكليوسوم ومؤشر نشاط مرض الذئبة الحمراء ضعيفة.

التوصيات: أن يتم عمل مستوى الاجسام المضادة للنيوكليوسوم للأطفال و المراهقين المصابين بمرض الذئبة الحمراء خاصة الذين لديهم الاجسام المضادة لشريط الحمض النووى المزدوج سلبية لان حساسيته للمرض أعلى كما نوصى بالمزيد من الدراسات لتأكيد علاقة الاجسام المضادة للنيكليوسوم بتشخيص و نشاط مرض الذئبة الحمراء.