Diagnostic and Prognostic Values of Antinuclear Immunoglobulin G in Pediatric Lupus Patients

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Introduction. Systemic lupus erythematous (SLE) as an autoimmune caused by self immunoglobulin. It was proposed that the chromatin including nucleosomes is the main antigen in the pathogenesis of SLE, and that antinuclear immunoglobulin G are associated with disease activity. Aim of the study was to study the diagnostic and prognostic value of serum levels of antinuclear immunoglobulin G as the most famous anti-chromatin immunoglobulin as a diagnostic tool and a disease activity marker in juvenile systemic lupus erythematous.

Methods. The work was conducted on 90 pediatric Lupus patients who attended to the Pediatric Nephrology Unit of Pediatric Department of Tanta University Hospital. Also on thirty apparently healthy children with matched age and sex served as a control group. All subjects were subjected to history in details, clinical examination, SLEDAI score, anti-dsDNA and antinuclear immunoglobulin G assay .

Results. The mean serum level of antinuclear immunoglobulin G was statistically significantly higher in patients than controls ($P < .001$). But there was no statistically significant difference between patients' subgroups. There was a weak positive correlation between serum antinuclear immunoglobulin G and SLEDAI score (r = 0.213) but strong correlation between anti-dsDNA antibody and SLEDAI score (r = 0.711). Antinuclear immunoglobulin G showed higher sensitivity but equal specificity to anti-dsDNA antibody for the diagnosis of ped.iatric lupus patients.

Conclusion. Antinuclear immunoglobulin G are more accurate than anti-dsDNA antibodies in the diagnosis of pediatric lupus patients in anti-dsDNA negative children as antinuclear immunoglobulin G have higher sensitivity but as regard to disease activity antidsDNA antibody is more accurate.

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INTRODUCTION

SLE was defined as a chronic, episodic and multisystem autoimmune disorder associated with multiple organ damages. SLE pathogenesis is a vicious cycle of autoantigen exposure, autoantibody production.[1]

It was assumed that the nucleosome is the main causative antigen in SLE, and that antinuclear immunoglobulin G (anti-Nuc) are associated with disease activity.[2-4]

Antinuclear immunoglobulin G have been recently shown to be a good diagnostic marker for SLE and, indeed, they represent the first serological marker described in association with adult lupus patients.[5-9] There are many publications on the role of antinuclear immunoglobulin G in active

lupus patients and their role in the evolution of disease activity in patients with SLE, suggesting that the determination of circulating antinuclear immunoglobulin G could be a useful parameter for early diagnosis and follow-up of SLE patients.[9-11]

The aim of this work was to study the potential utility of serum levels of antinuclear immunoglobulin G as the commonest used antichromatin antibodies as a diagnostic tool and disease activity marker in pediatric lupus patients

MATERIALS AND METHODS

Our study was carried out after approval from research ethical committee centre of faculty of medicine, Tanta university which coped with the Helsinki Declaration of 1975, as revised in 2000 and obtaining informed written or oral consents from parents of included children. This study was a prospective case-control study carried out in the pediatric nephrology Unit of Tanta university hospital (TUH) in the period from June 2017 to June 2018. 90 patients were included in the study fulfilling the revised criteria of American College of Rheumatology (ACR)[12] of SLE, 30 age and sex matched healthy subjects were taken as a control group. SLE patients were categorized into 3 groups: group A1 = 30 newly diagnosed cases, group A2 = 30 known cases of SLE during disease activity, and group A3 = 30 known cases of inactive SLE.

All enrolled and controls were subjected to:

- Complete history taking
- Through clinical examination
- Disease activity was evaluated according to the Systemic Lupus Erythematous Disease Activity Index (SLEDAI) score.
- Routine laboratory investigations: complete blood count, erythrocyte sedimentation rate, complete urine analysis, blood urea and serum creatinine, serum complements (C3 and C4) levels, anti-dsDNA and antinuclear immunoglobulin G
- Anti chromatin immunoglobulin G: by measuring antinuclear immunoglobulin G (IgG) which was done by enzyme-linked immunosorbent assay (ELISA)[13] 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 < .05 accepted as significant. Receiver operating curve (ROC) characteristic was used to determine cutoff value of anti-nucleosome antibody.[14]

RESULTS

Total number of patients was 90, 10 of them (11%) was males and 80 (88.9%) females and total number of controls was 30, 5 (16.7%) males and 25 (83.3%) females. Prevalence of the disease is higher in females with female to male ratio 8:1. The age in studied patients ranged between (6-18) years with a mean (± SD) of 13 ± 2.8 while in controls, age range was (7 - 17) years with a mean (+ SD) of 12.63 ± 2.6. There was no statistically significant difference between studied patients and controls as regard age and sex (P > .05) as shown in Table 1. Clinical manifestations of SLE were significantly higher in active (A1 and A2) than in inactive patients (A3) (P < .05) except for CNS manifestations which were present only in active patients but didn't show statistically significant difference (P > .05) as shown in Table 2.

There was significant difference between patients' subgroups regarding their SLEDAI score (P < .05) (Table 3). SLEDAI score was highest in newly diagnosed SLE patients and lowest in known inactive SLE patients. Patients had significantly higher levels of serum anti-dsDNA and anti-nucleosome antibodies than controls (P < .001) (Table 4). 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 antinuclear immunoglobulin G 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. The current study showed that there was a statistically non-significant positive correlation between serum antinuclear immunoglobulin G and SLEDAI score (r = 0.21, $P > .05$) (Figure 1) but there was a statistically significant positive correlation between serum anti-dsDNA antibody and SLEDAI score (r = 0.711, $P < .001$) (Figure 2) as shown in Table 5.

This study revealed that at cutoff point of > 30 U/mL, anti-Nuc antibody has a sensitivity of 97.8 % and a specificity of 93.3% for the diagnosis of SLE (Figure 3 and 4) and at cutoff point of > 40 U/mL, anti-dsDNA antibody has a sensitivity of 84.4% and a specificity of 93.3% for the diagnosis of SLE (Figure 4) as shown in Table 6. Antinuclear immunoglobulin G was positive in 44 patients (97.8 %) and Anti-dsDNA antibody was positive in 38 patients (84.4%). Anti-Nuc antibody was positive in 7 patients who were negative for anti-dsDNA antibody (Table 7).

Table 1. Age, Sex, and Disease Duration of Studied Subjects

	Groups										Chi-square	
	Patients						Controls (30)		Total			
	Group A1 (30)		Group A2 (30)		Group A3 (30)							
	N	%	N	%	N	%	N	%	N	%	X^2	*P*
Sex												
Male	4	13.3	2	6.7	4	13.3	5	16.7	15	13.3		
Female	26	86.7	28	93.3	26	86.7	25	83.3	115	86.7	0.87	> 0.05
total	30	100	30	100	30	100	30	100	120	180		
Age, y												
Range	6 - 18		10 - 18		10 - 17		7 - 17				ANOVA	
Mean ± SD	12.3 ± 3.6		13.8 ± 2.6		13 ± 2		12.6 ± 2.6				F	*P*
											0.91	> .05
Duration, mo												
Range, mo	-		12 - 120		6 - 72						t test	
											t	*P*
Mean ± SD	-		42.4 ± 38.2		33.2 ± 20.4						0.82	> .05

Table 2. Presentations of SLE in the Studied Subgroups

At Time of Examination	Subgroups								Chi-square	
	Group A1 (30)		Group A2 (30)		Group A3 (30)		Total			
	N	%	N	%	N	%	N	%	X^2	*P*
Hematological Manifestations										
No	8	26.7	10	33.3	30	100	48	53.3	19.821	< .001
Yes	22	73.3	20	66.7	0	0	42	46.7		
Renal Manifestations										
No	24	13.3	10	33.3	22	73.3	36	40	11.667	< .05
Yes	26	86.7	20	66.7	8	26.7	52	60		
Musculoskeletal Manifestations										
No	8	26.7	8	26.7	24	80	40	44.4	11.520	< .05
Yes	22	73.3	22	73.3	6	20	50	55.6		
Skin / MM Manifestations										
No	16	53.3	6	20	24	80	46	51.1	10.850	< .05
Yes	14	46.7	24	80	6	20	44	48.9		
Constitutional Manifestations										
No	2	6.7	2	6.7	22	73.3	26	28.9	21.6	< .001
Yes	28	93.3	28	93.3	8	26.7	64	71.1		
CNS Manifestations										
No	26	86.7	26	86.7	30	100	82	91.1	2.2	> .05
Yes	4	13.3	4	13.3	0	0	8	8.9		

Table 3. SLEDAI Score in Studied Patients

Subgroups	SLEDAI		ANOVA	
	Range	Mean ± SD	F	*P*
Group A1 (30)	10 - 29	18.1 ± 5.3	51.206	< .001
Group A2 (30)	8 - 25	13.4 ± 4.9		
Group A3 (30)	2 - 4	3 ± 0.9		
TUKEY'S Test				
Group A1 & Group A2	Group A1& Group A3		Group A2 & Group A3	
< .05	< .001		< .001	

Table 4. Anti-Nuc and Anti-dsDNA Antibodies of the Studied Subjects

					Mann-Whitney Test	
	Range	Median	IQR	Mean Rank	Z	*P*
Anti-dsDNA Antibody, U/mL						
Patients (90)	10 - 863	255	282.5	48.4	5.1	<0.001
Controls (30)	15 - 45	25	10	22.4		
Anti-Nuc Antibody, U/mL						
Patients (90)	30 - 120	52	34	52.3	6.9	<0.001
Controls (30)	10 - 55	18	7.8	16.5		

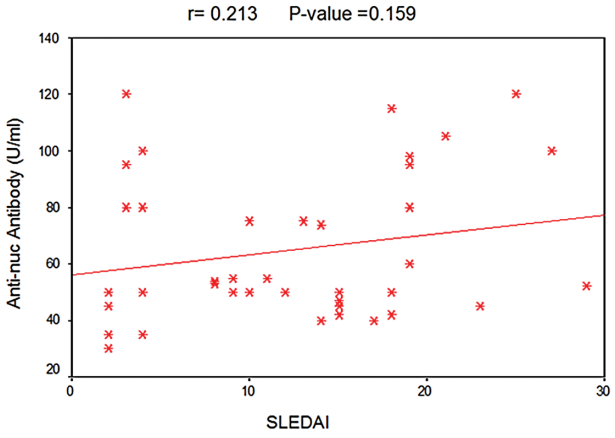

Figure 1. Serum Anti-nucleosome Antibody Level Among Studied Patients' Subgroups

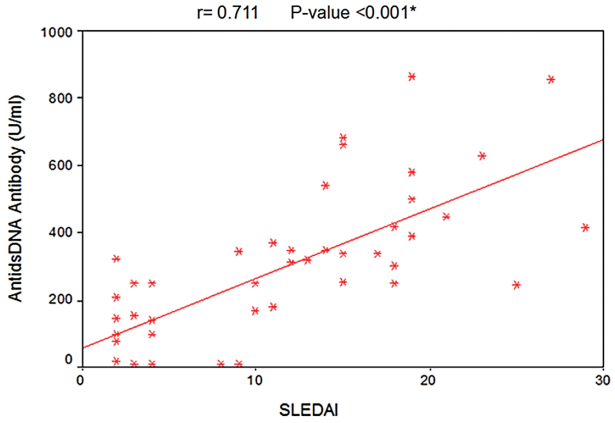

Figure 2. Studied Subgroups Regarding Anti-dsDNA Antibody

Table 5. Correlation Between Serum Anti-Nuc and Anti-dsDNA Antibodies and Disease Activity of the Studied Subjects

Correlations		
Spearman's rho	SLEDAI	
	r	*P*
Anti-Nuc Antibody (U/ml)	0.2	> .05
Anti-dsDNA Antibody (U/mL)	0.7	< .001

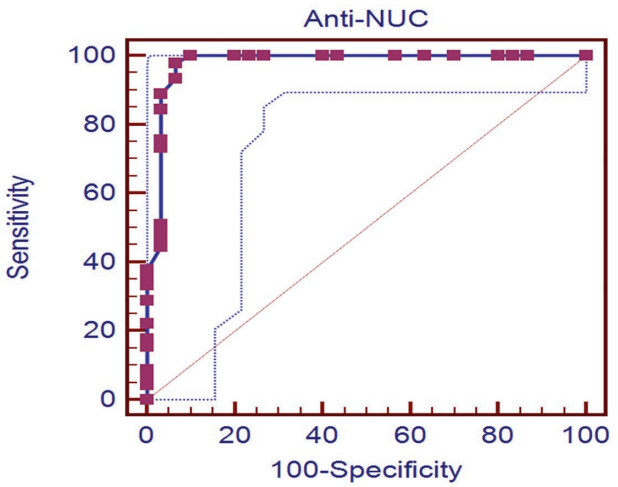

Figure 3. Anti-Nuc antibody Sensitivity and Specificity for the Diagnosis of SLE

DISCUSSION

There is no single diagnostic marker for pediatric lupus. Hence it was difficult to detect the disease in early stages especially in pediatric population.[15] In the present work, antinuclear immunoglobulin G showed high sensitivity (97.8%) for the diagnosis

Table 6. Validity of Anti-Nuc and Anti-dsDNA Antibodies for SLE as Diagnostic and Prognostic Markers

	ROC curve between Patients and Control					
	Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
Anti-Nuc Antibody	> 30	97.8	93.3	95.7	96.6	97.7%
AntidsDNA Antibody	> 40	84.4	93.3	95.0	80.0	88%

Table 7. The Overall Anti-dsDNA Antibody and Anti-Nuc Antibody Positivity Overall the Studied Subjects

	Anti-nucleosome Ab + ve	Anti-nucleosome Ab - ve	Total
Anti-dsDNA Ab + ve	74	2	78
Anti-dsDNA Ab - ve	14	zero	14
Total	88	2	90 (100%)

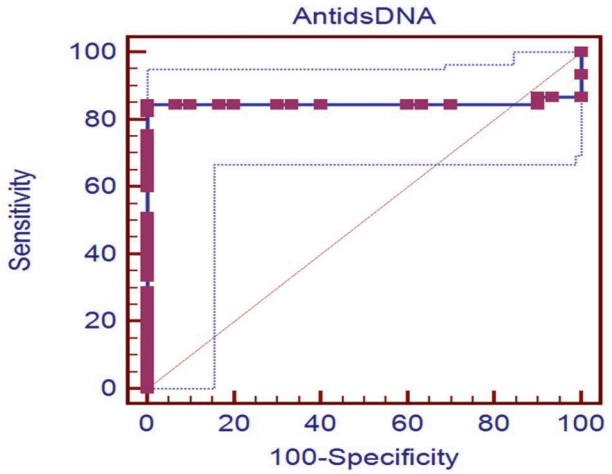

Figure 4. Anti-dsDNA Antibody Sensitivity and Specificity for the Diagnosis of SLE

of SLE. Nearly similar results were reported by Simon JA et al.[16] who said that the prevalence of antinuclear immunoglobulin G in SLE patients was 100% whereas in healthy controls was 3%. On the other hand, Ghirardello A et al.[17] reported less sensitivity of antinuclear immunoglobulin G (86.1%) for the diagnosis of SLE. This may be attributed to comparing SLE patients with other connective tissue diseases or patients with systemic infections. A low sensitivity and specificity of anti-Nuc antibodies for the diagnosis of SLE was also reported by different authors included Duzgun N et al.[2] who reported a lower sensitivity and specificity of antinuclear immunoglobulin G, 83.6% and 70%, respectively. In study by Tikly M et al.[18] overall sensitivity of anti-nucleosome antibody was 45.3%. Suleiman S et al.[15] reported that antinuclear immunoglobulin G had a lower sensitivity (52%) and specificity was 98%. Saigal R et al.[19] showed a low sensitivity (47.5%) for anti-nucleosome antibody. In the present work anti-dsDNA antibody showed a sensitivity of 84.4% and a specificity of 93.3% for the diagnosis of SLE. Specificity of antinuclear immunoglobulin G and anti-dsDNA antibody were equal but sensitivity of antinuclear immunoglobulin G was higher. There are many conflicting data regarding anti-Nuc antibodies level. Some authors for example Simon JA et al.,[16] Quattrocchi P et al.,[20] Suleiman S et al.,[15] Pradhan VD et al.,[11] Bizzaro N et al.,[5] and Saigal R et al.[19] reported that antinuclear immunoglobulin G were more sensitive than anti-dsDNA antibodies in the diagnosis of SLE. Others such as Min DM et al.[21] and Wu JF et al.[22] reported equal sensitivity for both antibodies in the diagnosis of SLE. Some authors reported that antinuclear immunoglobulin G were less sensitive than anti-dsDNA antibodies in the diagnosis of SLE (an examples is Campos LM et al.[23]). Many factors might contribute to such findings including the utilized method, types and number of the studied patients. In the present work, the studied children and adolescents were classified into three subgroups aiming better detection of the diagnostic validity of such serological tests. In this work, regarding the diagnosis of new SLE cases, an equal sensitivity of antinuclear immunoglobulin G and anti-dsDNA antibodies was reported while in children on anti-lupus medication, anti-dsDNA antibody levels declined and became negative in some patients (this finding was not reported in antinuclear immunoglobulin G results) and announced to better overall sensitivity of anti-Nuc antibodies when compared with anti dsDNA in the diagnosis of SLE. In the present work, anti-nucleosome antibodies were positive in 100% of active SLE children. On the other hand, anti-dsDNA antibodies were positive only in 90% of active-SLE patients while in inactive SLE children, antinuclear immunoglobulin G were positive in 93.3 % and

anti-dsDNA antibodies were positive in 73.3%. This study reported no statistically significant difference between the studied subgroups regarding serum anti-nucleosome antibody levels thus antinuclear immunoglobulin G levels couldn't differentiate between newly diagnosed, old active and old inactive SLE patients, on other side anti-dsDNA antibody showed statistically significant difference between patients' subgroups. Different authors have previously reported relationship between antinuclear immunoglobulin G levels and SLE disease activity. Horak P et al.[24] in their 6-month follow-up study reported higher antinuclear immunoglobulin G levels in patients with active disease compared with inactive disease but reported also a seldom variation in antinuclear immunoglobulin G levels at 3 points in their work. Ghirardello A et al.[17] in a two-year follow-up study reported no statistically significant relationship between antinuclear immunoglobulin G or anti-dsDNA antibodies and SLE disease activity or kidney damage. Quattrocchi et al.[20] did not report a statistically significant correlation between antinuclear immunoglobulin G and SLE disease activity. Duzgun N et al.[2] showed that antinuclear immunoglobulin G levels had strong relation with higher SLE activity compared with their other studied groups and added that there was no statistically significant difference between mild-to-moderate SLE disease activity and inactive group . On the opposite side, Suleiman S et al.[15] reported that antinuclear immunoglobulin G and anti-dsDNA antibodies had a statistically significant correlation with SLEDAI score, but the correlation coefficient for antinuclear immunoglobulin G with SLEDAI score was better than anti-dsDNA antibodies. Different authors including Simon JA et al.,[16] Campos LM et al.,[23] and Wu JF et al.[22] documented nearly similar results. The discrepancy in the results between our work and other studies might be due to variable factors. The clinical presentations of the included children, the parameter for assessment of SLE activity which was done by different disease activity indices, the different therapeutic modalities which might affect the level of antibody titers and technical issues regarding antigen preparations (quantitative versus qualitative kits). As anti-dsDNA Ab and complement are important components of SLEDAI score, the association of anti-NucAb with SLEDAI score might be a consequence of the strong correlation between antinuclear immunoglobulin G, anti-dsDNA Ab and complement, thus it is superior to use a modified SLEDAI score, in which anti-dsDNA Ab and complement were better to be excluded avoiding overestimation of the correlation. In our work, antinuclear immunoglobulin G was positive in 14 (15.5%) of children who were negative for anti-dsDNA and only 2 patients were negative for antinuclear immunoglobulin G but positive for anti-dsDNA antibody. Nearly similar results were previously reported by Suleiman et al.,[15] Campos et al.,[2] and Duzgun N et al.[2] The cut off value for positive antinuclear immunoglobulin G was variable between different studies which ranged from 10 – 55 u/mL; Simon JA et al.[16] reported a cut off 55 u/mL, Ghirardello A et al.[15] mentioned a cut off 10 u/mL, Wu JF et al.[22] announced a cut off 38.1 u/mL, Campos LM et al.[23] used a cut off 20 u/mL, and Suleiman et al.[15] reported a cut off 15 u/mL. The suggestion of the manufacture for the cutoff value, which was reported by Campos LM et al.[23] or 2 SD above normal controls, which was reported by Simon JA et al.16 or above 5 SD of normal controls reported by Wu JF et al.[22] or by ROC curve analysis reported by Ghirardello A et al.[17] This variation in the cut-off point of antinuclear immunoglobulin G might be due to the discrepancy between its usages as an indicator for diagnosis of disease activity.

CONCLUSION

Regarding diagnosis of SLE, anti-nuclear immunoglobulin G namely anti-nucleosome antibodies were reported as better markers than anti-dsDNA antibodies especially in anti-dsDNA negative children as they had higher validity (higher sensitivity). Regarding disease activity, anti-dsDNA antibody was reported to be more accurate than anti-nucleosome antibodies. Also anti-nucleosome antibody shows positive correlation with renal manifestations of SLE, which supports their role in developing lupus nephritis

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