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Serum β Lymphocyte Activating Factor of Tumor Necrosis Super family (BAFF) and a Proliferation Inducing Ligand (April): Correlation with Activity and Chronicity Indices in Egyptian Adolescent Lupus Patients with and Without Nephritis

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Abstract
Dysfunction of the B lymphocyte is considered to be involved in the pathogenesis of lupus nephritis (LN) intrarenal B cells have been found in several forms of inflammatory kidney disease. B lymphocyte stimulator signaling pathway by BAFF and its homologue APRIL has an important role in the selection, maturation and survival of B cells and plays a significant role in the pathogenesis of systemic lupus erythematosus (SLE).We aim at this study to investigate the serum level of BAFF, APRIL in Egyptian adolescent lupus nephritis patients and correlate their levels with grade and chronicity indices of LN and compare their result with their counterparts of adolescent lupus patients without lupus nephritis. This study included 60 adolescent patients: Group 1: 20 adolescent SLE patients with lupus nephritis. Group 2: 20 adolescent SLE patients without lupus nephritis. Group 3: 20 age and sex matched healthy subjects served as control group. In this study, BAFF ranged from 4.26-182., 3.25-166.0 and 2.1-30.0 with the mean of 88.6□42.6, 69.2□27.6 and 12.9□3.25 for group I, II and III respectively, there were statistical significant differences between the three studied groups regarding BAFF, group I has statistically higher values than group II and III, also group II has statistically higher values than group III. APRIL ranged from 3.0-40.0, 2.0-42.5 and 7.0-45.0 with the mean of 7.98±8.25, 9.12±7.88 and 14.89±7.98 for group I, II and III respectively, there were statistical significant differences between the three studied groups regarding APRIL, group III has statistically higher values than group I and II, also group II has statistically higher values than group I. Regarding group I, there was positive significant correlation between ANA, activity index and chronicity index with BAFF, there was negative significant correlation between ANA, renal activity index, and chronicity index with APRIL. Regarding group II, there was positive significant correlation between ANA and Anti-DNA with BAFF, while there was negative significant correlation between ANA with APRIL.

Key Words: *Adolescent SLE, lupus nephritis, BAFF, APRIL*

INTRODUCTION

Renal disease in systemic lupus erythematosus (SLE) carries significant morbidity and mortality.[1–5] Up to 26% of patients with diffuse proliferative lupus nephritis (LN) develop end-stage renal failure[6–9] and the mortality increases by eightfold as compared with the general population.[5]

Although a better understanding of autoimmunity in SLE has been achieved, reliable biomarkers of treatment response in both SLE and LN have yet to be found. As B cells have a pivotal role in the pathogenesis of SLE and autoantibody production, B cell activating cytokines have in recent years received increasing attention as both potential biomarkers and target molecules for new treatments.[5]

B lymphocyte stimulator (BLyS), also known as B cell activating factor belonging to the tumour necrosis factor family (BAFF), and a proliferation inducing ligand (APRIL) are members of tumor necrosis factor (TNF) family and are important regulators of B-cell maturation, survival and function.[6]

Over expression of BLyS led to autoimmune manifestations, including nephritis and arthritis.[7] In human studies, patients with SLE and rheumatoid arthritis have been shown to overexpress BLyS.[8–11] Renal lupus patients have also been shown to have higher levels of serum BLyS compared with SLE patients without renal involvement.[12]

A recent study demonstrated higher BLyS mRNA levels in glomeruli from patients with proliferative LN (PLN) compared with control tissue from pretransplant biopsies of living donors,[13] indicating an important role of BLyS in this LN subset.

APRIL is involved in the induction and maintenance of B and T cell responses.[14] In murine models, over expression of APRIL led to increased frequencies of B cells.[15] Some studies have demonstrated raised serum levels of APRIL in patients with SLE[16,17] while in others, APRIL levels did not differ from values regarded as normal.[18] APRIL levels have been shown to be lower in SLE patients with renal involvement compared with lupus patients without kidney disease,[12] and APRIL mRNA levels were higher in the glomeruli of PLN patients compared with tissue from living donors.[13]

Aim of the work

Given the rising critical role of BLys and APRIL play in β-cell homeostasis, we aim at this study to investigate the serum level of BAFF, APRIL in Egyptian adolescent lupus nephritis patients and correlate their level with grade and chronicity index of LN and compare their result with their counterparts of adolescent lupus patients without lupus nephritis

SUBJECT AND METHODS

This study included 60 adolescent patients;they were subdivided into 3 groups:

- Group 1: 20 adolescent SLE patients with lupus nephritis fulfilling the systemic lupus international collaborating clinics (SLICC) 2012 criteria for diagnosis of SLE[19]
- Group 2: 20adolescent SLE patients without lupus nephritis.
- Group 3: 20 age and sex matched healthy subjects served as a control group.

All patients were subjected to:

- Detailed history taking and complete physical and mental examination.
- Laboratory investigations done for the studied group of patients included:

- Complete blood picture,
- liver enzymes (ALT, AST),
- renal function test (blood urea, serum creatinine, creatinine clearance, 24 hour urine proteins and urinary albumin creatine ratio).
- complete urine analysis,
- erythrocyte sedimentation rate (ESR),
- C-reactive protein (CRP),
- Serum complement C3 and C4 (assessed by nephelometry).[20]
- lipid profile including serum cholesterol, triglycerides,
- antinuclear antibodies (ANA) titre.
- antidouble stranded DNA antibodies (anti-ds DNA) titre.
- Detection of serum BAFF level by enzyme-linked immunosorbent assay (ELISA).[20]
- Detection of serum APRIL level by ELISA.[22]

Renal biopsy

For the patients with Lupus Nephritis, All biopsies will be classified according to the modified WHO classification. [23]

Results of renal biopsies according to the modified World Health Organization Classification.[23]

Class	n
I. Normal glomeruli	Nil
A. Nil by all techniques	
B. Normal by light microscopy but deposits seen by electron or immunofluorescence microscopy	
II. Pure mesangial alterations (mesangiopathy)	16
A. Mesangial widening and mild hypercellularity (+)	11
B. Moderate hypercellulatiry (++)	05
III. Focal segmental glomerulonephritis	06
A. Active necrotizing lesions	05
B. Active and sclerosing lesions	01
C. Sclerosing lesions	Nil
IV. Diffuse glomerulonephritis	49
A. Without segmental lesions	Nil
B. With active necrotizing lesions	38
C. With active and sclerosing lesions	11
D. With sclerosing lesions	Nil
V. Diffuse membranous glomerulonephritis	07
A. Pure membranous glomerulonephritis	Nil
B. Associated with lesions of category II (A or B)	07
VI. Advanced sclerosing glomerulonephritis	Nil

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparison between different groups regarding categorical variables was tested using Chi-square test. Normally quantitative data was compared using student t-test, or F test (ANOVA), abnormally distributed data was compared using Mann Whitney test or Kruskal Wallis test, Correlations between two quantitative variables were assessed using Pearson or Spearman coefficient according to test of normality. Significance of the obtained results was judged at the 0.05 level.

RESULTS

Demographic data

Table (1) shows demographic data of the studied groups, it demonstrated that:

Age ranged between 11-18, 11-18 and 12-17 years with the mean of 15.1□2.66, 16.1□3.20 and 15.47□2.94 for group I, II and III respectively, there were no statistical significant differences between the three studied groups regarding age. (P=0.365)

Sex: this study include 3 (15.0%), 4 (20.0%) and 5 (25.0%) males and 18 (85.0%), 16 (80.0%) and 15 (75.0%) females for group I, II and III respectively, there were no statistical significant differences between the three studied groups regarding sex. (P=0.621)

Disease duration ranged between 3.0-20.0 and 4.0-24.0 months with the mean of 15.42□4.25, 16.01□5.08 months for group I and II respectively, there were no statistical significant differences between the two patients groups regarding disease duration. (P=0.407)

Table (1): Demographic data of the studied groups

	Group I "SLE patients with lupus nephritis" **"n=20"**	**Group II** "SLE patients without lupus nephritis" **"n=20"**	**Group III "control" "n=20"**	**p**
Age				
Range	11-18	11-18	12-17	0.365
Mean±S.D.	15.1±2.66	16.1±3.20	15.47±2.94	
Sex				
Male	3 (15.0%)	4 (20.0%)	5 (25.0%)	
Female	18 (85.0%)	16 (80.0%)	15 (75.0%)	0.621
Disease duration (months)			-	
Range	3.0-20.0	4.0-24.0	-	
Mean±S.D.	15.42±4.25	16.01±5.08	-	0.407

Clinical data

Table (2) shows clinical data of the two studied patients group, it illustrated that,

Regarding mucocutaneous manifestations, group Ihas higher values than group II regarding photosensitivity (60.0% and 60.0%), alopecia (30.0 and 15%) and vascular lesions (25.0% and 15.0%) respectively. While, group IIhas higher values than group I regarding oral ulceration (25.0%, 10.0%) respectively.

Regarding articular complaints, group Ihas higher values than group II regarding arthralgia (80.0% and 40.0%), arthritis (60.0% and 25.0%) respectively, while, group IIhas higher values than group I regarding myositis (15.0% and 5.0%) respectively.

Regarding constitutional manifestation, group Ihas higher values than group II regarding fatigue, loss of weight (55.0% and 35.0%), while group II has higher values than group I regarding fever (25.0 and 20.0%) respectively.

Regarding haematological, group Ihas higher values than group II regarding anemia (80.0% and 70.0), leucopenia (30.0% and 25.0) and thrombocytopenia (45.0% and 25.0%) respectively.

Group IIhas higher values than group I regarding ocular retinal changes (5.0% and 0.0%) respectively.

Group I has higher values than group II regarding hypertension (25.0% and 0.0%) respectively.

Regarding pulmonary manifestations, group Ihas higher values than group II regarding pleural effusion (15.0 and 10.0%), respectively.

Regarding renal manifestations, nephritic syndrome and renal failure were found in group I only (95.0% and 5.0%)

Regarding neuropsychiatric manifestations, seizure was found in 5.0% of group I only, while group I hashigher values than group II regarding headache (60.0% and 15.0%) respectively, group II has higher values than group I regarding depression (30.0% and 5.0%) respectively.

Table (2): Clinical data of the two studied patients group

	Group I "SLE patients with lupus nephritis" **"n=20"**		**Group II** "SLE patients without lupus nephritis" **"n=20"**	
	No.	%	No.	%
Mucocutaneous				
Oral ulceration	2	10.0	5	25.0
Photosensitivity	13	65.0	12	60.0
Alopecia	6	30.0	3	15
Discoid rash	0	0.0	0	0.0
Livedo-reticularis	0	0.0	0	0.0
Vascular lesions	5	25.0	3	15.0
Articular complaints				
Myositis	1	5.0	3	15.0
Arthralgia	16	80.0	8	40.0

Arthritis	12	60.0	5	25.0
Avascular necrosis of hip	0	0.0	1	5.0
Constitutional manifestation				
Fever	4	20.0	5	25.0
Fatigue, loss of weight	611	55.0	7	35.0
Haematological				
Anemia	16	80.0	14	70.0
Leucopenia	6	30.0	5	25.0
Thrombocytopenia	9	45.0	5	25.0
Ocular retinal changes	0	0.0	1	5.0
Hypertension	5	25.0	0	0.0
Cardiac				
Precardial effusion	2	10.0	3	15.0
Pulmonary				
Pleural effusion	3	15.0	2	10.0
Pulmonary Embolism	0	0.0	0	0.0
Renal				
Nephritic syndrome	19	95.0	0	0.0
Renal failure	1	5.0	0	0.0
Neuroyschiatric				
Seizure	1	5.0	0	0.0
CVS	0	0.0	0	0.0
Transvers myelitis	0	0.0	0	0.0
Depression	1	5.0	6	30.0
Headache	12	60.0	3	15.0

Laboratory investigations

Table (3) shows comparison between laboratory investigations in the two patients groups, it illustrated that,

Haemoglobin concentration (g/dl)

Haemoglobin concentration ranged between 8.00-11.27 and 8.32-11.38 with the mean of 9.85□1.86 and 10.25□1.68 for group I and II respectively with no statistical significant differences (P=0.108)

RBCs count (x10^3 cell/mm^3)

RBCs count ranged from 4.00-5.7 and 4.03-5.42 with the mean of 4.52□0.58 and 4.89□0.33 for group I and II respectively with no statistical significant differences (P=0.318).

WBCs count (x10^3 cell/mm^3)

WBCs count ranged from 2.11-7.1 and 2.78-8.77 with the mean of 4.52□1.72 and 5.01□2.17 for group I and II respectively with no statistical significant differences (P=0.281).

Platelet count (x10^3 cell/mm^3)

Platelet count ranged from 32.23-325.0 and 46.00-330.00 with the mean of 260.0□82.71 and 336.1□89.6 for group I and II respectively with no statistical significant differences (P=0.128)

ALT (U/L)

ALT ranged from 11.2-45.0 and 14.03-37.0 for group I and II respectively with no statistical significant differences between the two studied groups (P=0.285).

AST (U/L)

AST ranged from 25.0-43.6 and 21.0-38.0 with the mean of 34.11□9.75 and 29.87□8.25 for group I and II respectively with no statistical significant differences between the two studied groups (P=0.451).

ESR (mm)

ESR ranged from 30-100 and 25-95 with the mean of 68.0□30.1 and 65.1□26.7 for group I and II respectively with no statistical significant differences between the two studied groups (P=0.425).

CRP (mg/dl)

Positive CRP was found in 4 (20.0%) and 1 (5.0%), while negative CRP were found in 16 (80.0%) and 19 (95.0%) patients for group I and II respectively, with no statistical significant differences. (P=0.198)

Serum cholesterol (mg/dl)

Serum cholesterol ranged between 70-110 and 68.9-161.0 with the mean of 95.3□17.7 and 105.1□18.2 for group I and II respectively with no statistical significant differences (P=0.412).

Serum triglycerides (mg/dl)

Serum triglycerides ranged from 38-134 and 40-116 with the mean of 88.6□26.1 and 84.5□22.1 for group I and II respectively with no statistical significant differences (P=0.611).

Table (3): Comparison between laboratory investigations in the two patients groups

Laboratory investigations	**Group I** "SLE patients with lupus nephritis" **"n=20"**	**Group II** "SLE patients without lupus nephritis" **"n=20"**	**P**
HB (g/dl)			
Range	8.00 – 11.27	8.32 – 11.38	
Mean±S.D.	9.85 ±1.86	10.25±1.68	0.108
RBCs count(x10^3 cell/mm^3)			
Range	4.0-5.7	4.03-5.42	
Mean±S.D.	4.52±0.58	4.89±0.33	0.318
WBCs count(x10^3 cell/mm^3)			
Range	2.11 – 7.1	2.78 – 8.77	
Mean±S.D.	4.52±1.72	5.01±2.17	0.281
Platelet count(x10^3 cell/mm^3)			
Range	32.23 - 325.0	46.00 – 330.00	
Mean±S.D.	260.0±82.71	336.1±89.6	0.128
ALT(U/L)			
Range	11.2 – 45.0	14.03– 37.0	
Mean±S.D.	27.13±8.63	25.61±5.17	0.285
AST (U/L)			
Range	25.0 -43.6	21.0 -38.0	
Mean±S.D.	34.11±9.75	29.87±8.25	0.451
ESR (mm)			
Range	30-100	25-95	0.425
Mean□S.D.	68.0□30.1	65.1□26.7	
CRP (mg/dl)			
Negative	16 (80%)	19 (95.0%)	0.198
Positive	4 (20%)	1 (5.0%)	
Serum cholesterol (mg/dl)			
Range	70-110	68.9±161.0	
Mean□S.D.	95.3±17.7	105.1±18.2	0.412
Serum triglycerides (mg/dl)			
Range	38-134	40-116	
Mean□S.D.	88.6±26.1	84.5±22.1	0.611

Kidney function

Table (4) shows comparison between the two patients groups regarding kidney function, it demonstrated that,

Blood urea (mg/dl)

Blood urea ranged from 50-130 and 10-41 with the mean of 105.6±26.5 and 22.5±9.5 for group I and II respectively with statistical significant differences between the two studied groups, group I (SLE patients with lupus nephritis) has statistically higher values than group II (SLE patients without lupus nephritis) (P=0.001).

Serum creatinine (mg/dl)

Serum creatinine ranged from 1.4-6.0 and 0.3-1.01 with the mean of 3.65±1.22 and 0.81±0.26 for group I and II respectively with statistical significant differences between the two studied groups, group I has statistically higher values than group II (P=0.001).

Urinary Alb/creatinine ratio

It ranged from 28-227 and 15-27 with the mean of 115.6±69.8 and 19.8±5.69 for group I and II respectively with statistical significant differences between the two studied groups, group I has statistically higher values than group II (P=0.001).

Proteinurea

It ranged from640-6308 and 34-120 with the mean of 2520.6±780.77 and 85.9±12.69 for group I and II respectively with statistical significant differences between the two studied groups, group I has statistically higher values than group II (P=0.0001).

Table (4): Comparison between kidney function in the two patients groups.

	Group I "SLE patients with lupus nephritis" **"n=20"**	**Group II** "SLE patients without lupus nephritis" **"n=20"**	**P**
Blood urea			
Range	50-130	10-41	
Mean±S.D.	105.6±26.5	22.5±9.5	0.001*
Serum creatinine			
Range	1.4-6.0	0.3-1.01	
Mean±S.D.	3.65±1.22	0.81±0.26	0.001*
GFR			
Range	25-62	75-92	
Mean±S.D.	48.9±8.25	84.6±4.65	0.001*
Urinary alb./creatinine ratio			
Range	28-227	15-27	
Mean±S.D.	115.6±69.8	19.8±5.69	0.001*
Proteinurea(mg/24h)			
Range	640-6308	34-120	
Mean±S.D.	2520.6±780.77	85.9±12.69	0.0001*

Immunological profile

Immunological profile for the two studied patients groups were presented in Table (5), it showed that,

ANA

ANA ranged from 40-480 and 25-420 with the mean of 211.0±81.1 and 196.1±58.6 for group I and II respectively with no statistical significant differences between the two studied groups (P=0.214).

Anti-DNA

Anti-DNA ranged from30-275 and 30-285 with the mean of 125.6□62.5 and 132.6□52.8 for group I and II respectively with no statistical significant differences between the two studied groups (P=0.116).

C3

C3 ranged from 0.04-1.01 and 0.13-1.19 with the mean of 0.42±0.06 and 0.68±0.075 for group I and II respectively with statistical significant differences between the two studied groups, group II has statistically higher values than group I (P=0.041).

C4

C4 ranged from0.11-0.36 and 0.18-0.32 with the mean of 0.21□0.06 and 0.26□0.045for group I and II respectively with no statistical significant differences between the two studied groups (P=0.621).

Renal activity index

Renal activity index for group I (SLE patients with lupus nephritis) ranged between 0-8 with the mean of 4.0±2.56.

Renal chronicity index

Renal chronicity index for group I (SLE patients with lupus nephritis) ranged between 0-6 with the mean of 2.0±1.65.

WHO classification of lupus nephritis

For group I , class II was found in 6 (30.0%), class III was found in 9 (45.0%) and class IV was found in 5 (25.0%).

Lupus activity index: (SLE DAI)

Comparison between the two studied groups regarding the SLE DAI score was presented in table (6), it showed that, high activity score was found in 6 (30.0%) and 4 (20.0%), moderate activity score was found in 9 (45.0%) and 9 (45.0%), while low activity score was found in 5 (25.0%) and 7 (35.0%) for group I and II respectively, with no statistical significant differences. (P=0.123)

Table (5): Immunological profile for the two studied patients group

Immunological investigation	**Group I** "SLE patients with lupus nephritis" **"n=20"**	**Group II** "SLE patients without lupus nephritis" **"n=20"**	**P**
ANA Range Mean±S.D.	 40-480 211.0±81.1	 25-420 196.1±58.6	 0.214
Anti-DNA Range Mean±S.D.	 30-275 125.6±62.5	 30-285 132.6±52.8	 0.116
C3 Range Mean±S.D.	 0.04-1.01 0.42±0.06	 0.13-1.19 0.68□0.075	 0.041*
C4 Range Mean±S.D.	 0.11-0.36 0.21±0.06	 0.18-0.32 0.26±0.045	 0.621
Renal activity index Range Mean±S.D.	 0 - 8 4.0 ±2.56	 - -	
Renal chronicity index Range Mean±S.D.	 0-6 2.0±1.65	 - -	
WHO classification of lupus nephritis **Class II** **Class III** **Class IV**	 6 (30.0) 9 (45.0%) 5 (25.0%)	 - - -	

Table (6): Comparison between the two studied groups regarding the SLE DAI score

	Group I "SLE patients with lupus nephritis" **"n=20"**		**Group II** "SLE patients without lupus nephritis" **"n=20"**	
	No	%	No.	%
High	6	30.0	4	20.0
Moderate	9	45.0	9	45.0
Low	5	25.0	7	35.0
p	0.123			

BAFF and APRIL

Table (7) shows BAFF and APRIL in the studied groups, it demonstrated that:

BAFF

BAFF ranged from 4.26-182., 3.25-166.0 and 2.1-30.0 with the mean of 88.6±42.6, 69.2±27.6 and 12.9±3.25 for group I, II and III respectively, there were statistical significant differences between the three studied groups regarding BAFF, group I has statistically higher values than group II and III, also group II has statistically higher values than group III. (P=0.001)

APRIL

APRIL ranged from3.0-40.0, 2.0-42.5 and 7.0-45.0 with the mean of 7.98±8.25, 9.12±7.88 and 14.89±7.98 for group I, II and III respectively, there were statistical significant differences between the three studied groups regarding APRIL, group IIIhas statistically higher values than group I and II, also group II has statistically higher values than group I. (P=0.0025)

Table (7): BAFF and APRIL in different studied groups

	Group I "SLE patients with lupus nephritis" **"n=20"**	**Group II** "SLE patients without lupus nephritis" **"n=20"**	**Group III "control" "n=20"**	**p**
BAFF				
Range	4.26-182.0	3.25-166.0	2.1-30.0	0.001*
Mean±S.D.	88.6±42.6	69.2±27.6	12.9±3.25	
APRIL				
Range	3.0-40.0	2.0-42.5	7.0-45.0	
Mean±S.D.	7.98±8.25	9.12±7.88	14.89±7.98	0.0025*

Correlations

Table (8) shows correlations between serum BAFF and APRIL with immunological profile, disease duration and activity of disease in the two patients groups, it illustrated that,

Regarding group I, there was positive significant correlation between ANA, activity index and chronicity index with BAFF, there was negative significant correlation between ANA, activity index, and chronicity index with APRIL.

Regarding group II, there waspositive significant correlation between ANA and Anti-DNA with BAFF, while there was negative significant correlation between ANA with APRIL.

Table (9) shows relation between disease activity and BAFF, APRIL levels, it demonstrated that, the mean of BAFF values was 98.8±38.6, 80.2±35.9 and 71.6±39.5 for high, moderate and low in group I, while in group II the mean of BAFF values was 82.6±21.3, 74.2±26.5 and 60.2±31.2 for high, moderate and low disease activity, with statistical significant differences

The mean of APRIL value was16.25±3.01, 10.12±2.78, 8.23±3.95 for high, moderate and low in group I, while in group II the mean of APRIL valuewas11.6±3.41, 9.58±3.21 and 7.98±2.85 for high, moderate and low disease activity, with statistical significant differences

Table (8): Correlation between BAFF and APRIL and immunological profile and disease duration and activity of disease in the two patients group

	Group I "SLE patients with lupus nephritis" **"n=20"**		**Group II** "SLE patients without lupus nephritis" **"n=20"**	
BAFF #	**r**	**p**	**r**	**p**
ANA	0.411	0.01*	0.511	0.003*
Anti-DNA	0.125	0.236	0.258	0.046*
C3	0.098	0.456	0.107	0.365
C4	0.11	0.277	0.206	0.211

Activity index	0.369	0.013*		
Chronicity index	0.468	0.002*		
APRIL#				
ANA	0.398	0.021*	0.426	0.015*
Anti-DNA	0.223	0.107	0.109	0.365
C3	0.17	0.269	0.11	0.411
C4	0.221	0.11	0.207	0.288
Activity index	0.39	0.019*		
Chronicity index	0.44	0.002*		

Table (9): Relation between disease activity and BAFF, APRIL level

	Group I "SLE patients with lupus nephritis" **"n=20"**	**Group II** "SLE patients without lupus nephritis" **"n=20"**
BAFF		
High	98.8±38.6	82.6±21.3
Moderate	80.2±35.9	74.2±26.5
Low	71.6±39.5	60.2±31.2
p	0.012*	0.003*
APRIL		
High	16.25±3.01	11.6±3.41
Moderate	10.12±2.78	9.58±3.21
Low	8.23±3.95	7.98±2.85
p	0.012*	0.014*

DISCUSSION

Lupus nephritis is one of the most frequent and serious complications for patients with SLE and has a profound effect on both morbidity and mortality. Dysfunction of the B cells, an important component of adaptive immunity, is thought to be important in the pathogenesis of SLE/LN. The production of pathogenic antibody has been traditionally viewed as the principle contribution of B cells to the pathogenesis of immune-mediated glomerulonephritis [(24)].

B-cell activating factor (BAFF, also known as B-lymphocyte stimulator, BLyS) belongs to the tumor necrosis factor (TNF) superfamily and can be produced by myeloid cells such as monocytes, macrophages, dendritic cells, and neutrophils. BAFF contributes to B-cell proliferation and differentiation, and it is important in immunoglobulin class switching[(25)]. Many researchers have demonstrated that high levels of BAFF may relax B-cell selection and contribute to autoantibody production, exacerbating proteinuria and renal inflammation in SLE [(26)]. Like BLyS, APRIL is a member of the TNF family, and is thought to have a regulatory role in B cell proliferation.

The aim of this study was to investigate the serum level of BAFF, APRIL in Egyptian adolescent lupus nephritis patients and correlate their level with grade and chronicity index of LN and compare their result with their counterparts of adolescent lupus patients without lupus nephritis. This study included 60 adolescent patients: Group 1: 20 adolescent SLE patients with lupus nephritis. Group 2: 20 adolescent SLE patients without lupus nephritis. Group 3: 20 age and sex matched healthy subjects served as control group.

In this study, serum BLyS levels was statistically higher in group I (SLE with nephritis) than group II (SLE without nephritis) and the least was in the control group.

In agreement with our study, numerous studies have shown that serum BLyS levels are elevated in patients with SLE compared with controls,.[(27)]

Our study showed that, serum APRIL level ingroup III has statistically higher values than group I and II, also group II has statistically higher values than group I.

In disagreement with our study, APRIL levels have been shown to be elevated in patients with lupus compared with healthy controls, although one study has found that levels may be lower in patients with lupus nephritis compared with patients who have lupus without kidney involvement.[28,29]

Vincent, et al., (2013) demonstrated that, there was a trend toward a higher BAFF/APRIL ratio amongst SLE patients with renal disease. These data indicated that among patients with renal involvement, serum concentrations of BAFF and APRIL were significantly different to those without these manifestations.[29]

In agreement with our study, Vincent, et al., (2013) determine whether serum concentrations of B cell activating factor from the tumour necrosis factor family (BAFF) and/or a proliferation-inducing ligand (APRIL) are associated with clinical manifestations of systemic lupus erythematosus (SLE). They found that, serum BAFF was significantly increased, and APRIL decreased, in patients with renal lupus. In contrast, in cross-sectional analysis, there was no correlation between disease activity (SLEDAI-2k) and serum BAFF or APRIL, while the only disagreement with our study, was the positive significant correlation of serum BAFF with SLE activity index.[29]

Petri, et al., (2008)[30] and Hegazy et al., (2010)[31] illustrated that, disease activity levels have been correlated with serum BAFF and APRIL, but this association was not observed in other studies.[32,33]

The lack of correlation of serum BAFF and APRIL concentrations with disease activity in cross-sectional analysis does not preclude the possibility that measurement of these cytokines could be associated with disease activity in individual patients over time, for example because of differences between subjects' baseline concentrations.[29]

Many studies of potential biomarkers have failed to yield evidence of useful correlations with composite measures of disease activity.[34] It has recently been suggested that the investigation of phenotypic subsets based on clinical manifestations, in addition to analysis of overall disease activity, may have merit.[35] Several lines of evidence support this approach. Murine studies suggest that different manifestations of SLE may be determined by different immunological mechanisms.[36], Moreover, studies in human SLE of the IFNα pathway suggest that the expression of IFN-induced genes associates with clinical subgroups, such as patients with renal disease, despite not varying with overall disease activity.[37] Of note, the actions of IFNα include upregulation of BAFF expression.[38]

In agreement with our study, Petri, et al., (2008)[30] and Hegazy et al., (2010)[31] showed that, anti-dsDNA antibodies levels have been correlated with serum BAFF and APRIL, but this association was not observed in other studies[39,40], our study showed no significant correlation between serum APRIL and anti-DNA levels, while it showed a positive significant correlation with ANA levels

CONCLUSIONS

From our study, we concluded that, serum BAFF and APRIL concentrations could be used as new noninvasive biomarkers that could
distinguish a clinical subset of SLE patients, in this case those with renal SLE and the use of Anti BAFF (belimumab) as a new hope for treatment of patients with lupus nephritis.

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