Original article

Serum interleukin-17 expression in a group of Egyptian patients with juvenile systemic lupus erythematosus

Background: *Systemic lupus erythematosus (SLE) is a chronic multi-organ systemic autoimmune disease. Interleukin-17 (IL-17) is a powerful proinflammatory cytokine that is involved in the development of several autoimmune diseases, including SLE.* ***Objective:*** *We aimed to evaluate the serum IL-17 expression in pediatric SLE and correlate this to the disease activity and other biomarkers of disease activity.* ***Methods:*** *Thirty-six patients diagnosed with pediatric SLE were enrolled in the study and were classified according to the SLE disease activity index (SLEDAI) score into two subgroups; mild activity (SLEDAI <5) and moderate to severe activity (SLEDAI ≥ 5). Routine laboratory work-up of SLE was done. IL-17 level was assessed by ELISA in the patients' group (n=36) as well as in 17 age and sex-matched healthy subjects.* ***Results:*** *Our patients were 32 females (88.9 %) and 4 males (11.1 %). Their mean age at enrollment was 13.7 ± 2.7 years. The median (IQR) serum IL-17 level was significantly higher in patients than controls [138 pg/nl (68.5-200.15) versus 8.6 pg/nl (5.98-11.55) respectively]. There was no significant correlation between serum levels of IL-17 levels and disease activity scores. SLE patients with mild activity were comparable to those with moderate to severe activity in terms of IL-17 expression.* ***Conclusion:*** *SLE in children is associated with significantly increase in serum IL-17, whatever the activity status is, suggesting a potential role in the pathogenesis of the disease. Our conclusion is limited by the sample size.*

Keywords: Serum Interleukin-17, Systemic Lupus Erythematosus, Lupus activity.

Abbreviations: ACR: American College of Rheumatology, dsDNA: Double stranded DNA, IL: Interleukin, INF: interferon, SLE: Systemic lupus erythematosus, SLEDAI: Systemic lupus erythematosus Disease activity Index

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multi-organ systemic autoimmune disease characterized by autoantibody production to nuclear antigen resulting in inflammation and damage to numerous organs particularly kidneys.[1] It appears in genetically prone individuals and is triggered by ill-defined environmental factors. The deposition of autoantibodies occurs in vulnerable vascular beds frequently in skin, joints and renal glomeruli causing local inflammation and tissue destruction that may magnify the autoimmune response creating.[2]

Till date the complete understanding of SLE pathogenies is unclear. However, it is well known that dysregulation of B-and T-cell activation will lead to disruption in immune system, and this is considered a key role in SLE pathogenies.[3] In addition, proinflammatory cytokines contribute to the pathogenesis of SLE. These include interleukin (IL)-1 1β, IL-6, IL-17 and tumor necrosis factor (TNF)-α and their levels may correlate with SLE activity.[4]

Interleukin-17 (IL-17) is produced by T-helper 17 (Th17) cells and other immunological cells.[5] IL-17 consists of six protein members [IL-17A, IL-17B, IL17-C, IL-17D, IL-17E , and IL-17F] of which IL-17A and IL-17F are responsible for the activity of Th17 cells in the induction of other cytokines and chemokines. [6,7] IL-17, is a pleiotropic pro-inflammatory cytokine that enhances T-cell priming and stimulates epithelial, endothelial, and fibroblastic cells to produce other multiple proinflammatory mediators such as TNF-α, IL-1β, and IL-6.[5] [IL]-17 plays a critical role in innate and adaptive immune systems by promoting

inflammation, cytokine production, B-cell proliferation, and autoantibodies production.[7]

Being a powerful proinflammatory cytokine, IL17 is involved in the development of several autoimmune diseases, including SLE.[8] The serum level of IL-17A and numbers of IL-17–producing T cells were reported to be increased both in patients with SLE and in a mouse model of lupus.[8,9]

Several IL-17A pathway inhibitors such as anti-IL-17 monoclonal antibody have been proposed as a potential treatment for different autoimmune disease. Those autoimmune diseases are psoriasis, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, and non-infectious uveitis.[10] However, the conflicting results of whether the level IL-17 correlated with disease activity or not, makes such medication not suitable to every patient. And this will lead us to precision medicine which depends on assessing IL-17 before commencing treatment and providing it to those who need it.[11] A similar strategy is currently used for rheumatoid arthritis.[12] In our study we aimed to assess the level of IL-17 in a sample of Egyptian paediatric SLE patients and correlate it to disease activity.

METHODS

This is a controlled cross-sectional study that was conducted on 36 patients with pediatric SLE who were recruited consecutively from the Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Ain Shams University, during the period between January 2018 to January 2019. All patients fulfilled at least four of the diagnostic criteria of the American College of Rheumatology (ACR)[13] for SLE diagnosis. An informed consent was obtained from the parents/caregivers and the study protocol was approved by the Local Research Ethics' Committee of Ain Shams University. A 17 age- and sex- matched healthy children were enrolled as a control group. They were recruited from Pediatric Outpatient Clinic, after taking their parents' consent.

Patients were subjected to detailed history and clinical examination to assess disease activity. SLEADI score was used to assess the disease status activity and based on the achieved score patients were categorized as moderate to severe activity (score ≥ 5) or remission to mild activity (score < 5)[14]

They underwent the following laboratory parameters:

- Complete blood count using coulter counter (Coulter AXMUG- HL –CCI) and Leishman-stained peripheral blood film examination for manual differential white blood cell counting
- Erythrocyte sedimentation rate (ESR) by Westergren Method,
- Serum anti-nuclear antibody (ANA) by indirect immuno-fluorescence, and anti-double stranded deoxyribonucleic acid (anti-ds DNA) by ELISA and complement-3 (C3) by nephelometry.
- Complete urine analysis was performed using freshly collected random urine specimen in sterile plastic container including chemical analysis using dipsticks and microscopic examination with special emphasis on the presence of albuminuria, hematuria, pyuria, and urinary casts.
- 24-hour-urinary protein measurement using Synchron CX7 autoanalyzer (Beckman Inc., California, USA).
- Serum IL-17 was assessed in the patient and control groups by Human Interleukin 17 ELISA kit manufactured by Sun Red Biological Technology Co., Ltd (Hutai Road, Baoshan District, Shanghai, China)

Statistical analysis

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented with suitable analysis according to the type of data obtained for each parameter. Descriptive statistics: Mean, Standard deviation (± SD) and range for parametric numerical data. Median and Interquartile range were used for non-parametric numerical data. Analytical statistics: Student t Test was used to assess the statistical significance of the difference between two study group means. Correlation analysis (using Pearson's method and spearman's rho) to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables. r= 0-0.19 is regarded as very weak correlation, r=0.2-0.39 as weak correlation, r=0.40-0.59 as moderate correlation, r=0.6-0.79 as strong correlation, r= 0.8-1 as very strong correlation. The ROC Curve (Receiver Operating Characteristic) is used to evaluate the sensitivity and specificity of serum IL-17 for pediatric SLE. Probability (p) values < 0.05 is considered significant.

RESULTS

We enrolled 32 girls (88.9%) and 4 boys (11.1%) with a female to male ratio of 8:1. Their ages at

diagnosis ranged from 8 to 17 years with a mean of 14.2 ± 2.6 years. Their mean age at enrollment was 13.7±2.7 years. The duration of illness ranged from 6 months to 7 years with a mean of 2.14±1.8 years. Thirty-four patients (94.4%) had lupus nephritis (LN) and 4 (11%) had lupus cerebritis. Patients with LN comprised 12 patients (35%) with class II, 10 (29.4%) with class III, 7 (20.5%) with class IV and 5 patients (14.7%) had class V. The demographic and laboratory data of the SLE patients are presented in **(table 1).** The control, group included 9 females (53%) and 8 males (47%). Their mean age at enrollment was 11.3±1.8 years.

Serum levels of IL-17 were significantly higher among patients as compared to healthy controls with a median (IQR) of 138 pg/nl (68.5-200.15) versus 8.6 pg/nl (5.98-11.55), respectively (p=0.001); (Figure1). Receiver-operating characteristic (ROC) curve showed that the cut off level of serum IL-17 was 29.3 pg/mL with sensitivity of 100%, specificity of 100%, positive predicative value of 100% and negative predictive value of 100% (Figure 2).

We analyzed the IL-17 expression in relation to type of organ involvement. Patients with CNS lupus had a higher median level than those with lupus nephritis [195.3pg/ml versus139.9pg/ml, respectively]; however, the observation is limited by the small number of patients with lupus cerebritis. No significant correlations could be elicited between serum IL-17 and any of SLE activity markers namely 24 hours urinary protein level, anti-dsDNA titer and C3-level (p >0.05). We also found no correlation between serum IL-17 level and patients' age or disease duration (r=-0.06, p=0.729; r=0.235, p=0.168 respectively).

Based on the SLEADI score at the time of the study, there were 20 SLE patients with mild disease activity (SLEADI score ≤ 5 (group A) and 16 patients with moderate to severe disease activity (SLEDAI ≥ 5 (group B). The serum IL-17 median (IQR) levels were comparable between both groups being147.17 pg/ml (61.9- 435) in patients with mild and 118.84 pg/ml (39.3-264.5) in patients with moderate to severe disease activity (p=0.34). We correlated IL-17 to different laboratory markers of activity in in each disease activity group **(Table 2).** The only significant correlation observed was between IL-17 and the ESR in patients with mild activity (p=- 0.005). The findings are indeed limited by the sample size.

Table 1. Demographic and laboratory data of SLE patients

Variable	Patients (n= 36)					
	Patients with mild activity n=16 (44%)		Patients with moderate to severe activity n= 20 (56%)		t value	p value
	Mean±SD	Range	Mean±SD	Range		
Weight (Kg)	50.58 ± 14.5	25 – 80	47.80 ±14.63	19-65	0.55	0.584
Height (m)	1.47 ± 0.11	1.3 - 1.65	1.52 ±0.14	1.2-1.65	-1.01	0.321
TLC ($\times 10^9$/L)	6.97 ± 4.04	2.5 - 19	6.19± 2.13	2.5-10.1	0.68	0.500
Lymphocytic count ($\times 10^9$/L)	2.16 ± 0.94	1 - 4.5	1.56±0.84	0.3-3.7	1.94	0.061
Hemoglobin (gm/dl)	11.96 ± 1.82	6.8 - 14.9	10.52±2.02	5.9-13.8	2.19	0.036
Platelet ($\times 10^9$/L)	282.84 ± 84.12	50 - 453	253.27±93.83	78-420	0.97	0.341
ESR (1st hour)	34.89 ± 25.57	4 - 120	60.53±39.29	10-125	-2.19	0.039*
C3 (mg/dl)	116.16 ± 37.18	38 - 181	72.20±26.61	25-107	3.86	0.001*
Creatinine (mg/dl)	0.68 ± 0.13	0.5 - 0.9	0.59±0.20	0.3-0.9	1.61	0.117
BUN (mg/dl)	8.32 ± 2.11	5 - 14	13.53±5.72	8-30	-3.36	0.004*
IL17 (ng/ml)	147.17 ± 90.71	61.9 - 435	118.84±71.43	39.3 - 264.5	0.97	0.341

* Significant; BUN: blood urea nitrogen; C3: complement 3; SLEDAI: systemic lupus erythematosus disease activity index

Table 2. Correlation between serum Il-17 and other lab markers in SLE patient groups

Variable	IL-17			
	Patients with mild activity (n=20)		Patients with Moderate to severe activity (n=16)	
	r	p - value	R	p – value
TLC	-0.244	0.314	-0.027	0.927
Lymphocytes	-0.327	0.172	0.332	0.246
Platelets	-0.042	0.865	-0.155	0.598
ESR	**0.621**	**0.005***	-0.049	0.867
Anti-DNA	0.143	0.558	-0.149	0.610
C3	-0.418	0.075	-0.054	0.855
24-hour Protein	-0.233	0.338	-0.261	0.368

* Significant; BUN: blood urea nitrogen; C3: complement 3; ESR: erythrocyte sedimentation rate; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; r=rho; SLEDAI Score: systemic lupus erythematosus disease activity index score; TLC: total leukocyte count.

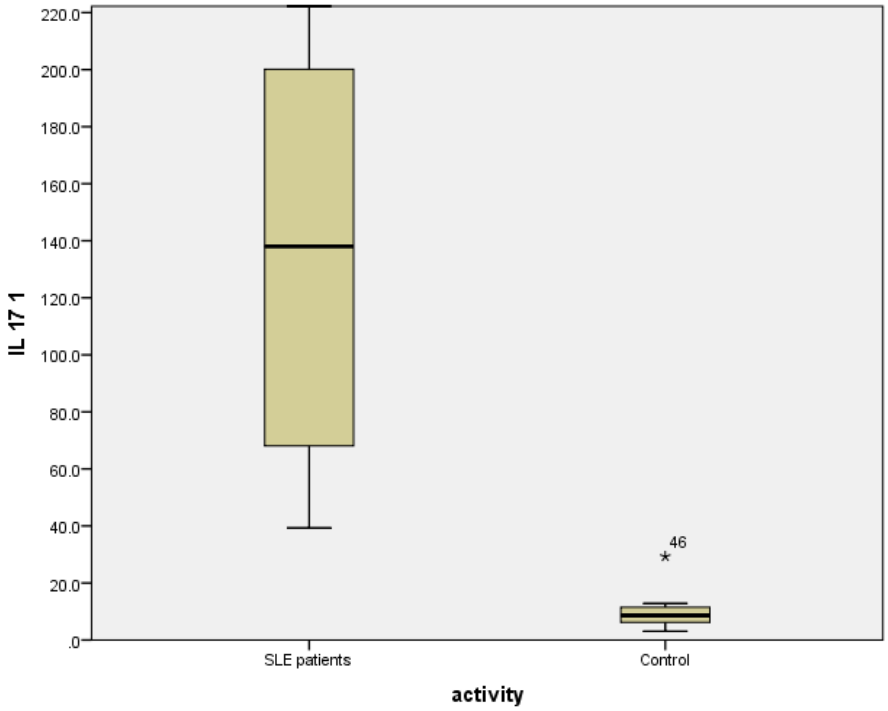

Figure 1. Box plot indicating difference in serum IL 17 between patients and controls.

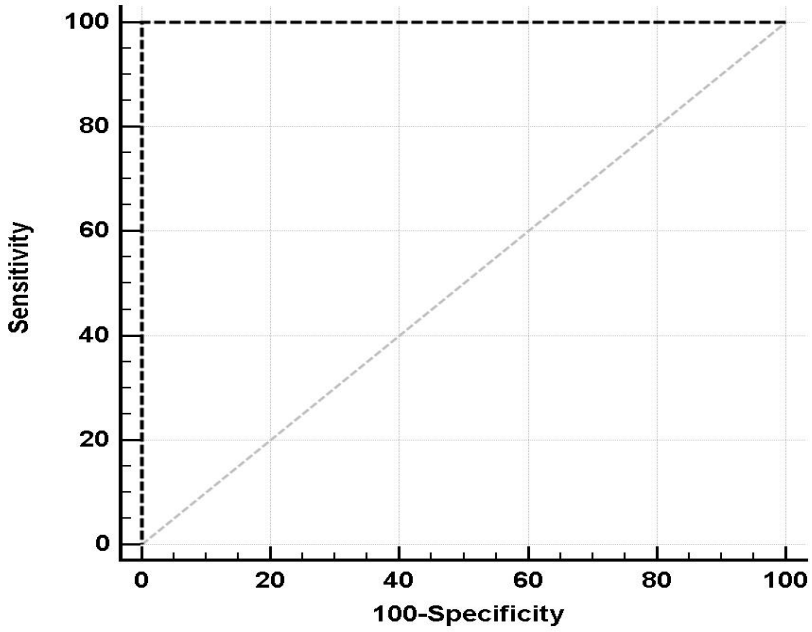

Figure 2. Receiver-operating characteristic (ROC) curve for discrimination between patients of SLE and controls using serum IL-17.

The Receiver-operating characteristic (ROC) curve shown in figure 1 depicted the true positive fractions (sensitivity) and false positive fractions (1-specificity) for serum IL17 at various cut points in healthy subjects and patients. The calculated area under the curve was found to be 2 which means that the variable (serum IL17) can be used to differentiate between patients and controls. The natural log-transformed cut point (cut off value/ threshold) that maximize the combined sensitivity and specificity for serum IL17 is 29.3 pg/mL with sensitivity of 100% and specificity of 100%. Below or above this value it is considered abnormal. The positive predicative value is 100% and the negative predictive value is 100%.

DISCUSSION

The involvement of IL-17 axis in many inflammatory and autoimmune diseases is well established leading to the development of successful targeted therapies. Its role in SLE is less described. However, data from animal models and patients strongly suggest that IL-17 and its producing cells are involved in SLE pathogenesis and are increased in serum and involved organs.[11]

There was significant elevation of serum IL-17 levels among our patients as compared to the control group. Moreover, the cut-off level of differentiation between patients and controls was 29.3pg/ml with sensitivity and specificity of 100% which supports the postulated involvement of IL-17 in the immune dysregulation of SLE. The same was reported by Wong et al,[15] who reported that adult SLE is associated with significantly higher IL-17 than in control (76.5±45.7, 37.6±35.3 respectively). In addition, studies conducted on adult Egyptian SLE patients showed overexpression of IL-17.[16-18] Abdel-Galil et al[16] noted a cut off level of 19.7 pg/ml to differentiate between patients and controls with 93.3.5% sensitivity and 92.9% specificity.[16] Several international studies on adults proved increase in IL-17 gene expression and/or increase in serum levels.[19-27] In a recent meta-analysis, IL-17 levels were significantly higher in SLE than healthy controls (standardized mean difference was1.045, 95% confidence interval 0.521-1.568, $p<0.001$).[7] Such elevation is explained by many assumptions including the constant release of inflammatory cytokines which promotes production of IL-17 by T Lymphocytes and the stimulatory effect of IL-23 on innate immune cells to secret IL-17.[21]

Interestingly, IL-17 was reported to vary according to ethnicity being higher in Asians followed by Arabs and less among Latin Americans.[7] Several studies reported the risk of IL-17 gene polymorphism in SLE but did not point to ethnic differences.[26-28]

We could not find a significant difference in serum IL-17 according to SLE activity scores. This could be due to small sample size. However, the relation of IL-17 to SLE activity was a point of debate in various studies. For instance, Talaat et al.[29] found no difference in IL-17 level among SLE patients in activity as compared to those in remission. On the other hand, Abdel-Galil et al found a significant difference between IL-17 level

in patients with SLE activity and those in remission based on the SLEADI index,.[16] Several other studies demonstrated significant association of serum IL-17 with SLEDAI lupus activity scores.[15,30-35] Also, Chen et al.[36] found that glomerular IL-17 positively correlated with renal SLEADI and histological index of LN patients which supports the role of IL-17 in LN pathogenesis and activity. In contrast, others denied any significant correlation with disease activity.[37,38] Such contradictory findings warrant further studies investigating the association of IL-17 with lupus flare.

We did not observe any significant correlation between serum IL-17 expression and other markers of disease activity except for a positive correlation with the ESR. However, Abdel-Galil et al[16] found no significant correlation to the ESR but it was positively correlated to the 24-hour urinary protein excretion and anti-DNA and negatively to the serum C3. Such conflict might be explained by the small sample size. The serum IL-17 levels seemed higher in lupus cerebritis (4 patients) than LN (17 patients); however, the discrepancy in patient numbers did not allow for statistical comparison. The observation of higher IL-17 levels in lupus cerebritis was also made by Vincent et al.[31] It is possible that IL-17 expression has organ predilection in SLE, but this observation needs further evaluation.

Our study limitations are the small sample size and the consecutive manner of patient recruitment. The latter led to heterogenicity in the size of subgroups classified according to activity and organ involvement. In addition, we did not adjust our findings according to the effect of obesity which is known to influence the proinflammatory effect of IL-17. Obesity is a comorbidity in SLE due to the long-term steroid therapy and sedentary life pattern.

CONCLUSIONS

Pediatric SLE is associated with higher levels of serum IL-17 suggesting a potential role in the pathogenesis of the disease. Further wider-scale longitudinal studies with adequate representation of various organ involvement are required before considering IL-17 as potential target for biological therapy in pediatric SLE.

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