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The Correlation between Plasma Interleukin-18 Level and Disease Activity in Patients with Systemic Lupus Erythematosus

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Abstract
Background: Interleukin *18 (IL-18) is a newly defined cytokine that has an important role in the Th1 type immune response and it shares similar functional properties with IL-12. Elevation of IL-18 levels in autoimmune diseases such as Systemic Lupus Erythematosus (SLE) has been reported in previous studies.* ***Aims & Objectives:*** *To study the IL-18 levels in the plasma of Jordanian patients suffering from SLE and to correlate the disease activity and IL-18 level.* ***Materials and method:*** *The study includes forty-one RA patients in experimental group, and forty-one as a control group, sex and age matched apparently healthy subjects. Plasma IL-18 levels were determined using Enzyme-Linked Immuno Sorbent Assay (ELISA).****Results:*** *IL-18 levels were significantly elevated in the SLE patients compared to the controls ($p< 0.0001$) and the level of IL-18 was significantly correlated with the disease activity in SLE patients ($r= 0.602$, $p= 0.000$).* ***Conclusion:*** *Elevated IL-18 levels were noticed in patients with SLE and IL-18 levels are significantly correlated with disease activity in SLE patients so this finding may be of used for monitoring the disease activity in SLE patients.*

Keywords: *Disease Activity, Plasma Interleukin-18 Level, Systemic Lupus Erythematosus*

I. Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterized by the activation of Polyclonal B lymphocytes, production of auto antibodies, and formation of immune complexes causing tissue and organ damage [3].

Interleukin (IL)-18, formerly called IFN-γ-inducing factor, is a novel Th1 cytokine produced by kupffer cells, activated macrophages, keratinocytes, intestinal epithelial cells, osteoblasts and adrenal cortex cells [2]; [3]. It plays an important role in the Th1 response to toxic shock and shares functional similarities with IL-12 [4]. IL-12 can induce the production of IL-18 and has a synergistic effect with IL-18 on the activation of natural killer (NK) and cytotoxic T lymphocytes (CTL) [5].

The association of IL-18 with pathological condition had been evaluated in many diseases including the hemophagocytic lympho histiocytosis[6], Crohn's disease [7] and leukemia [8]. Connective tissue diseases are important causes of morbidity and mortality. They are autoimmune in nature with variable manifestations of both clinical course and management strategies. Factors that govern severity, response to treatment and outcome are largely unknown. Genetic factors, cytokines and environmental factors have been indicated in the pathogenesis and pathology of these diseases.

1.1. Aims & objectives

This study aims at measuring levels of Interleukin-18 (IL-18) in plasma samples taken from Jordanian patients suffering from Systemic Lupus Erythematosus (SLE) and to correlate plasma IL-18 levels with disease activity.

II. Materials & Methods

2.1. Sample selection

This research was conducted on blood samples obtained from patients referred to the rheumatology Out Patient Clinic of the Jordan University Hospital. The blood samples were collected from 41 patients (32 females and 9 males) with an age range between 16 and 69 years, all patients had confirmed diagnosis of SLE, according to the 1982 revised American Rheumatism Association criteria [9]. Apparently healthy individuals with 41 age and sex matched were included as a control.

2.2. Data collection methods:

2.2.1. Blood specimen collection

Seven ml of peripheral blood were collected from each patient and control individual into EDTA containing tube using Vacutainer system (Becton Dickinson Vacutainer System, France). Plasma was separated within 4 hours by centrifugation at 2000g at 4°C for 10 minutes, then it was aliquoted and stored at -70°C until it was analyzed [10].

2.2.2. Evaluation of disease activity

The evaluation of the disease activity of SLE patients was performed according to the SLE Disease Activity Index (SLEDAI) [11]. The disease was considered active when one or more of these clinical manifestations were present, and inactive in the absence of these clinical manifestations.

2.2.3. IL-18 Determination assay

Plasma IL-18 concentrations of patients and control subjects were measured by Enzyme Linked- Immuno-Sorbent Assay (ELISA) using human IL-18 ELISA Kit manufactured by Medical and Biological Laboratories (Nagoya, Japan).

2.2.4. Data analysis and interpretation

Quantitative continuous measurements were expressed as mean, median, standard deviation (SD) and range. Two-tailed T-test was used for comparison between two independent sample populations at 95% confidence level ($P<0.05$). Spearman's correlation coefficient was used to test the correlation between IL-18 concentration and SLE Disease Activity Index. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) statistical software for windows, Version 9.0 (SPSS, Chicago, IL, USA). A probability (P) value of <0.05 was considered as indicating a significant difference.

III. Results

3.1. SLE patients and their control group

Forty-one Jordanian patients with SLE consists of 32 females and 9 males, (mean age ± SD = 32.5±10.1 yr), were recruited for this study. The mean duration of the disease at the time of the patient's evaluation was 4.7 ± 3.7 yr, ranging from 0.5-15.0 yr. Forty-one, sex-and-age-matched, apparently healthy, 32 female and 9 males, (mean age ± SD = 32.7 ± 9.5 yr), ranging from 20-57 yr were recruited as control subjects.

***3.2. IL-18 level in the plasma of SLE patients and their* controls**

The mean concentration of IL – 18 in SLE patients was 620 ± 269 pg/ml ranging from 179 to 1229 pg/ml. the levels of plasma IL – 18 of the control group were ranging from 66 to 452 pg/ml with a mean value of 282 ± 73. The comparison of both patients versus controls IL – 18 levels was statistical significant, ($p< 0.0001$). When the levels of IL-18 was studied according to the disease activity, there were significant differences between the levels of IL-18 as shown in Table 1.

3.3. Correlation between IL-18 level and SLE Disease Activity Index (SLEDAI) Score

When we studied the correlation between IL-18 level and SLE disease activity, a significant positive correlation was demonstrated ($r= 0.602$, $p= 0.000$) as shown in Fig 1.

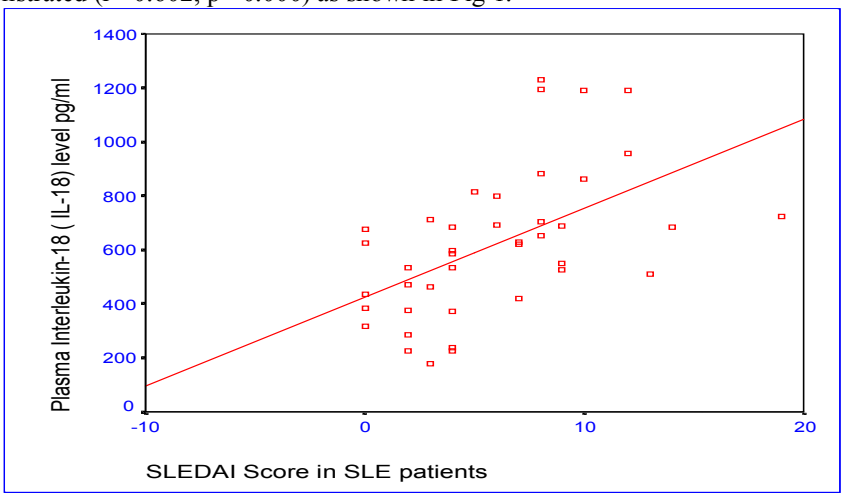

Figure (1): Correlation between IL- 18 level and SLEDAI Score in SLE patients

IV. Discussion

In the current study our findings showed that the plasma IL-18 levels were significantly elevated in patients with SLE as a group and as active and inactive subgroup in comparison to the control group (621 pg/ml VS 280 pg/ml respectively with p< 0.0001). Moreover, there was a significant difference in IL-18 level between patients of active and inactive disease.

These findings were in agreement with those reported by other authors (Wong, et al., 2000)[10], were they found that the concentrations of plasma IL-18 in SLE patients were significantly higher than those in control subjects. They also indicated that there was a significant positive correlation between IL-18 concentration and SLEDAI score which was comparable to our findings (r=0.499, p= 0.004) (Wong, et al., 2000)[10].

Wong, et al. also reported that there was a significant in IL- 18 levels between the patients of SLE with Renal SLE and those without similar results, and this elevation was correlated with the disease activity . They estimated the plasma, but there was no significant difference between the levels in SLE patients without renal involvement and the control group[12].

Amerio, et al. showed that Th1 and Th2 cytokine can be elevated in SLE patients and that only IL-18 level correlated with disease activity [13].

Animal experiments on conducted on MRL/Ipr mice (the animal model for spontaneous lupus-like autoimmue disease) were also in agreement that exogenous IL- 18, can induce similar clinical picture. Such as vasulitis, proteinuria , the presence of immune globulins in the skin and higher production of anti-dsDNA antibodies as well as pro inflammatory monokines were developed in MRL/ Ipr mice[14].

V. Conclusion

Elevated IL-18 levels were noticed in patients with SLE. IL-18 levels are significantly correlated with disease activity in SLE patients. This finding may be of used for monitoring the disease activity in SLE patients.

Recommendation:

We recommended to evaluate other types of autoimmune diseases such as Rheumatoid Arthritis (RA) and Behcet's disease, and correlate plasma interleukin -18 level with disease activity. Further study can be conducted using large sample.

Table (1): Plasma Levels of IL-18 of SLE and the control group (values in pg/ml)

1L-18 Pg/ml	All SLE N=41 (a)	Active SLE N=22 (b)	Inactive SLE N=20 (c)	Control Group N=41 (d)	Statistical comparisons (P value)
Mean+_SD Median Range	620 +_ 269 620 (179-1229)	787+_243 704 (418-1229)	446+_ 169 449 (179-712)	282+_73 280 (66-452)	(a)/(d)*p.< 0.0001 (b)/(d)*p.< 0.0001 (c)/(d)*p.< 0.0001 (b)/(c)*p.< 0.0001
*p(significant)					

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