Section: Internal Medicine

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Study of Interleukin-17 as an Add-on Biomarker for Evaluation of Lupus Nephritis Activity

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Abstract

Background: The T helper 17 (Th17)/interleukin-17 (IL-17) axis is characterized primarily by its effector and proinflammatory properties. Present serologic and urine indicators are not linked well with nephritic activity in systemic lupus erythematosus (SLE), despite the great efficacy of biomarkers for the diagnosis of SLE.

Aim and objectives: We plan to study the role of adding IL-17 to C3 and C4 as a complementary indicator of lupus nephritis (LN) activity.

Patients and methods: This cross-sectional observational research, includes 60 patients selected from attendee of immunology and allergy center, AL-Azhar University.

Results: There was a statistically significant variance among our research populations regarding contrast amongst erythrocyte sedimentation rate (ESR) 1st H and C-reactive protein (CRP), C3 and C4. Contrast amongst the three examined groups regarding to anti-DNA and antinuclear antibodies (ANA) and contrast among the three examined groups regarding to IL-17 (ng/l). There was a statistically substantial negative association amongst IL-17, C3 and C4 with P value of 0.001, and less than 0.001 in all participants, statistically significant negative correlation with C4 in SLE cases with active renal disease and statistically significant negative association between IL-17 and C3 in SLE cases without active renal disease.

Conclusion: Not all cases of LN have consumed complement C3 and C4. Some cases have normal C3 and C4, serum IL-17 can be utilized as an adjunctive marker for LN activity in addition to complement C3 and C4 and substantial association of serum IL-17 with SLE when compared with markers of SLE activity like anti-dsDNA antibodies and urinary A/C ratio.

Keywords: Biomarker, Interleukin-17, Lupus nephritis activity

1. Introduction

Clinical exacerbations and remissions define systemic lupus erythematosus (SLE), a chronic autoimmune illness that may impact any organ system at any time. The pathophysiology of SLE is unclear and complicated, as it involves several subsets of the immune system.¹

The serum levels of interleukin-17 (IL-17) and IL-23 were higher in both active and inactive SLE cases, but IL-22 levels were lower in those with active lupus. However, lupus nephritis (LN) was not associated with either IL-6 or IL-10 levels. Elevated levels of IL-6 and tumor necrosis factor alpha (TNF-a) were both associated with disease activity in their own investigations.²

The chance of getting SLE is greatly increased in those with a family history of complement C4 insufficiency, but C3 deficiency is relatively infrequently linked to SLE-like disease. It is hypothesized that in lupus, there is a failure in the clearance of immunological complexes and/or apoptotic debris, both of which are aided in large part by complements. By facilitating the negative selection of self-
reactive B cells, the innate immune system, which includes complement, protects against lupus.\(^3\)

These Th17 cells release a pleiotropic proinflammatory cytokine known as IL-17. Increased production of IL-1, IL-6, TNF-α, and chemokines is the result of this compound’s ability to induce the differentiation of epithelial, endothelial, and fibroblastic cells. Although IL-17 performs a crucial function in the immune response against germs and fungi, it has also been linked to the development of a number of inflammatory and autoimmune illnesses, for example, psoriasis, RA, IBD, SSc, and SLE. The conditions under which it is made have a substantial impact on its final characteristics.\(^4\)

The main aim of the study was as complement C3 and C4 are not constantly in linear correlation with LN activity, we plan to study the role of adding IL-17 to C3 and C4 as a complementary indicator of LN activity.

2. Patients and methods

The present research was designed as a comparative cross-sectional research was conducted at Center of Allergy & Immunology, Faculty of Medicine, Al-Azhar University. The research included 60 patients; all participants were separated into two subgroups. Group A (case group): 40 cases diagnosed with SLE and group (B) (control group): 20 healthy age-matched patients. The research protocol has been approved by the local ethics committee, and all participants have given their written informed permission.

Inclusion criteria: cases must be at least 18 years old and have SLE confirmed by autoantibody testing (antinuclear antibody titers \(^3\)1 : 80, anti-double-stranded DNA antibodies, or both) according to the American College of Rheumatology categorization criteria for SLE as per Shiboski et al.\(^5\)

Exclusion criteria: cases with other autoimmune or rheumatic disorders, patients with renal diseases besides LN, patients with infections or other comorbidities, and malignant tumors.

Sample size: Epi Info STATCALC was used to determine the sample size of this investigation, with the use of the following assumptions drawn from the work by Galil et al.\(^6\) The odds ratio was determined to be 1.115 at a 95 % two-sided confidence level, with an 80 % power and 5 % error. From the Epi-Info output, the maximum possible sample size was drawn to be 49. As a result, the number of patients was doubled to 60 in order to account for potential dropouts throughout the follow-up phase.

2.1. Methods

All participants divided into two subgroups: group A (case group): 40 patients diagnosed with SLE and group (B) (control group): 20 healthy age-matched patients.

All patients were subjected to: every patient gives their permission after being fully informed, full documentation of the past, extensive medical checkup (general examination and systemic examination; musculoskeletal and renal), disease activity assessment, laboratory evaluation, and serum cytokines estimation.

Patients with SLE were split into two groups: 20 cases with newly diagnosed active LN (group A1) and 20 cases with SLE without renal disease (group A2) (inactive group) were studied.

Serum cytokines estimation: estimated IL-17 blood concentrations at baseline were performed on all study populations (healthy controls, active, and inactive patient groups). Using a commercially available human development kit, they used sandwich enzyme-linked immunosorbent assay to get a quantitative determination. The test was conducted in agreement with the manufacturer’s guidelines indicated in the brochure provided. At the time of the patient’s clinical evaluation and evaluation of SLE disease activity, blood was drawn to measure serum levels of cytokines and to conduct additional laboratory tests.

2.2. Statistical analysis of the data

Data analysis was carried out utilizing IBM SPSS, version 20.0 (IBM Corp., Armonk, New York, USA). Quantitative and percentage descriptions were utilized for qualitative data. Normality was determined with the utilization of the Shapiro–Wilk test. The minimum and maximum values, as well as the mean, SD, median, and interquartile range, were utilized to characterize the quantitative data. The acquired findings were deemed significant at the 5 % level.

3. Results

Table 1.

There was no statistically substantial variance was found between SLE cases with active renal disease, and SLE cases without renal disease as regards demographic data except for residence being frequency of urban residence more among inactive renal disease with \(P\) value of 0.001 (Table 2).

There was statistically significant higher erythrocyte sedimentation rate (ESR) and C-reactive
protein (CRP) among SLE patients compared to control group with $P$ value of 0.020, and less than 0.001, respectively (Table 3).

There was statistically substantial lower C3 and C4 among SLE cases with nephritis and without nephritis than control group with $P$ value less than 0.001, with more consumption of C3 and C4 in cases without nephritis (Table 4).

There was a statistically substantial positive anti-nuclear antibodies (ANA) and anti-dsDNA among...
SLE cases with active renal disease and SLE cases without active renal disease compared to control group with \( P \) value less than 0.001, respectively (Table 5).

There was a statistically significant higher IL-17 among SLE cases with active renal disease contrasted with SLE cases without active renal disease and control group with \( P \) value less than 0.001 (Table 6).

There was a statistically substantial negative association among IL-17, C3 and C4 with \( P \) value 0.001, and less than 0.001 in all participants, statistically significant negative correlation with C4 in SLE cases with active renal disease with \( P \) value less than 0.024, and statistically significant negative correlation between IL-17 and C3 in SLE cases without active renal disease with \( P \) value 0.047 (Fig. 1).

4. Discussion

SLE is a complex autoimmune disease that can manifest in a variety of ways. There is a 9:1 female to male ratio, with the peak onset age occurring...
amongst the late teens and the early 40’s in women. Although there is a complicated genetic basis for SLE and some environmental triggers, including sun exposure and certain medications, no one cause has been discovered.7

The main results were as follows.

As regard to comparison between the three examined groups regarding to demographic data we found that there was no statistically substantial variance found amongst SLE cases with active renal disease and SLE patients with inactive renal disease as regards demographic data except for residence being frequency of urban residence more among inactive renal disease with P value of 0.001.

Our study was consistent with Hussain et al. who intended to measure serum complement C3 and C4 concentrations in LN cases in order to determine if these simple measurements would provide valuable information to the clinician managing these cases. As in LN cases, 14 (82.35 %) were women and 3 (17.64 %) were men. Mean age at study entry was 28.1 years (range: 11–60).8

In our study as regard to contrast amongst the three examined groups regarding to C3 & C4 we found that there was statistically significant lower C3 and C4 among SLE cases with nephritis and without nephritis than control group with P value<0.001, with more consumption of C3 & C4 in cases without nephritis.

In SLE, there is often a decrease in the levels of complement proteins C3 & C4 due to increased consumption, autoantibody-mediated consumption, impaired synthesis, and genetic factors. This can lead to an increased susceptibility to infections, particularly those caused by encapsulated bacteria, and an increased risk of LN. In LN cases, the levels of complement proteins C3 & C4 are often decreased due to complement activation, autoantibodies against complement proteins, and genetic factors. This can lead to an elevated hazard of infections and disease progression.9

In our study, SLE patients with active LN have higher C3 & C4 contrasted with cases without renal disease. Our explanation is that during active phase of LN, it is possible that there may be some increase in the levels of complement proteins C3 &C4, as complement activation can occur in the kidneys in response to immune-mediated inflammation. This may cause a transient increase in the levels of complement proteins.

Our study was in disagreement with Hussain et al.9 who found that in LN, C3, and C4 are generally associated. Both C3 and C4 levels were reduced but C4 concentrations were more often and greater depressiveness than C3 concentration.

Also, our study was consistent with Contreras et al.10 who found that C3 levels were higher than C4 levels.

In our study as regard to contrast among the three examined groups regarding to IL-17 (ng/l) we found that there was a statistically significant higher IL-17 among SLE cases with active renal disease contrasted with SLE cases without active renal disease and control group with P value less than 0.001.

Our study was consistent with Wu et al.11 who aimed to study ‘IL-1β and IL-6 are highly expressed in RF + IgE + SLE subtype’ as there was a statistically substantial variance amongst the examined groups as regards IL-17 (P = 0.003).

Also, our study was consistent with Merrill et al.12 who aimed to study ‘the biomarkers of lupus disease study: a bold approach may mitigate interference of background immunosuppressants in clinical trials’ as there was a statistically substantial variance among the examined groups regarding IL17RA (P = 0.01).

In our study as regard to correlation between IL-17 (ng/l) and different parameters in each group we found that there was a statistically substantial negative association amongst IL-17, C3, and C4 with P value 0.001 and less than 0.001 in all participants, statistically significant negative correlation with C4 in SLE cases with active renal disease with P value less than 0.001, and statistically substantial negative association among IL-17 and C3 in SLE cases without active renal disease with P value of 0.087.

The negative association amongst IL-17 and C3/ C4 levels in SLE cases with active renal disease may be due to the activation of the complement system by IL-17. IL-17 has been shown to activate the complement system by stimulating the production of complement including C3 and C4, making immune complexes and their consumption in the serum. This can lead to the formation of the membrane attack complex, which can cause tissue damage in the kidneys and other organs.13

As regard to contrast among the three examined groups regarding to ESR 1st H and CRP we found that there was a statistically significant higher ESR and CRP among SLE cases with active renal disease compared with SLE cases without active renal disease with P value of 0.020, and less than 0.001, respectively. This difference could not be explained easily, as any form of lupus activity (whatever renal or nonrenal) is associated with high levels of ESR and CRP. As patients with LN have many comorbidities other than renal affection including hypertension and hyperlipidemia, this may explain the significant increase in their CRP levels in our study,
yet this finding may need further assessment and research.

As regards to contrast among the three examined groups regarding to anti-DNA and ANA we found that there was a statistically substantial positive ANA and anti-dsDNA among SLE cases with active renal disease and SLE cases without active renal disease compared with control group with \( p < 0.001 \).

Our study was consistent with Alba et al.\(^{14}\) who aimed to study the ‘immunological and demographic factors associated with the development of LN’ as positive anti-dsDNA was 68.5 (72.1) and negative was 41.5 (71.7).

Our study was in disagreement with Wolf et al.\(^{15}\) who aimed to study ‘development of biomarker models to predict outcomes in LN’ as there was no statistically substantial variance among the examined groups as regards anti-dsDNA (\( p = 0.660 \)). This finding may need further assessment and research.

### 4.1. Conclusion

Not all cases of LN have consumed complement C3 and C4, some cases have normal C3 and C4, serum IL-17 can be used as an adjunctive marker for LN activity in addition to complement C3 and C4 and significant association of serum IL-17 with SLE when compared with markers of SLE activity like anti-dsDNA antibodies and urinary A/C ratio.

### Conflicts of interest

There are no conflicts of interest.

### References