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Original Article

The Role of IL-17 in the Pathogenesis of Acute Rheumatic Fever

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ABSTRACT

Objective: In this study, our aim is to determine the interleukin 17 (IL-17) and interleukin 22 (IL-22) levels in acute rheumatic fever (ARF) and rheumatic heart disease (RHD) patients and their relationship with rheumatic fever pathogenesis.

Methods: Newly diagnosed 7 ARF patients and 14 RHD patients who are followed by Akdeniz University Faculty of Medicine, Pediatric Cardiology Department and 15 age and sex-appropriate healthy children as the control group were enrolled in this study. Interleukin 17 and interleukin 22 levels were determined with an enzyme-linked immunosorbent assay.

Results: IL-17 levels were undetectable, while the IL-22 level was increased in 1 patient in the ARF group. Eleven of 14 RHD patients had IL-17 under detectable levels, while 3 had detectable levels. None of the patients had detectable IL-22 levels. In the control group, none had detectable IL-17 or IL-22 levels.

Conclusion: Our results showed that IL-17 and IL-22 do not have an important role in ARF pathogenesis.

Keywords: Acute rheumatic fever, interleukin 17, interleukin 22, rheumatic heart disease

INTRODUCTION

Acute rheumatic fever (ARF) is thought to be an autoimmune disorder caused by *Streptococcus pyogenes* (*S. pyogenes*). Non-treated or undertreated *S. pyogenes* throat infections and immunologically susceptible children are also necessary for the occurrence of ARF. Genetic factors, Streptococcus pyogenes infection and environmental factors affect the development of the disease.[1] Acute rheumatic fever is a significant cause of mortality and morbidity in developing countries.[2] The pathogenesis of ARF is still unrevealed. Cellular and humoral responses against group A beta-hemolytic Streptococcus have cross-reactions with heart, joint, brain, and skin tissues of genetically susceptible persons. It is thought that helper T (Th) cells (especially Th17) have a significant role in this developing immune response.[1]

Th 17 cells provide neutrophils and macrophages recruited to infected tissue and also contribute to host defense. Among the cytokines they secrete, interleukin 17 (IL-17) has a pro-inflammatory effect, while interleukin 22 (IL-22) has a regenerative and protective effect on epithelial cells.[3] Studies have revealed that IL-17A gene expression is found to be higher in peripheral blood T cells of people with chronic rheumatic heart disease (RHD) compared to healthy individuals.[1] Collagen-induced arthritis (CIA) is accepted as the experimental model of ARF, in which Th17 cells have an important role.[4-7] These data demonstrate that Th17 cells may have an important role in the inflammatory response in ARF.

In this study, IL-17 and IL-22 levels in patients diagnosed with ARF were evaluated during the active phase of the disease, during treatment, and at the end of treatment, and also IL-17 and IL-22 levels in cases diagnosed with chronic RHD were evaluated.

MATERIALS AND METHODS

Patients

Seven patients who applied to Akdeniz University Pediatric Cardiology Polyclinic and were diagnosed with ARF, as well as 14 patients who were followed up with a previous

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diagnosis of ARF, were included in the study. Ethical commitee approval for the study was received from Akdeniz University School of Medicine Ethical Committee (03.09.2010/69). An informed consent form was obtained from the patients and their parents who agreed to participate in the study. After detailed history and examination of the patients, acute-phase reactants were studied. Patients were evaluated with electrocardiography (ECG) and echocardiography (ECHO). Patients were diagnosed with ARF according to Jones's criteria. Peripheral blood serum samples were separated for IL-17 and IL-22 studies before treatment, on the 15th day of treatment, and 1 week after the completion of treatment. Peripheral serum samples of 15 age-matched healthy children were collected as a control group. Samples were stored at −80°C until testing. The patients were evaluated in terms of demographic characteristics, heart valve involvement, and joint involvement. Stored serum samples were studied with enzyme-linked immunosorbent assay (ELISA) for IL-17 and IL-22.

MATERIALS AND METHODS

Enzyme-linked İmmunosorbent Assay

Serum samples were frozen at −80°C until studying samples. On the same day, according to the manufacturer's protocol, the test was performed (eBioscience Human IL-17A and IL-22 Platinum Elisa Kit) and was run in duplicate.

Electrocardiography

PR distances were measured by taking a 12-lead surface ECG in the patients.

Echocardiography

At the time of diagnosis, patients were evaluated by echocardiography, performed by an experienced cardiologist with a GE Vivid 7Pro, (Horten, Norway) ECHO instrument using 3.5 and 7-MHz probes.

Statistics

The statistical software SPSS (SPSS Inc.; Chicago, IL, USA) for Windows (version 16.0.0) was utilized to conduct all statistical analyses. Qualitative variables were described using frequency and percentage data. The Mann–Whitney *U* test was used to evaluate ELISA results, with statistical significance defined as $P < .05$.

MAIN POINTS

Our study suggests that:

- Interleukin 17 (IL-17) and interleukin 22 (IL-22) do not have an important role in the pathogenesis of acute rheumatic fever.
- Interleukin 17 may have an important role in rheumatic heart disease
- Interleukin 22 doesn't have an important role in rheumatic heart disease

RESULTS

Demographics and Clinical Data

Cases Diagnosed with ARF

Seven patients diagnosed with ARF were involved in the study. Among these patients, 5 (71.4%) were male and 2 (28.6%) were female. The mean age of the cases was 11.57 ± 2.07 years (min-max: 10-16 years).

The mean erythrocyte sedimentation rate (ESR) of the patients was 74.14 ± 19.22 mm/h (min-max: 45-95 mm/h). The mean C-reactive protein (CRP) values ranged between 3.25 ± 2.39 mg/dL (min-max: 0.63-6.4 mg/dL).

Anti-streptolysin O (ASO) values measured in all patients (mean: 1697.28 ± 628.52 IU/mL) (min-max: 849-2760 IU/mL) were high (Table 1).

In the ECGs of the patients, the axis of the heart, rhythm, velocity, voltage criteria in terms of hypertrophy, and PR distance were evaluated. Prolongation of the PR distance was detected in 3 of the patients. At the time of diagnosis, 6 of the cases had carditis, and 1 had heart failure with carditis. Of the patients with carditis, 2 had mitral insufficiency, 1 had aortic insufficiency, and 4 had aortic and mitral insufficiency. Arthritis accompanied these findings in 4 of the patients. There were 2 patients who were started on aspirin therapy at the time of admission.

Interleukin 17 (min-max: 1.6-100 pg/mL) was not detectable in any of the cases; the IL-22 level (min-max: 31.3-2000 pg/mL) was found to be high in 1 case. The case was using aspirin at the time of admission, and the IL-22 value at admission was 59.2 pg/mL, and 49.3 pg/mL (min-max: 31.3-2000 pg/mL) on the 15th day of treatment (patient 6). However, it could not be evaluated because the patient was out of follow-up after treatment.

Table 1. Clinical Findings of ARF Patients

	Min	Max	Mean
Age	10	16	11.57
CRP	0.63	6.4	3.25
ESR	45	95	74.14
ASO	849	2760	1697.28

ASO, anti-streptolysin O; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Cases with a Previous Diagnosis of ARF

Fourteen patients with a previous diagnosis of ARF were involved in this study. Among these patients, 10 (71.42%) were male and 4 (28.6%) were female. The mean age of the cases was 13.85 ± 2.24 years (min-max: 10-17 years). The mean age at diagnosis of ARF ranged between 9.78 ± 1.96 years (min-max: 6-12 years). Ten of the cases were presented with arthritis, 11 with carditis, 8 with both carditis and arthritis, and 1 with chorea.

When IL-17 levels were evaluated, it was below measurable values in 11 of the cases, and it was at a measurable level in 3 of them (1.64; 2.29; 1.82 pg/mL) (min-max: 1.6-100 pg/mL). However, IL-22 was not detected at a measurable level in any of the cases.

Control Group

The mean age of the 15 patients involved in the control group was 11.66 ± 4.09 years (min-max: 5-18 years). Ten of the cases were male (66.7%) and 5 were female (33.3%). IL-17 and IL-22 values were not detectable in any of the control group.

DISCUSSION

In developing countries, ARF is the leading cause of acquired heart disease. It causes remarkable morbidity and mortality. The pathogenesis of the disease is still not clearly understood.

The Th17 cells have a significant role in host defense. Interleukin 17, one of the cytokines released from Th17 cells, ensures the survival and migration of macrophages and is also effective in neutrophil migration. It also has a role in the production of pro-inflammatory cytokines and antimicrobial peptides, and they establish a relationship between innate and adaptive immunity.

Although IL-17 has strong pro-inflammatory effects, IL-22 protects and regenerates the epithelial cells. Interleukin 22 induces re-epithelialization, supports the migration and proliferation of epithelial cells, and inhibits keratinocyte differentiation.[8]

We did not encounter any study on IL-17 and IL-22 levels in ARF cases in the literature. However, there are studies about chronic RHD patients and IL-17.[1,15]

An increase in the Th17 cell percentage and a decrease in the Treg cell percentage compared to the control group was shown in a study conducted with rheumatic mitral valve disease (MVD) patients.[15] Serum levels of Th17-related cytokine, interleukin 17A, were found to be high compared to the control group; the Th17/Treg ratio was remarkably high in rheumatic MVD patients ($P = .0001$).[15]

In a study by Guilherme et al.,[1] IL-17A gene expression in peripheral blood T cells was found to be high in cases with chronic RHD compared to healthy controls.

In an experimental rat model study of RHD in China in 2015, serum IL-17 and IL-6 levels and IL-17, IL-21, IL-6, and IL-23 levels studied from mitral valve tissue were found to be remarkably high.[9]

Interleukin 17 has a relationship with many autoimmune and inflammatory diseases like RHD and inflammatory bowel disease.[9-10,11] Wen et al.[9] showed that serum IL-17 and IL-6 levels and mitral valve IL-17 and IL-6 expression levels are increased in the early and late periods of the experimental RHD model. In the same study, it was reported that in patients with RHD, the expression of IL-17, IL-21, IL-6, and IL-23 in mitral valve tissues is increased significantly. In another study, it was shown that serum IL-17 and IL-23 levels were high in cases with rheumatic mitral valve stenosis.[12] In recent studies, it has been reported that the IL-17A rs2275913 variant is effective in both the pathogenesis and severity of RHD and is significant in defining susceptibility.[13]

Although these data suggest that Th17 cells may be related to the inflammatory response in rheumatic heart disease, in our study, IL-17 is not measurable in any of the cases. Also, the IL-22 level was found high in only 1 of the ARF cases. IL-22 was high in a single case, so it could not be evaluated statistically. Since IL-22 has a significant role in the proliferation and re-epithelialization of epithelial cells, it is noteworthy that it has increased especially after the initiation of treatment. In a study by Sayın et al., it was shown that aspirin and ibuprofen strongly inhibit IL-17 production *in vitro*.

Interleukin 17 values were found to be measurable in 3 of the patients who were followed up with RHD. This may be due to the disappearance of the inhibitory effect after discontinuation of medicines such as aspirin. It is thought that IL-17 and IL-22 values were below measurable levels because there was no inflammation in the control group.

The number of cases in our study is limited. The association between IL-17 and IL-22 could not be demonstrated in patients due to different reasons such as the time of diagnosis and the difference between symptom onset and admission to our center. Our results suggest that these cytokines do not have an important role in the pathogenesis of ARF, but further studies with large case series are needed.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval for the study was received from Akdeniz University School of Medicine Ethical Committee (03.09.2010/69).

Informed Consent: Written and verbal consent were obtained from patients, their parents and hospital management for the use of patient data.

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