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Immunological Features of Reactive Arthritis of Various Etiologies

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Abstract

The pathogenetic mechanisms of reactive arthritis (ReA) are not fully understood. According to some studies, arthritis in ReA is a consequence of hyperproduction of pro-inflammatory cytokines, the results of others indicate that in ReA the Th1 immune response is reduced in favor of the Th2 immune response. The aim of our work was to study the levels of IL-17A and TNF-α in the blood serum of patients with ReA of various etiologies. The study revealed a significant increase in the content of IL-17A and TNF-α in patients with ReA compared with the control group. There were no significant differences in the cytokine profile of patients with ReA and infection-associated arthritis. The data obtained, in general, indicate the pro-inflammatory Th1 nature of the cytokine profile of the ReA patients examined by us and confirm the currently most common hypothesis of ReA pathogenesis, which is based on an imbalance of cytokines.

1. Introduction.

Reactive arthritis (ReA) is an inflammatory disease of the joints that occurs after a previous intestinal or urogenital infection and is a systemic clinical manifestation of this infection. Reactive arthritis occurs in people of predominantly young and middle age, most of whom are carriers of the HLA-B27 histocompatibility gene. The pathogenetic mechanisms of ReA are not fully clear. Particular importance is currently attached to the study of the immune response in this disease. Many researchers are inclined to believe that the basis of the pathogenesis of ReA is an imbalance of cytokines. Proinflammatory Th1-type cytokines such as IFNγ and TNFα are known to play a leading role in the eradication of an infectious agent, especially in the case of an intracellular bacterium. However, the results of cytokine profile studies in ReA are inconsistent.

Some authors are inclined to believe that in ReA, the antibacterial Th1-immune response (production of IFNγ, TNFα, IL-2 and IL-12) is reduced in favor of the Th2-immune response (synthesis of IL-4 and IL-10), other researchers point to a pro-inflammatory cytokine profile in ReA. In the literature, there are only isolated reports of a study of cytokines in this disease depending on the infection that caused it. The effect of the activity and nature of the course of the disease on the cytokine profile in ReA also requires clarification.

The purpose of this work was to study the content of IL-17A and TNF- α in serum in patients with ReA of various etiologies in comparison with arthritis associated with infection.

2. Materials and methods.

120 ReA patients were examined (72 women and 48 men), as well as 30 healthy volunteers. All patients had mono- or oligoarthritis and a laboratory-confirmed infection or clinic of prior infection. A separate group included HLA-B27 (+) patients with typical clinical manifestations of ReA, in whom an etiological factor was not identified. The average age of ReA patients was 32,2±1,8 years, the average duration of the disease was 20,4±7,9 months. Patients with ReA who had not previously received basic therapy were included in the study. 46 patients had a prolonged course of the disease (disease duration from 2 months to 1 year), 47 patients had a chronic course (disease duration more than 1 year), and 27 patients had a recurrent course of the disease (development of joint attack after disease remission lasting at least 6 months). I degree of disease

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activity was registered in 77 (64.2%) patients with ReA, II and III - in 43 (35.8%) patients. The group of patients with ReA of urogenital etiology was 65 (54.2%) patients, postenterocolytic ReA - 35 (29.2%) patients, the group of HLA-B27 (+) ReA of unknown etiology - 20 (16.7%) patients. The average age of patients with arthritis associated with infection was 34,9±5,2 years, the average duration of the disease was 4,9±1,7 months.

The levels of IL-17A and TNF- α in patients were determined by solid-phase enzyme-linked immunosorbent analysis using the Cytokine reagent kit (St. Petersburg, Russia). Statistical processing of the obtained data was carried out using the program "Statistica 5.5 for Windows." The methods of non-parametric statistics (Mann-Whitney test, median chi-square and ANOVA module), as well as the calculation of correlation coefficients were used. Differences $p < 0.05$ were considered statistically significant.

3. Results.

It was found that the level of cytokines in the studied blood sera of patients with ReA varied widely. Comparative analysis of disease activity indices showed the highest rates in the group of patients with II and III degree of activity (table 1).

Table 1. Comparative analysis of inflammation and activity indicators in patients with ReA

Activity rate of ReA	Groups of patients with ReA		p
	I degree of activity	II+III degree of activity	
Back pain, points	6,0 (7,0; 9,0)	8,0 (7,0; 9,0)	<0,0001
Nighttime back pain, points	7,0 (6,0; 8,0)	8,0 (6,0; 8,0)	<0,0001
BASDAI points	6,6 (4,4; 8,85)	8,2 (4,4; 8,85)	<0,0001
ASDAS-CRP, points	3,8 (3,5; 4,4)	4,3 (3,5; 4,4)	<0,0001
NPV	2,0 (1,0; 4,0)	3,0 (1,0; 4,0)	<0,0001
CRP, mg/l	12,3±3,9	42,4±5,7	<0,0001
ESR, mm/h	19,3±6,7	30,4±7,8	<0,0002

Statistical processing of the data also showed a significant increase in IL-17A and TNF-α in the group of patients with ReA compared with the control group. In patients with ReA, there were no significant differences in the content of the studied cytokines depending on the activity of the disease (Table 2). Analysis of the levels of cytokines in the group of patients with ReA, depending on the presence of the histocompatibility gene HLA-B27, showed a higher level of all the studied cytokines in the group of HLA-B27(+) patients, however, there were no significant differences in the groups. The study of cytokine levels depending on the nature of the course of ReA revealed a significantly higher content of serum IL-17A in the chronic course of the disease compared with protracted and recurrent (Table 2).

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Table 2. Comparative analysis of cytokine profile indicators in groups

Parameters	Patients with ReA	Control	p
IL-17A	19,1±12,1	22,2±13,1	<0,01
TNF-α	12,4±8,6	6,1±4,3	<0,01

4. Discussions.

The performed study showed a significant increase in the content of pro-inflammatory cytokines IL-17A and TNF-α ($p<0.01$) in the blood serum of patients with ReA in comparison with the control group, as well as the presence of direct correlations between IL-17A and TNF-α with activity indices diseases, which indicates the pro-inflammatory nature of the cytokine profile of the ReA patients examined by us. Several previous studies have demonstrated low levels of pro-inflammatory cytokines in the synovial fluid and serum of patients with ReA. Thus, Yin Z. (1997) determined an increased content of IL-17A in the synovial fluid of patients with ReA, the results of a study by Braun J. and Yin Z. (1999) showed that in patients with ReA, the level of secretion of TNF-α by T-lymphocytes at the onset of the disease is reversed. proportional to the duration of the disease. The results of our study, which included only patients with prolonged, chronic, and recurrent ReA, also indicate that the duration of the disease largely determines the pro-inflammatory nature of the cytokine profile in ReA patients. Recent studies have shown an important role of IL-17A in the pathogenesis of chronic inflammation in many rheumatic diseases and an increase in its content in the blood serum of patients with rheumatoid arthritis, ankylosing spondylitis and systemic lupus erythematosus. In our study, the level of IL-17A in the blood serum of patients with ReA was also higher in the chronic course of the disease compared with protracted and recurrent ($p < 0.05$).

And also, the average values of all studied cytokines were higher in the group of HLA-B27(+) patients with ReA in comparison with HLA-B27(-), however, significant differences could not be obtained. There were no significant differences in the content of cytokines in patients with ReA and depending on the activity of the disease. Analysis of the cytokine profile of ReA patients depending on the etiology showed a significantly higher content of TNFα in the HLA-B27(+) group of patients with ReA of unknown etiology in comparison with ReA of urogenital and postenterocolitic etiologies, which, in our opinion, requires dynamic monitoring of this group of patients in in terms of possible transformation into ankylosing spondylitis or other variants of seronegative spondyloarthropathies. There were no significant differences in the cytokine profile of patients with ReA and infection-associated arthritis.

5. Conclusions.

Thus, ReA is a heterogeneous group of inflammatory joint diseases associated with urogenital or intestinal infection. Probably, it is the heterogeneity of ReA that is one of the reasons for the mixed results of laboratory studies, including those regarding the cytokine status. Studies of the cytokine profile in patients with rheumatic diseases in recent years have become increasingly relevant due to the emergence of new drugs - biological agents. Our data generally point to the pro-inflammatory Th1 nature of the cytokine profile of the examined patients with ReA and confirm the currently most common hypothesis of the pathogenesis of ReA, which is based on an imbalance of cytokines. However, the inconsistency of the results of many ongoing studies, as well as the lack of unified views on the nature of the cytokine profile in ReA, require further research in this direction.

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