Interleukin 8 and tumor necrosis factor-α level in acute rheumatic fever and chronic rheumatic heart disease

Wafa Benzabya
Department of cardiology and bacteriology, Libya

Abstract: Forty children were included in this study with age ranging between 5 - 15 years. They were divided into four groups according to clinical presentation. Group I with acute rheumatic arthritis, group II with chorea, group III with clinical carditis and group IV with chronic heart disease. Twenty healthy children were investigated for IL-8 and TNF-α as a control group. We found that the serum level of IL-8 was significantly higher than the control group and in carditis than arthritis. TNF-α was significantly higher in acute rheumatic fever than control group. The result showed that the level of IL-8 and TNF-α were significantly higher in patients with chorea than arthritis. These parameters also were significantly higher in rheumatic chorea than chronic rheumatic heart disease. The recurrence of rheumatic activity and development of chronic rheumatic heart disease was high in patients with high levels of interleukins in acute phase.

Introduction

Beta-haemolytic streptococcal pharyngitis may induce rheumatic fever and rheumatic heart disease in susceptible individuals, weeks or years after acute infection. Immunologic response is directed primarily against M-protein, a major component of streptococcal cell surface that presents antiphagocytic properties. M-protein shares structural homology and antibody cross-reactivity with α-helical coiled fibrous proteins like myosin and tropomyosin in heart muscle (1). Acute rheumatic fever (ARF) is a common and serious public health problem in developing countries (2). Rheumatic valvular heart disease is an important sequel to rheumatic fever and remains the most common acquired heart disease world-wide (3). Rheumatic heart disease is associated with a considerable disability in children (2). Rheumatic fever is one of autoimmune diseases with a known infectious etiology (4). Immune-activation and immune-reaction may play an important role in rheumatic fever pathogenesis (5). It was shown that streptococcal M-protein may be a superantigen, stimulating a large number of T-cells which are the major source of cytokines, a fact that can has an important immune-pathological consequences (6). Excessive production of IL-7 and IL-8 throughout the active period of rheumatic fever was demonstrated by Kuterkcuer and Norin (7). Interleukins and serum insoluble receptors for TNF-α may play an important role in rheumatic fever pathogenesis (5). The aim of this work is to study the level of IL-8 and TNF-α in patient with acute rheumatic fever (ARF) and chronic rheumatic heart disease (CRHD).

Materials and methods

This study was done in cardiology and bacteriology department. The work included 40 patients and 20 healthy children as a control group. The age of all studied children was ranged from 5 - 15 years. Patients: Forty children were divided into 4 groups: group I: 12 patients with acute rheumatic arthritis without clinical carditis and without rheumatic chorea. Group II: 13 patients with acute rheumatic arthritis and had clinical evidence of carditis. Group III: 8 children with chorea

as the main symptom and Group IV included 7 with chronic rheumatic heart disease (CRHD).
Materials: ELISA kits for Interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-α)**.** (Medgenix diagnostics S-A Zonning Industrial B-6220-Flurin, Belgium)**.** All patients were subjected to clinical examinations. Doppler Echocardiography study, E.S.R, CRP and ASO titer were taken. Estimation of plasma levels of IL-8 and TNF-α for control group and during acute phase and after 6 month for patients groups by ELISA technique (8).

Results

Table 1 shows that there is a high significance difference in IL-8 concentration level among groups I, II and III than the control group. Table 2 shows the level of TNF-α in patient group (I, II & III) and control group, there is a highly significant difference.

Table 3 shows that there is no a statistical difference between group IV and control group with regard to IL-8 and TNF-α serum levels. Table 4 shows that there is no statistical difference in all patients 6 months after acute phase and control group as regard to serum levels of IL-8 and TNF-α.

Table 5 shows the follow-up study of patients with ARF for 6 months based on clinical and Doppler-echocardiography study. Tow in group I showed rheumatic reactivity, but 7 in group II, 3 in group III showed reactivity. None in group I developed CRHD, but 5 in group II and 2 in group III developed CRHD.

Table 1: Comparative analysis between ARF and control group as regard to serum level of IL-8

	group I	**group II**	**group III**	**control**	**p value**	**significant**
range	60 - 92	83 - 116	88 - 135	0 - 82	< 0.001	highly significant
mean	68.6	96.2	102.9	23.2		
± SD	± 7.1	± 11.56	± 13.6	± 15.7		

Table 2: Comparative analysis between patients with ARF and control group as regard to serum level of TNF-α

	group I	**group II**	**group III**	**control**	**p value**	**significance**
range	28 - 48	28 - 49	24 - 54	0 - 12		highly
mean	31	36	36.2	7.1	< 0.001	Significant
± SD	± 5.1	± 6.2	± 3.98	± 3.9		

Table 3: Patient with CRHD and control group as regard to IL-8 and TNF-α serum levels

	group IV mean ± SD	**control mean ± SD**	**p value**	**significance**
Il-8	26 ± 18	23.2 ± 15.7	> 0.05	non-significant
TNF-α	9.1 ± 5	7.1 ± 3.9		

Table 4: All patients groups after 6 months of acute phase and control group

	All patients after 6 months mean ± SD	control mean ± SD	p value	significance
IL-8	19.6 ± 13.4	23.2 ± 15.7	< 0.05	non-significant
TNF-α	9.5 ± 4.1	7.1 ± 3.9		

Table 5: Follow up data based on clinical and Doppler echocardiograph

groups	No.	IL-8	TNF-α	rheumatic reactivity No. of cases	valvular HD (after follow-up)
I	12	68.6 ± 7.1	31 ± 5.1	2	none developed RHD
II	13	96.2 ± 11.56	36 ± 6.2	7	5 developed RHD 3 → MS 1 → MS & AR 1 → MS & MR
III	8	102.9 ± 13.6	36.2 ± 3.98	3	2 developed RHD Both had MS

MS = Mitral stenosis **AR** = Aortic regarge **MR** = Mitral regarge **RHD** = Rheumatic heart disease

Discussion

In patients with rheumatic fever, there is an exaggerated humeral response to several cardiac nuclear and streptococcal antigens (9). Although most patients exhibit cross reactive antibodies, these antibodies do not seen to contribute to tissue damage. It was shown that streptococcal M. protein may be super-antigen, a fact that can be important as immunopathological consequences (6). Narin and others (10) demonstrated that there is an increased cellular immune response evidenced by increased percentages of $CD4^+$ cells and interleukins. In this study, it was found that IL-8 plasma level was significantly higher in patients with acute rheumatic arthritis than control. Also, IL-8 plasma level in patients with carditis and chorea was significantly higher than in patients with rheumatic arthritis. It was stated that there is an excessive production of IL-8 probably by cellular infiltrate throughout the active period of rheumatic fever (7). Morris and others (11) showed that there was a significant high level of immune response indices mainly interleukin, $CD4^+$, $CD22^+$ B cells in patients with ARF. In this study, it was found that the plasma level of TNF-α was significantly higher in patients with ARF than control group. Also, the level of TNF-α was significantly higher in patients with carditis and chorea than in patients with arthritis. Our results showed that there was no statistically difference in plasma level of IL-8 and TNF-α among all patients after 6 months from active phase of rheumatic fever patients with CRHD and control group. This may mean that these cytotoxic agents may play an important role in the active phase of ARF. Narin et al. (7) showed that there was a highly significant level of TNF-α in active period of rheumatic fever in comparison to control and CHD.

In our study, we found that there were high levels of IL-8 and TNF-α in patients presented with chorea in comparison to acute rheumatic arthritis alone. Analysis of our results after 6 months of following, the study showed that the development of CRHD is more common in patients with carditis and chorea than in arthritis patients, where the level of IL-8 and

TNF-α were significantly higher in these groups. Also the individual levels of IL-8 and TNF-α were high in patients with more recurrent attacks of rheumatic reactivity and in those who developed CRHD. Samsonov et al. (5) stated that higher level of TNF-α in patient with ARF is related to the development of chronic valvular heart disease.

In conlusion, high level of IL-8 and TNF-α in patient with ARF may play a role in pathogenesis of ARF and development of CRHD. Thus, it recommends a follow-up of patients with ARF with high level of interleukins concentration and the effort must be directed to suppress their cytotoxic reactions to avoid the development of CRHD.

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