

# Diagnostic Aspects of Changes in the Concentration of Cytokines in the Blood Serum in Patients with Chronic Uveitis

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**Abstract** Uveitis is a group of severe inflammatory diseases of the eyeball that can lead to such serious complications as decreased vision and even blindness. Of great importance in the pathogenesis of inflammation of the vascular layer of the eyeball is dysregulation of immune mechanisms, carried out by a large number of humoral mediators. Among them, cytokines occupy a special place. **Purpose:** to study the concentration of a number of cytokines in blood plasma and analyze changes in the cytokine profile depending on the severity of the inflammatory process in uveitis. **Materials and methods.** The subjects of the study were 45 patients (20 men and 25 women), examined and treated with a diagnosis of chronic uveitis in the hospital of the Bukhara branch of the Republican Specialized Scientific and Practical Medical Center for Eye Microsurgery (Bukhara, Uzbekistan). 22 patients who did not have inflammatory diseases in the organ of vision were selected as a control group. Quantitative determination of cytokines in blood serum was carried out by enzyme-linked immunosorbent assay using “Vector Best” kits (Russia) for tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and interleukins (IL) IL-1 $\beta$  and IL-10. **Results.** Regulation of the immune response in patients with a positive result in the group of patients with a good expected outcome of uveitis occurs due to the balanced production and interaction of mediators of the acute phase of inflammation, activation of local cellular reactions. In the group of patients with uveitis that has become a chronic form of the inflammatory process of the eye or recurrent, a defect in the cytokine network is associated with an imbalance of the pro-inflammatory and anti-inflammatory effects of inflammation; the transition to a pathological process with their hyperproduction is described. **Conclusions.** In the blood serum of patients with varying degrees of severity of chronic uveitis, a statistically significant increase in the concentrations of IL-1 $\beta$ , IL-10 and TNF $\alpha$  was noted. The level of cytokines in the blood serum in chronic uveitis must be taken into account when assessing the severity of inflammation of the choroid.

**Keywords** Uveitis, Cytokines, Interleukin, Diagnosis of uveitis, Immunoinflammatory process

## 1. Introduction

Uveitis is an important cause of blindness in both developing and developed countries. Its prevalence in children and the elderly is estimated to be around 5–16% and 6–21%, respectively [1,2].

Uveitis is a general term for inflammation of the uveal tract from any cause and usually includes a large group of diverse diseases affecting not only the uveal tract, but also the retina and vitreous. Despite a long period of study, uveitis is one of the most complex inflammatory diseases of the organ of vision; many issues of the development of uveitis remain unexplored. To date, no ideal method has been found

to treat and prevent exacerbations of the disease [3,6,14].

The etiology of uveitis is difficult to determine because the exact cause of uveitis is often unknown. The relationship between uveitis and systemic diseases is well known. In earlier studies, most cases were associated with autoimmune diseases, while recent reports show an association with various generalized diseases [4,5].

With the development of uveitis, the lack of a clear understanding of the mechanisms of initiation of the inflammatory process in the internal structures of the eyeball and the reasons for the chronicity of the pathological process in the eye does not allow timely and effective pathogenetic therapy of the disease. This, in turn, leads to the chronic nature of the disease and a significant decrease in vision [5,6,11].

According to many authors, dysregulation of immune mechanisms, carried out by a large number of humoral mediators, is of great importance in the pathogenesis of

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inflammation of the vascular layer of the eyeball. Among them, cytokines occupy a special place. These are low molecular weight proteins that ensure the process of intercellular interaction [7,8].

Various studies have highlighted the importance of cytokines in the development and progression of various forms of infectious and non-infectious uveitis [9,10].

In patients with uveitis, an increase in the level of pro-inflammatory cytokines such as IL 1 ( $\text{IL-1}\beta$ ) and IL-6, which is similar in biological properties, was found. It was also revealed that the concentration of IL-6 in the eyes of patients with uveitis exceeds its level in the blood serum. However, IL-6 is not a specific marker of uveitis, since its level increases both in diabetic retinopathy and retinal detachment and other eye diseases [12,13]. Studies of anti-inflammatory cytokines are also described in the literature. A number of authors suggest a protective role of interleukin-10 (IL-10) in patients with uveitis, since its higher level was noted in patients with good visual functions in the outcome of the disease [15,16].

## 2. Purpose

To study the concentration of a number of cytokines in blood plasma and analyze changes in the cytokine profile depending on the severity of the inflammatory process in uveitis.

## 3. Material and Methods

The subjects of the study were 45 patients (20 men and 25 women), examined and treated with a diagnosis of chronic uveitis in the hospital of the Bukhara branch of the Republican Specialized Scientific and Practical Medical Center for Eye Microsurgery (Bukhara, Uzbekistan). The age group of patients ranged from 21 to 65 years. As a control group, 22 patients were selected who did not have inflammatory diseases in the organ of vision, but had

refractive diseases (myopia, hyperopia, astigmatism) in the eyes, corresponding to the above comparison group by age and gender.

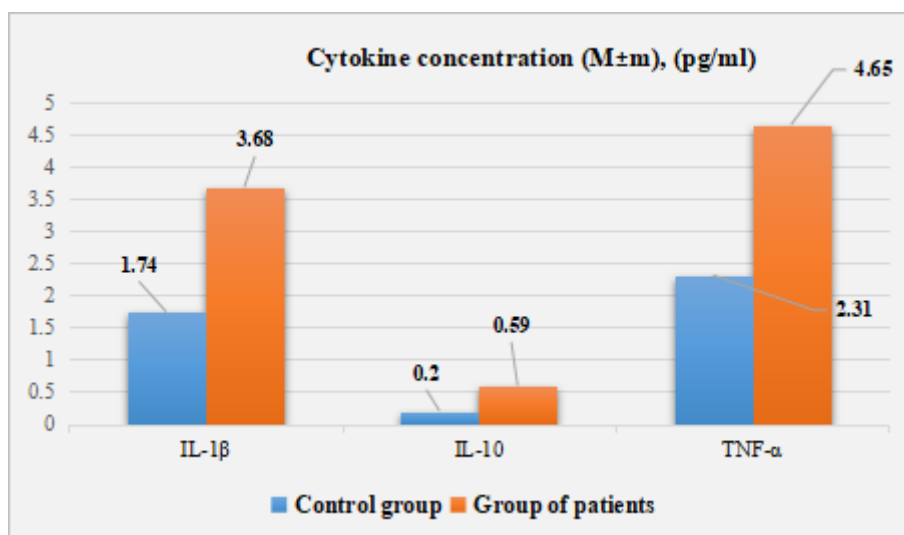
For immunological studies, the same amount of blood was taken from the antecubital vein from all patients on an empty stomach. Quantitative determination of cytokines in blood serum was carried out by enzyme-linked immunosorbent assay using Vector Best kits (Russia) for tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and interleukins (IL) IL-1 $\beta$  and IL-10.

Intracellular cytokines are determined using modern methods based on the principles of proteomics and genomics. The cytokines produced are determined using various methods that allow them to be measured even at low concentrations [17].

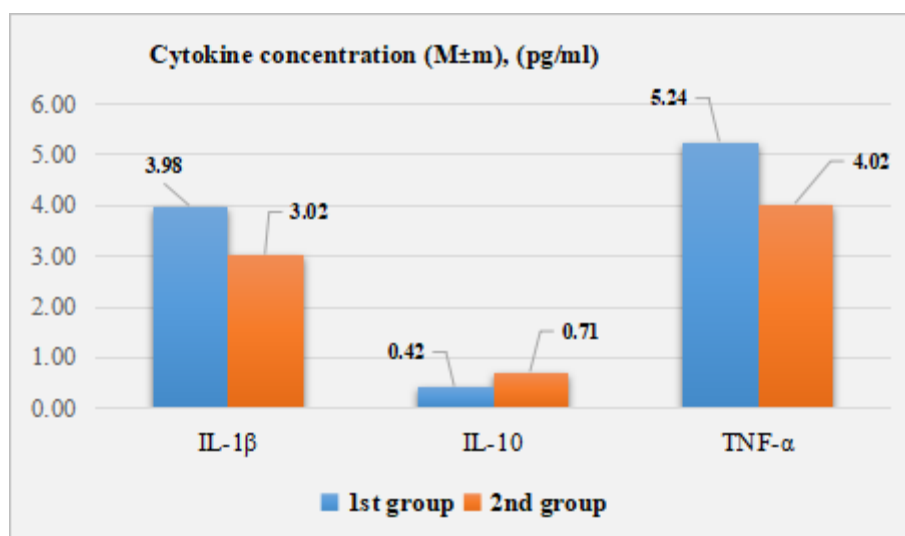
Statistical processing of the data obtained and collected as a result of the study was carried out using parametric analysis methods using Student's t-test. Pearson correlation analysis was performed by calculating linear and multiple correlation coefficients to determine the relationship between characteristics.

## 4. Results and Discussions

Since hospitalization, all patients with chronic uveitis showed statistically significant changes in cytokine levels. The indicators of all studied groups of cytokines in patients were significantly higher than those of patients in the control group. The concentrations of IL-1 $\beta$ , IL-10 and TNF $\alpha$  in the group of patients were  $3.68 \pm 0.11$ ;  $0.59 \pm 0.04$ ;  $4.65 \pm 0.29$  pg/ml, respectively. The level of IL-1 $\alpha$ , one of the main mediators responsible for the formation of a local inflammatory reaction in the eye, was 2.1 times higher than in patients in the control group. The concentration of IL-10, which is responsible for inhibiting the synthesis of anti-inflammatory cytokines, was 2.95 times higher than the values of patients in the control group. The values of TNF $\alpha$ , the concentration of which increases during infection and the entry of endotoxins of various natures into the body, were 2 times higher than in the control group (Fig. 1).



**Figure 1.** Cytokine profile at disease onset in patients with uveitis and controls



**Figure 2.** Cytokine profile of uveitis patients with different disease outcomes

In order to increase the efficiency of the study and deepen the data on changes in the concentration of various cytokines in the blood during inflammatory processes in the eye, the group of patients with chronic uveitis was divided into two subgroups.

23 patients in the 1st subgroup: patients with chronic uveitis, but local inflammatory activity in the eye is slow; patients with a good expected outcome of the disease; patients whose eye condition has clinically improved over the course of 24 hours;

22 patients in the 2nd subgroup: patients with chronic uveitis, but with active local inflammatory process in the eye or relapse of chronic uveitis; patients whose expected outcome of the disease is unfavorable or who are at high risk of various complications;

In the subgroups, already at the onset of the disease, differences were revealed in the concentrations of interleukins involved in the initiation and development of the inflammatory process.

Thus, the level of IL-1 $\beta$  in subgroup 1 is 2.3 times higher than in patients in the control group. This indicator is 1.32 times higher compared to the indicators of patients with uveitis of the 2nd subgroup. The results show that the plasma concentration of IL-1 $\beta$  in uveitis patients with poor outcome is lower than that in uveitis patients with good outcome (Fig. 2).

It can be seen that the concentration of TNF $\alpha$  in the 1st subgroup is 2.27 times higher than in patients in the control group. It was found that this indicator is 1.3 times higher compared to the indicators of patients with uveitis of the 2nd subgroup. The results showed that serum TNF $\alpha$  concentrations as well as IL-1 $\beta$  levels were higher in uveitis patients with good outcome compared with uveitis patients with poor outcome.

The concentration of IL-10 in the blood serum of patients of the 1st subgroup was 2.1 times higher than that of the control group. But on the other hand, when we compared the concentration of IL-10 in the blood serum of both subgroups, it turned out that the indicators in the 1st subgroup were 1.7

times lower than the indicators in the 2nd subgroup. From the results, it can be seen that serum IL-10 concentration is lower in uveitis patients with good outcome compared to uveitis patients with poor outcome, in contrast to the above two parameters.

**Discussion.** When analyzing the interaction of the studied indicators in the groups of the 1st subgroup, a negative relationship of medium strength was found between IL-1 $\beta$  and IL-10 and a weak direct relationship between IL-1 $\beta$  and TNF $\alpha$  ( $r = +0.341$ ). In the 2nd subgroup with an unfavorable outcome of uveitis, one correlation was identified: a strong inverse correlation between the concentrations of IL-1 $\beta$  and IL-10 ( $r = -0.784$ ).

It is difficult to determine which of the above indicators is the best indicator of change. However, the role of IL-1 $\beta$  and TNF $\alpha$  as a pro-inflammatory cytokine can be emphasized in the results between groups.

We know from several sources that TNF is an anti-inflammatory cytokine that is associated with many other inflammatory conditions. In modern studies, the simultaneous determination of TNF $\alpha$  in cyst fluid with other indicators may be an additional parameter for the clinical diagnosis of inflamed cysts. [18,19].

Analysis of the cytokine status of the blood serum of patients with chronic uveitis shows that the immune mechanism plays an important role in the pathogenesis of this disease. In patients with chronic uveitis, changes in the concentration of cytokines may be the main factor in the development of the intraocular inflammatory process.

Regulation of the immune response in patients with a positive result in the group of patients with a good expected outcome of uveitis occurs due to the balanced production and interaction of mediators of the acute phase of inflammation, activation of local cellular reactions. Positive and negative feedback mechanisms are observed between IL-1 $\beta$ , IL-10 and TNF $\alpha$ , which is confirmed by correlation interaction analysis. In the group of patients with uveitis that has become a chronic form of the inflammatory process of the

eye or recurrent, a defect in the cytokine network is associated with an imbalance of the pro-inflammatory and anti-inflammatory effects of inflammation; the transition to a pathological process with their hyperproduction is described.

As with most studies, the current study design has limitations. There were difficulties in obtaining reliable sources to confirm the validity of the data collected during the study.

## 5. Conclusions

In the blood serum of patients with varying degrees of severity of chronic uveitis, a statistically significant increase in the concentrations of IL-1 $\beta$ , IL-10 and TNF $\alpha$  was noted. The level of cytokines in the blood serum in chronic uveitis must be taken into account when assessing the severity of inflammation of the choroid. Determining the concentration of a number of cytokines (IL-1b, IL-10 and TNF $\alpha$ ) in the blood serum of patients with chronic uveitis can become a promising direction for the early diagnosis of uveitis and the development of new treatment methods.

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