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ORIGINAL PAPER

Aqueous humor IL-8, IL-10, and VEGF levels in Fuchs' uveitis syndrome and Behçet's uveitis

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Abstract
Purpose This study investigated the levels of interleukin (IL)-8, IL-10, and vascular endothelial growth factor (VEGF) in the aqueous humor (AqH) of patients with Behçet's uveitis (BU) and Fuchs' uveitis syndrome (FUS) during an inactive period and compared these levels with those in the AqH of noninflammatory healthy control subjects.
Methods This prospective and case–control study included 33 patients (16 patients with BU and 17 patients with FUS) and 35 control subjects. IL-8, IL-10, and VEGF levels in the AqH were quantified by performing sandwich enzyme-linked immunosorbent assay. Kruskal–Wallis test was used to compare the cytokine levels in the different groups, and statistical significance was set at $p < 0.05$.
Results IL-8 levels were significantly higher in the AqH of patients with BU and FUS than in the AqH of control subjects ($p < 0.001$ and $p < 0.001$, respectively). IL-10 levels were significantly lower in the AqH of patients with BU than in the AqH of patients with FUS and of control subjects ($p = 0.001$ and $p < 0.001$, respectively). Although VEGF levels were higher in the AqH of patients with FUS than in the AqH of patients with BU and of control subjects, the difference was significant only between patients with FUS and control subjects ($p < 0.001$).
Conclusions We observed a significant decrease in IL-10 levels in the AqH of patients with BU and a significant increase in VEGF levels in the AqH of patients with FUS compared to controls. IL-8 and VEGF levels showed no significant difference among uveitis patients.

Keywords Behçet's uveitis · Fuchs' uveitis syndrome · IL-8 · IL-10 · VEGF

Introduction

Cytokines are low-molecular-weight bioactive polypeptides that perform critical biological roles in intercellular interaction, cellular differentiation and activation, and tissue repair and destruction [1]. Cytokines are released by various cells, including lymphocytes, leukocytes, endothelial cells, macrophages, and natural killer cells, and affect other surrounding or distant target cells by spreading through the hematogenous and/or endocrine routes.

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Some interaction between pro- and anti-inflammatory cytokines in tissues is essential for maintaining a healthy immune microenvironment. Earlier studies have shown that dysregulation in the pro- and anti-inflammatory cytokine balance leads to various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease, inflammatory bowel disease, and multiple sclerosis and to immunosuppression, anergy and immune unresponsiveness, and tumor formation [2–5].

Uveitis, which affects the anterior or posterior segment of the eye in an extreme broad spectrum, is characterized by the inflammation of the uvea irrespective of its etiology. Moreover, uveitis is characterized by an inflammatory response induced by various cytokines in the ocular immune microenvironment irrespective of its etiology, i.e., infective or noninfective. Previous animal and experimental studies on autoimmune uveitis have reported altered immune response in the intraocular microenvironment [6, 7]. Moreover, many studies have concluded that T cells play a primary role in inflammation observed in uveitis [8, 9].

Interleukin (IL)-8 is a cytokine that promotes inflammation through its chemoattractant and proinflammatory activities [10, 11]. An animal study by Ferrick et al. showed that neutrophil infiltration induced by intravitreal IL-8 injection promoted intraocular inflammation [12]. Other studies have reported elevated IL-8 levels in the aqueous humor (AqH) of patients with idiopathic uveitis, Behçet's disease, sarcoidosis, and Vogt-Koyanagi-Harada (VKH) disease [13, 14].

IL-10 is referred to as a cytokine synthesis inhibitory factor because it inhibits cytokine synthesis in Th1 lymphocytes. IL-10 inhibits IL-2 and interferon-γ (IFN-γ) production in Th1 cells and antigen-specific T cell activation; in addition, it inhibits cytokine production in monocytes and macrophages [1]. Different studies have reported different IL-10 levels in the AqH of patients with uveal diseases. While Calder et al. [15] reported low IL-10 levels in the AqH of patients with idiopathic uveitis, Muhaya et al. [16] reported high IL-10 levels in the AqH of patients with Fuchs' uveitis syndrome (FUS). However, IL-10 levels showed no significant changes in the AqH of patients with Behçet's uveitis (BU) compared to controls [13, 17].

Vascular endothelial growth factor (VEGF) functions both as a growth factor for endothelial cells and as a cytokine with proinflammatory activity [18]. VEGF synthesis is induced under hypoxia and by various inflammatory processes. Increased VEGF levels are associated with ocular pathologies such as proliferative retinopathies, neovascularization, age-related macular degeneration, and primary open-angle glaucoma. Although no comprehensive study has investigated VEGF levels in patients with uveal diseases, some studies have reported that VEGF levels are increased in experimental models of autoimmune uveitis and quiescent uveitis [19, 20].

Therefore, the present study investigated the levels of IL-8 and VEGF, which function as proinflammatory and angiogenic cytokines, and the level of IL-10, which functions as an anti-inflammatory cytokine, in the AqH of patients with BU and FUS and compared these levels with those in the AqH of healthy subjects.

Patients and methods

Patients and control subjects

The present study included 33 eyes of 33 uveitis patients (n = 16 with BU, n = 17 with FUS) who visited the uveitis unit of a tertiary referral center in Turkey. These patients underwent phacoemulsification and intraocular lens implantation for a complicated cataract that developed secondary to uveitis. One eye of each patient who underwent phacoemulsification surgery was included in the study. The control group comprised 35 eyes of age- and sex-matched 35 control subjects who underwent phacoemulsification and intraocular lens implantation for a cataract and who had no systemic or other ocular pathology. Patients with idiopathic uveitis besides FUS and BU and those with ocular pathologies, including glaucoma; inflammatory ocular diseases; and retinal diseases such as diabetic retinopathy, age-related macular degeneration, and retinal artery/vein occlusion, which may influence cytokine levels, were excluded from the study. Moreover, patients with systemic inflammatory/autoimmune diseases (such as rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, juvenile idiopathic arthritis, and scleroderma) and those with a history of ocular surgery and trauma were excluded from the study. All study

procedures were conducted in accordance with the Declaration of Helsinki, and the study was approved by the Ethical Committee of Ankara Numune Education and Research Hospital (report number E-15-637). Before performing the phacoemulsification procedure, all the patients were informed about the potential adverse effects of the treatment and their consent was obtained. All the patients were Turkish Caucasians.

Diagnosis of BU was based on the International Study Group for Behçet's Disease Criteria [21]. Patients with FUS were diagnosed based on the presence of a combination of clinical signs based on criteria described by Kimura et al. [22].

The demographic characteristics of the patients such as age and sex, etiology of uveitis (BU and FUS), preoperative best-corrected visual acuity (BCVA) value according to ETDRS chart, preoperative intraocular pressure (IOP), and findings of the preoperative examination of the anterior and posterior segments of the eyes were recorded. After biomicroscopic examination of the anterior segment, dilated fundus examination was performed indirectly by using a + 90-diopter lens. IOP was measured using a noncontact pneumotonometer.

Collection of the aqueous humor

AqH sample (approximately 100 µL) was collected from the anterior chamber of the eye of each patient by using a 30-gauge insulin syringe at the beginning of the phacoemulsification procedure. After this, the routine phacoemulsification procedure was continued.

The AqH samples obtained were kept in a freezer at − 76 °C until analysis. IL-8, IL-10, and VEGF levels were analyzed by performing enzyme-linked immunosorbent assay (ELISA) at the Biochemistry Laboratory of Hacettepe University Faculty of Medicine, Ankara.

Cytokine assays

IL-8, IL-10, and VEGF levels were measured using IL-8, IL-10, and VEGF human ELISA kits (Affymetrix, eBioscience, Thermo Fisher Scientific, Waltham, Massachusetts, USA), according to the manufacturer's instructions. A 25 µL of AqH sample was used for each measurement. Absorbances were read at 450 nm by using a microplate reader (ELx800; BioTek Instruments, Inc. Winooski, Vermont, USA). The assay ranges for VEGF, IL-8, and IL-10 were 15.6–1000, 2–250, and 2–300 pg/mL, respectively.

Statistical analysis

Data were analyzed using Predictive Analytics Software for Windows (version 18.0 program; SPSS Inc., Chicago, IL, USA). Normality of data was analyzed using visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. Nonparametric tests were performed because of the limited number of patients and the high standard deviation values. Kruskal–Wallis test was used for comparing AqH cytokine levels in the three groups. Mann–Whitney U test was used to test the significance of pairwise differences by using Bonferroni correction to adjust for multiple comparisons. Spearman correlation test was used for performing correlation analysis of cytokine levels. A p value of < 0.05 was considered statistically significant.

Results

The study included 33 patients with uveitis (16 patients with BU and 17 patients with FUS) and 35 noninflammatory healthy control subjects. Although no significant difference was observed among the groups with respect to age, sex, and IOP level ($p = 0.098$, $p = 0.119$, and $p = 0.739$, respectively), a significant different was observed among the groups with respect to BCVA value ($p = 0.001$). The BCVA (LogMAR) value was significantly lower in the BU group than in the FUS and control groups ($p < 0.001$ and $p < 0.001$, respectively; Table 1).

The IL-8 level was significantly higher in the BU (median 28.77 pg/mL) and FUS (median 32.51 pg/mL) groups than in the control group (median 16.99 pg/mL) ($p < 0.001$ and $p < 0.001$, respectively). However, the difference in the IL-8 level between the two uveitis groups was not significant ($p = 0.292$; Table 2).

The IL-10 level was significantly lower in the BU group (median 7.06 pg/mL) than in the FUS (median 9.88 pg/mL) and control groups (median 10.60 pg/mL) ($p = 0.001$ and $p < 0.001$, respectively). There was no significant difference between FUS and control groups in terms of AqH IL-10 level. ($p = 0.183$; Table 2).

Table 1 Clinical features in patients with uveitis and control subjects

	BU (n = 16)	FUS (n = 17)	Control (n = 35)	p
Age (year)	46.43 ± 14.75	43.52 ± 9.53	49.31 ± 11.79	.098
Range	(26–79)	(28–63)	(15–69)	
Sex (m/f)	13/3	8/9	23/12	.119
BCVA (LogMAR)	1.73 ± 0.85	0.84 ± 0.51	0.91 ± 0.68	.001
Range	(0.40–3.10)	(0.40–2.10)	(0.30–3.10)	
IOP (mmHg)	15.81 ± 2.88	16.52 ± 4.09	15.88 ± 2.87	.739

Data are presented as means ± SDs as appropriate

BU Behçet's uveitis; *FUS* Fuchs uveitis' syndrome; *BCVA* best-corrected visual acuity; *IOP* intraocular pressure; *min* minimum; *max* maximum; *m* male; *f* female

p Kruskal–Wallis tests for age, BCVA, and IOP; Chi-square test for sex

Table 2 Comparison of aqueous humor cytokine profiles between groups

Cytokines	BU (n = 16)	FUS (n = 17)	Control (n = 35)	p
IL-8 (pg/ml)	46.05 ± 52.07	39.90 ± 18.34	17.83 ± 4.10	$< 0.001^{*}$
Median	28.77	32.51	16.99	$< 0.001^{a}$, $< 0.001^{b}$, 0.292^{c}
Range	14.9–229.9	22.1–87.4	12.3–29.6	
IL-10 (pg/ml)	7.23 ± 1.73	11.70 ± 6.60	10.62 ± 1.64	$< 0.001^{*}$
Median	7.06	9.88	10.60	$< 0.001^{a}$, 0.183^{b}, 0.001^{c}
Range	4.9–10.8	6.1–28.7	7.3–15.8	
VEGF (pg/ml)	350.33 ± 177.02	511.74 ± 337.82	246.67 ± 148.56	$< 0.001^{*}$
Median	330.0	373.33	260.0	0.051^{a}, $< 0.001^{b}$, 0.113^{c}
Range	49.0–653.5	107.2–1524.4	13.4–661.4	

BU Behçet's uveitis; *FUS* Fuchs' uveitis syndrome

*Significance among three groups (Kruskal–Wallis test)

[a]Significance between BU and control groups (pairwise comparison)

[b]Significance between FUS and control groups (pairwise comparison)

[c]Significance between BU and FUS groups (pairwise comparison)

The VEGF level was higher in the FUS group (median 373.33 pg/mL) than in the control group (median 260.0 pg/mL) ($p < 0.001$). There was no significant difference in VEGF levels between the BU (median 330.0 pg/mL) and control groups ($p = 0.051$). And also, there was no significant difference between the BU and FUS groups ($p = 0.113$; Table 2).

The correlation analysis of AqH cytokine levels showed a significant moderately positive correlation between IL-8 and VEGF levels in the control group ($p = 0.011$, $r = 0.425$) but showed no significant correlation between IL-8 and VEGF levels in the patient group ($p = 0.347$, $r = 0.170$). Moreover, no significant correlation was observed among the other cytokine levels in the patient and control groups (Table 3).

Table 3 Analysis of correlation between aqueous humor cytokine levels in patients with uveitis and control group

	Patient group		Control group	
	r	p	r	p
IL-8 and IL-10	0.205	0.255	− 0.066	0.719
IL-8 and VEGF	0.170	0.347	0.425	0.011
IL-10 and VEGF	0.206	0.291	0.190	0.346

r, Spearman correlation coefficient

Discussion

The present study compared IL-8, IL-10, and VEGF levels in the AqH of patients with BU and FUS and of noninflammatory healthy subjects. Although IL-8 levels were increased in the AqH of patients with BU and FUS, IL-10 levels were significantly decreased in the AqH of patients with BU and VEGF levels were significantly increased in the AqH of patients with FUS compared to controls.

Many studies have reported high IL-10 levels in patients with uveitis [17, 23, 24]. This increase in IL-10 levels is suggested to occur for regulating an activated proinflammatory pathway. In contrast, Lacomba et al. [25]. and Kooij et al. [26] observed no significant difference in IL-10 levels in the AqH of patients with uveitis compared with control subjects. However, Kooij et al. [26] reported higher IL-10 levels in patients with active uveitis than in patients with inactive uveitis. Similarly, El-Asrar et al. [27] reported higher IL-10 levels in the AqH of patients with active uveitis than in the AqH of control subjects; therefore, they concluded that increased IL-10 levels were a potential indicator of activation. However, Curnow et al. determined that no significant difference in IL-10 levels between patients with active idiopathic uveitis ($n = 37$) and noninflammatory control subjects ($n = 12$) [13]. In addition to its association with disease activation, IL-10 is suggested to be associated with infective or noninfective uveitis. Consistently, Curnow et al. detected significantly increased IL-10 levels in the AqH of patients with polymerase chain reaction (PCR)-proven herpetic uveitis compared with those in the AqH of patients with noninfectious uveitis [13]. Takase et al. [23] also detected significantly increased IL-10 levels in the AqH of patients with infectious uveitis ($n = 8$) compared with those in the AqH of patients with noninfectious ($n = 9$). This increase in IL-10 levels was suggested to be caused by an infection and/or indicated that IL-10 functioned as an activation marker. In the present study, there was no significant difference between the FUS group and the control group in terms of IL-10 levels. However, IL-10 levels were significantly lower in the AqH of patients with BU than in the AqH of patients with FUS and of control subjects.

Behçet's disease is a multifactorial systemic disease of unknown etiology, with genetic susceptibility, environmental factors, and infectious and immune disorders suggested to be the potential risk factors of this disease. Intense Th1 activation, increased proinflammatory cytokine levels, and low immunosuppressive status play a role in the immunological pathway of the etiology [28, 29]. El-Asrar et al. [27] found that IL-10 levels were lower in patients with Behçet's disease than in patients with HLA-B27-associated uveitis and VKH disease, with the difference approaching statistical significance ($p = 0.0532$). In the present study, lower IL-10 levels in the AqH of patients with BU and the proinflammatory agents becoming predominant may be a cause or triggering factor for the development of BU. Th1 cells are predominant in the immune environment of patients with BU, and the level of IL-10, which suppresses overexpression of Th1 response, is significantly decreased in these patients [30]. In addition, differences in IL-10 genotype and low IL-10 expression play a role in the pathogenesis and prognosis of Behçet's disease [31–33].

Hill et al. found that IL-10 levels were higher in the AqH of patients with FUS than in the AqH of patients with acute anterior uveitis; however, the difference was not statistically significant ($p = 0.051$) [34]. Similarly, Muhaya et al. [16] found that IL-10 levels in the AqH of patients with FUS were higher but not significant different than those in the AqH of patients with idiopathic acute anterior uveitis. In accordance with the literature, there was no significant difference in IL-10 levels of FUS patients compared to controls.

IL-8 is a proinflammatory cytokine with chemoattractant characteristics and is released by T cells, neutrophils, and macrophages during acute local or systemic inflammation. Because of its characteristics, IL-8 initiates and aggravates an inflammatory response by promoting the rapid accumulation of prostaglandins and polymorphonuclear leukocytes in its environment [35]. Moreover, because IL-8 is an angiogenic cytokine, it exacerbates inflammation by enhancing vascular permeability.

Previous studies have reported increased IL-8 levels in the AqH of patients with uveitis, including patients with intermediate uveitis [36], Behçet's disease [37], FUS [13], and VKH disease [38]. El-Asrar et al. compared three groups of patients with uveitis (Behçet's disease, VKH disease, and HLA-B27-associated uveitis) and observed no significant difference among these patients with respect to AqH IL-8 levels [39]. In the present study, we also observed no statistically significant difference in IL-8 levels

between the patients with BU and FUS. The lack of a significant difference among the patient groups with respect to IL-8 levels is because IL-8 is not a disease-specific cytokine and shows a nonspecific increase in level during inflammation.

VEGF is an angiogenic growth factor produced primarily by endothelial cells, T cells, and macrophages. VEGF release is promoted particularly under ischemic conditions. Moreover, VEGF increases vascular permeability and local angiogenesis and induces inflammation [40, 41]. Although a vascular disorder is not the main pathology in most patients with uveitis, proinflammatory cytokines released from an inflammation area increase VEGF levels. In addition to promoting angiogenesis, VEGF enhances inflammation. Increased VEGF level has been observed in a rat model of experimental autoimmune uveitis [19].

Previous studies have reported increased VEGF levels in the plasma of patients with Behçet's disease and in the AqH of patients with uveitis, which induce cystoid macular edema [42, 43]. Bae et al. [37] detected higher VEGF levels in the AqH of patients with active BU ($n = 7$) and Paroli et al. [20] detected higher VEGF levels in the AqH of patients with inactive uveitis ($n = 13$) than that in the AqH of control subjects. These findings suggest that VEGF is an important factor affecting the inflammatory process involved in the pathogenesis of uveitis even in the absence of neovascularization or cystoid macular edema. In the present study, VEGF levels were higher in the AqH of patients with FUS and BU than in the AqH of control subjects; however, VEGF elevation was statistically significant only in patients with FUS.

Uveitis rarely progresses with neovascularization and is characterized by VEGF production even in the absence of neovascularization, as demonstrated in previous studies, suggesting that VEGF performs a proinflammatory role rather than an angiogenic role in the pathogenesis of uveitis [19, 20].

In patients with FUS, hemorrhage may occur in fragile iris vessels (Amsler–Verrey sign), particularly during surgical paracentesis and less commonly during gonioscopy, applanation tonometry measurement, and trauma. However, it is unclear whether these fragile vessels of the iris and anterior chamber angle in patients with FUS undergo neovascularization or abnormal vascularization [44, 45]. The results of the present study suggest that increased VEGF levels in the AqH of patients with FUS may be associated with the formation of these abnormal fragile vascular tissues.

The present study has some limitations. First, the number of patients included in this study was limited because of the inclusion of only patients with cataract secondary to FUS and BU. Therefore, additional studies involving increased number of patients may help in determining a precise difference in AqH cytokine levels. Second, we only assessed the levels of three cytokines because of the limited quantity of the AqH sample.

In summary, the levels of IL-8, a nonspecific proinflammatory cytokine, increase in patients with different uveal diseases, whereas the level and genotypic diversity of IL-10 seem to be significant, particularly during the clinical course of Behçet's disease. VEGF may function both as an angiogenic and as an important proinflammatory cytokine and may be a target molecule for treating patients with uveitis. Furthermore, VEGF may play an important role in the etiopathogenesis of FUS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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