Serum TNF-α and IL-1β levels in patients with RNFL thinning in uveitis complicated by optic nerve inflammation

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Purpose: *To assess serum tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) levels in patients with retinal nerve fiber layer (RNFL) thinning in uveitis complicated by optic nerve inflammation.*
Material and Methods: *One hundred and thirty-two patients underwent examination and treatment. Serum TNF-α and IL-1β levels were determined by commercially available enzyme-linked immunoassay kits.*
Results: *The serum TNF-α level was more than 1.5 times higher in patients with uveitis complicated by optic nerve inflammation who had reduced RNFL thickness compared to patients with normal RNFL thickness ($p < 0.05$), and the serum IL-1β level was 17% higher in the former patients than in the latter patients ($p > 0.05$).*
Conclusion: *In the active stage of uveitis, the serum TNF-α level was significantly higher in patients with RNFL thinning due to uveitis complicated by optic nerve inflammation compared to patients with normal RNFL thickness, and the serum IL-1β level was higher in the former patients than in the latter patients, but the difference was not statistically significant. The results of the study may justify the use of biologic therapy in the treatment of uveitis complicated by optic nerve inflammation.*

Keywords:
uveitis complicated by optic nerve inflammation, TNF-α, IL-1β

Introduction

Tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) are important in the pathogenesis of uveitis, which is indicated by their increased levels in the aqueous humor [1-4], vitreous [5, 6], and serum [7-11] of patients with the disease. Aqueous humor TNF-α [1], serum TNF-α [10] and aqueous humor IL-1β [4] levels have been found to correlate with disease activity in uveitis.

However, opinions vary regarding the role of TNF-α and IL-1β in optic nerve injury or lesion.

Experimental studies have demonstrated that IL-1β promotes the induction of retinal autoimmune disease such as autoimmune uveoretinitis [12] and is involved in caspase-1-mediated cell death, known as "pyroptosis" [13].

In addition, an increase in TNF-α expression has been correlated with optic nerve injury [14]. Susceptibility to experimental autoimmune uveoretinitis (EAU) and endotoxin-induced uveitis (EIU) in vivo is correlated with the extent of TNF production by retinal Müller glia (RMG) and retinal pigmented epithelium (RPE) cell types under in vitro conditions [15].

Findings of retinal ganglion cell and optic nerve axon death after intravitreal administration of TNF-α have become the basis for a generally recognized experimental model of optic nerve degeneration [16-18]. The role of TNF-α in the development of retinal ganglion cell apoptosis has been demonstrated in the experimental corneal alkali burn model [19].

However, an experimental study by Mac Nair et al [14] found that TNF-α has an early protective effect on retinal ganglion cells after optic nerve crush. Obviously, the question requires further exploration.

The purpose of this study was to assess serum TNF-α and IL-1β levels in patients with RNFL thinning in uveitis complicated by optic nerve inflammation.

Material and Methods

The study protocol complied with the tenets of the Declaration of Helsinki. Inclusion criteria were men and women aged 18 years or younger, with uveitis complicated

by optic nerve inflammation. Exclusion criteria were diabetes; acute infections; cardiovascular diseases; abnormal circulation in the major ocular vessels; history of ocular surgery; pregnancy; or breast feeding.

One hundred and thirty-two patients (53 men and 79 women) aged 18 to 74 years were involved in the study and underwent examination and treatment for uveitis complicated by optic nerve inflammation. The duration of uveitis ranged from one month to 14 years.

Patients underwent a routine eye examination, including, but not limited to, ultrasound biomicroscopy and optical coherence tomography (OCT).

Serum TNF-α and IL-1β levels were determined by commercially available enzyme-linked immunoassay kits. Sera of 40 healthy volunteers were used as controls.

Statistica 6.1 software was used for the statistical analyses. Significance of differences was determined by Student's t-test, Pearson's chi-square or Fisher's Exact test, as appropriate. Mean values are presented as the mean ± standard error.

Results

The current and our previous studies [20] found that the serum TNF-α level in patients with active uveitis complicated by optic nerve inflammation was significantly increased compared with healthy donors (15.8 ± 1.02 pg/ml and 4.1 ± 1.52 pg/ml, respectively, $p < 0.05$). In addition, the serum TNF-α level in patients with RNFL thinning due to uveitis complicated by optic nerve inflammation (Fig. 1) was 1.5 times higher compared to patients with normal RNFL thickness (20.5 ± 1.24 pg/ml vs 12.4 ± 1.47 pg/ml, respectively, $p < 0.05$).

The serum IL-1β level in patients with active uveitis complicated by optic nerve inflammation was significantly increased compared with healthy donors (67.3 ± 5.24 pg/ml vs 35.6 ± 4.1 pg/ml, respectively, $p < 0.05$). Fig. 2 shows serum IL-1β levels in patients with uveitis complicated by optic nerve inflammation who had not vs had RNFL thinning.

The serum IL-1β level in patients with active uveitis complicated by optic nerve inflammation who had RNFL thinning was 17% higher than in those who had not RNFL thinning (Fig. 2), but the difference was not significant (74.9 ± 6.3 pg/ml and 64.1 ± 5.2 pg/ml, respectively, $p > 0.05$).

Discussion

The current study found that both the total study sample of patients with active uveitis complicated by optic nerve inflammation, and those with RNFL thinning, had significantly increased TNF-α and IL-1β levels compared to healthy controls. These findings are consistent with other reports on elevated serum TNF-α levels in such patients [8-11, 21, 22]. However, our findings differ from those of some studies [2, 5, 23] that have reported no significant difference in serum TNF-α levels between uveitis patients and healthy controls.

Our finding of elevated TNF-α levels in RNFL thinning secondary to uveitis are indirectly confirmed by a study by Katome et al. (2013) [24], who found that the reduced production of microglial TNF-α after optic nerve injury results in the higher rate of retinal ganglion cell survival in apoptosis signal-regulating kinase 1 (ASK1) knockout mice.

Another finding of the current study is significantly increased serum IL-1β levels in patients with uveitis complicated by optic nerve inflammation, with a 17% difference in serum IL-1β level between those who had and those who had not RNFL thinning secondary to uveitis. This is in line with findings of increased serum IL-1β levels in patients with Behçet's disease by Chekaoui et al [7] and Evereklioglu et al [9], but does not confirm reports of the absence of significant changes in serum IL-1β levels in patients with uveitis in studies by others [2, 4].

Our findings should be considered in conjunction with (1) those by Tseng et al [13] (2013) who found that IL-1β is involved in caspase-1-mediated cell death, known as "pyroptosis", and (2) those by Bariş et al [25] (2016) who reported that the IL-1β gene polymorphism was statistically correlated with the presence of an ocular lesion in patients with Behçet's disease.

We also found that, in active stage of uveitis, (1) the serum TNF-α level was significantly, more than 1.5 times, higher in patients with RNFL thinning due to uveitis complicated by optic nerve inflammation compared to patients with normal RNFL thickness, and (2) the serum IL-1β level was higher in the former patients than in the latter patients, but the difference was not significant. This is in agreement with findings of Kitaoka et al [26] (2016) that IL-1β was upregulated in astrocytes in the optic nerve in TNF-induced optic nerve degeneration in rats, and with findings of Sivakumar et al [27] (2011) that excess production of TNF-α and IL-1β by microglia can induce retinal ganglion cell death in the retina of one-day-old Wistar rats subjected to hypoxia.

Moreover, our findings of elevated serum TNF-α levels in patients with RNFL thinning are in indirect agreement with the results of our previous study [28] that concentration of matrix metalloproteinase-9 in uveitis complicated by optic nerve inflammation correlated with the development of partial optic nerve atrophy, since Yamada et al [29] showed in their experimental study that the expression of MMP-9 increased in the presence of TNF-α.

Therefore, the current study demonstrated that, in active stage of uveitis, (1) the serum TNF-α level was significantly, more than 1.5 times, higher in patients with RNFL thinning due to uveitis complicated by optic nerve inflammation compared to patients with normal RNFL thickness, and (2) the serum IL-1β level was 17% higher in the former patients than in the latter patients, but the difference was not significant. The results of the study may justify the use of biologic therapy in the treatment of uveitis complicated by optic nerve inflammation.

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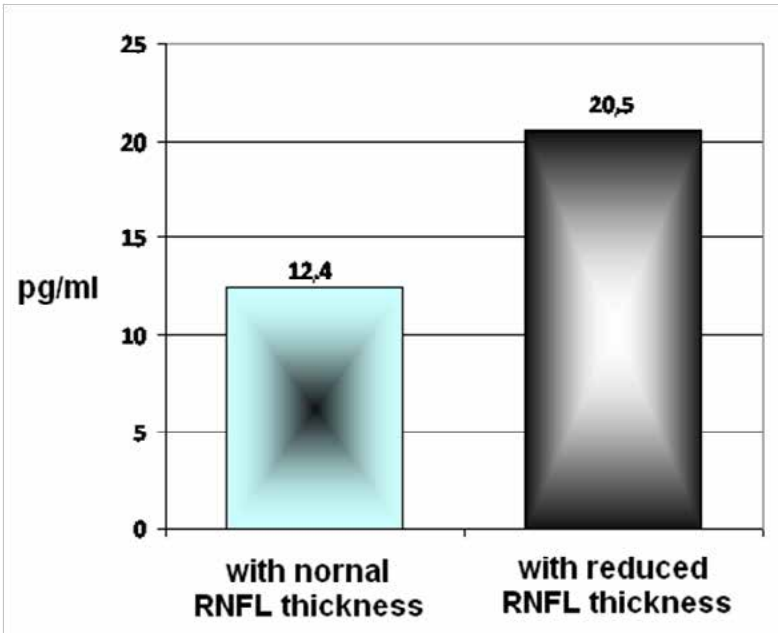

Fig. 1. Serum TNF-α levels (pg/ml) in patients with active uveitis complicated by optic nerve inflammation who had normal or reduced retinal nerve fiber layer (RNFL) thickness

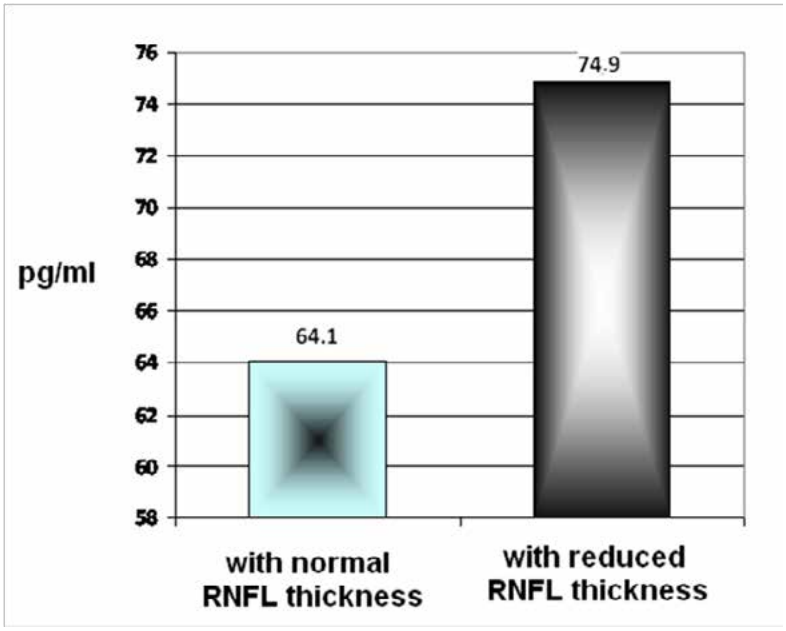

Fig. 2. Serum IL-β levels (pg/ml) in patients with active uveitis complicated by optic nerve inflammation who had normal or reduced retinal nerve fiber layer (RNFL) thickness