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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

A connection between levels of soluble Fas and Fas ligand in the aqueous humor and the parameters of structural and functional damage of glaucoma patients

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SUMMARY

Introduction/Objective Fas ligand (FasL) induces apoptosis when interacting with the Fas-receptor. The aim was to determine the concentration of soluble Fas (sFas) and soluble FasL (sFasL) in the aqueous humor (AH) of open-angle glaucoma patients, and establish a connection between these markers of apoptosis and the parameters of structural and functional glaucoma damage.

Methods This study examined 88 AH samples; 35 primary open-angle glaucoma with elevated intraocular pressure (POAG-HTG) patients, 24 open angle pseudoexfoliative glaucoma patients (XFG) and 29 patients with senile cataract (CAT). The concentration of sFas and sFasL was determined by commercial ELISA tests in the AH.

Results The conducted study showed that AH sFas concentration was the highest in XFG (720.14 ± 167.39 pg/ml), and slightly lower in POAG-HTG (713.43 ± 162.69 pg/ml), than in cataract patients (632.46 ± 217.11 pg/ml), without statistical significance. There was a significant negative correlation of sFas concentration and thickness of the peripapillary nerve fibers of the retina (RNFL) inferior thickness in POAG-HTG ($p < 0.05$). The concentration of sFasL was the lowest in POAG-HTG (9.28 ± 0.551 pg/ml), higher in XFG (9.45 ± 0.61 pg/ml; $p = 0.0566$), and the highest in the cataract group (9.48 ± 0.73 pg/ml). A negative correlation of sFasL and MD in the POAG-HTG, and a negative correlation with RNFL superior in the XFG were significant.

Conclusion sFasL has an active role in the regulation of the inflammatory process in glaucoma. sFas and sFasL, as markers of apoptosis, are associated with the parameters of structural, RNFL thinning, and functional glaucoma damage, namely visual field defects.

Keywords: Fas; FasL; aqueous humor; open angle glaucoma; hypertensive glaucoma; pseudoexfoliation

INTRODUCTION

Fas is a transmembrane glycoprotein, and a type I membrane protein of the tumor necrosis family (TNF), which binds Fas ligand (FasL) to its receptor [1]. In addition to its role in the apoptosis induction, Fas causes a pro-inflammatory response of cytokines [2]. The interaction of Fas and FasL is important in controlling the T-cell immune response and affecting cell death via cytotoxic T-lymphocytes (T-Ly) [1–4].

FasL is a type II membrane protein. As a member of the TNF-cytokine family, FasL induces apoptosis when interacting with the Fas receptor. The membrane bound FasL (mFasL) can become a soluble form (sFasL), by acting of a matrix metalloproteinase as an enzyme. FasL binding to Fas leads to receptor oligomerization and causes apoptotic cell death. FasL is predominantly expressed in activated T-Ly and natural killer cells, and in tissues and immune privileged organs, such as the testicles, placenta, brain and the eye (retina, uvea and cornea) [2, 5, 6, 7].

Wax et al. [8] have indicated that the T-cell mediated degeneration of the retinal ganglion cells (RGC) takes place via the Fas/FasL signaling pathway. Some studies have shown reduced capacity of naturally produced sFasL to induce apoptosis compared to membrane-bound FasL, indicating the selectivity of sFasL. The sFasL in the aqueous humor (AH) may be present due to high FasL expression in intraocular cells [9, 10].

Primary open-angle glaucoma with elevated intraocular pressure (POAG-HTG) is closely related to elevated intraocular pressure (IOP), which may occur due to difficult outflow of humor aqueous through trabecular meshwork (TM) [11]. A finding in POAG patients suggests that the number of TM-cells is significantly reduced in relation to a healthy population of the same age. Aging-related loss of TM cells is thought to occur due to an increased rate of cell death. Also, an increased rate of apoptosis may cause loss of TM cells in POAG. Agarwal et al. [12] showed that after receptor activation by monoclonal Ig M, TM-cells express the Fas receptor and undergo transient apoptosis. Preventing the binding of membranous Fas

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to FasL, by binding soluble Fas (sFas) to FasL, can block Fas-mediated apoptosis. Therefore, it can be hypothesized that the increase in the rate of cell death from TM results from decreased levels of sFas or increased levels of FasL in glaucoma [1, 12, 13]. Also, in glaucoma, FasL expressed in microglia promotes neuroinflammation via activation of Fas+ astrocytes, Müller cells and microglia, as well as apoptosis of Fas+ RGCs [5, 14]. Membrane-associated FasL (mFasL) and soluble FasL (sFasL) fragment show opposite effects on glaucoma development.

In the healthy eye, FasL is constitutively cleaved and sFasL maintains a non-inflammatory homeostatic environment. In experimental glaucoma models with IOP, microglia activation occurs and FasL expression increases, resulting in a shift from sFasL to mFasL that contributes to RGC apoptosis. When FasL cleavage is disabled, accelerated and much more severe glaucoma occurs. While stimulated production of sFasL by long-lived neurons provides significant neuroprotection of RGCs and axons [5, 15].

Recent studies revealed a paradoxical phenomenon related to FasL function within the eye, where ocular expression of mFasL promotes immunoreactivity. Even though it has been shown in some studies that sFasL antagonizes the functional effect of mFasL, and in others that sFasL can bind to ocular matrix proteins and thus trigger potent apoptotic activity, it remains unclear how immune-privileged sites regulate FasL activity and control the potentially dangerous consequences associated with inflammation and apoptosis [2, 16].

The aim of this study was to determine the concentration of sFas and FasL in the AH of open-angle glaucoma patients and establish a connection between these markers of apoptosis and the parameters of structural and functional glaucoma damage.

METHODS

This study examined 88 AH samples; 35 patients suffering from POAG-HTG (hypertensive glaucoma), 24 open-angle pseudoexfoliative glaucoma patients (XFG), and 29 patients with senile cataract (CAT).

The Ethical Committee of the Faculty of Medicine in Niš (decision number 01-2625-18, dated 08/04/2014) and the Ethical Committee of the University Clinical Center Niš (decision number 338/43, dated 13/01/2015) granted approval for conducting the research. Prior to engaging in the research, all participants signed informed consent according to the Declaration of Helsinki.

Clinical examination included: demographic characteristics of the patients, detailed medical history, visual acuity with refraction (Snellen chart), biomicroscopy, Goldmann applanation IOP tonometry, three mirrors Goldman gonioscopy, indirect ophthalmoscopy using a 90D lens and determination of the cup size of the optic nerve head (C/D ratio), standard automatic perimetry (Humphrey Visual Field Analyzer, Threshold Test 24-2, Carl Zeiss Meditec, Inc., Dublin, CA, USA) with determining changes in the visual field: mean deviation (MD), optical coherent tomography (OCT, Stratus, Carl Zeiss Meditec, Inc.) and measuring the average thickness of the peripapillary nerve fibers of the retina (RNFL Avg), in the superior (RNFL Sup) and the inferior (RNFL Inf) quadrants [17].

Diagnostic criteria for POAG-HTG included elevated IOP, characteristic arcuate Bjerrum scotoma, and/or paracentral scotoma, and/or Rönne's nasal step, and other corresponding visual scotomas, and/or thinning of the nerve fibers on OCT, gonioscopy open angle finding, and the absence of a secondary cause of glaucomatous optic neuropathy. Patients with a history of inflammatory eye diseases, uveitis, congenital or normotensive glaucoma and systemic factors (systemic rheumatologic and inflammatory diseases) and systemic drug usages, previous administration of corticosteroids, previous trauma, that would affect the level of the examined markers, were excluded from the study [17].

Patients with XFG had been previously diagnosed according to established criteria: elevated IOP, visual field changes, RNFL thinning, such as for POAG-HTG, with the presence of pseudoexfoliation on the anterior lens capsule and/or along the pupil margin.

Patients with POAG-HTG and XFG subjected to antiglaucomatous surgery had intraocular pressure values greater than 21 mmHg during daytime with antiglaucomatous therapy. They had had a confirmed diagnosis of glaucoma for several years and maximum drug therapy in the form of drops (prostaglandin, beta blocker, carbonic anhydrase inhibitor).

The control group consisted of patients referred for CAT surgery, without serious systemic diseases and with no personal and family history of glaucoma. Glaucoma was excluded in these patients applying the same diagnostic criteria used to diagnose POAG-HTG or XFG, i.e., after the same ophthalmological examination and procedures.

The AH sampling was performed at the very beginning of the antiglaucomatous surgery and ultrasound cataract surgery, in sterile conditions, by limbal paracentesis. Sterile insulin syringe 1 ml/cc with a needle 29G X 1/2" was used, whereas any contact with the corneal endothelium, iris and lens was avoided. Special care was taken to ensure the samples did not contain blood. The AH samples (100–150 μL) were immediately stored at -80°C.

The concentration of sFas and sFasL in the AH of the patients was determined by commercial enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions (ELH-Fas and ELH-FASL-1, RayBiotech, Peachtree Corners, GA, USA). The concentration was determined using the standard curve and expressed in pg/ml. The minimum detectable dose (MDD) for Fas was 5 pg/ml and for Fas ligand was 2 pg/ml, with no significant cross-reactivity or interference with other proteins.

Statistical processing was performed with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). We used descriptive statistical parameters (absolute numbers, relative numbers, arithmetic mean, standard deviation, median, and an interval of variation: minimum and maximum values). The Mann–Whitney U-test or the Student's

t-test for independent samples were used for two groups of subjects, the Kruskal–Wallis test and ANOVA were used for multiple groups, the Student's t-test and ANOVA were used for continuous variables with normal distribution. Spearman's rank correlation coefficient was used to test the strength of the association between two continuous variables. Univariate linear regression analysis was used to test the influence of independent, predictor variables on the value of the continuous dependent variable. A value of $p < 0.05$ was used as a threshold of statistical significance.

RESULTS

Demographic characteristics of 88 participants (35 POAG-HTG + 24 XFG + 29 CONTROL- CATARACT), basic clinical parameters of glaucoma (IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf), and AH levels of sFas and sFasL are shown in Table 1.

The results of this study showed no significant difference in age between the examined groups (Kruskal–Wallis test and Mann–Whitney test). POAG-HTG and XFG were found to be more prevalent in men (54.28%, i.e., 58.33%), whereas, in the control group, women were more prevalent (51.73%); however, there was no significant difference between the groups. The highest IOP value was found in XFG patients. IOP values in both glaucoma groups were significantly higher compared to the control group ($p < 0.001$). The values of the C/D ratio were almost identical in the POAG-HTG and the XFG group, without significant difference. Although the absolute value of MD was higher in XFG, it was not significantly different from the value of this parameter in POAG-HTG. All POAG-HTG and XFG patients were in the second and the third group according to the Hadopp classification, without statistically significant differences in distribution. Average RNFL thickness, RNFL thickness in the superior and inferior quadrants, were higher in XFG patients, however, not significantly compared to POAG-HTG patients.

We did not determine significant differences in sFas concentration in the AH between the groups although sFas in the AH was the highest in XFG patients (720.14 ± 167.39 pg/ml), and higher in POAG-HTG patients (713.43 ± 162.69 pg/ml), compared to the control group (632.46 ± 217.11 pg/ml). The difference between POAG-HTG and the control was nearly significant ($p = 0.0505$), whereas the difference between XFG and the control was also very close to statistical significance ($p = 0.0657$).

In addition, no differences were found in the sFasL concentration of POAG-HTG and XFG patients and

Table 1. Demographic and clinical characteristics, and aqueous humor levels of sFas and sFasL in glaucoma patients and the control group of subjects with cataract

Parameters	POAG-HTG (n = 35)	XFG (n = 24)	Control (n = 29)	Tests
Age (year) X ± SD (Me) Min–Max	70.95 ± 7.93 70 58–87	73.41 ± 6.25 76 59–84	71.77 ± 9.38 74 51–88	Kruskal–Wallis test Mann–Whitney test
Gender (M/F)	19 (54.28%) /16(45.72%)	14 (58.33%) /10 (41.67%)	14 (48.27%) /15 (51.73%)	/
IOP (mmHg) X ± SD (Me) Min–Max	21.86 ± 7.37^{c***} (20) 10–48	**23.58 ± 11.31**^{c***} (20.50) 10–56	14.76 ± 2.39 (14) 8–20	c- *vs*. control, ***-p < 0.001 Kruskal–Wallis and Mann–Whitney test
C/D X ± SD (Me) Min–Max	0.64 ± 0.20 (0.60) 0.4–1	0.63 ± 0.18 (0.55) 0.4–1	not determined	Mann–Whitney test
MD (dB) X ± SD (Me) Min–Max	-11.73 ± 9.05 (-8.46) -0.38–-31.27	-12.72 ± 11.21 (-8.62) -0.07–-29.69	not determined	Mann–Whitney test
RNFL Avg (µm) X ± SD (Me) Min–Max	78.09 ± 24.39 (80.98) 24.46–143.71	78.62 ± 21.54 (81.63) 45.77–103.69	not determined	Mann–Whitney test
RNFL Sup (µm) X ± SD (Me) Min–Max	92.38 ± 34.50 (96) 26–180	100.64 ± 37.66 (104) 44–161	not determined	Mann–Whitney test
RNFL Inf (µm) X ± SD (Me) Min–Max	94.41 ± 37.55 (101) 29–157	96.10 ± 31.11 (91) 57–144	not determined	Mann–Whitney test
sFas (pg/ml) X ± SD (Me) Min–Max	713.43 ± 162.69 (759.80) 369.95–958.22	720.14 ± 167.39 (776.63) 166.99–921.60	632.46 ± 217.11 (727.79) 83.83–862.33	Kruskal–Wallis and Mann–Whitney test
sFasL (pg/ml) X ± SD (Me) Min–Max	9.28 ± 0.551 (9.35) 8.33–10.78	9.45 ± 0.61 (9.60) 8.52–10.40	9.48 ± 0.73 (9.46) 8.44–10.82	Kruskal–Wallis, Mann–Whitney test, and Student's t-test

n – number of participants/eyes and examined samples of the aqueous humor; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; Control – control group with cataract; IOP – intraocular pressure; C/D – cup/disk ratio; MD – mean deviation; RNFL Avg – average peripapillar retinal nerve fiber layer thickness; RNFL Sup – peripapillar retinal nerve fiber layer thickness in the superior quadrant; RNFL Inf – peripapillar retinal nerve fiber layer thickness in the inferior quadrant; sFas – soluble Fas; sFasL – soluble Fas ligand

Table 2. Spearman's rank correlation coefficient for sFas and the examined clinical parameters in glaucoma patients

ρ FAS (pg/ml)	VA	IOP	C/D	MD	RNFL Avg	RNFL Sup	RNFL Inf
POAG-HTG	-0.12	0.06	0.06	0.07	-0.29	-0.20	*-0.33
XFG	0.06	-0.22	-0.17	-0.38	-0.35	-0.43	-0.28
All glaucoma patients	0.01	0.14	0.03	-0.01	*-0.31	-0.27	*-0.35

*p < 0.05, - ρ – Spearman's rank correlation coefficient;
sFas – soluble Fas; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; VA – visual acuity; IOP – intraocular pressure; C/D – cup/disk ratio; MD – mean deviation; RNFL Avg – average peripapillary retinal nerve fiber layer thickness; RNFL Sup – peripapillary retinal nerve fiber layer thickness in the superior quadrant; RNFL Inf – peripapillary retinal nerve fiber layer thickness in the inferior quadrant

Table 3. Spearman's rank correlation coefficient for sFasL and the examined clinical parameters of glaucoma patients

ρ FasL (pg/ml)	VA	IOP	C/D	MD	RNFL Avg	RNFL Sup	RNFL Inf
POAG-HTG	0.11	0.18	0.17	*-0.32	-0.31	-0.27	-0.30
XFG	-0.11	-0.11	-0.12	-0.29	-0.43	*0.62	-0.07
All glaucoma patients	-0.11	-0.08	0.10	*-0.31	*-0.32	*-0.35	*-0.31

*p < 0.05, - ρ – Spearman's rank correlation coefficient;
sFasL – soluble Fas ligand; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; VA – visual acuity; IOP – intraocular pressure; C/D – cup/disk ratio; MD – mean deviation; RNFL Avg – average peripapillary retinal nerve fiber layer thickness; RNFL Sup – peripapillary retinal nerve fiber layer thickness in the superior quadrant; RNFL Inf – peripapillary retinal nerve fiber layer thickness in the inferior quadrant

eyes with CAT (9.48 ± 0.73 pg/ml). The concentration of sFasL in the AH was the lowest in POAG-HTG patients (9.28 ± 0.551 pg/ml); almost significantly lower in relation to XFG patients (9.45 ± 0.61 pg/ml; p = 0.0566). Spearman's rank correlation coefficient was tested for the association of sFas concentration in the AH and visual acuity, IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf of the examined patients (Table 2). POAG-HTG patients had a statistically significant negative correlation between sFas concentration in the AH and RNFL Inf (p < 0.05). All glaucoma patients (POAG-HTG and XFG) had the significant negative correlations of sFas concentration with morphological parameters obtained by OCT: RNFL Avg and RNFL Inf (p < 0.05). Spearman's rank correlation coefficient was also tested for the association of sFasL concentration in the AH and visual acuity, IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf of the examined glaucoma patients (Table 3). In the group of patients with POAG-HTG, the negative sFasL correlation with MD (p < 0.05) was statistically significant. In the group of XFG patients, a negative correlation with RNFL Sup (p < 0.05) was statistically significant. All glaucoma patients had significant negative correlations of sFasL with the functional visual field parameter MD, and morphological OCT parameters RNFL Avg, RNFL Sup, and RNFL Inf (p < 0.05).

Univariate linear regression analysis was used to assess the effect of sFas and sFasL concentration on the values of IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf parameters and confirmed FasL, as the only factor that significantly affects RNFL Sup in XFG patients (Table 4).

DISCUSSION

Various proapoptotic stimuli lead to the initiation of biochemical processes and activate a large family of proteases and caspases, which are the major executors of apoptosis. The outer and inner pathway of caspase activation is equally admixed into glaucoma, in the reduction of trabecular cellularity and RGC apoptosis, including TNF-α, FasL, IL-1α, IL-1β, and IL-6 [18, 19, 20]. However, Rolle et al. [20] state that in neurodegenerative diseases, as well as in glaucoma, necroptosis as a genetic form of cell death plays a major role. It is very similar to necrosis, and is characterized by cell swelling, granular cytoplasm, chromatin fragmentation, and cell lysis, but differs from apoptosis because the cell contents move into the extracellular matrix passively through an altered cell membrane. TNF-a, Fas, apoptosis-inducing ligand interferons can induce necroptosis [20].

Our study showed that sFas concentration in AH was the highest in XFG, and higher in POAG-HTG patients compared to the cataract group, without significant differences between the tested groups. This is not entirely in line with the results obtained by Razeghinejad et al. [1], who found the highest Fas values in XFG, followed by CAT, and POAG, respectively, nor with the results of Sugita et al. [7]. However, Okamura et al. [21] found that apoptosis plays an important role in the development of cataracts with DR, but not in CATs. Hence, there is no explanation for higher levels of sFas in cataract patients. We found a significant negative correlation between sFas concentration in AH and RNFL Inf of POAG-HTG patients (p < 0.05). Therefore, sFas may be an indicator of glaucoma damage in the inferior quadrant.

Our study showed that the AH concentration of sFasL was the lowest in POAG-HTG patients. Although the sFasL values in POAG were similar to those found by Razeghinejad et al. [1], we did not find a significant

Table 4. Estimation of the influence of sFas and sFasL factors on the values of RNFL Sup (μm); results of univariate linear regression analysis for patients with POAG-HTG and XFG

Parameters	POAG-HTG				XFG			
Factor	t	p	B	95% CI for B	t	p	B	95% CI for B
sFas (pg/ml)	-0.65	0.5209	-0.02	-0.07 - 0.04	-1.11	0.2967	-0.20	-0.62 - 0.21
sFasL (pg/ml)	-0.67	0.5100	-5.86	-23.74 - 12.02	-2.29	0.0479	*-48.47	-96.39 - -0.55

*p < 0.05;
t – statistical test value; p – statistical significance; B – regression coefficient; 95% CI for B – 95% confidence interval for B; POAG-HTG – primary open-angle glaucoma with elevated intraocular pressure, hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; sFas – soluble Fas; sFasL – soluble Fas ligand

connection, contrary to their findings. The current study confirmed a significant ($p < 0.05$) negative correlation of sFasL with MD, and a nearly significant ($p = 0.0594$) negative correlation with RNFL Avg, in the group of POAG-HTG patients. In the group of XFG patients, a negative correlation with RNFL Sup was significant ($p < 0.05$). This leads to the connection between the concentration of FasL and both structural and functional parameters of glaucoma patients.

Razeghinejad et al. [1] showed no significant difference in the sFas concentration between the XFG and the cataract group ($p = 0.72$). Although our values of sFasL are similar to those of Razeghinejad et al. [1], no significance has been confirmed either. Also, they found no correlation between sFas levels, as well as sFasL concentration, and vertical C/D ratio in POAG and XFG ($p = 0.52$, $p = 0.65$; $p = 0.58$, $p = 0.64$). The level of sFas in POAG, which was significantly lower than in the control group, was explained by the binding of FasL to Fas and a higher rate of trabecular cell apoptosis, which ultimately led to increased resistance to AH outflow [1].

Sugita et al. [7] showed significant AH levels of sFasL in patients with CAT and no ocular inflammation, thus indicating that AH in its normal condition contains significant amounts of sFasL. Contrary to these results, Borkenstein et al. [18] reported that levels of cytokines (TNF-α, IL-1α and FasL) were below the detection limit, in a multiplex bead study conducted by analyzing the AH samples of 25 patients with POAG and 29 patients with cataract, which were interpreted by choosing various methods [18–23].

This discrepancy between studies may be caused by different conditions of the puncture and sampling of the AH from the anterior chamber, as well as the use of different ELISA tests. The amount of sFasL detected in the AH can be affected by a contact of the syringes with ocular structures, blood contamination from the limbal blood vessels, or tear film with its own concentration of sFasL. In our study, special care was taken to avoid contact of needles and the iris. Samples contaminated with blood were not processed. Only 100–150 μl of AH was taken, and a certain amount always remained in the anterior chamber. On the other hand, Sugita et al. [7] extracted a critical amount of HA of 0.2 ml.

Gregory-Ksander and Marshak-Rothstein [5] in their recent studies in mice have shown that under homeostatic conditions membrane-bound FasL is preferentially cleaved into a soluble fragment, sFasL. Soluble-FasL contributes to the mechanisms responsible for immune privilege and may alter the inflammatory effects of mFasL, blocking both apoptosis and inflammation. When pathogenic mFasL isoform levels exceed normal, immune privilege is revoked and destructive inflammation begins or the onset of other ocular pathology. Therefore, it is important to study the roles of all FasL isoforms in the pathology of eye diseases [5, 20]. The neurodestructive effect of sFas in glaucoma can be blocked via sFaL or a small Fas-inhibitor peptide that blocks the activation of Fas and mFasL and prevents the neuroinflammation development and provides neuroprotection for RGCs and their axons. [5, 20, 24].

Hence, in glaucoma we can expect an increase in sFas and mFasL, while there is no increase in sFasL, the only isoform that can be measured by ELISA tests in the AH, which is partially in line with our research results.

Considering that sFasL has an active role in limiting eye inflammation, this opens up new possibilities for new therapeutic applications of sFasL in regulating the inflammatory process in glaucoma and other eye disorders [5, 20, 24, 25]. Rolle et al. [20] outlined various molecular mechanisms and new therapeutic possibilities, mentioning ONL1204. It is a small peptide antagonist of the Fas receptor, that blocks microglial activation and inhibits the induction of multiple genes involved in glaucomatous disease, and significantly reduces RGC death and axonal loss [20].

Due to all these conflicting results, the role of Fas/FasL in glaucoma is only partially elucidated. Finally, our findings do not clarify the influence of Fas/FasL, but this study shows that a larger, adequately powered, and well-designed study is needed to explore the role of sFas and sFasL in glaucoma genesis.

CONCLUSION

sFasL has an active role in the regulation of the inflammatory process in glaucoma. sFas and sFasL, as markers of apoptosis, are associated with the parameters of structural, RNFL thinning, and functional glaucoma damage, namely visual field defects.

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Веза између нивоа растворљивих Фас и Фас-лиганда у очној водици и параметара структурног и функционалног оштећења код болесника са глаукомом

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САЖЕТАК

Увод/Циљ Фас лиганд (ФасЛ) индукује апоптозу када је у интеракцији са Фас рецептором. Циљ овог истраживања је био да се утврди концентрација растворљивих Фас и ФасЛ у очној водици болесника са глаукомом отвореног угла и успостави веза између ових маркера апоптозе и параметара структурног и функционалног оштећења изазваног глаукомом.

Методе Овом студијом испитано је 88 узорака очне водице, 35 болесника оболелих од примарног глаукома отвореног угла са повишеним интраокуларним притиском (*POAG-HTG*), 24 болесника са псеудоексфолијативним глаукомом отвореног угла (*PEKSG*) и 29 испитаника са сенилном катарактом. Концентрација растворљивих Фас и ФасЛ одређена је комерцијалним ЕЛИСА тестовима у очној водици.

Резултати Спроведена студија показала је да је концентрација растворљивог Фас у очној водици највећа код болесника са *PEKSG* (720,14 ± 167,39 *pg/ml*), нешто нижа код болесника са *POAG-HTG* (713,43 ± 162,69 *pg/ml*), а најнижа код катаракте (632,46 ± 217,11 *pg/ml*), без статистичке значајности. Постојала је статистички значајна негативна корелација између концентрације растворљивог Фас и дебљине перипапиларних ретиналних нервних влакана (*RNFL*) у доњем квадранту код болесника са *POAG-HTG* ($p < 0,05$). Концентрација растворљивог ФасЛ била је најнижа код болесника са *POAG-HTG* (9,28 ± 0,551 *pg/ml*), виша код болесника са *PEKSG* (9,45 ± 0,61 *pg/ml*; $p = 0,0566$), а највећа у групи са катарактом (9,48 ± 0,73 *pg/ml*). Значајна је била негативна корелација растворљивог ФасЛ и средње девијације у групи болесника са *POAG-HTG*, као и негативна корелација са *RNFL* у групи болесника са *PEKSG*.

Закључак Растворљиви ФасЛ активно регулише инфламаторни процес код глаукома. Растворљиви Фас и ФасЛ, као маркери апоптозе, повезани су са параметрима структурног оштећења, истањења *RNFL*, и функционалног глаукомног оштећења, односно испада у видном пољу.

Кључне речи: Фас; ФасЛ; очна водица; глауком отвореног угла; хипертензивни глауком; псеудоексфолијација