Original Research Article: full paper

(2020), «EUREKA: Health Sciences»
Number 6

PROGNOSIS OF POSTOPERATIVE PROGRESSION OF GLAUCOMA OPTIC NEUROPATHY AT PRIMARY OPEN-ANGLE GLAUCOMA

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Abstract

Search for new informative markers and methods of prognosis prediction glaucomatous optic neuropathy (GON) in primary open-angle glaucoma (POAG) is an urgent task. We have established efficiency surgical treatment of POAG, but the progression of GON is observed in 10–15 % patients. It is known that the main mechanism of GON is apoptotic death retinal ganglion cells, a marker of which is recognized as tumour necrosis factor-α (TNFα), Fas-ligand (FasL) and a soluble form of the Fas-receptor (sFas/APO-1).

The aim of the study: to find out the possibility of using apoptosis factors (TNFα, FasL and sFas/APO-1) to predict postoperative progression of GON at POAG.

Methods. 69 patients (69 eyes) with POAG stage I–III were examined, who underwent trabeculectomy with implantation of an Ex-Press shunt. In intraocular fluid (IOF) markers of apoptosis was determined by the method enzyme-linked immunosorbent assay. Repeated ophthalmological examination was performed in 1 year. The control group consisted of 25 patients who were operated on about phacoemulsification of cataracts. For statistical and regression analysis used software package GLZ (Statistica 10, StatSoft, Inc. USA) and module of analysis of operational characteristics of regression models – ROC-diagrams (MedCalc 18.9.1, MedCalc Software, Belgium).

Results. Multivariate regression analysis showed that the progression of GON determine the content in IOF of TNFα and sFas/Apo-1 before surgery and intraocular pressure after three months. Based on these indicators, it is calculated satisfactory model of GON progression prediction with 95.4 % accuracy. One-factor logistic regression analysis proved the influence of the content of TNFα, FasL and sFas/Apo-1 for the presence or absence of progression of GON during the year after operations: direct dependence took place for TNFα and FasL and inverse – for sFas/Apo-1. The critical limits of the content in the IOF markers are calculated apoptosis, in which the progression of GON is unmistakably predicted during year after surgery.

Conclusions. The obtained results prove the significant influence of the studied markers apoptosis on the progression of GON after surgery. Direct pathogenetic influence belongs to TNFα and FasL.

Keywords: primary open-angle glaucoma, surgical treatment, glaucoma optic neuropathy, TNFα, FasL, sFas/APO-1.

DOI: 10.21303/2504-5679.2020.001476

1. Introduction

In Ukraine, as in other countries, primary open-angle glaucoma (POAG) is one of the priority problems of ophthalmology due to its large medical and social significance [1, 2]. Yes, POAG ranks second among causes of blindness in different countries [3, 4]. The issues remain relevant timely diagnosis of glaucoma, determination of the rate of progression diseases and improvement of surgical treatment methods [5, 6].

Therefore, the search for new informative markers and forecasting methods progression of glaucoma optic neuropathy (GON) is relevant today problem [7, 8]. Our previous research has established the effectiveness of the use of trabeculectomy (TE) for the surgical treatment of POAG with implantation of the Ex-Press shunt [9], which coincides with the data of the latter meta-analysis [10].

Despite numerous studies of POAG, the mechanisms of development diseases continue to be studied because the pathogenesis is not yet final clarified [5, 7, 8]. The main links in the pathogenesis of POAG, in addition to violations outflow of aqueous humor and ischemic damage to the optic disc is development of GON and atrophy of retinal ganglion cells [11, 12].

Important inducers of GON include tumour necrosis factor-α (TNFα), which induces apoptosis of retinal ganglion cells; marked correlation between its level in the retina and the rate of ganglion death cells [13, 14]. Under the influence of TNFα, matrix activation occurs metallopro-

teinases, which lead to degradation of intercellular components substances that modulate the tissue of the optic disc, disrupt hemato-ophthalmic barrier [15].

Among the markers of apoptosis related to the development of GON, the most studied is the Fas-receptor (APO-1), the connection of which with another transmembrane protein – Fas-ligand (FasL) leads to the start apoptosis [16, 17]. TNFα, the level of which increases in the retina during inflammation, oxidative stress, ischemic injury promotes the binding of Fas-receptor with FasL and initiation of apoptosis by receptor and mitochondrial by [18, 19]. There is also a dissolved form of the Fas-receptor – sFas/APO-1, which is associated with antiapoptic effects [20, 21].

The aim of the study is to determine the possibility of using factors apoptosis (TNFα, FasL and sFas/APO-1) for the prognosis of postoperative progression of GON in POAG.

2. Materials and methods

All studies were conducted at the Dnepropetrovsk Regional Clinical Ophthalmological Hospital, which is the clinical base of the Dnepropetrovsk Medical Academy of the Ministry of Health of Ukraine in the period from 2016 to 2019.

Data from 69 patients (69 eyes) with stage I–III POAG were analyzed. All research was conducted in compliance with basic bioethical norms and requirements Declaration of Helsinki adopted by the General Assembly of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant regulations of the WHO, the International Council of Medical scientific societies, the international code of medical ethics (1983) and Order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009. All patients who received participation in the study signed an informed consent.

Patients before surgery and one year later performed visometry, static perimeter on the Humphrey Field Analyzer model 540i by Carl Zeiss Meditec in the 30-2 Threshold program for research local defects of the field of view, indicators of MD (integral indicator deviation of the level of light sensitivity in the field of view depending on the age norm and not more than 5.8 dB) and PSD values, the degree of local defects, no more than 1.78 dB), tonometry, refractometry, keratopachymetry, biomicroscopy, ophthalmoscopy with Volk Double aspheric or Ocular Small Pupil, optical coherence tomography (OCT) on the device Optovue RTVue 100-2 (program version A6.11.0.12; for objectification progression of GON investigated the indicators of the RNFL layer of nerve fibers retina and GSS-complex of ganglion cells), if necessary, performed examination of the anterior segment of the eye (A-OCT).

The stage of the disease was determined by classification perimetric changes of glaucoma [5, 8]. Patients underwent trabeculectomy (TE) with Ex-Press shunt implantation [10]. The operations were performed under local anaesthesia by one team of surgeons.

Given the data on the reduction of intraocular pressure (IOP) after surgical treatment and the negative value of postoperative hypotension [5, 6, 11], remeasurement of IOP was performed three months after surgery.

Intraocular fluid (IOF) collection was performed through paracentesis anterior chamber before surgery by aspiration of 0.05–0.1 ml through disposable syringe (Hemoplast, Etalon+, Ukraine) with a volume of 1.0 ml. Determination of apoptosis markers (TNFα, FasL and sFas/Apo-1) in IOF was performed by the method of solid-phase enzyme-linked immunosorbent assay using commercial test systems «Bender MedSystems» (Austria). Conducted twice dilution of the samples, the results were expressed in pg/ml (TNFα and FasL) and in ng/ml (sFas/Apo-1).

During the follow-up, four patients dropped out of the study, therefore, the results of determining markers of apoptosis were analyzed in 65 patients who were examined one year after surgery. The control group was formed 25 patients of the same age without glaucoma who were operated on about phacoemulsification of cataracts.

Statistical analysis of the results of clinical trials was performed by using the software package SPSS 11.0, MedStat. Calculated the average (M) and its standard deviation (SD). For pairwise comparisons used Tukey HSD test for unequal sample sizes. In all cases, the critical significance level was assumed to be 0.05.

To build a prognostic model, multifactor logistic regression technology with step-by-step inclusion of independent variables from the GLZ software package (Statistica 10, StatSoft, Inc. USA)

was used. As dependent variable regression equation used binomial identifier of the presence/absence of progression of GON during the year after operations. The identifier was assigned an indicator value of «0», which corresponded to a stable postoperative period and – «1», in the presence of progression of GON. Independent variables were selected from the following indicators, which were transformed as follows: «gender» – a binomial variable converted to indicator values: «men» = 101, «women» = 102; «age» – the ordinal variable is converted into indicator values: «30–39 years» = 101; «40–49 years» = 102; «50–59 years» = 103; «60–69 years» = 104. Transformation, similar to the latter, made with the variable «duration of the disease»: «less than 1 year» = 101; «1–2 years» = 102; «3–4 years» = 103; «more than 4 years» = 104. Continuous variables «IOP», «TNFα», «FasL», «sFas/Apo-1» are used in its quantitative representation. Selection of optimal predictors from above labeled was carried out by the method of maximum authenticity. The effectiveness of selection was evaluated by an interval method based on statistics Wald, and the overall adequacy of the model – using the chart operating characteristics (ROC), which calculated the area under ROC-curve – AUC, its error and 95 % probable interval (95 % PI). Evaluated probability of differences from the null hypothesis. Used software GLZ package (Statistica 10, StatSoft, Inc. USA) and operating system analysis module characteristics of regression models – ROC-diagrams (MedCalc 18.9.1, MedCalc Software, Belgium).

3. Results

The percentage error was not calculated in this situation because the data were not statistically compared. Percentages are given for a simple description of the distribution of patients by sex and age, and characteristics of study groups, indicate the random nature of such distribution.

Among patients with POAG 12 people (18.5 %) had stage 1 disease, 24 (36.9 %) – 2nd and 29 (44.6 %) – 3rd. There were 32 women in the study (49.2 %), men – 33 (50.8 %), according to the stages of POAG there was no difference by sex ($p = 0.911$).

The age of patients ranged from 30 to 69 years, up to 39 years there was one patient (1.5 %), ages from 40 to 49 years – three (4.6 %), from 50 to 59 years – 13 (20.0 %) and from 60 to 69 years – 48 (73.8 %); the difference in the distribution of age by stages of POAG was not significant ($p = 0.072$). Patients were divided according to the duration of the disease as follows: less than one year – 12 (18.5 %), from one to two years – 20 (30.7 %), from three to four years – 15 (23.1 %), more than four years – 18 (27.7 %); the difference in distribution by stages of POAG was not significant ($p = 0.074$).

IOP before surgery ranged from 15.0 to 34.0 mmHg and on average amounted to 24.2 ± 0.4 mmHg. Three months after the operation IOP was normalized in all eyes and averaged 20.1 ± 1.8 mmHg. The content of markers of apoptosis in the control group was: TNFα – 1.11 ± 0.76 pg/ml, FasL – 22.44 ± 3.77 pg/ml, sFas/APO-1 – 0.05 ± 0.12 ng/ml. By stages of POAG content of TNFα and FasL was higher (**Fig. 1**).

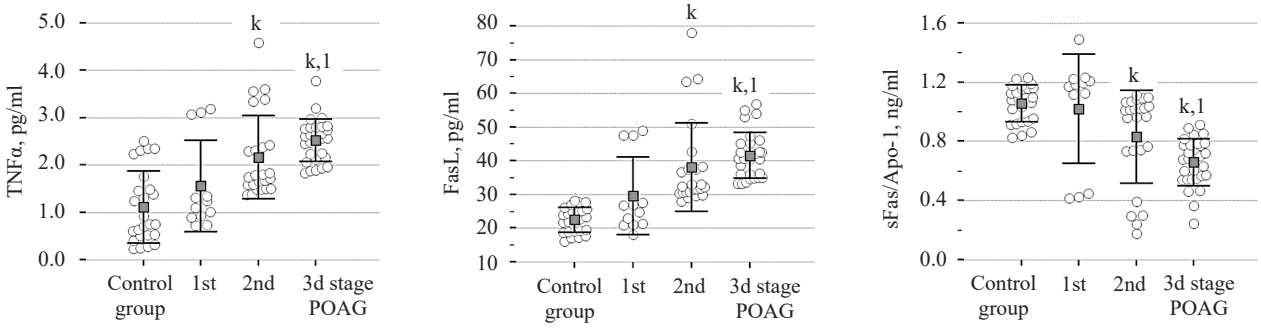

Fig. 1. The content of markers of apoptosis in IOF by stages of POAG.
On horizontal axis: 1st, 2nd, 3rd – stages of POAG. In the pictures above columns marked k – comparison with the control is statistically significant ($p < 0.05$), 1 – comparison with the 1st stage is statistically significant ($p < 0.05$). Differences for the 2nd and 3rd stages on any indicator are not statistically significant ($p > 0.05$). For each indicator, the circles indicate the actual data, the square – M, error bars – SD.

At the same time, it significantly exceeded the control group in the 2nd and 3rd stages of POAG. The content of sFas/APO-1 for stages of POAG was less than in the control, especially – in the 3rd stage.

During the year of observation, the progression of GON, which was determined by narrowing of the field of view according to the static perimeter of Humphrey, was identified in 8 patients (12.3 %). In 57 patients (87.7 %) the field of view remained at the preoperative level or expanded.

In this plan, to clarify the relationship of indicators, which was determined before operations, regression analysis was performed on the progression of GON. Calculation β-coefficients of the multifactor regression model of probability prediction GON progressions for independent variables (predictors) of logistic regression and their statistical significance is given in **Table 1**. The analysis was selected three indicators that had a significant impact on the progression of GON: a direct relationship was found for TNFα, an inverse relationship for IOP and sFas/Apo-1.

Table 1

Indicators of multifactorial regression model of the forecast probabilities of GON progression and their statistical significance

Indicators	β±SE	Wald	95 % PI	*p*
Selected predictors				
IOP	–0.304±0.121	6.34	–(0.541–0.068)	0.012
TNFα	7.592±2.105	13.00	3.466–11.718	< 0.001
sFas/Apo-1	–18.886±5.013	14.19	–(28.712–9.061)	< 0.001
Rejected predictors				
Sex	–0.035±0.308	0.01	–0.640–0.570	0.909
Age	–0.934±0.928	1.01	–2.752–0.884	0.314
Duration of disease	0.733±0.973	0.57	–1.173–2.641	0.451
FasL	–0.130±0.109	1.44	–0.344–0.083	0.231

Note: β±SE – regression equation coefficients and their standard error; Wald – Wald's statistics; 95 % PI – 95 % probable interval for regression coefficients; p is the probability of differences from the null hypothesis (accepted at p < 0.05)

As a mathematical expression of the developed forecast model progression of GON in the postoperative period can be used as follows formula:

$$P_{GON} = 1/(1+e^{-(7.592*«TNFa»-0.304*«IOP»-18.886*«sFas/Apo1»)}), \quad (1)$$

where P_{GON} – the probability of progression of GON; «TNFα» – the content of TNFα in IOF (pg/ml); «sFas/Apo1» – the content of sFas/Apo-1 in IOF (ng/ml); «IOP» – the value of the measurement of IOP three months after surgery (mmHg).

The adequacy of the developed regression model provides a ROC-diagram of operational characteristics (**Fig. 2**). The values between the previous and final, multiplied models describe the following parameters: AUC = 0.978 ± 0.170 (95 % CI 0.945–1.000). These values are statistically significant for the value of AUC = 0.500, which is accepted for the null hypothesis ($p < 0.001$).

Classification characteristics of the model for the standard cut-off point of two opposite in content forecast results (positive and negative; cut off = 0.5) are shown in **Table 2**.

Thereby, the analysis showed that using the developed model can be achieved error-free prediction of the progression of GON in patients in the postoperative period for one year with an overall accuracy of 95.4 %.

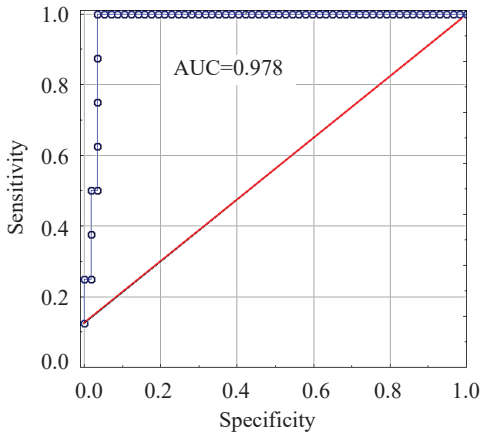

Fig. 2. ROC-diagram for the model of calculating the probability of progression of GON in the postoperative period. The solid red line marks the limit of the null hypothesis (AUC = 0.5)

Table 2

Classification characteristics of the regression model prognosis of GON progression

Cut-off	Probability values and forecast	In fact (n)	According to the forecast (n)	Correctness of the forecast (%)	Model accuracy (%)
0.5	$PP_{GON} \geq 0.5$: presence of progression	8	8	100.00	95.38
	$PP_{GON} < 0.5$: lack of progression	57	54	94.74	

Note: cut-off – probability value for the point that divides the data forecast; PP_{GON} – the probability of progression of GON

In order to determine the limit concentrations in the IOF of the selected markers, a regression analysis based on a series of logistic one-factor equations was performed. The binomial identifier for the presence/absence of GON progression was used as the dependent variable of the regression equations. The identifier was assigned an indicator value of «0» with a stable course and – «1», with disease progression. As independent variables (predictors) the content of the studied markers of apoptosis is included in the equation. Finding the limit concentrations of markers was carried out using diagrams of the sensitivity and specificity of the developed regression models on the concentration of TNFα, FasL or sFas/Apo-1. The value of the marker was considered critical, at which it was possible to accurately predict the progression of the POAG stage (maximum sensitivity) with minimal error in predicting a stable course of the postoperative period (maximum possible specificity).

The result of calculations of β-coefficients for independent variables of one-factor logistic regressions that simulate the effect of TNFα, FasL and sFas/Apo-1 on the presence or absence of GON progression in the postoperative period and their statistical significance are shown in **Table 3**.

Signs of β-coefficients indicated a direct dependence of the probability of prediction on the content of IOF to the operation of TNFα and FasL and the inverse – on the content of sFas/Apo-1. The analysis of the general statistical indicators of the models revealed the greatest correspondence between the predictor and the final variable for the regression equation, which describes the effect of sFas/Apo-1 on the progression of GON in the postoperative period (-2*log = 17.75; $\chi^2 = 30.74$; $p < 0.001$; $R^2 = 0.717$).

The adequacy of the developed regression models is characterised by ROC-diagrams of operational characteristics (**Fig. 3**).

The following data indicate satisfactory computational properties of regression equations and confirm the significance of the relationship between predictors and the final variable: for the model of the influence of the content in the intraocular fluid TNFα: AUC = 0.978 ± 0.017 (95 % PI 0.907–0.999; $p < 0.001$); for FasL: AUC = 0.947 ± 0.028 (95 % PI 0.862–0.987; $p < 0.001$) and for sFas/Apo-1: AUC = 0.978 ± 0.017 (95 % PI 0.907–0.999; $p < 0.001$). These indicators show a significant difference from the null hypothesis ($p < 0,001$).

Table 3

Predictor coefficients of one-factor regression models for predicting the probability of GON progression by the content of apoptosis markers, their statistical significance and general statistical characteristics of the models

Indicators	β±SE	Wald	95 % PI	*p*
Model for TNFα (-2*log=18,35; χ^2=30,14; p<0,001; R^2=0,706)				
Constant variable	–17.738±6.051	8.59	–(29.599–5.789)	0.003
TNFα	5.517±1.962	7.909	1.672–9.362	0.005
Model for FasL (-2*log=26,58; χ^2=21,91; p<0,001; R^2=0,544)				
Constant variable	–10.868±5.296	12.50	–(18.894–4.842)	<0.001
FasL	0.201±0.064	9.86	0.075–0.326	0.002
Model for sFas/Apo-1 (-2*log=17,75; χ^2=30,74; p<0,001; R^2=0,717)				
Constant variable	6.182±2.481	6.21	1.319–11.045	0.013
sFas/Apo-1	–15.549±5.535	7.89	–(29.397–4.701)	0.005

*Note: β±SE – coefficients of the regression equation and their standard error; Wald – Wald's statistics; 95 % PI – 95 % probable interval for regression coefficients; -2*log – maximum authenticity factor for the complete model; χ^2 – Pearson's xi-square criterion; R^2 – coefficient of pseudo-determination of Nigelkerk; p – probability of differences from the null hypothesis (accepted when p < 0.05)*

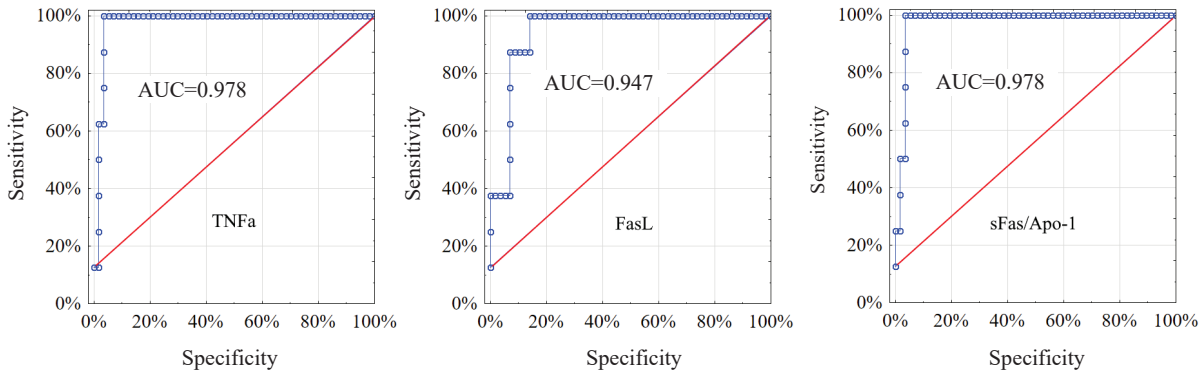

Fig. 3. ROC-diagram for one-factor regression models of the influence of TNFα, FasL and sFas/Apo-1 content in IOF (indicated on the diagrams) on the probability of GON progression in the postoperative period. The solid red line marks the limit of the null hypothesis (AUC=0.5)

Finding the limit concentrations of markers is demonstrated on the diagrams of the dependence of sensitivity and specificity of the developed regression models on the concentration of TNFα, FasL and sFas/Apo-1 (**Fig. 4**).

When analyzing the diagrams of the dependence of sensitivity and specificity on the concentration of TNFα, FasL and sFas/Apo-1, the values of markers at which the sensitivity is 100 % are established, so it is possible to accurately predict the progression of GON, and at the same time the maximum possible values of specificity are reached, which indicate the minimum error of the forecast of the stable course of the postoperative period.

These values for TNFα – 3.04 pg/ml, for FasL – 42.67 pg/ml and for sFas/Apo-1 – 0.45 ng/ml. Given the direction of dependence of the final variable on these predictors, we can state this conclusion in the following wording: the probability of progression of GON during the year after surgery is unmistakably predicted when the values in the intraocular fluid TNFα and FasL more than 3.04 pg/ml and 42.67 pg/ml, respectively and not more than 0.45 ng/ml for sFas/Apo-1.

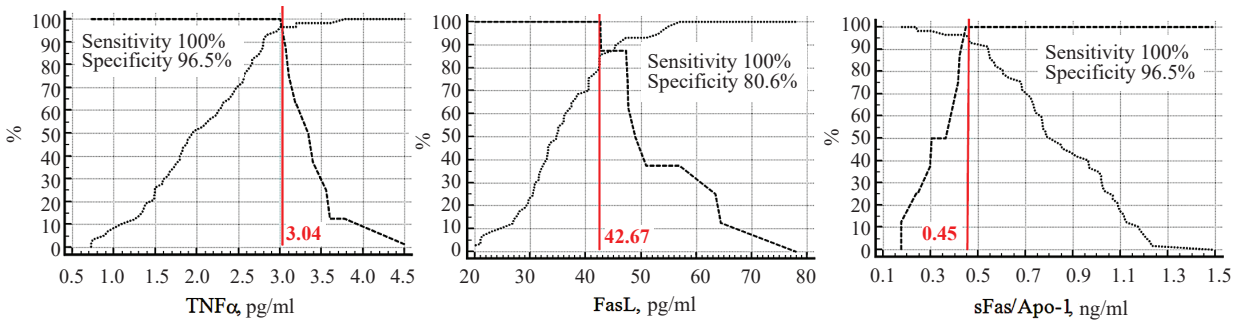

Fig. 4. Diagrams of the dependence of sensitivity (indicated by a large dotted line) and specificity (indicated by a small dotted line) as a percentage (along the vertical axis) of the concentration of TNFα, FasL and sFas/Apo-1 (along the horizontal axis). The limits for the values of these markers that satisfy the selection conditions (see sensitivity and specificity) are shown by a vertical solid red line

Table 4 shows the classification characteristics of the developed models with the above parameters.

Table 4

Classification characteristics of one-factor regression models of dependence of GON progression on the content of apoptosis markers

Marker	Content value and forecast	In fact (n)	According to the forecast (n)	Correctness of the forecast (%)	Model accuracy (%)
TNFα	> 3.04 pg/ml: presence of progression	8	8	100.00	96.92
	≤ 3.04 pg/ml: lack of progression	57	55	96.50	
FasL	> 42.67 pg/ml: presence of progression	8	8	100.00	87.69
	≤ 42.67 pg/ml: lack of progression	57	49	85.96	
sFas/Apo-1	≤ 0.45 ng/ml: presence of progression	8	8	100.00	96.92
	> 0.45 ng/ml: lack of progression	57	55	96.50	

4. Discussion

Thereby, the obtained results prove a significant effect of the studied markers of apoptosis on the development of POAG by stages and progression of GON after surgery. Thus, this directly indicates that the progression of GON is due to the activity of apoptotic processes.

In our opinion, the fact that there is a negative relationship between IOP and the probability of progression of GON during the year after surgery was very interesting (see **Table 1** and Equation 1). According to the above calculations, it turns out that the lower the IOP three months after surgery, the greater the likelihood of progression of GON. At first glance, this contradicts the classical notion of the importance of high IOP for the development of GON [5]. But it is known that post-operative hypotension has a negative effect on the progression of IOP and excessive reduction of IOP after surgery for POAG worsens the long-term results of surgical treatment [9–11]. Our results confirm this opinion – the decrease IOP after surgery has a significant effect on the progression of GON after one year ($p = 0.012$).

Direct pathogenetic influence on the progression of GON belongs to TNFα and FasL. The content of TNFα in IOF reflects its formation in the retina by activated astrocytes under the action of inflammatory mediators, free radicals, end products of glycation (AGE), products of ischemic injury [7, 12, 13]. In POAG, a correspondence was found between the increase in the content of TNFα in the retina and the rate of death of ganglion cells [14]. Through its specific receptors, this

cytokine induces the formation of the proapoptotic complex DISC (death-inducing signalling complex) and activates the subsequent kinase cascade (MARK/ERK kinase-1/JNK/caspase-8) [18]. The proapoptotic effects of TNFα in POAG are realised by activating the binding of the Fas-receptor to FasL [13, 22], which stimulates both receptor and mitochondrial pathways of apoptosis activation [16, 19]. Today, the opinion about the effectiveness of specific blocking of TNFα receptors for neuroprotection in glaucoma is well-founded [22].

The negative relationship between the content of IOF sFas/Apo-1 with the development of POAG and the progression of GON after surgery is consistent with the data [20] and confirms the antiapoptotic effect of this marker, the content of which decreased with POAG progression. The content of sFas/Apo-1 corresponded to a decrease of retinal sensitivity and an increase the area of scotoma [21].

Study limitation. The results of this study cannot be used in patients with diabetes, chronic inflammatory diseases of the eye; in patients who have undergone eye surgery and / or have CNS diseases that can damage the optic nerve.

Prospects for further research. In the future, it is planned to introduce and test on a clinical basis the proposed model of the progression of glaucomatous optic neuropathy and test the calculated critical values of the content of markers in the intraocular fluid.

5. Conclusions

1. Multivariate regression analysis showed that the progression of GON during the year after surgery is determined by the content in the IOF of TNFα and sFas/Apo-1, as well as IOP three months after surgery. Based on these indicators, a satisfactory model for predicting the progression of GON was calculated (AUC = 0.978 ± 0.170; 95 % PI 0.945–1.000; $p < 0.001$). The accuracy of the model was 95.4 %.

2. One-factor logistic regression analysis proved the effect of the content of TNFα, FasL and sFas/Apo-1 in IOF on the presence or absence of GON progression in the postoperative period. Signs of β-coefficients indicated a direct dependence of the probability of prediction on the content of IOF to the operation of TNFα and FasL and the inverse – on the content of sFas/Apo-1. The sensitivity of the calculated models to the progression of GON was 100.0 %.

3. The critical limits of the content of apoptosis markers in IOF were calculated, at which the progression of GON during the year after the operation is unmistakably predicted: TNFα – more than 3.04 pg/ml; FasL – more than 42.67 pg/ml, sFas/Apo-1 – less than 0.45 ng/ml.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Received date 11.08.2020
Accepted date 04.11.2020
Published date 30.11.2020