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ORIGINAL RESEARCH

Inflammation and Neurodegeneration in Glaucoma: Isolated Eye Disease or a Part of a Systemic Disorder? - Serum Proteomic Analysis

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Introduction: Glaucoma is the most common optic neuropathy and the leading cause of irreversible blindness worldwide, which affects 3.54% of the population aged 40–80 years. Despite numerous published studies, some aspects of glaucoma pathogenesis, serum biomarkers, and their potential link with other diseases remain unclear. Recent articles have proposed that autoimmune, oxidative stress and inflammation may be involved in the pathogenesis of glaucoma.

Methods: We investigated the serum expression of 92 inflammatory and neurotrophic factors in glaucoma patients. The study group consisted of 26 glaucoma patients and 192 healthy subjects based on digital fundography.

Results: Patients with glaucoma had significantly lower serum expression of IL-2Rβ, TWEAK, CX3CL1, CD6, CD5, LAP TGF-beta1, LIF-R, TRAIL, NT-3, and CCL23 and significantly higher expression of IL-22Rα1.

Conclusion: Our results indicate that patients with glaucoma tend to have lower levels of neuroprotective proteins and higher levels of neuroinflammatory proteins, similar to those observed in psychiatric, neurodegenerative and autoimmune diseases, indicating a potential link between these conditions and glaucoma pathogenesis.

Keywords: glaucoma, inflammation, neurodegeneration, proteomics, Olink

Introduction

Glaucoma is the most common optic neuropathy and the leading cause of irreversible blindness worldwide. On average, it affects 3.54% (2.09–5.82%) of the population aged 40–80 years.[1,2] Although there are many advanced treatment options: pharmacological, laser, or surgery, it is estimated that in 2040 glaucoma will distress 111.8 million people.[3] Glaucomatous neuropathy is caused by progressive neurodegeneration of the optic nerve and loss of retinal ganglion cells (RGCs) due to apoptosis,[4,5] which is observed as a characteristic pattern of morphological changes of the optic nerve head (ONH). It is primarily the consequence of a persistent increase in intraocular pressure (IOP); therefore, glaucoma treatment aims to reduce IOP. However, glaucoma can also develop in patients with normal IOP. Furthermore, glaucomatous optic neuropathy in some patients is known to progress despite implementing medications or surgical treatment. This suggests that some undefined underlying molecular mechanisms lead to glaucoma onset and progression, which is why the search for new therapeutic approaches is continually underway. Therefore, it is crucial to find biomarkers of glaucoma that would enable timely diagnosis and expand the understanding of disease pathogenesis. Recent articles have proposed that autoimmune, oxidative stress and inflammation may be involved in the pathogenesis of glaucoma.[6–8] Some studies have found elevated levels of growth factors or cytokines in aqueous humor and serum, suggesting that inflammation involved in their pathophysiology could thus serve as a biomarker for the pathogenesis,

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development, or severe course of glaucoma.[9–11] Khalef et al[9] reported increased levels of IL-6, IL-8, transforming growth factor β1, tumour necrosis growth factor α and serum amyloid A. Vidal-Villegas et al[6] found increased levels of IL-12, IL-13, and monocyte chemoattractant protein-1 (monocyte chemotactic and activating factor) in aqueous humor glaucomatous patients.

Neuroprotection is a therapeutic approach to preserve neural condition and utility.[5] This area is attracting growing attention in glaucoma as it refers to non-IOP-related actions that enable one to prevent or postpone the apoptosis of RGCs. This may be achieved with neurotrophic factors, which regulate the survival, migration, differentiation, proliferation, and maintenance of several classes of neurons. Few studies indicate a possible connection between brain-derived neurotrophic factor, nerve growth factor, ciliary neurotrophic factor, and glaucoma.[12–15]

This article overviews 92 inflammatory and neurotrophic factors in the Polish Caucasian glaucomatous patient population and in healthy controls. This work aims to detect agents that may serve as serum biomarkers for glaucoma and their link with other general diseases. Although most studies focus on selected biomarkers associated with glaucoma, this study is the first to investigate such a broad spectrum of inflammatory and neurodegeneration serum biomarkers.

Our study was performed on the basis of Bialystok PLUS Study - a cohort study designed to identify novel risk factors for lifestyle diseases, by investigating a broad spectrum of biological, social, emotional, and environmental factors. It is the only study of its kind in Poland and one of the few worldwide. The aim of the study is to invite 10,000 Bialystok residents aged 20–80 to participate in the study. Participants were randomly selected from the Bialystok City Council registry, using stratified sampling based on sex and age strata (10-year intervals) to ensure a representative gender and age distribution. All participants underwent a detailed and comprehensive health evaluation.

Materials and Methods

Bialystok PLUS Study

We have enrolled in a study 218 participants from the Bialystok PLUS study, a prospective population-based cohort providing broad information on the health of the residents of Bialystok, Poland.[16] Data were collected from 02/2019 to 02/2021.

The study population was divided into two subgroups based on the findings of the digital fundography. The glaucoma subgroup consisted of 26 subjects with diagnosed glaucomatous optic neuropathy (20 subjects with both eyes affected and 6 with one eye affected). The healthy individuals group consisted of 192 subjects without any pathological findings in fundography.

We have excluded from study population the individuals diagnosed with a history of psoriasis, rheumatoid arthritis, other types of inflammatory arthritis, systemic lupus, inflammatory bowel disease, systemic scleroderma, and fibromyalgia. Moreover, we have excluded from control group all individuals treated for eye diseases.

The clinical characteristics of the study population are available in Table 1.The study design was consistent with the Declaration of Helsinki and was reviewed and approved by the local ethics committee of the Medical University of Bialystok under the number: R-I-002/108/2016. The informed consent obtained from the study participants prior to study commencement.1

Laboratory Analyses

Biochemical assessments were conducted utilizing a Cobas c111 machine (Roche, Basel, Switzerland), while blood morphology was examined using a Mythic 18 machine (Cormay, Warsaw, Poland). Proteomic analyses were carried out employing the Olink Inflammation Panel (Olink Proteomics AB, Uppsala, Sweden). Following a minimum 8-hr fasting period, peripheral vein blood samples were collected. Plasma was obtained through centrifugation at 1810 G for 10 min at room temperature. Subsequently, immediate biochemical tests were conducted using an automated biochemical analyzer (Cobas c111 machine, Roche). Blood count analysis was performed on blood collected in an EDTA anticoagulant tube (Mythic 18 machine, Cormay).

For proteomic analysis, plasma samples were stored in a biobank at −80 ◦C, thawed at 4 ◦C, prepared, and sent to the Olink Proteomics laboratory (Uppsala, Sweden) for analysis. Biomarker levels were measured using the proximity extension assay (PEA) multiplexing method, which relies on quantitative PCR. This method provides relative levels of peptides expressed in NPX units (Normalised Protein eXpression) rather than absolute values of biomarker concentrations.

Table 1 Clinical Characteristics – Continuous Variables

	Healthy Controls		Glaucoma Subgroup		p value
	Median	Q1 - Q3 (IQR)*	Median	Q1 - Q3 (IQR)	
Age [years]	43.00	36.00–58.00 (22.00)	53.00	37.75–66.25 (28.50)	0.085
BMI [kg/m^2]	26.09	23.39–30.02 (6.63)	26.23	23.56–29.03 (5.47)	0.859
SBP [mm Hg]	121.00	112.25–133.00 (20.75)	122.25	112.88–134.75 (21.87)	0.910
DBP [mm Hg]	81.00	75.00–87.50 (12.50)	79.00	73.38–82.00 (8.62)	0.088
RBC¶ [10^6/μL]	4.70	0.44	4.66	0.35	0.579
PLT [10^3/μL]	227.00	193.00–256.25 (63.25)	221.50	176.25–255.25 (79)	0.420
WBC [10^3/μL]	5.70	4.90–6.60 (1.70)	6.25	5.30–8.05 (2.75)	**0.046**
LYM [10^3/μL]	1.80	1.60–2.10 (0.50)	1.80	1.63–2.28 (0.65)	0.594
GRA [10^3/μL]	3.50	2.90–4.20 (1.30)	4.15	3.50–4.83 (1.33)	**0.025**
MON [10^3/μL]	0.30	0.30–0.40 (0.10)	0.30	0.30–0.40 (0.10)	0.556
CRP (mg/L)	0.69	0.31–1.32 (1.01)	1.14	0.50–1.83 (1.33)	0.106
Fasting glucose [mg/dL]	99.00	92.00–105.25 (13.25)	100.50	91.25–109.75 (18.50)	0.407
HbA1c [%]	5.40	5.10–5.60 (0.50)	5.60	5.05–6.08 (1.03)	0.093
Total cholesterol [mg/dL]	184.50	160.00–212.50 (52.50)	172.00	152.50–198.50 (46.00)	0.093
HDL-C [mg/dL]	58.81	49.00–70.86 (21.86)	57.06	47.25–68.46 (21.21)	0.632
LDL-C [mg/dL]	120.15	96.30–146.20 (49.90)	112.05	91.88–134.65 (42.78)	0.213
TG [mg/dL]	88.50	63.00–131.25 (68.25)	85.00	77.25–139.75 (62.50)	0.492
TSH [uIU/mL]	1.67	1.16–2.28 (1.12)	1.67	1.24–2.52 (1.28)	0.752
FT3 (pg/mL)	5.22	4.77–5.61 (0.84)	5.39	4.72–6.27 (1.55)	0.328
FT4 (ng/mL)	16.66	15.15–18.28 (3.13)	16.90	15.44–18.37 (2.93)	0.303
Creatinine(μmol/L)	69.80	60.85–78.45 (17.60)	67.05	62.75–79.60 (16.85)	0.701

Notes: Compared with Welch's *t*-test, mean and standard deviation are reported instead median and interquartile range (IQR); other comparisons were made with Mann–Whitney *U*-test, The bold means that the data reached the level of statistical significance.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RBC, red blood cell count; PLT, platelet count; WBC, white blood cell count; LYM, lymphocyte count; GRA, granulocyte count; MON, monocyte count; CRP, C-reactive protein concentration; HbA1c - percent of the glycated A1c fraction of hemoglobin, HDL-C; high density lipoproteins concentration, LDL-C; low density lipoproteins concentration, TG; triglycerides concentration, TSH, thyroid stimulating hormone activity; fT3, free triiodothyronine concentration; fT4, free thyroxine concentration.

Digital Fundography

All participants underwent nonmydriatic fundography with a 35^O digital colour fundus camera (Canon CR-2 PLUS AF, New York, NY, USA). Digital colour images and autofluorescence images were taken for each eye. The image evaluation was performed by trained specialists (ŁL, MMK). This included an evaluation of the optic nerve, macula, and central vessels with their branches visible in field photography. The protocol for detailed evaluation of ONH included its dimensions, shape, colouring, vascularization, tilting, evaluation of neuroretinal rim and cup-to-disc ratio, presence of optic disc haemorrhages and assessment of parapapillary atrophy.

The diagnosis of glaucomatous optic neuropathy was based on characteristic optic disc changes observed on stereoscopic photographs, which was proposed as the best reference standard for disease diagnosis according to the European Glaucoma Guidelines.[17] To evaluate the damage to ONH, the Disc Damage Likelihood Scale (DDLS) was used.[18,19] ONH

with grade DDLS ≥6 was classified as glaucomatous. In addition, special attention was drawn to signs of focal damage to the optic nerve disc, such as optic disc hemorrhages, peripapillary atrophy, and the thickness of the retinal nerve fibre layer.[20,21] Fundography findings were coded per eye and summed to achieve binary information per patient. (Figures 1-4).

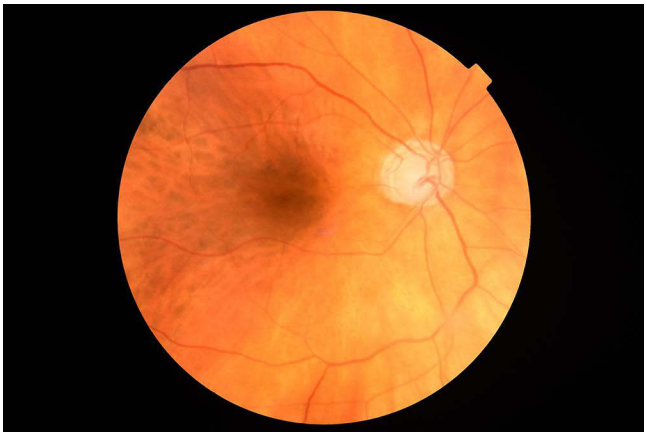

Figure 1 Funduscopic image of glaucomatous optic disc in 74-year female (right eye).

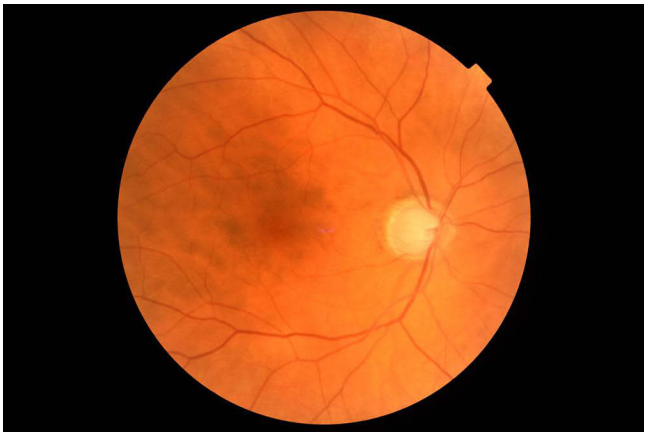

Figure 2 Funduscopic image of glaucomatous optic disc in 72-year male (right eye).

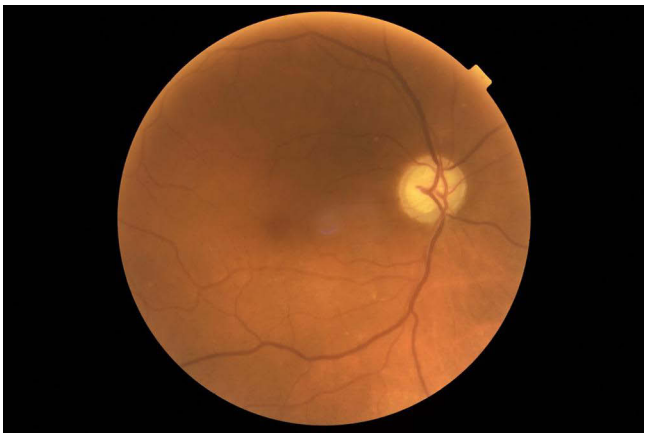

Figure 3 Funduscopic image of glaucomatous optic disc in 65-year female (right eye).

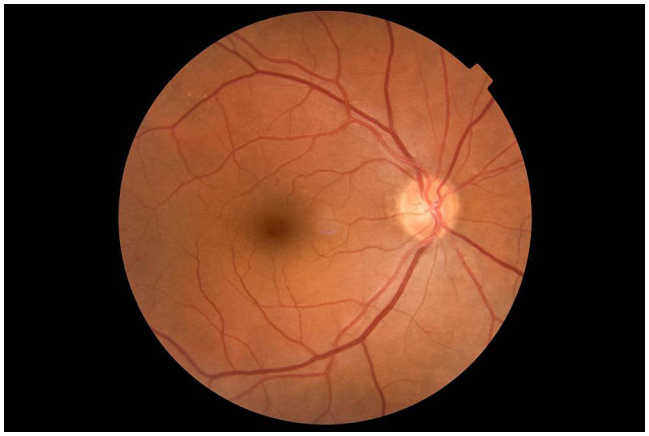

Figure 4 Funduscopic image of healthy optic disc in 61-year female (right eye).

Statistical Analyses

The Shapiro–Wilk test was performed on continuous variables. Subsequently, clinical characteristics were compared with Welch's *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for non-normally distributed continuous variables, and chi-square tests for categorical variables. Protein expressions are compared with Generalized Linear Model. All models were controlled after fitting. We assumed three models per protein: Model-1 - without covariate correction, Model-2 - with sex, age, and current tobacco smoking status correction and the final Model-3 with sex, age, current tobacco smoking status, diabetes mellitus, and hypertension correction. The statistical significance was established as $p < 0.05$. The R software was used to perform analyses.[22] All results are available in Supplement 1.

Results

Clinical Characteristics of Groups

Glaucoma patients, more frequently had diabetes ($p = 0.02$) and hypertension ($p = 0.02$) and also had higher counts of white blood cells ($p = 0.046$) and granulocytes ($p = 0.025$) than healthy controls. Detailed data are available in Table 1 and Table 2.

Serum Proteomics

In the final Model-3 patients with glaucoma had significantly lower serum expression of

IL-2Rβ (coefficient = −0.215, p = 0.005), TWEAK (coefficient = −0.146, p = 0.020), CX3CL1 (coefficient = −0.145, p = 0.021), CD6 (coefficient = −0.194, p = 0.025), CD5 (coefficient = −0.137, p = 0.026), LAP TGF-beta1 (coefficient = −0.163, p = 0.026), LIF-R (coefficient = −0.091, p = 0.035), TRAIL (coefficient = −0.128, p = 0.040), NT-3 (coefficient = −0.121, p = 0.044), CCL23 (coefficient = −0.168, p = 0.048) and significantly higher expression of IL-22Rα1 (coefficient = 0.294, p = 0.007).

Detailed data are available in Table 3.

Table 2 Clinical Characteristics – Categorical Variables

Variable	Glaucoma	Healthy	p-value
Sex = Female n(%)	14 (53.8)	112 (58.3)	0.64
Current tobacco smokers n(%)	8 (30.8)	33 (17.2)	0.10
Diabetes* n(%)	5 (19.2)	12 (6.3)	**0.02**
Hypertension history n(%)	11 (42.3)	40 (20.8)	**0.02**

Notes: *Based on the ADA guidelines and diabetes history.[23] The bold means that the data reached the level of statistical significance.

Table 3 Serum Proteomics – Olink Inflammation Panel

Protein	UniProt ID	Model-1 Coefficient	Model-1 pvalue	Model-2 Coefficient	Model-2 pvalue	Model-3 Coefficient	Model-3 pvalue
IL-2Rβ	P14784	−0.207	0.005	−0.204	0.007	−0.215	**0.005**
IL-22Rα1	Q8N6P7	0.301	0.004	0.284	0.008	0.294	**0.007**
TWEAK	O43508	−0.170	0.006	−0.153	0.013	−0.146	**0.020**
CX3CL1	P78423	−0.124	0.052	−0.165	0.009	−0.145	**0.021**
CD6	Q8WWJ7	−0.187	0.025	−0.197	0.021	−0.194	**0.025**
CD5	P06127	−0.112	0.061	−0.136	0.025	−0.137	**0.026**
LAP TGF-beta1	P01137	−0.132	0.066	−0.136	0.063	−0.163	**0.026**
LIF-R	P42702	−0.050	0.247	−0.076	0.077	−0.091	**0.035**
TRAIL	P50591	−0.083	0.190	−0.137	0.027	−0.128	**0.040**
NT-3	P20783	−0.119	0.042	−0.128	0.030	−0.121	**0.044**
CCL23	P55773	−0.130	0.123	−0.170	0.044	−0.168	**0.048**

Note: Bold text, statistical significance.

Abbreviations: IL-2Rβ, Interleukin 2 receptor subunit beta; IL-22Rα1, Interleukin-22 receptor subunit alpha 1; TWEAK, TNF-related weak inducer of apoptosis; CX3CL1 - C-X3-C motif chemokine ligand 1; CD6, Cluster of differentiation 6; CD5, Cluster of differentiation 5; LAP TGF-beta1 - Latency associated peptide transforming growth factor beta-1; LIF-R, Leukemia inhibitory factor receptor; TRAIL, TNF-related apoptosis-inducing ligand; NT-3, Neurotrophin-3; CCL23, CC chemokine 23.

Discussion

Blood Smear Differences

We reported a higher total count of white blood cells and granulocytes in the blood of glaucoma patients compared to healthy individuals. The results confirm peripheral blood smear disturbances that have been widely described in the literature.[24–28] Patients with various types of glaucoma tend to have a higher neutrophil count, generally reported to have a higher neutrophil-to-lymphocyte ratio. We have not measured the fractions of granulocytes, although our findings probably depend on the neutrophil count, as they are the main fraction of granulocytes.[24–28]

Diabetes Mellitus and Hypertension

Our research found a significantly higher occurrence of diabetes in glaucoma than in the control group. Literature suggests that diabetic patients are nearly 1.5 times more likely to develop glaucoma than non-diabetic ones.[29] Moreover, the risk of glaucoma increases by 5% each year of diabetes. Diabetes' impact on glaucoma development has been studied thoroughly. The current theory about the association between these two diseases is that diabetes leading to microvascular damage and vascular dysregulation of the retina and the optic disc is causing glaucomatous damage to the optic nerve head. Diabetes also may disrupt the trabecular meshwork function, thereby elevating IOP.[30,31]

We have also shown that elevated blood pressure (BP) was significantly more often in the glaucoma group. These results coincide with the literature data – when untreated – hypertension results in a greater risk for open-angle glaucoma.[32] Meta-analyses show a risk ratio of 1.69 (95% CI 1.50 to 1.90) in the hypertension group.[33]

IL-2Rβ

Interleukin 2 receptor subunit beta, also called IL-2Rβ or CD122, is a subunit common to Interleukin 2 receptor (IL-2R) and Interleukin 15 receptor (IL-15R), playing an essential role in the human immune system, taking part in the process of proliferation, activation, differentiation, and survival of T-cells, altogether maintaining the autoimmune homeostasis. Being shared with mentioned cytokine receptors, it belongs to the hematopoietin receptor family, also called type I cytokine receptor superfamily. IL-2Rβ, along with alpha (IL-2Rα/CD25) and gamma (γc/CD132) chains, forms heterotrimeric IL-2R complex (IL-R2αβγc) binding Interleukin 2 (IL-2) with high affinity.[34–36]

IL-2Rβ is constitutively expressed on the surface of resting or activated natural killer cells (NK), cytotoxic T cells (Tc), regulatory T cells (Treg), B cells, macrophages, monocytes, eosinophils, and dendritic cells (DC).

Furthermore, concentration of subunit correlated negatively with common biomarkers of inflammation: C-reactive protein (CRP), and procalcitonin (PCT), as well as with acute physiology and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores, reflecting severity of the disease. Some authors draw attention to IL2RB gene (encoding IL-2Rβ) as a potential biomarker and target for novel sepsis therapy.[37–41]

The role of expression and active signalling of IL-2Rβ in ophthalmology has been pretty well studied, but mainly in the context of other diseases (dry eye disease, ocular sarcoidosis, ocular malignancies) than glaucoma.[42–46]

Elevated concentration of soluble form of IL-2R (sIL-2R) or IL-2Rβ (sIL-2Rβ) can be detected in serum of individuals in course of inflammatory or pseudoinflammatory conditions, which corresponds to its fundamental role. In general adult population study, Alende-Castro et al distinguished potential factors influencing serum sIL-2R concentration.[47] Individuals over 65 years of age, males, smokers, individuals with atopy, metabolic syndrome, or a history of ischemic heart disease presented higher serum values of the receptor than the standard reference range.

Elevated serum/plasma concentrations of sIL-2R and sIL-2Rβ are observed in the course of many systemic conditions. Cai et al reported increased sIL-2R plasma levels in patients with Diabetes Mellitus type 2 (DM2).[48] Furthermore, the authors noted a negative correlation between plasma sIL-2R concentration and high-density lipoprotein (HDL), low-density lipoprotein (LDL) and cholesterol levels. Interestingly, sIL-2R seems to be a valuable biomarker for the assessment of sarcoidosis diagnosis, chronicity, remission, and treatment monitoring.[49–53] Furthermore, elevated serum/plasma concentration of sIL-2R/sIL-2Rβ and polymorphisms of IL2RB gene have also been associated with depression, Parkinson's disease, and several other autoimmune or cardiovascular diseases.[54–71]

Interestingly, there is a lack of evidence on possible causes of lowered serum sIL-2R and sIL-2Rβ.

Available serum proteomic results made on glaucoma patients are opposite to our findings. Yang et al reported raised mean concentration of sIL-2R in the serum of patients with primary open-angle glaucoma (POAG) and normal pressure glaucoma (NPG), compared to healthy individuals.[72] Interestingly, authors did not observe aberrations in IL-2 levels among control and study groups. Contrary to these findings, Huang et al demonstrated comparable serum sIL-2R and IL-2 concentrations in healthy controls and patients with various severity of POAG.[73] Whereas in our study, the participants with glaucomatous neuropathy presented lower serum expression of sIL-2Rβ compared to the control group. However, we need to underline one essential difference in our research model. In their studies, Yang et al and Huang et al detect a complex of sIL-2R (containing alpha, beta, and gamma chains), while we measured the concentration of its single beta subunit.[72,73] Our approach seems to deliver more detailed and concretized data about the potential role of the immune system in the pathogenesis of glaucoma.

Upon activation, natural killer (NK) cells could undergo surface receptor consumption through processes such as receptor internalization, degradation, or regulation of receptor gene expression. We speculate that decreased sIL-2Rβ serum levels could potentially correspond with greater subunit utilization by activated NK and T cells, underlining the systemic nature of the disease.[74]

IL-22Rα1

Interleukin 22 Receptor Subunit Alpha 1 (IL-22Rα1) is a long-chain transmembrane protein, representative of the type II cytokine family, highly specific for Interleukin-22 (IL-22), Interleukin-20 (IL-20), and Interleukin-24 (IL-24). Unlike IL-22, alpha 1 subunit secretion is highly tissue-specific and expressed only by certain nonimmune epithelial cells, fibroblasts, hepatocytes, and pancreatic stellate cells, but also tissues of the digestive and respiratory systems. Interestingly, IL-22Rα1 expression was also discovered in the ocular surface of mice and trabecular meshwork cells.[75,76] IL-22 receptor (IL-22R) consists of IL-22Rα1 and IL-10Rβ subunits. A high-affinity initial binding of IL-22 to IL-22Rα1 is followed by recruitment of IL-10Rβ to stabilise the ligand/receptor complex. The heterodimeric receptor mediates IL-22-activated downstream signalling through JAK/TYK2/STAT3, NF-κB, MAPK, and Akt pathways, playing an essential role in epithelial integrity and homeostasis, stimulation of tissue repair and resistance against extracellular pathogens.[77–79]

In systemic disorders, the increased expression of IL-22Rα1 constitutes an essential part of the neuroprotective cascade induced by IL-22 during many liver conditions. IL-22Rα1 mediated signalling attenuates fibrosis caused by increased activity of hepatic stellate cells, inhibits cell apoptosis, and promotes mitosis of the hepatocytes.[80]

On the other hand, IL-22Rα1 overexpression may become a valuable marker and potential treatment target for certain rheumatoid diseases.[81] Interestingly, overexpression of IL22RA1 was also associated with psoriasis, and therefore inhibition of Il-22Rα1 signalling, both on genetic and proteomic levels, may constitute a novel therapy for the disease.[82,83]

Regarding genetics, IL2RA1, the gene encoding IL-22Rα1, seems to be an important target for future diagnostic and therapeutic processes of malignant conditions. Zhang et al identified 11 types of cancer associated with upregulated transcript levels of IL22RA1.[84] The authors noted that patients' poor survival was linked to greater gene expression. IL22RA1 polymorphisms were also linked with chronic rhinosinusitis occurrence and severity.[85,86]

Concerning ocular conditions, increased expression of Il-22Rα1 by retinal glial Müller cells was reported in the posterior segment of mice globes with experimentally induced autoimmune uveitis. IL-22-induced signalling inhibits pro-inflammatory and promotes anti-inflammatory pathways, improving the survival of retinal ganglion cells (RGC) and enhancing the neurotrophic and neuroprotective effects of upregulated glial cell-derived neurotrophic factor and nerve growth factor.[87] Contrary to these findings, Lindborg et al suggested that IL-22 secreted by neurons (RGCs or other neuronal cells) may restrict axon development through paracrine signalling via immune or glial-expressed IL-22Rα1.[88] IL-22Rα1 was previously described as a potentially important factor in pathogenesis of DR and fungal keratitis, but there is a lack of evidence on its role in glaucoma pathogenesis.[79,89,90]

Our study shows the increased serum expression of IL-22Rα1, which is indirectly consistent with the research conducted by Zhao et al.[91] The overexpression of IL22RA1 in human Tenon's capsule fibroblasts of individuals with glaucoma is related to intensified cell migration, proliferation, fibrosis, and autophagy, modulated by NR_003923 – long noncoding RNA (lncRNA). Summarized effects of increased activity of IL22RA1 and NR_003923 were associated with glaucoma progression. The above findings may be a valuable link to understanding the true pathophysiology of glaucoma, developing novel therapeutic targets, and improving glaucoma surgery outcomes.[89,92]

TWEAK and TRAIL

Tumor necrosis factor-related weak inducer of apoptosis (TWEAK) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) are members of the tumor necrosis factor superfamily (TNFSF). TNFSF members are involved in inflammatory and autoimmune pathways, including nervous system diseases.

TWEAK is a cytokine regulating multiple processes such as cell survival and proliferation, angiogenesis, and induction of other cytokines. It is expressed in multiple tissues, on immune cells and endothelial cells, and it arises as soluble TWEAK (sTWEAK) after cleavage. Membrane-bound as well as soluble forms of TWEAK act via receptor-fibroblast growth factor-inducible protein 14 (Fn14), activating the ERK, PI3K/Akt, and NF-κB signalling pathways.[93–95]

Interestingly, in rodents, the Fn14 expression in excitatory thalamocortical neurons of the dorsal lateral geniculate nucleus is induced by the vision expression signals from the retina. The lack of Fn14 provides physiological deficits and changes in synaptic morphology.[96] Actions mediated by TWEAK-Fn14 seem to be important in microglial-regulated postsynaptic remodelling in the dorsal lateral geniculate nucleus.[97]

Considering eye diseases, the TWEAK-Fn14 pathway role was reported to be important in retinal pathologies – mainly neovascularization.[98–100] Current evidence shows only local effects of TWEAK overexpression, which is difficult to match with lowered serum TWEAK expression that we report.

Serum/plasma levels of sTWEAK were reported in multiple inflammatory and autoimmune diseases. Maarouf et al reported statistically higher sTWEAK serum levels in patients with multiple sclerosis than in healthy controls, especially during relapses of the disease.[101]

Karadag et al reported significantly higher plasma concentration of sTWEAK in patients with bipolar depression than in healthy controls, but not between patients with major depression and healthy controls or bipolar depression patients.[102] Contrary to these findings, Schmidt et al and Melin et al reported decreased sTWEAK in patients with depression compared to healthy controls, although research conducted by Melin et al was conducted on patients with depression and type 1 diabetes.[103,104]

In our results, we report lowered sTWEAK in glaucoma patients compared to the controls, which could be evidence of a link between glaucoma and depression, especially since this type of link has been previously established by Gubin et al who reported that the severity of depression is positively related to RGCs loss.[105]

Multiple publications report lowered sTWEAK as a biomarker of atherosclerosis-associated diseases, which could be a possible link with the atherosclerotic theory of glaucoma.[106–110]

TRAIL is a cytokine that plays an important role in regulating innate and adaptive immune systems. Similarly to TRAIL and other TNFSFs, it can be expressed as a trans-membrane protein (ie on epithelial, mucosal cells, neurons, and oligodendrocytes) and as a soluble form (sTRAIL). TRAIL could act via multiple receptors – DR4 and DR5 to induce caspase-dependent apoptosis, DcR1, DcR2, and osteoprotegerin to activate the NFκB pathway.[93,111,112]

TRAIL also acts as a suppressor of autoimmunity via inducing Th1 cells apoptosis, which changes the ratio of Th1/Th2 cells because Th2 cells are more resistant to TRAIL-induced apoptosis. Moreover, it promotes the growth of Treg cells.[113,114] Regarding our results, the lowered serum sTRAIL expression in glaucoma patients seems to be difficult to interpret because, in the available evidence, patients with glaucoma tend to have lower concentrations of the circulating Th1 cells and increased concentrations of Tregs – what theoretically should be supported with TRAIL overstimulation.[115,116] Although our results are based only on circulating sTRAIL, thus we cannot evaluate trans-membrane TRAIL expression on cells. Unfortunately, we did not assess circulating levels of Th1, Th2, and Treg cells to compare with the available evidence.

In the context of eye diseases, TRAIL seems to be important in ophthalmic oncology – also as an additional treatment to traditional medications. It also acts as an antiangiogenic cytokine, which might be crucial in neovascular retinal diseases such as proliferative diabetic retinopathy (PDR). Interestingly, patients with PDR have decreased expression of sTRAIL in the conjunctival sac fluid. On the other hand, TRAIL might also have a dark side – mutations in DR4 receptor genes and low serum levels of DcR1 receptor provide a higher risk for age-related macular degeneration development.[111]

Serum/plasma proteomic research also shows a possible connection between sTRAIL concentration and autoimmune and cardiometabolic diseases. Moreno et al's findings have not shown differences in serum sTRAIL concentration between patients with MS and healthy individuals, but they have noticed significant sTRAIL decrement during MS relapses.[117] They suggested the sTRAIL concentration decrement could relate to enhanced survival of pathogenic T lymphocytes.

Interestingly, Cheng et al reported that serum sTRAIL concentrations positively correlate with total cholesterol and LDL, while Mori et al have found a negative correlation between serum sTRAIL and coronary artery disease severity.[118,119]

Regarding our results, lowered sTRAIL serum expression might be a supporting argument for the autoimmune, neuroinflammatory, and atherosclerotic pathways in glaucoma development.

CX3CL1

C-X3-C motif chemokine ligand 1 (CX3CL1), known as fractalkine, is a chemokine mainly expressed by neurons. It has an interesting profile of action because it could act pro- and anti-inflammatory. Moreover, it is a chemoattractant for immune cells. It is expressed by microglia, natural killer cells, dendritic cells, monocytes, T cells, and macrophages. Fractalkine is probably involved in pathways of neuroinflammatory diseases.[120] Animal models showed that fractalkine signalling is important in glaucoma RGCs protection and reduction of inflammatory cytokines in diabetic retinopathy.[121,122] Interestingly, inhibition of fractalkine signalling via blockade of the fractalkine receptor – CX3CR1 improved the recovery of neurological function in the rat model of spinal cord injury.[123]

Begum et al reported increased serum expression of fractalkine in athletes with sport-related traumatic brain injury, hypothesizing that fractalkine increases microglia activity in response to neurotoxicity and protects them from apoptosis.[124] In clinical studies on patients with Alzheimer's, serum expression of fractalkine was decreased and correlated with the level of cognitive impairment.[125]

In the context of our study, the decreased serum expression of fractalkine in glaucoma patients could be interpreted as reduced neuroprotective abilities and a possible link with Alzheimer's disease.

CD5 and CD6

Cluster of differentiation 5 (CD5) is a transmembrane protein expressed mainly on the surface of T-cells and B-1a cells. Expression of CD5 is upregulated during T-cells' strong activation. Due to this, CD5 remains a good immunohistochemical marker for T-cells, although less sensitive than the currently used CD3. For this reason, CD5 should be considered an

indirect marker of T lymphocyte activity, including autoimmune activity, consistent with the autoimmune theory of glaucoma development.[126]

It is suggested that CD5 negatively regulates TCR signalling from the onset of T-cell activation and therefore plays a key role in regulating cell survival and apoptosis. It could even inhibit the development of autoimmune reactions or cancer.[127]

In addition, circulating, soluble forms of CD5 (sCD5) could be found in healthy individuals' serum in the pico/nanomolar range due to proteolytic cleavage following lymphocyte activation. Furthermore, elevated levels of soluble CD5 (sCD5) have been detected in the serum of patients with various autoimmune and inflammatory conditions (Sjogren syndrome, septic syndromes, atopic dermatitis, and various rheumatoid diseases).[128–133] However, the exact importance of the release of sCD5 following lymphocyte activation remains unknown, and it needs further research.[133]

Due to those mentioned above, we could speculate if sCD5 and CD5 expression levels inhibit autoimmunity and inflammation development. Our study shows a decreased serum expression of CD5 in glaucoma patients, supporting this notion.

In our research, we have also found a decreased soluble CD6 serum expression. Literature has no direct association between CD6 expression and glaucoma or neurodegeneration.

We speculate that decreased CD6 expression in the glaucoma group could suggest inhibited T-cell activation because of counterregulatory, anti-inflammatory mechanisms, similar to CD5.

LAP TGF-beta1

Transforming growth factor-beta 1 (TGF-β1) is the multifunctional polypeptide cytokine that takes part in the regulation of cell proliferation, growth, differentiation, and apoptosis, especially in bones but not only TGF-B1 is secreted as a latent form as a dimer consisting of latency-associated peptide (LAP) and TGF-β1.

Smag proteins inhibit TGF-β1 signalling. This counter-regulation plays an important role in eg inflammatory bowel disease, fibrosis, and cancer (especially colorectal cancer).[134]

The association between increased expression of proteins from the transforming growth factor beta family and glaucoma and DR is well established. Few studies show elevated TGF1 alpha and beta concentrations in aqueous humour and vitreous fluid. TGF-β1 plays a crucial role, eg in scar formation after glaucoma surgery.[106]

TGF-β1 is also associated with the pathogenesis of pseudoexfoliation glaucoma since it activates TGF-βpathway.[135]

In neuroinflammation and neurodegeneration, TGF-β1 is linked with possible Alzheimer's disease pathogenesis. TGF1 beta is involved in neuronal development and synaptic plasticity as a trophic factor. Impaired TGF-β1 signalling results in increased Amyloid β deposition and enhanced neurodegeneration.[136]

Chronic inflammation and ageing-associated processes reduce TGF-β1/Smad signalling, resulting in cytotoxic activation of microglia and further neurodegeneration.

High levels of TGF-β1 have been associated with increased production of extracellular matrix components, such as fibronectin and collagen, which can lead to excessive deposition and remodelling of the extracellular matrix in the trabecular meshwork and optic nerve head.

In our glaucoma study group, we have found that a decreased expression of LAP-TGFβ-1 seems reasonable – higher free TGFB1 expression in glaucoma patients results in a decreased propeptide expression due to increased dissociation of TGFB1.

Soluble LIF-R

Leukemia Inhibitory Factor Receptor Complex (LIF-R) is a receptor for Leukemia Inhibitory Factor (LIF) and other cytokines such as Oncostatin M, Cardiotrophin-1, Ciliary Neurotrophic Factor, Cardiotrophin-Like cytokine. LIF-R expressed on cell membrane provides a signalling pathway for mentioned cytokines, but interestingly soluble LIF-R (sLIF-R) plays a different role. sLIF-R binds circulating LIF and inhibits signal transduction from LIF to membrane-bound LIF-R. It is hypothesized that sLIF-R prevents the generalized action of LIF, allowing LIF to bind only to local receptors.[137]

How sLIF-R interacts with other ligands for membrane-bound LIF needs to be clarified. Available evidence reports only interaction between Oncostatin M and soluble gp130 unit, which is part of the LIF-R complex. High concentrations of soluble gp130 could attenuate LIF and Oncostatin M mediated proteoglycan resorption in cartilage tissue.[138]

LIF and other LIF-R receptor ligands were reported as neuroprotective proteins for retinal cells in animal models.[139–141]

Referring to our results, decreased sLIF-R serum expression in glaucoma patients could result in generalized and stronger action of LIF and probably other LIF-R ligands, which could result in intensified neuroprotection. However, we have not noticed a significant difference in LIF and Oncostatin M expression between glaucoma patients and healthy individuals. Unfortunately, expressions of other ligands were not investigated in our research. sLIF-R serum expression was not examined for diseases caused by inflammation or neurodegeneration. Thus, possible connections with glaucomatous optic nerve degeneration are difficult to be assessed.

NT-3

Neurotrophin-3 (NT3) is a member of the neurotrophin family, which are proteins essential for appropriate nervous system functioning. They play an important role in neuron development, survival, and synaptic plasticity.[142] Interestingly, NT-3 is not a tissue-specific protein, and its highest NT-3 RNA expression was reported in female reproductive system tissues.[143]

The available literature referring to the involvement of neurotrophins in glaucoma pathophysiology mainly focuses on the failure of axonal transport in RGCs, which potentially results in disturbed retrograde transport of neurotrophins from target cell to RGC soma, and anterograde transport of neurotrophin receptors from RGCs soma to axon termini.[144]

Neurotrophins interact with tropomyosin receptor kinase (Trk) receptors A, B, and C with different binding affinities. The most selective Trk receptor for NT-3 is TrkC. All neurotrophins could also influence processes of survival/apoptosis via p75 - "death receptor". Furthermore, p75 receptor expression regulates Trk activities by determining when NT-3 binds with TrkA (which typically has a lower affinity to bind NT-3 than TrkC).[145] Interestingly, TrkA and TrkC could trigger neuron death in NT-3 deficient environment, and adding NT-3 could prevent that process.[146]

Referring to The Human Protein Atlas and the transcriptome atlas of the adult human retina, TrkC receptor RNA is expressed in Rod photoreceptors, Muller glia, bipolar cells, horizontal cells, and RGCs.[147,148]

An optic nerve transection model showed that expression ratios between Trk receptors mRNA in RGCs change over time after cell damage.[149] Results from another study show that a change in Trk mRNA expression does not have to be accompanied by a change in protein expression. TrkC mRNA and protein expression decline in the described IOP-induced injury model but TrkB mRNA declines without change in TrkB protein expression after injury.[150] Ogłodek et al reported that NT-3 serum concentrations were lower in patients with depression than in healthy controls and were inversely related to the severity of symptoms, which is further supported by the results by Gubin et al, mentioned above.[105,151]

Concluding both publications, we could hypothesise that NT-3 may be a link between glaucoma and depression.

Our findings of reduced serum expression of NT-3 in glaucoma patients could be a new piece in the glaucoma pathophysiology puzzle, in addition to pointing to a probable link with depression.

CCL23

CC-chemokine ligand 23 (CCL23) cytokine, which mechanisms of action are poorly described due to the lack of this cytokine in rodent models. In research on human diseases, CCL23 was described mainly in the context of oncological and haematological diseases.[152] Shih et al reported that CCL23 suppresses the production and release of polymorphonuclear leukocytes and monocytes, which might explain why glaucoma patients in our research had increased granulocyte count compared to the healthy controls.[53]

In the context of inflammation and neuroinflammation-driven pathology in diseases, current proteomic reports showed only increased levels of CCL23 in patients. Dallas Heart Study Report showed elevated plasma levels of CCL23 were associated with coronary artery calcium.[153] At the same time, Faura et al found that higher plasma levels of CCL23 predict the progression of mild cognitive impairment to Alzheimer's disease.[154] Therefore, based on current evidence, lowered serum expression of CCL23 could be only linked with increased granulocyte count, which the main subgroup – neutrophils were reported to be increased in all types of glaucoma, as we described above.

Limitations

The main limitation of our study is using quite a limited evaluation of the optic nerve head based only on fundography, which is an imperfect diagnostic method. Advanced imaging solutions would make the diagnosis of glaucoma more reliable; however, several studies have shown that DDLS is strongly correlated with the degree of glaucomatous visual field damage and other diagnostic modalities. Moreover, according to the literature, the DDLS system has a good interobserver agreement (Cohen's kappa 0.902),[19] and research suggests that DDLS is a more accurate method of detecting and monitoring glaucomatous disc changes compared to other scales.[155,156] Therefore, DDLS is recommended for glaucoma detection schemes and referral guidelines. Another limitation is the relatively small study group; however, the number of glaucoma subjects reflects the general population.

Conclusion

In summary, our research indicates that patients with glaucomatous neuropathy tend to have lower levels of neuroprotective proteins and higher levels of neuroinflammatory proteins. However, identifying a single serum biomarker as a reliable tool for diagnosing and monitoring glaucomatous neuropathy seems to be impossible at this stage of knowledge. Future, more comprehensive research should focus on identifying a certain risk phenotype associated with glaucoma, including specific pro-inflammatory and neuroprotective factors. Additionally, similar proteomic changes have been observed in psychiatric, neurodegenerative, and autoimmune diseases, indicating a potential link between these conditions and glaucoma pathogenesis. Further studies are needed to explore this possible connection and develop new therapeutic strategies for glaucoma and possibly related neurodegenerative disorders. Proteomics appears to be a promising avenue in searching for new glaucoma medications. Interestingly, in this context, only the proteome of retinal cells has been studied so far.[157] Therefore, our work provides potentially new insights from the perspective of the peripheral proteome.

Disclosure

The authors report no conflicts of interest in this work.

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