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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**EPIDEMIOLOGY, REGIONAL HEMODYNAMICAL
FEATURES AND CLINICAL-IMMUNOLOGICAL
EXAMINATIONS OF OCULAR TOXOPLASMOSIS**

Specialty: 3202.01 – Epidemiology
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RELEVANCE AND RESEARCH DEGREE OF THE SUBJECT

Toxoplasmosis is a widespread parasitic disease belonging to the group of zoonoses. This infection can be found everywhere. The number of people infected with toxoplasmosis reaches 1.5 billion people in the world ^{1, 2}. Toxoplasmosis is widespread in the Republic of Azerbaijan, but research on this invasion was conducted 20-30 years ago. Although the proportion of people infected with toxoplasmosis and with clinically significant manifestations of the disease is not high (5-7% of the total number of patients with symptomatic forms of toxoplasmosis), they are younger, more socially active individuals, which raises questions about the disease. This group includes patients with chorioretinitis, patients with chronic intoxication, patients with lymphadenitis, pregnant women at risk of developing congenital toxoplasmosis in the fetus ^{3,4}. One of the most essential manifestations of toxoplasmosis is damage to the visual organ in the form of chorioretinitis in immunocompetent individuals. It has been recently proved that toxoplasmosis is considered to be one of the leading causes of chorioretinitis in one in three patients with chronic toxoplasmosis. However, the factors that determine the likelihood of developing eye damage during toxoplasmosis and the degree of manifestation of eye pathology remain unclear. Information on changes that occur in the markers, which characterize the immune system in patients with ocular toxoplasmosis, is limited to incomplete information on congenital toxoplasmosis and role of the HLA system

¹ Zemlyansky O.A. (2015). Actual principles of diagnosis, treatment and prevention of toxoplasmosis during pregnancy. *Medical Parasitology and Parasitic Diseases*, 3, 13-17.

² Shkarin V.V., Borodina V.A. (2017). Features of the epidemiology of protozoa in combination with infectious diseases and helminthiases. *Infectious Diseases. News. Treatment. Training*, 5, 39-49.

³ Burnett A. J., Shortt S. G., Isaac Renton J. et al. (2017). Multiple cases of acquired toxoplasmosis retinitis presenting in an outbreak. *Ophthalmology*, 6(105), 1032-1037.

⁴ Dolgikh T.I., Zapariy N.S. (2017). Antibacterial activity of granular carbon sorbents. *Pathological Physiology and Experimental Therapy*, Moscow, 3, 76-82.

(some antigens act as receptors for toxoplasmosis, facilitating their fixation and entry into the cell)^{5, 6}. The ophthalmological view of the fundus is similar in chorioretinitis of different etiologies. In addition, the characteristics of the immune response to eye damages reveal that serological and molecular-genetic tests of peripheral blood carried out for etiological verification of chorioretinitis are relatively less significant^{7, 8, 9}.

The complexity of the treatment of ocular toxoplasmosis is that severe impairment of visual function is not always associated with obvious general disorders, and therefore the choice of optimal antibacterial therapy should be based not only on clinical symptoms but also on specific diagnostic criteria for infection.

Thus, by considering high level of cases of infection to toxoplasmosis among world population, and as well as observation of the cases of infection among the population of the Republic of Azerbaijan and realization of the researches in connection with infection of toxoplasmosis in our country 25-30 years ago, it is necessary to improve the diagnostics and treatment of patients with chronic toxoplasmosis based on development of algorithm of assessment of the risk of damage of visual organ and scientific-based instructions for carrying out of prevention of development of lesion of toxoplasmosis etiology with medicine.

⁵ Filip M., Dragne C., Filip A., Măgureanu M. (2016). Toxic anterior segment syndrome. *Oftalmologia*, 50 (4), 27—29.

⁶ Paola P., Massimo A., La Cava M. (2016). Endogenous uveitis: an analysis of 1,417 cases. *Ophthalmologica*, 210, 234.

⁷ Panova I.E., Drozdova E.A. (2014). Uveitis: A Guide for Physicians. *Medical Information Agency*, Moscow, 144.

⁸ Pokrovsky V.V., Ermak T.N., Belyaeva V.V., Yurin O.G. (2017). The spread of toxoplasmosis and sarcocystosis in humans and animals, legal regulation of the organization of the fight against them. *Russian Parasitological Journal*, Moscow, 1, 35-41.

⁹ Avdeeva M.G., Konchakova A.A., Andreeva E.I. (2017). Opportunistic infections and immunological deficiency in women with ineffective IVF cycles. *Epidemiology and Infectious Diseases*, Moscow, 4, 183-189.

Object of research. 148 patients aged from 5 to 45 years were affected by toxoplasmosis of the eyes. 66 sick men, 82 sick women. 215 eyes were examined. Control group: 48 healthy people. According to the issues raised, depending on the mechanism of infection, the main group (148 people) was divided into 2 subgroups: patients with congenital toxoplasmosis - 65 patients, patients with acquired toxoplasmosis - 83 patients

Research purpose. Features of clinical-immunological examinations, regional hemodynamics, and epidemiology of ocular toxoplasmosis were studied.

Research objectives

1. To conduct prospective clinical-laboratory and instrumental-diagnostic examinations of patients with ocular toxoplasmosis.

2. To study the clinical and epidemiological features of patients with ocular toxoplasmosis.

3. To examine hemodynamic indications in the vessels of the visual organ in the context of eye damage caused by toxoplasmosis.

4. To study the changes in the basic indicators of cellular and humoral immunity in patients with ocular toxoplasmosis.

5. To give proposals on optimization of methods of diagnosis, treatment and prevention of damage to the visual organ caused by toxoplasmosis.

Research methods. A number of modern examination methods, including clinical, epidemiological, parasitological, immunological, statistical, etc. methods were used in the complex researches conducted.

The main provisions of the defense:

- Clinical and immunological characteristics of ocular toxoplasmosis;
- The clinical course of ocular toxoplasmosis is closely related to the nature of hemodynamic changes in the vessels of the eye and orbit;
- Optimization of diagnosis of ocular toxoplasmosis based on the study of clinical, regional hemodynamic, immunological, and epidemiological features.

Scientific novelty of the research:

- For the first time in Baku, clinical-epidemiological and instrumental-diagnostic examinations of patients with ocular toxoplas-

mosis were performed.

– It was found out that hemodynamic parameters recorded by ultrasound dopplerography are important criteria in the diagnosis of chorioretinitis and are considered promising in terms of studying the pathogenesis of the proliferative process in the tissues of the eye and substantiating the occurrence of focal reactions.

– Immunological features of eye damage motivated by toxoplasmosis were revealed. It was revealed that in patients with posterior toxoplasmosis uveitis in the context of general lymphopenia, a cellular and humoral specific immune response to toxoplasmosis is formed, as evidenced by the results of skin and focal tests with toxoplasmosis, the formation of specific IgM, IgG antibodies.

– The predominance of the number of cells with early – CD25 / CD95 (1.83 ± 0.21) and especially late - CD71 / CD95 and HLA-DR / CD95 (2.52 ± 0.34 ; 4.02 ± 0.49 , respectively) positive activation markers over the number of cells expressing negative activation markers, as well as an increase in the level of interferon-gamma in the blood (24.31 ± 4.6) are new data.

– Measures for early diagnosis, treatment and prevention of ocular toxoplasmosis were developed. The uses of azithromycin and trimethoprim / sulfamethoxazole in the treatment of ocular toxoplasmosis were compared.

Practical significance of the research. The identified clinical and immunological features of ocular toxoplasmosis are of practical importance for ophthalmologists in the early diagnosis of a specific process in the eye. The identified features of epidemiological, hemodynamic and immunological tests allow for timely verification and optimization of the diagnosis of toxoplasmosis of the eyes. Significant changes in the basic parameters of the immune cell ring in ocular toxoplasmosis: a significant reduction in the relative and absolute number of T-helpers and a decrease in the immunomodulatory index are key factors. Disorders manifested by an increase in the concentration of IgM antibodies in the humoral ring of immunity have been confirmed. Immunosuppression associated with toxoplasmosis plays a vital role in the development of organ and systemic damage in patients, as well as a factor in the development of other etiological diseases. Optimization

of the diagnosis of chronic toxoplasmosis uveitis is possible by purposeful identification of symptoms of posterior uveitis, detection of hemodynamic instrumental signs of the vascular-exudative phase of inflammation, using clinical-immunological methods.

Approbation and application of the dissertation. The materials of the dissertation were discussed: At the scientific-practical conference "Actual Problems of Medicine" dedicated to the 100th anniversary of the Azerbaijan Democratic Republic (Baku, 2018); at the international scientific-practical conference dedicated to the 100th anniversary of the Medical Faculty (Baku, 2019); and at the international scientific-practical conference dedicated to the 100th anniversary of the Department of Human Anatomy and Medical Terminology of the Azerbaijan Medical University (Baku, 2019), "Modern Medicine: new approaches and current research" at the International Scientific-practical Conference (Moscow, 2019), "Tbilisi International Ophthalmological Conference" (Tbilisi, 2019).

The dissertation materials were presented and discussed at the interdepartmental meeting held jointly by the profile departments of Azerbaijan Medical University (AMU) (Baku, 2021, protocol no.1) and at the scientific seminar of the approbation commission under BFD 2.28/1 Dissertation Council of Azerbaijan Medical University (AMU) (Baku, 2021, protocol no.5). The materials of the dissertation are used in the teaching process of the departments of epidemiology and ophthalmology of AMU, and the proposed practical recommendations are applied.

Use of scientific research work. The work was performed at the Educational-Surgical Clinic and departments of Epidemiology and Ophthalmology of Azerbaijan Medical University.

Publishing. 12 scientific works on the topic of dissertation were published.

Volume and structure of the thesis. The thesis is presented on 160 pages of computer text (172.479 characters) and consists of an introduction (10.100 characters), list of references (48.000 characters), research materials and methods (15.350 characters), 3-chapter research results and their discussion (35.650 + 37.100 + 28.550 characters), summary, conclusions, practical recommendations (38.750

characters), bibliography covering 201 sources, including works by Azerbaijani authors. The thesis contains 19 tables, 18 graphics and 5 figures.

MATERIALS, VOLUME AND METHODS OF RESEARCH

The research was carried out in 2015-2017 within the scientific program of the departments of Epidemiology and Ophthalmology of AMU. Laboratory and instrumental-diagnostic examinations were performed on the basis of the departments of Epidemiology and Ophthalmology of AMU and the educational-clinical Epidemiological laboratory of the department of epidemiology.

As a result of serological examinations for toxoplasmosis during our observation in 2015-2017, we found 148 people aged 5-45 years, whose eyes were damaged by toxoplasmosis and who formed the main observation group. The mean age of the patients was 12.60 ± 2.5 . The study included 66 men ($44.5 \pm 4.1\%$) and 82 women ($55.5 \pm 4.1\%$). A total of 215 eyes were examined with this pathology. In this case, 148 patients in the main group were divided into 2 subgroups, depending on the mechanism of infection with toxoplasmosis. The first subgroup (65 patients) was formed by patients with congenital toxoplasmosis (CT). The second subgroup involved 83 patients with acquired toxoplasmosis. In the course of the study, the consent of all patients and their parents was obtained to participate in the study, which was defined by a standard protocol and acquainted with the content in advance. The control group consisted of 48 healthy individuals.

The etiology of toxoplasmosis of the disease was determined as a result of medical history data, complex clinical, instrumental, laboratory examinations and diagnosis of toxoplasmosis. Ophthalmological examinations include: visometry, tonometry, perimetry, biomicroscopy, direct and indirect (reverse) ophthalmoscopy, according to a request, compimetry, gonioscopy, tonography, and ultrasound examination using the method of dopplerographic examination of blood flow in the vessels of the eye. Following the instructions, gen-

eral clinical, serological, immunological, hormonal, and microbiological examinations were carried out and consulted with a therapist, hematologist, otolaryngologist, infectious disease specialist, neurologist and surgeon.

Laboratory diagnosis of toxoplasmosis is grounded on a set of laboratory tests aimed at the direct detection of the causative agent, its antigens or DNA (parasitological method, immunofluorescence reaction, polymerase chain reaction – PCR), or indirect (serological) detection of antibodies against individual proteins of the parasite in immunoblot (line-blot) and antibodies from IgM, IgA, IgG and IgG classes via enzyme-linked immunosorbent assay (ELISA) (in order to confirm the specificity and determine the phase of the infectious process). Standard mathematical statistical methods were used in processing the results of the examinations. The determination of the accuracy of the difference of the average mathematical error between two sample numbers was based on Student's t-test. When the accuracy of the difference between the compared figures is higher than 95% ($p \leq 0.05$), the difference is considered valid.

RESULTS OF PERSONAL OBSERVATIONS AND THEIR DISCUSSION

Studies have shown that the age of the majority of patients with ocular toxoplasmosis vary between 25-45 years ($31.8 \pm 3.6\%$). The distribution of patients according to the symmetry of the lesion taking the age factor into consideration showed that unilateral process was found in 81 patients (81 eyes, $54.7 \pm 4.1\%$), bilateral process was found in 67 patients (134 eyes, $45.3 \pm 4.1\%$). The age characteristics of the patients were given in Table 1.

Depending on the mechanism of infection with toxoplasmosis, congenital toxoplasmosis was found in 65 patients ($43.9 \pm 4.1\%$) and acquired toxoplasmosis in 83 patients ($56.1 \pm 4.1\%$; $\chi^2 = 76.32$; $p < 0.01$). The distribution of patients according to the symmetry of the lesion depending on the mechanism of infection showed that during congenital toxoplasmosis, unilateral process was detected in 43 eyes ($53.0 \pm 5.5\%$) and bilateral process in 22 eyes ($32.8 \pm 5.7\%$). During

acquired toxoplasmosis, unilateral process was found in 38 eyes ($47.0 \pm 5.5\%$; $\chi^2 = 74.23$; $p < 0.01$) and bilateral process in 45 eyes ($67.2 \pm 5.7\%$; $\chi^2 = 22.48$; $p < 0.01$).

Table 1
Distribution of examined groups of patients according to their age and symmetry of the lesion

Age	Total				Total (n=148)		Control group (n=48)	
	Unilateral process (n=81)		Bilateral process (n=67)					
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
5-6	8	9.9 ± 3.3	-	-	8	5.4	3	6.2
7-10	7	8.6 ± 3.5	4	6.0 ± 2.9	11	7.4 ± 2.2	5	10.4 ± 4.5
11-14	9	11.1 ± 3.3	6	8.9 ± 3.6	15	10.1 ± 2.5	6	12.5 ± 4.8
15-18	12	14.8 ± 3.9	16	23.9 ± 5.2	28	18.9 ± 3.2	8	16.7 ± 5.4
19-24	17	20.9 ± 4.5	22	32.8 ± 5.8	39	26.4 ± 3.6	12	25.0 ± 6.2
25-45	28	34.7 ± 5.3	19	28.4 ± 5.5	47	3.8 ± 3.6	14	29.2 ± 6.5

In the distribution of patients according to the mechanism of infection depending on age, it was determined that congenital toxoplasmosis (CT) predominates starting from the age group of 5-6 years and at the age of 7-10 years (19 children, 100%; $p < 0.01$). In the 11-14 age group, unilateral process of CT ($13.8 \pm 4.3\%$) and bilateral process of CT were noted in most cases ($4.6 \pm 2.6\%$; $p < 0.01$). In the age group of 15-18 years, in most cases, the bilateral process of AT ($18.1 \pm 4.2\%$) and the unilateral process of CT ($7.7 \pm 3.3\%$; $p < 0.01$) were noted. In the 19-24 age group, unilateral AT process ($21.7 \pm 4.5\%$) and bilateral CT process ($10.8 \pm 3.8\%$; $p < 0.01$) were recorded in most cases. In the 25-45 age group, unilateral AT process ($16.7 \pm 4.1\%$) and bilateral AT process ($25.5 \pm 4.8\%$; $p < 0.01$) were recorded in most cases.

Strabismus, microphthalmia, cataracts, optic nerve atrophy, and nystagmus may be associated with congenital diseases. The infection causes inflammation of a specific area of the retina, which can usually be removed spontaneously. However, the infection can form localized scar tissue (covering the retina and vascular membrane) in

which the toxoplasmosis is inactive. Chorioretinal scars do not affect vision unless the scar tissue is connected to the central part of the retina (macula).

Acquired toxoplasmosis was manifested in the following clinical forms: acute (9 patients, $10.8 \pm 3.4\%$), semi-acute (12 patients, $14.5 \pm 3.9\%$), chronic (47 patients, $56.7 \pm 5.4\%$), inapparent (9 patients, $10.8 \pm 3.4\%$) and causative agent (6 patients, $7.2 \pm 2.8\%$)

The host's immune response induces the conversion of parasitic forms from tachyzoites to bradyzoites and their enzymes. The cyst, along with parasites, can remain inactive for a long time in or near the scar tissue, but retinitis can reactivate when the cyst breaks down and the organisms enter the surrounding retina. It is known that reactivation of retinitis develops at the border of old scars and is explained by the collapse of tissue cysts located in old lesions. However, sometimes new lesions are found far from the old scars. Recurrences of acquired toxoplasmosis were observed in 51 patients ($61.4 \pm 5.3\%$) ($n = 83$). Unilateral process was detected in 43 patients with recurrences ($84.3 \pm 4.0\%$), bilateral process was detected in 8 patients ($15.7 \pm 4.0\%$). In this case, the new chorioretinal foci usually appeared on or near the old foci, and in rare cases in the uninjured eye. In the group of patients with congenital toxoplasmosis ($n = 65$), the distribution of patients according to the degree of disease was as follows: 13 people with mild disease ($20.0 \pm 4.9\%$), 21 people with moderate disease ($32.3 \pm 5.8\%$), and 31 people with severe disease ($47.7 \pm 6.2\%$; $t = 3.65$; $p < 0.001$). In the group of patients with acquired toxoplasmosis ($n = 83$), according to the degree of the disease, patients were divided as follows: mild – 21 people ($25.3 \pm 4.8\%$), moderate – 28 people ($33.7 \pm 5.2\%$), and severe – 34 people ($41.0 \pm 5.4\%$; $t = 3.21$; $p < 0.001$). During the unilateral process ($n = 81$), the number of patients with mild form of the disease was 11 ($13.6 \pm 3.8\%$; $t = 4.23$; $p < 0.001$), the number of patients with moderate form was 38 ($46.9 \pm 5.5\%$; $t = 6.38$; $p < 0.001$), the number of patients with severe form was 32 ($39.5 \pm 5.4\%$; $t = 2.25$; $p < 0.001$). Complications of ocular toxoplasmosis include increased intraocular pressure (76 patients, $51.3 \pm 4.2\%$), cystic macular degeneration (41 patients, $27.7 \pm 3.7\%$), cataracts (62 patients, $41.8 \pm 4.1\%$), secondary

glaucoma (26 patients, $17.7 \pm 3.2\%$), keratopathy (38 patients, $25.6 \pm 3.6\%$), and retinal detachment and rupture (19 patients, $12.8 \pm 2.8\%$). Chorioretinal dystrophy (108 patients, $72.9 \pm 3.6\%$) was identified as a delayed complication of ocular toxoplasmosis. Other complications of ocular toxoplasmosis cover secondary paralysis and paresis of the motor muscles of the eye, leading to impairment and disability.

In order to study the state of regional hemodynamics (Acuson Aspen), 16 patients (32 eyes) aged 5-45 years, whose eyes were damaged by toxoplasmosis, were examined. Hemodynamic parameters were studied in the ophthalmic artery (OA), central retinal artery (CRA), central retinal vein (CRV), short posterior ciliary arteries, and long posterior ciliary arteries. The following parameters were evaluated: maximum systolic velocity (V_{\max}), minimum diastolic velocity (V_{\min}), mean blood flow rate over time, cm/s, peripheral resistance index (RI), pulsation index (PI), systolic-diastolic ratio (S/D). Analyzing the data obtained, it should be noted that in all patients, the maximum systolic velocity of blood flow in the ocular artery was higher than in the internal carotid artery and was clearly lower in the eye with unilateral process. This tendency also applies to short and long ciliary arteries and the central retinal artery. Study of hemodynamic parameters in the ophthalmic and orbital vessels showed a significant decrease in maximal blood flow rate, pulse index and systolic-diastolic ratio in the central retinal artery and allowed to determine the decrease in maximum blood flow velocity, resistance index, and maximal systolic-diastolic ratio in short posterior ciliary arteries, as well as systolic-diastolic ratio in long posterior ciliary arteries in case of ocular toxoplasmosis.

Instrumental evaluation of hemodynamic parameters of the ophthalmic and orbital vessels in case of ocular toxoplasmosis in the central retinal artery (V_{\max} (11.8 ± 0.2), V_{\min} (3.3 ± 0.01), RI (0.71 ± 0.01), PI (1.54 ± 0.01)), in the short posterior ciliary arteries (V_{\max} (10.1 ± 0.3), V_{\min} (3.5 ± 0.01), RI (0.81 ± 0.01), PI (1.45 ± 0.02)), and in the long posterior ciliary arteries (V_{\max} (13.9 ± 0.1), V_{\min} (2.2 ± 0.01), RI (0.81 ± 0.01), PI (1.66 ± 0.01)) was reliably found to decrease. Hemodynamic parameters recorded by ultrasound dopplerography are important criteria in the diagnosis of chorioretinitis

and are considered promising in terms of studying the pathogenesis of the proliferative process and substantiating the formation of a focal reaction in the tissues of the eye. Ultrasound dopplerography was also performed in 13 patients (13 eyes) diagnosed with toxoplasmosis chorioretinitis (8 women, 5 men, mean age 25.0 ± 18.5). In this group of patients, proliferation was recorded in the form of perifocal edema of the retina in the focal area, inflammatory infiltration of various degrees in the vitreous, the formation of epiretinal membranes. During the study of ultrastructural changes in the retina at different stages of the inflammatory process (exudation, infiltration, initial absorption), a violation of the differentiation of the retinal layers in the area of the inflammatory focus was identified in all patients during the observation period. Perifocal thickening of the ganglion cells, inner plexiform, inner nuclear layers, and outer plexiform and outer nuclear layers of the retina was determined in the focal zone. Among the early complications in the studied groups were: retinal vasculitis symptoms (3 patients, 3 eyes), macular pathology (6 patients, 6 eyes), neuropathy (2 patients, 2 eyes), posterior vitreous detachment (4 patients, 4 eyes), preretinal progressive fibrosis (2 patients, 2 eyes), and formation of epiretinal membranes (3 patients, 3 eyes). Changes in the macular area are clinically manifested in some cases by the formation of cystic cavities and layered retina along with retinal edema in the macular area. According to optical coherent tomography (OCT, Cirrus HD OCT-3000 Carl Zeiss), peripapillary increase in the height of the neuroepithelium (on average up to $513.0 \text{ mm} + 31.6$) and “smoothing” of the excavation of the optic disc was noted. In “En Face” mode, according to OCT, a homogeneous dark zone at the level of the choriocapillary layer in the area of the inflammatory focus is visualized, which is most likely due to exudative changes at the level of the retina and special vascular membrane. OCT data indicate a violation of the differentiation of the retinal layers in all cases in the focal zone. At the end of the formation of inflammatory process and chorioretinal scar, a decrease in the thickness of the neuroepithelium in the area of inflammation is observed in all patients. During the active pathological process, an increase in the height of the neuroepithelium in the area of inflammatory focus is

observed.

The identified nature of regional hemodynamic changes allows predicting the development of complications and relapses of ocular toxoplasmosis and should be taken into account in the diagnosis of this pathology and the development of pathogenetically differentiated treatment. Comprehensive examination of patients with ocular toxoplasmosis should include ultrasound dopplerography of the ophthalmic and orbital vessels, which allows determining the nature of hemodynamic disorders. The decrease in the blood flow rates of the central retinal artery, short posterior ciliary arteries, and long posterior ciliary arteries is clearly observed in the relapsed course of the process. The use of hemodynamic indicators in practice to predict the occurrence of complications and relapses of ocular toxoplasmosis shows that they can provide a high level of information in solving the proposed clinical tasks. In the study of the differential-diagnostic features of clinical manifestations in patients with ocular toxoplasmosis, it was found that ocular lesions with toxoplasmosis occur in 4 clinical forms with different frequencies: $47.9 \pm 4.1\%$ of cases with centrally localized focal chorioretinitis (71 people), $29 \pm 3.7\%$ of cases with equatorial and centrally localized focal chorioretinitis (43 people), $13.5 \pm 2.8\%$ of cases with disseminated chorioretinitis and diffuse choroiditis (20 people), and $9.5 \pm 4.5\%$ of cases with panuveitis (14 people) were found. Centrally localized focal chorioretinitis was detected in 71 patients ($47.9 \pm 4.1\%$). The process was mainly unilateral – in 55 patients ($77.5 \pm 4.9\%$) and bilateral – in 16 patients ($22.5 \pm 4.9\%$). In 23 patients ($32.4 \pm 5.6\%$), central chorioretinitis was detected for the first time and chronic recurrent course was detected in 48 people ($67.6 \pm 5.6\%$). Central chorioretinitis is characterized by the location of the foci in the macular and paramacular areas, along the veins up to the preequatorial zone. Macular and paramacular localization of foci (in 28 patients, $39.4 \pm 5.8\%$) was accompanied by a sharp onset, a sharp decrease in vision, “spotted” vision, and distortion of objects. Ophthalmologic examination revealed one (27 patients, $38.0 \pm 5.8\%$) or several (44 patients, $62.0 \pm 5.8\%$) chorioretinal foci. The foci were yellowish in color, with indistinct borders, localized, secondary vasculitis, accompanied by varying degrees of

perifocal inflammatory reaction.

During bilateral lesions, a clinical form identical to the first affected eye was observed in the second eye of 11 patients. Chronic recurrent course of centrally localized chorioretinitis was observed in all cases of bilateral eye damage. Centrally localized focal chorioretinitis was characterized by high frequency (58 patients, $81.6 \pm 4.6\%$) and a variety of complications (58 patients, $81.6 \pm 4.6\%$), including neuropathy (31 patients, $53.4 \pm 6.6\%$), maculopathy (18 patients, $31.0 \pm 6.0\%$), secondary maculodystrophy (9 patients, $15.6 \pm 4.8\%$). In 31 patients ($43.7 \pm 5.9\%$) with centrally localized focal chorioretinitis, the lesion was located in the superior papilla. Jensen's juxtapapillary chorioretinitis was found in $20.9 \pm 3.3\%$ of all lesions of toxoplasmosis etiology of the eyes. The process was mostly unilateral (25 patients, $80.6 \pm 7.0\%$). Bilateral process was detected in 6 patients ($19.4 \pm 7.0\%$). Recurrent course was observed in 7 patients ($22.5 \pm 7.6\%$). Equatorial and peripheral localized chorioretinitis was detected in 43 patients ($29.1 \pm 3.7\%$). The nature of the lesion was mainly monolateral (27 patients, $62.8 \pm 7.4\%$). Symptomatic chorioretinitis was detected for the first time in 17 patients ($39.5 \pm 7.4\%$), and chronic recurrent nature of the process was noted in 26 patients ($60.5 \pm 7.4\%$). Aggravation of the disease was detected in 29 ($67.4 \pm 7.2\%$) patients. Early complications were dominated by neuropathy (11 patients, $37.9 \pm 9.0\%$) and maculopathy (5 patients, $17.2 \pm 6.9\%$), while late complications were more common in uveal cataracts (7 patients, $24.2 \pm 8.6\%$) and vitreous fibrosis (6 patients, $20.7 \pm 8.4\%$).

Panuveitis was found in 14 patients ($9.5 \pm 4.5\%$). The chronic relapsing nature of the process was observed in 11 of 14 patients ($91.7 \pm 7.2\%$), and the monolaterality of the lesion was noted in 2/3 of the cases. Patients complained of impaired visual acuity and blurred vision. Changes in the anterior part of the eyeball were observed in all patients. In the context of the treatment, foci of different localization were formed: peripheral – 10 patients ($71.4 \pm 12.1\%$), central – 3 patients ($21.5 \pm 10.8\%$), and disseminated – 1 patient ($7.1 \pm 5, 8\%$). The mean duration of this form of posterior toxoplasmosis chorioretinitis was 182.4 ± 38.5 days. In all patients, the process was

complicated, with exudative retinal detachment (5 patients, $35.7 \pm 12.8\%$) and traction retinal detachment (3 patients, $21.5 \pm 10.8\%$) predominating among the complications. Disseminated chorioretinitis and diffuse choroiditis were identified in 20 patients ($11.5 \pm 2.8\%$). The lesion was usually bilateral (16 patients, $80.0 \pm 8.9\%$). In this clinical form, it is not possible to judge the frequency of relapses and the duration of remissions, because patients are usually examined at a late visit to the doctor, in the period of diffuse specific damage to the fundus with secondary dystrophic changes in the macular area. The disease was detected in 4 patients ($20.0 \pm 8.9\%$) during relapse. In our study, dynamic observations were observed in 62 patients ($41.9 \pm 4.1\%$) without chronic relapse of ocular toxoplasmosis, and in 86 patients ($58.1 \pm 4.1\%$) recurrent course of the process.

As a result of our research, we found that the symptoms of general immunosuppression, which are characteristic for the clinical manifestation of toxoplasmosis, were observed. A decrease in the total number of leukocytes and lymphocytes in the blood was revealed together with a decrease in the CD3, CD4, CD8 populations (0.77 ± 0.04 ; 0.42 ± 0.02 ; 0.31 ± 0.01 , respectively), in the cells with positive activation markers – HLA DR (0.24 ± 0.01), and in the immune regulatory index – D3 / CD8 (1.6 ± 0.01). The decrease in the number of these cells may be due to disruption of leukopoiesis and lymphopoiesis, migration of lymphocytes to the site of invasion of the parasite, as well as changes in apoptosis. The apoptosis realization index, which reflects the mortality rate of lymphocytes expressing programmed cell death preparation markers in patients with toxoplasmosis, was significantly higher than in the control group (103.1 ± 22.01), which may be one of the mechanisms underlying the reduction of the total number of T-lymphocytes and their subpopulations identified in our study. We found that patients with posterior toxoplasmosis uveitis develop a cellular and humoral specific immune response to toxoplasmosis in the context of general lymphopenia, which is confirmed by the results of skin and focal tests with toxoplasmin *in vivo*, an increase in the functional activity of lymphocytes against toxoplasmosis *in vitro*, as well as an increase in specific IgM, IgG antibodies. The predominance of cells with early – CD25 / CD95

(1.83 ± 0.21) and especially late – CD71 / CD95 and HLA-DR / CD95 (2.52 ± 0.34 ; 4.02 ± 0.49 respectively) positive activation markers compared with cells expressing negative activation markers from the formation of a specific immune response and clonal expansion of lymphocytes, as well as the increase in interferon-gamma levels in the blood (24.31 ± 4.6) also proves it. Under such conditions, the ratio of cells with positive activation markers in the circulation to cells with negative activation markers may also depend on the intensive death of apoptosis-ready cells (lymphocytes expressing CD95 receptors). Changes in the humoral ring of immunity are not only specific, but they also reflect changes in the effector ring of humoral immunity in the form of an increase in the level of total immunoglobulins of the primary IgM (1.64 ± 0.06) and secondary IgG (14.02 ± 0.32) immune response, an increase in the level of circulating immune complexes (67.21 ± 4.25), as well as an increase in the activity of the initial – C1 components (78.22 ± 4.26) and a decrease in the terminal – C5 components (53.12 ± 3.32) of the complement system. The identified changes in the functional activity of neutrophils – an increase in spontaneous HCT-test (35.32 ± 3.65) – indicate a high oxygen content of neutrophils and reflect the strengthening of the effector ring of the humoral immune system. The formation of a specific cellular immune response during toxoplasmosis uveitis suggests a lymphocyte blast transformation reaction (LBTR) with a positive cutaneous and focal response to toxoplasmosis, predominance of cells with early (C025 / CO 95) and delayed (C071/C095 and HLA DR /CO95) positive activation markers over the number of cells with signs of inactivity, as well as an increase in serum gamma-interferon levels. In ocular toxoplasmosis, humoral immunity is characterized by an increase in the total level of primary (IgM) and secondary (IgG) immune response immunoglobulins, as well as specific immunoglobulins, increased levels of circulating immune complexes, and changes in effector mechanisms of humoral immunity (complement and phagocytic microbial activity). Decreased ability of leukocytes to produce α -IFN (54.8%) and γ -IFN (51.6%) in more than $\frac{1}{2}$ subjects examined in interferon status indicates an unsatisfactory immune response. In 19 children with congenital toxoplasmosis, the

life quality was measured. The tool for studying the quality of life (QOL) in children aged 5-14 years was the Russian-language version of the general questionnaire Pediatric Quality of Life Inventory – PedsQL™4.0. In children with CT, all QOL parameters in all age groups – 5-7 years, 8-12 years and 13-14 years – differed significantly from the control indicators for both child and parent forms ($p < 0.05$), which characterizes the obvious psychosocial and physical disabilities of children. The level of quality of life in children with developmental disabilities associated with CT was age-dependent. Children aged 5-7 assessed their quality of life negatively for all physical and psychosocial characteristics. In children aged 8-12 years, the indicators improved and differed significantly from the healthy group only due to rheumatoid factor (RF) as a more sensitive criterion of physical condition (49.8 ± 7.9 – children, 71.1 ± 5.2 – parents, $76.8 \pm 11, 5$ – healthy group). Parents of children with CT rated their children’s quality of life as good. There were differences in physical characteristics only in the 8-12 age group compared to the control group ($p < 0.05$). FF was 68.6 ± 7.4 in parents compared to 82.6 ± 12.5 in healthy children. RF was also lower than the control values (72.0 ± 14.8).

The goal of treatment is to stop the growth of parasites during active damage and to minimize damage to the retina and optic disc. Various treatment options are currently available, but classic chemotherapy with pyrimethamine and sulfadiazine in combination with corticosteroids remains the most widely used method. In addition, patients are treated for ocular toxoplasmosis individually. Some patients can recover in a few weeks without antibiotics. However, there are opinions about the benefits of using antibiotics because antibiotics reduce the number of relapses and can help speed up the resolution of inflammation. We conducted research to establish combinations with less adverse outcomes and better intake regimens (due to the reduction in the number of tablets per day). Trimethoprim/sulfamethoxazole and oral prednisolone are alternative treatments. During a clinical examination of the fundus of the eye, acute lesions were noted in 26 patients (88.9%) 4 weeks after the start of treatment. Acute lesions were reported 4 weeks after initia-

tion of treatment in 11 patients (78.6%) in the azithromycin group and 13 patients (100%) in the trimethoprim / sulfamethoxazole group. Other treatment options include intravitreal injection of clindamycin and dexamethasone, which are considered promising. Intravitreal drug crosses the ocular barriers and thus provides a high concentration of the drug, bypassing the systemic effects in the intra-ocular tissues and the risk of its complications. Thus, intravitreal treatment may be easier with a higher safety profile and increased access to the drug, as well as a further reduction in subsequent referrals and hematological assessments. In this regard, we scheduled intravitreal injection of clindamycin for 3 patients in the azithromycin group. With good intracellular penetration, clindamycin enters cells and provides a high intracellular / extracellular ratio compared to other antibiotics such as erythromycin and levofloxacin. 1.5 mg of clindamycin used intravitreally was non-toxic to the retina and the elimination half-life was 5-6 days. After intravitreal injection of 1 mg of clindamycin, its concentration remained ≥ 1.6 mg / ml for approximately 40 hours, which was higher than the 50% inhibitory concentration for *Toxoplasma gondii*. Intravitreal therapy may be favorable for the treatment of ocular toxoplasmosis. A better understanding of the clinical and pathophysiological features can lead to the identification of more effective strategies for the prevention and treatment of common causes of vision loss.

As a result of our research, we have developed a set of measures that can reduce the intensity of toxoplasmosis transmission in the population, revealing the main routes of transmission of toxoplasmosis in the population and the circulatory characteristics of the parasite in Baku. The following principles should be followed to select patient examination tactics:

- comprehensive approach to diagnosis, taking into account epidemiological, anamnestic, clinical and laboratory data, as well as the results of functional examinations;
- to determine the indicators that identify the condition of the fetoplacental system in pregnant women;
- to assess the condition of the cell ring (if possible), humoral ring (total IgA, IgM, IgG), and complement system (most important-

ly C3 and C4) and, if possible, to determine the amount of key cytokines and interferons;

- to detect (exclude) mixed infection;
- to explore the form and activity of the infectious process;
- to study the main etiological factor in the formation of pathology, which is especially important during co-infection;
- to identify factors that complicate the process (hormonal deficiency, autoimmune diseases, hestosis, chronic fetoplacental insufficiency, etc.).

Thus, the results of the study allowed identifying socio-epidemiological patterns of toxoplasmosis in the population and proposing measures to reduce them, as well as developing a comprehensive treatment tactic available to the population of all ages due to its high efficiency and lack of side effects.

RESULTS

1. Our research results determined that the main proportion of patients with ocular toxoplasmosis is patients aged 25-45 years ($31.8 \pm 3.6\%$). The age-related distribution of patients according to the symmetry of the lesion showed that a unilateral process was detected in 81 patients (81 eyes, $54.7 \pm 4.1\%$), and a bilateral process in 67 patients (134 eyes, $45.3 \pm 4.1\%$). Depending on the mechanism of infection with toxoplasmosis, the distribution of patients was as follows: congenital toxoplasmosis in 65 patients ($43.9 \pm 4.1\%$), acquired toxoplasmosis in 83 patients ($56.1 \pm 4.1\%$) were found [2,8,9].

2. In the study of the differential-diagnostic features of clinical manifestations in patients suffering from ocular toxoplasmosis, it was found that ocular lesions with toxoplasmosis occur in 4 clinical forms with different frequencies: $47.9 \pm 4.1\%$ of cases with centrally localized focal chorioretinitis (29 people), $71.1 \pm 3.7\%$ of cases – equatorial and peripheral localized focal chorioretinitis (43 people), $13.5 \pm 2.8\%$ of cases – disseminated chorioretinitis and diffuse chorioretinitis (20 people), and $9.5 \pm 4.5\%$ of cases – panuveitis (14 people) was detected [3].

3. Instrumental examination of hemodynamic parameters of the ophthalmic and orbital vessels in case of ocular toxoplasmosis in the central retinal artery (V_{\max} (11.8 ± 0.2), V_{\min} (3.3 ± 0.01), RI (0.71 ± 0), PI (1.54 ± 0.01)), short posterior ciliary arteries (V_{\max} (10.1 ± 0.3), V_{\min} (3.5 ± 0.01), RI (0.81 ± 0.01), PI (1.45 ± 0.02)), and long posterior ciliary arteries (V_{\max} (13.9 ± 0.1), V_{\min} (2.2 ± 0.01), RI (0.81 ± 0.01), PI (1.66 ± 0.01)) showed a significant decrease [5].

4. Studies have shown that S-antigenemia (S-AG) was found in the majority of patients examined in AMU compared with the control group (0.22 ± 0.02). At the same time, general immunosuppressive symptoms characteristic of the clinical manifestation of toxoplasmosis were observed. A decrease in the total number of leukocytes and lymphocytes in the blood together with a decrease in the CD3, CD4, CD8 populations (0.77 ± 0.04 ; 0.42 ± 0.02 ; 0.31 ± 0.01 , respective-

ly), in the cells with positive activation markers – HLA DR (0.24 ± 0.01), and in the immune-regulatory index – CD3 / CD8 (1.6 ± 0.01) was detected. The identified changes in the functional activity of neutrophils – an increase in spontaneous HCT-test (35.32 ± 3.65) – indicate a high oxygen content of neutrophils and reflect the strengthening of the effector ring of the humoral immune system [4,7].

5. The identified clinical and immunological features, the nature of changes in regional hemodynamics and immunological parameters allow predicting the development of complications and relapses of posterior toxoplasmosis uveitis and should be taken into account in the diagnosis of this pathology and the development of pathogenetically differentiated treatment [1,6,12].

PRACTICAL RECOMMENDATIONS

1. The nature of hemodynamic disorders in posterior toxoplasmosis uveitis is manifested by a decrease in the velocity of blood flow in the central retinal artery, short posterior and long posterior ciliary arteries.

2. Changes in the humoral ring of immunity are not only specific, but they also reflect changes in the effector ring of humoral immunity in the form of an increase in the level of total immunoglobulins of the primary IgM and secondary IgG immune response, an increase in the level of circulating immune complexes, as well as an increase in the activity of the initial – C1 components and a decrease in the terminal – C5 components of the complement system.

3. Comprehensive examination of patients with ocular toxoplasmosis should include ultrasound dopplerography of the ophthalmic and orbital vessels, which enables to determine the nature of hemodynamic disorders: in the central retinal artery, short posterior and long posterior ciliary arteries.

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