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ABSTRACT

of the Dissertation for the degree of Doctor of Philosophy

**CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF
UVEITIS CAUSED BY ENTEROVIRUS (EV) INFECTION**

Specialty: 3202.01 – Epidemiology
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Field of science: Medicine

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GENERAL CHARACTERISTICS OF WORK

Relevance of the subject. In modern times, enterovirus (EV) infection remains one of the most pressing health problems. New and severe forms of enterovirus infection – acute hemorrhagic conjunctivitis caused by enterovirus 70 and poliomyelitis-like diseases caused by enterovirus 71, enterovirus infection manifesting itself with uveitis, retinal diseases caused by enterovirus Coxsackie B4 have occurred over the last 30 years^{1,2}. Enterovirus type B is the most common type and includes all Coxsackie B viruses and ECHO (except ECHO 1, as well as Coxsackie A9 virus and enteroviruses types 69, 73, 77, 78). Enterovirus C includes other types of Coxsackie A viruses, including 1, 11, 13, 15, 17–22, and 24. Types of enterovirus D and E are relatively small, including 2 (enterovirus 68 and 70) and 1 (A2 plaque virus), respectively. Enterovirus diseases, first reported in the mid-20th century, have spread around the globe and are not declining^{3,4}. On the contrary, their role in human pathology has been growing in recent years. One of the features of enterovirus infection is the polymorphism of clinical symptoms i.e., from catarrhal to serous meningitis, from acute hemorrhagic uveitis to acute paralytic syndrome and myocarditis, long-term viral transmission, the possibility of chronic process, lack of specific prophylactic methods^{5,6}. Tropism of the causative agent against

¹ Scott M., Whitcup M.D., Robert B., Nussenblatt M. (2016). Immunologic Mechanisms of Uveitis. *Ocular immunology and inflammation*, vol. 1, no.11, 255-260.

² Ibid., 255-260.

³ Suhler E.B., Smith J.R., Wertheim M.S. (2016). A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol.*, vol. 123, no. 7, 903-912.

⁴ Paola P., Massimo A., La Cava M. (2016). Endogenous uveitis: an analysis of 1,417 cases. *Ophthalmologica*, vol. 210, 234.

⁵ Дроздова Е.А. Вопросы классификации и эпидемиологии увеитов [Issues of classification and epidemiology of uveitis]. *Russian Journal of Clinical Ophthalmology / РМЖ «Клиническая офтальмология»*, 2016, № 3, с.155–159.

⁶ Chan C., Li Q. (2017). Immunopathology of uveitis. “Eye” An International Journal of Ophthalmology, Cambridge Ophthalmological Symposium Royal College of Ophthalmologists, vol. 11- part 2, 91-95.

tissues, age-related immune reactivity, T-cell and humoral deficiency, activation of free radical oxidation processes, changes in hormonal regulation are of great importance in the pathogenesis of EV infections. When infected with enterovirus, a temperature of 38-39° C and over, the involvement of the upper respiratory tracts in the process, in many cases a rash, often the growth of parenchymal organs and peripheral nodes are observed in children. Because of these, but often after a drop in temperature, acute anterior uveitis is found in children, which is characterized by quite specific symptoms. However, uveitis, despite the involvement of the ciliary body in the process, is not accompanied by precipitation of precipitates, but only by diffuse edema of the endothelium, which is noted in a small number of patients. A characteristic feature of anterior uveitis is atrophy of the pigmented surface of the iris^{7,8,9,10}. At first there occur defects, through which the reflex at the base of the eye is clearly visible, and then (during heavy walking) it is possible to see almost complete destruction of the pigment layer^{11,12,13,14}. Another feature of anterior uveitis is the

⁷ Романенкова Н.И., Бичурина М.А. Сезонные подъемы заболеваемости энтеровирусными инфекциями на Северо-Западе России [Seasonal rises in the incidence of enterovirus infections in the North-West of Russia]. *Proceedings of the All-Russian Annual Congress "Infectious Diseases in Children: Diagnosis, Treatment and Prevention"* / Сб. материалов Всероссийского ежегодного конгресса «Инфекционные болезни у детей: диагностика, лечение и профилактика». Санкт-Петербург, 13-14 октября 2016 г. Журнал инфектологии, 2016, Т.8, №3, с.104-105.

⁸ Телетаева Г.М. Цитокины и противоопухолевый иммунитет [Cytokines and anti-tumor immunity]. *Practical Oncology / Практическая онкология*, 2017, Т. 8, № 1, с. 211–218.

⁹ Anitua E., Muruzabal F., Tayebba A., Riestra A. (2015). Autologous serum and plasma rich in growth factors in ophthalmology: preclinical and clinical studies. *Acta Ophthalmol.*, no. 8, 605–614.

¹⁰ Carreño E., Portero A., Herreras J.M. (2016). Cytokine and chemokine tear levels in patients with uveitis. *Acta Ophthalmologica* (32), 92-95.

¹¹ Batts A.F., Jalalat S.Z. (2016). Exacerbation of bullous pemphigoid after hand, foot, and mouth disease treated with rituximab. *JAAD Case Rep.*, vol. 8, no. 2(1), 7-9.

development of hypotony, which is difficult to treat¹⁵. In some children, this type of hypotony can lead to subatrophy of the eye. In many children, gray-yellow inflammatory foci are found on the eyelid margins. Another feature, as noted by some authors, is the rapid development of cataracts, which is not typical for anterior uveitis of other origins. The retina becomes diffusely opaque, then partially absorbed in the cataract, which is still not the case with uveitis of other etiologies. Also, there is virtually no data in the literature on epidemiological studies of enterovirus infection accompanied by uveitis¹⁶. In this case, new foci of inflammation can appear both in the area where the old foci are localized, and in a new place, including the healthy eye. In addition to the systemic and locally detection of glucocorticosteroids of chorioretinitis, the widely accepted and well-known method of treatment with antiprotozoal drugs prevents the acute process and does not always lead to relapses. However, little is known about the epidemiology of enterovirus infection. Thus, the study of clinical and epidemiological features of enterovirus uveitis (EU) in children is undoubtedly of great scientific and practical interest.

Object of research. 150 patients with enterovirus (EV) infection of the eyes aged from 3 months to 14 years.

Research purpose

A study of the clinical and epidemiological aspects of enterovirus uveitis (EU) in children in the Gakh region of Azerbaijan

¹² Chung E.J. (2017). Tonic spasms in acute transverse myelitis. *J. Clin. Neurosci.*, vol. 17, no. 1, 165-166.

¹³ Dowdle W.R. (2017). The principles of disease elimination and eradication. *Bull of the WHO*, vol. 76 (Suppl. 2), 22–25.

¹⁴ Ferguson T.A., Griffith T.S. (2017). The role of Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL) in the ocular immune response. *Chem. Immunol. Allergy.*, vol. 92, 140-154.

¹⁵ Graham E.M., Stanford M.R. (2017). Diagnostic value of ophthalmological features. *Br J Ophthalmol.*, vol. 73, no. 8, 714-721.

¹⁶Nix W.A., Oberste M.S. (2006). Sensitive seminested PCR amplification of VP1 sequences for direct identification of all enterovirus serotypes from original clinical specimens. *Clin. Microbiol.*, vol. 44, no. 6, 2698–2704.

was conducted to develop a system of adequate regional anti-epidemic measures and key aspects of epidemiological surveillance.

Research objectives

1. To carry out clinical-laboratory and functional examination of patients with enterovirus infection of the eyes;
2. To identify and study the features of the clinical course of enterovirus damage to the visual organs;
3. To explore the relationship between the cytokine profile and the degree of expression of the inflammatory response in patients with different degrees of enterovirus infections of the eyes;
4. To develop an algorithm for assessing the risk of developing visual impairment in children with enterovirus infection;
5. To learn key aspects of epidemiological surveillance in relation to topical enterovirus infections and develop a regional system of anti-epidemic measures.

Research methods

The complex research includes a number of modern examination methods, including clinical, epidemiological, immunological, sociological, computational, statistical and other methods.

The main provisions of the research defense

1. Dynamics of biochemical, clinical and immunological indicators in blood and tears under the influence of treatment.
2. When assessing the severity of enterovirus uveitis, the score-rating system allows screening of the patient at the pre-admission level of inpatient services.
3. Principles and methods of complex treatment of enterovirus uveitis (EU) in children.

Scientific novelty of the research

- For the first time, clinical-functional examination of patients with enterovirus infection of the eyes was performed.
- For the first time, a score-rating system was established to assess the severity of enterovirus uveitis, which allows screening of

the patient's condition at the pre-admission level of inpatient services.

– It was found that immunological parameters in blood serum and tears correlate with the severity of the disease in patients with enterovirus infection of the eyes.

– A conceptual model of epidemiological control over enterovirus infections and a system of regional anti-epidemic measures have been developed on the basis of the conducted examinations.

Practical significance of the research

The detected clinical features of enterovirus uveitis (EU) are of great practical importance for ophthalmologists in the timely clinical diagnosis of a specific process occurring in the eye. The score-rating system can be recommended for ophthalmologists, pediatricians and other specialists in the search for the causes of uveitis as a pre-hospital screening assessment.

At the clinical stage, the examination plan includes the study of the general and local cytokine profile, determination of serum IL-8 and TNF- α in the blood serum and detection of IL-6 in tears to predict the course of the disease. The proposed epidemiological surveillance system allows ensuring the implementation of preventive and anti-epidemic measures aimed at reducing the incidence of enterovirus infections.

Approbation and application of the dissertation

The materials of the dissertation were discussed:

The results of the research were reported in 2016 at the V Azerbaijan National Congress on “Allergology, Immunology and Immunorehabilitation” in Baku, in 2016-2017 at the scientific-practical conference “Modern achievements of Azerbaijani medicine” in Baku, at the scientific-practical conference “Actual problems of medicine” dedicated to the 100th anniversary of the Azerbaijan Democratic Republic (Baku, 2018), and at the international scientific-practical conference dedicated to the 100th anniversary of the Medical Faculty (Baku, 2019). The dissertation materials were discussed at the interdepartmental meeting held jointly by the profile departments of Azerbaijan Medical University (Baku, 2021, protocol no. 1), at the

scientific seminar of the Approbation Commission under BFD 2.28/1 Dissertation Council (Baku, 2021, protocol no. 2). The materials of the dissertation are used in the teaching process of the departments of Epidemiology and Ophthalmology of AMU; the proposed practical recommendations are applied in practice.

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. According to the results of the study, 6 articles and 5 theses on the topic of dissertation were published.

Volume and structure of the thesis. The thesis is presented on 164 pages of computer text (215704 characters) and consists of an introduction (9417 characters), list of references (45451 characters), research materials and methods (19977 characters), 3-chapter research results (99455 characters) and their discussion (28.550 characters), summary(35138), conclusions(2336), practical recommendations (894 characters), bibliography covering 208 sources, including works by Azerbaijani authors. The thesis contains 30 tables and 21 figures.

MATERIALS AND METHODS OF THE RESEARCH

The research work was conducted in 2015-2017 on the scientific program of the departments of Ophthalmology and Epidemiology of Azerbaijan Medical University. Examinations were carried out using the prospective method on the basis of the departments of Ophthalmology and Epidemiology of AMU and Gakh Central District Hospital. Under our observation, in 2015-2017, there were 150 children with enterovirus (EV) infection of the eyes aged from 3 months to 14 years. The mean age was 7.50 ± 2.5 years, of which 63 were boys ($42.0 \pm 4.0\%$) and 87 were girls ($58.0 \pm 4.0\%$). In order to compare indicators and determine the degree of their difference from the physiological norm, we examined a control group of 50 somatic and ophthalmologically healthy individuals of the same age as EVU patients. For the examination, analytical, laboratory, epidemiological, information-educational and statistical methods were

used. The analysis of the data and the study of the correlation between a number of ophthalmological and laboratory parameters allowed us to distinguish a group of patients with different clinical course of EVU. The age distribution of the lesions according to the symmetry of the lesion showed that a unilateral process was found in 61 children (61 eyes) and a bilateral process in 89 children (178 eyes). A total of 239 eyes were involved in the process.

The number of patients in the first clinical group (severe) was 70 people. Young children predominated in this group, and the clinical course of EVU was characterized by the development of vitreoretinal pathology with low vision. The number of children in the second clinical group (moderate) was 48. In the second group, the majority of sick children were children and adolescents aged 7-14 years. In this group, visual impairment was observed mainly due to the opacity of the vitreous. In the third clinical group, we called it the “satisfactory” group, because in patients with EVU, visual acuity was maintained at a high level for a long time, and pathological changes in the vitreous were moderate, and older sick children predominated. Here includes 32 children with EVU. At the time of the examination, the duration of the disease varied from 2 to 9 years, taking into account the data of outpatient medical histories. The number of children and adolescents in the study groups varied.

The study included the following clinical and laboratory examinations of patients: general clinical; biochemical; determination of IgG-specific in IFA; and quantitative determination of enterovirus DNA by PCR test. Visual acuity in children was identified with or without correction using the Orlova and Golovin-Sivtsev tables with the Rott apparatus (illuminator), as well as through optotypes on the screen of a Canon projector and a set of standard lenses. Comprehensive assessment of intravitreal changes in patients with EVU was performed on the basis of biomicroscopy data describing the volume, configuration, and mobility of the vitreous, and was implemented on an UltraScan device equipped with an Alcon (USA) black-and-white and color display. Instrumental

methods include ECG, fluorography, ultrasound imaging. These methods were applied in only some patients. All patients should be advised by a rheumatologist, ENT, cardiologist, and dentist. Final examination and diagnosis of general pathology was performed by a pediatrician.

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 figures was based on the Student's t-test (t). 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

The data show that different strains of enteroviruses were identified in the materials we studied in 150 patients with EVU. Identification by a specific serum neutralization reaction allowed substantiating the etiological role of 2 groups of enteroviruses: ECHO 19 and ECHO 11. ECHO 19 virus was found in 63 children ($42.0 \pm 4.0\%$) and ECHO 11 virus in 48 children ($32.0 \pm 3.8\%$). Elevated titer of antibodies to ECHO 19 virus in the blood of 23 children with uveitis ($15.3 \pm 2.9\%$) and ECHO 19 in 16 children ($10.7 \pm 2.6\%$) was detected.

Given the clinical picture of the disease – 108 patients with uveitis ($72.0 \pm 3.7\%$) in the prodromal period and at the beginning of the fever period, it can be assumed that the infection is spread mainly by airborne-droplet transmission. The presence of intestinal syndrome in 42 ($28.0 \pm 3.7\%$) patients in the first 2-3 days of the disease (it occurs in violation of the anti-epidemic regime) suggests the presence of fecal-oral transmission of the disease.

The prevalence of EVU among children is quite high, mainly in regions with inadequate water supply. A more detailed analysis of EVU morbidity was conducted in the Gakh region of Azerbaijan in 2013-2017 (Figure 1).

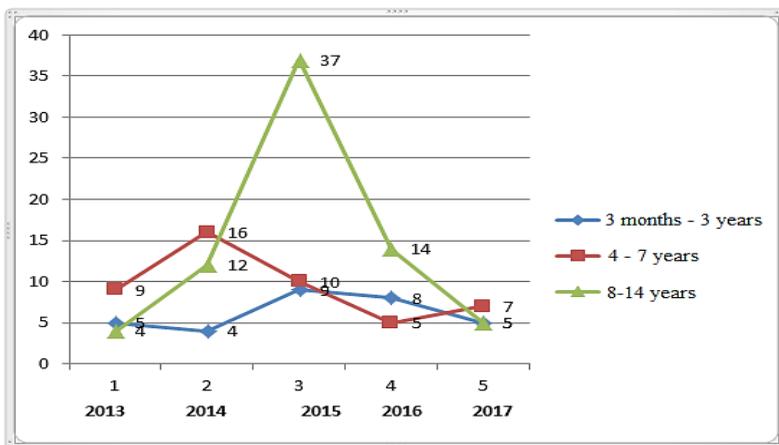


Fig.1. Age dynamics of the incidence rate with EVU in the Gakh region of Azerbaijan during 2013-2017.

Morbidity rates have changed according to the age groups of children and in 2015 compared to children aged 3 months to 3 years (9 children) the rates in the age group of 8-14 years (37 children) increased by 4.1 times and to 10 children in the age group of 4-7 years. The increase in morbidity in children aged 8-14 years was particularly intensive in 2014, 2015 and 2016: 16.6% (12 children), 51.4% (37 children) and 19.4% (14 children), respectively. There is an impression that there are outbreaks of EVI in this region, which mainly involve older children and, to a lesser extent, children under 6 years of age. In 2013, the morbidity rate among children was 6.9% (5 children), and in 2017 the lowest morbidity rate was observed – 5.7% (4 children). The examinations show that during the analyzed period, the incidence of EVU is unstable for the children of the region, which is characterized by a curved trend. This trend reflects the effectiveness of preventive and anti-epidemic measures. It was found that EVU is characterized by a predominance of disease in winter and autumn, i.e. the maximum monthly indicators of the autumn-winter seasons are in September (18 cases, 12.0%), October (21 cases, 14.0%), November (29 cases, 19.3%) and in December (33 cases, 22.0%). The minimum incidence was observed in the summer months: starting from May – 3 cases (2.0%), June (6 cases, 4.0%), July (4 cases, 2.8%), and August (5 cases, 3.3%).

The age characteristics of children and adolescents in the examination groups were in different percentages. The majority of patients with EVU were children aged 4 to 14 years ($79.3 \pm 3.3\%$). The distribution of children according to age regarding the symmetry of the lesion showed that the unilateral process was found in 61 children (61 eyes, $40.7 \pm 4.0\%$) and the bilateral process in 89 children (178 eyes, $59.3 \pm 4.0\%$). According to the etiology of EVU were distributed as follows: enteroviral – in 82 children ($54.7 \pm 4.1\%$), viral-bacterial – in 42 children ($28.0 \pm 3.7\%$; $\chi^2 = 77.64$; $p < 0, 01$), viral-allergic was found in 26 children ($17.3 \pm 3.1\%$; $\chi^2 = 14.36$; $p < 0.01$). In viral-bacterial etiology, the unilateral process was observed in 19 eyes ($31.1 \pm 5.9\%$; $\chi^2 = 72.46$; $p < 0.01$), and the bilateral process was observed in 46 eyes ($61.8 \pm 3.6\%$; $\chi^2 = 22.65$; $p < 0.01$). In viral-allergic etiology, the unilateral process was observed in 15 eyes ($24.6 \pm 5.5\%$; $\chi^2 = 12.43$; $p < 0.01$), and the bilateral process was observed in 22 eyes ($12.4 \pm 2.5\%$; $\chi^2 = 0.95$; $p > 0.05$). During the distribution of patients on the etiology of uveitis depending on age, it was found that in the age group of 3 months-3 years, viral-bacterial etiology ($58.1 \pm 8.9\%$; $\chi^2 = 18.24$; $p < 0.01$) and viral-allergic etiology of uveitis ($41.9 \pm 8.9\%$; $\chi^2 = 21.61$; $p < 0.01$) predominate. In the 4-7 age group, viral ($51.1 \pm 7.3\%$) and viral-bacterial uveitis ($36.1 \pm 7.0\%$; $\chi^2 = 65.18$; $p < 0.01$) were reported in most cases.

However, uveitis of viral-allergic etiology was found in $12.8 \pm 4.9\%$ of cases ($\chi^2 = 36.17$; $p < 0.01$). In the older age group (8-14 years), uveitis of enterovirus etiology ($80.6 \pm 4.6\%$; $\chi^2 = 16.27$; $p < 0.01$) predominated. The number of children with uveitis for the first time was only 78 people ($52.0 \pm 4.1\%$), with recurrent uveitis – 72 people ($48.0 \pm 4.1\%$).

Also, all children were distributed according to the localization of the process as follows: mainly damage to the anterior part of the eye – anterior uveitis in 76 children ($50.7 \pm 4.1\%$; $t = 4.72$; $p < 0.001$), peripheral uveitis in 54 children ($35.0 \pm 3.9\%$; $t = 2.64$; $p < 0.001$), posterior vascular lesions – chorioretinitis in 7 children ($4.7 \pm 2.1\%$; $t = 2.65$; $p < 0.001$), panuveitis in 13 children ($9.6 \pm 3.1\%$; $t = 1.78$; $p < 0.001$).

The characteristics of the groups of patients according to the severity of the disease showed that the number of patients in the first

clinical group (severe) was 70 people ($46.7 \pm 4.1\%$). The number of patients in the 2nd group with moderate severity of the disease was 48 people ($32.0 \pm 3.8\%$; $t = 4.54$; $p < 0.001$). In the third clinical group (with a satisfactory course), the number of patients was 32 ($21.3 \pm 3.3\%$; $t = 3.65$; $p < 0.001$). Many complications were found in children with enterovirus lesions, for example, in the first-time uveitis, acute opacity was observed in $52.6 \pm 5.7\%$ of cases, and in the recurrent form – $52.8 \pm 5.9\%$. In half of the patients retinal detachment was involved in the process: peripapillary edema in the first-time uveitis – $83.3 \pm 4.2\%$, in the recurrent form – $41.6 \pm 5.8\%$, macular edema of the retina in the first-time uveitis - $16.7 \pm 4.3\%$ of cases, in the recurrent form – $58.4 \pm 5.8\%$ ($p < 0.001$). In addition, 5.3% of patients developed optic neuritis.

In recent years, EVU is often accompanied by some complications: consecutive cataract – in $38.0 \pm 3.9\%$ of cases, corneal dystrophy – $22.0 \pm 3.4\%$, chorioretinal dystrophy $22.7 \pm 3.4\%$ ($p < 0.001$) and so on. This fact is due to the timely prevention of ocular complications of viral uveitis (Table 1).

Complications	Enterovirus Uveitis (EU)					
	First-time (n=78)		Recurrent (n=72)		Total (n=150)	
	Abs	%	Abs.	%	Abs.	%
Corneal dystrophy	11	14.1±3.9	22	30.6±5.5	33	22.0±3.4
Posterior synechiae	36	28.1±5.1	12	16.7±4.4	48	32.0±3.8
Acute opacity of the vitreous	41	52.6±5.7	38	52.8±5.9	79	52.6±4.1
Consecutive cataract (uveal)	24	30.8±5.2	33	45.8±5.8	57	38.0±3.9
Hemophthalmos	1	1.3	1	1.4	2	1.3
Eye bleeding	3	3.8	6	8.3	9	6.0
Retinal detachment (serous)	2	2.6	1	1.4	3	2.0
Macular edema of the retina	13	16.7±4.3	42	58.4±5.8	55	36.7±3.9
Retinal vasculitis	20	25.6±4.9	17	23.6±5.0	37	24.7±3.5
Chorioretinal dystrophy	16	20.5±4.6	18	25.0±5.1	34	22.7±3.4
Peripapillary edema	65	83.3±4.2	30	41.6±5.8	95	63.3±3.9
Optic neuritis	4	5.1	4	5.6	8	5.3
Subatrophy of the eyeball	3	3.8	1	1.4	4	2.7

Table 1. Complications accompanying the first-time and recurrent uveitis (in percentage)

Recurrences during EVU occurred alongside the development of many complications, including: multiple posterior synechiae – $16.7 \pm 4.4\%$ of cases, vitreous opacity – $45.8 \pm 5.8\%$ ($p < 0.001$), cataracts – $45.8 \pm 5.8\%$ of cases, chorioretinal dystrophies in $25.0 \pm 5.1\%$ ($p < 0.001$) of cases, etc. The retina and its vessels are almost always involved in the process: macular edema – $58.4 \pm 5.8\%$ of cases, peripapillary edema – $41.6 \pm 5.8\%$ ($p < 0.001$). Eye bleeding was noted in 8.3% of cases. The number of children with a first-time uveitis was only 78 people ($52.0 \pm 4.1\%$), with recurrent uveitis – 72 people ($48.0 \pm 4.1\%$, $p < 0.001$).

The score-rating system allows to develop the right tactics of follow-up of the patient in the pre-hospital stage, as well as to predict the course of the disease and its consequences. The following features were taken into account: edema of the cornea, corneal dystrophy, presence of precipitates in the endothelium of the cornea, changes in the shape of the pupil as a result of synechiae, and edema and dilation of the vessels of the iris during anterior uveitis. Pathological changes (floating opacities, exudate, fixed opacities) occurring in the vitreous during peripheral uveitis were also assessed. All symptoms were assessed on a 5-point scale. When there are common signs, the points are added to the sum of the individual points.

When studying the nature of changes in regional hemodynamics in patients with EVU, it was found that in the first group, with respective to V_s in TMA – 9.74 ± 0.18 cm / sec, V_d – 2.84 ± 0.04 cm / sec, as well as V_s in AGSA – 7.38 ± 0.45 cm / sec and V_d – 2.64 ± 0.14 cm / sec and R_i - 0.78 ± 0.02 , one or more pathological changes or secondary maculodystrophies in the form of cystosis maculopathies of macular edema of the vitreous-macula interface, cubretinal neovascular membrane, macular foramen were clinically recorded. In the second group, acceleration of the main parameters of hemodynamics: V_s , V_d in TMA and AGSA was recorded, and the aggravated course of EVU was not observed at all.

When studying the state of visual function in children with EVU, it was found that the decrease in visual acuity, as a rule

(86.0%) has a combined origin, and sometimes it is impossible to determine the role of each factor and the underlying cause. Sometimes the key factor has changed in the development of complications of the disease. Low vision is not only due to macular pathology (edema, membrane formation, dystrophy), which is sometimes accompanied by post-inflammatory changes of the optic disc or opacity of the vitreous in the optic region (45.3%) or crystal opacity.

Due to the treatment, there is a decrease in the total number of leukocytes in all groups: 23.3% in the first group, 19.6% in the second group, and 13.8% in the third group.

Enterovirus uveitis (EVU) was characterized by a significant increase in mean levels of TNF- α , IL-6, and IL-4 ($p < 0.01$) compared with control group levels during the acute phase of the disease. Significant increases in IFN- α and IFN- γ levels ($p < 0.05$) level in blood serum were observed in patients with EVU during the acute phase of the disease, which remained within the norm in the control group.

It is essential to determine the relationship between the levels of the studied cytokines and the relative number of major subpopulations of lymphocytes and the amount of class A, M, G immunoglobulins in the serum of patients with uveitis. No significant changes in the number of major subpopulations of lymphocytes in the blood of patients with EVU were found. However, during the EU, there was a significant decrease in the number of T-helpers (CD4 +) and the immune regulatory index (CD4 + / CD8 +) compared to the control group. Conversely, the number of CD8 + lymphocytes, blood cells with high proliferative activity expressing the CD71 + receptor, and CD95 + lymphocytes has increased, which is considered a normal immune response of the body against the virus antigen. A correlation ($r = 0.78$, $p = 0.054$) was established between the level of TNF production and the number of CD95 + during EV infection, which indicates an increase in the amount of IFN-g, as well as the development of Th1 response during viral infection of the eyes. In each of the study groups, the serum levels of

class A and M immunoglobulins (Ig) were significantly higher than in the control group ($p < 0.01$). The correlation between the number of B-cells (CD19 +) in the acute phase of the disease and the amount of IgM in patients with EU ($r = 0.7642$, $p = 0.022$), most likely, indicates the production of anti-uveal antibodies to this class of Ig. Their appointment is vital for the detection and assessment of the degree of expression of autoimmune syndrome, as well as the selection of an adequate treatment regimen for uveitis.

Since scores are determined on the basis of a set of clinical symptoms in the scoring system, it is possible to draw a conclusion on the basis of the correlation of scores with cytokines that the amount of cytokines corresponds to the clinical course of the disease. A strong direct correlation ($r = 0.9$, $r = 0.8$, $r = 0.6$) was established between the clinical course of the disease and TNF- α in all groups. The higher the TNF- α values, the more severe the disease is. With the help of this cytokine, the course of uveitis can be predicted, which dictates the need for additional tests to study its level in the blood at different stages of the disease. According to our studies, IL-6 and INF- γ may be markers of inflammatory processes in the vascular membrane during certain local immunity.

In children with allergic eye diseases associated with infectious changes, a significant decrease in secretory immunoglobulin A occurs on average up to 24.0% ($p < 0.05$), whereas in the group associated with allergic changes, the level of sIgA in tears increases to 21.0% ($p < 0.05$). Antibodies to eye tissues, mainly Ig and IgM class antibodies may be formed in children examined for infectious changes in the eye during this type of reaction. Analysis of the examination data shows a 2.3-fold increase in the level of class M antibodies and a 3.6-fold increase in class G antibodies ($p < 0.05$).

Based on the analysis of clinical and laboratory data of uveitis, as well as the analysis of the literature on the mechanisms of inflammation and immunopathology of the eye, we have developed and implemented the principles and methods of complex treatment of uveitis in children.

Treatment of EVU was carried out by different methods, in connection with which patients were divided into 2 groups, regardless of the severity of the disease. Group 1 included 57 patients receiving traditional treatment (general and local antiviral therapy) for uveitis. Group 2 included 93 patients receiving complex treatment of EVU (antibacterial, antiviral, detoxification, antioxidant, vascular-strengthening therapy). Prior to treatment, low visual acuity (up to 0.2) in $22.5 \pm 4.4\%$ of cases, 0.2-0.7 visual acuity in $45.2 \pm 5.2\%$ of cases, and high visual acuity (0.8-1.0) was recorded in $32.3 \pm 4.8\%$ of cases. Because of the complex treatment, the following dynamics of visual acuity was observed in all patients. Visual acuity lower than 0.2 in $9.8 \pm 3.1\%$ of cases, visual acuity of 0.2-0.7 in $12.8 \pm 3.5\%$ of cases, and high visual acuity was recorded in $77.4 \pm 4, 3\%$ of cases.

In the group receiving traditional treatment, low visual acuity (up to 0.2) was noted in 10.1% of cases, visual acuity of 0.2-0.6 – in 40.5%, high visual acuity of 0.7-1.0 – in 49% of cases. In the traditional treatment group, visual acuity of up to 0.2 in $12.3 \pm 4.3\%$ of cases, visual acuity of 0.2-0.7 cases in $42.1 \pm 6.5\%$ of cases, and visual acuity of 0.8-1.0 was recorded in $45.6 \pm 6.6\%$ of cases. After a traditional treatment, visual acuity was in the range of 0.8-1 in $59.6 \pm 6.5\%$ of cases, 0.2-0.7 in $31.6 \pm 6.4\%$ of cases, and less than 2 in $8.8 \pm 3.3\%$ of cases. In the day-to-day assessment of visual function dynamics, positive dynamics were observed in both groups for 4–5 days, regardless of treatment method, followed by faster positive dynamics of visual acuity in the complex treatment group, on average 1.5 days earlier than in the traditional treatment group.

Positive dynamics of the pathological process was observed in both groups. However, some symptoms of uveitis, such as weakening of the pericorneal injection, reduction or disappearance of precipitates, reduction of edema of the cornea and iris, reduction of edema of the eye, and decreased exudation of the vitreous, occurred rapidly in the complex treatment group. During EVU, the weakening of pericorneal injection in group 2 occurred on day 4.6 ± 0.93 ($p \geq 0.05$), decrease in the number of precipitates on day 5.9 ± 0.26

($p \geq 0.05$), reduction of corneal edema on day 6.66 ± 0.97 ($p \geq 0.05$), reduction of iris edema on day 6.44 ± 0.30 ($p \geq 0.05$), the beginning of absorption of exudate in the vitreous on day 11.10 ± 0.01 ($p < 0.05$), reduction of edema in the eye on day 10.39 ± 0.01 ($p < 0.05$). Weakening of pericorneal injection in the group receiving conventional treatment during EVU (group 1) occurred on day 4.52 ± 0.89 ($p \geq 0.05$), decrease in the number of precipitates on day 7.0 ± 0.35 ($p \geq 0.05$), reduction of corneal edema on day 6.66 ± 0.87 ($p \geq 0.05$) and reduction of iris edema on day 7.07 ± 0.41 ($p \geq 0.05$), the onset of exudation in the vitreous on day 16.15 ± 0.02 ($p < 0.05$), the reduction of edema in the eye on day 15.05 ± 0.06 ($p < 0.05$).

In group 2, the duration of treatment was reduced by 3-6 days (from 21 to 17 days) compared to group 1. The average length of stay in hospital was 18.42 ± 1.27 days in group 2 (in the group who received traditional treatment was 22.33 ± 1.69 days). The recovery dynamics of visual acuity was positive in all groups, but occurred at different rates. The onset of positive dynamics of visual acuity was observed on average 3 ± 0.92 days in the group with satisfactory level of the disease, 6 ± 0.76 days in the group with moderate level, and 8 ± 0.88 days in the group with severe level. In the majority of patients, visual acuity reached 1.0 in the group with satisfactory level on the 16th day, in the group with moderate level on the 27th day, and in the group with severe level practically less than 1.0.

In the group with severe disease, the absence of injection occurred on average 5.2 ± 0.75 days. The decrease or complete disappearance of the number of precipitates occurred on day 9.4 ± 1.4 . The cornea became transparent, sweating and edema disappeared on day 8.13 ± 1.06 . Iris edema disappeared on average day 9.4 ± 0.76 . The onset of exudation in the vitreous was on average day 20.6 ± 0.9 , and the reduction of edema in the eye occurred on day 18.8 ± 1.06 . In the group with a satisfactory course of the disease, the absence of injection occurred on average day 4.2 ± 0.38 , the number of precipitates decreased or disappeared on day 4.8 ± 0.54 , the cornea became transparent, sweating and edema disappeared on day $5.5 \pm$

0.45, iris edema disappeared on average day 3.9 ± 0.38 . Decreased exudation in the vitreous occurred on average day 7.57 ± 1.4 , and the onset of edema in the eye occurred on day 6.35 ± 1.3 . The basis of epidemiological surveillance is the assessment of health status, identification of causes and conditions of enterovirus infection, identification of regional features of the cause-and-effect relationship between the health status of the population and its determining factors, and identification of specific environmental factors that adversely affect the health of the population.

Thus, enterovirus infection is a common intestinal infection among children, and the lack of specific prophylaxis makes it easier for infection to occur and for morbidity to increase. Early diagnosis allows the selection of adequate therapy, rapid prevention of symptoms of the disease, as well as the timely implementation of preventive measures. The data of the examinations allow us to identify the epidemiological patterns of the spread of EV infection among children and suggest measures to reduce their level, as well as to develop comprehensive tactics for the treatment and prevention of this disease.

Results

1. According to clinical and laboratory examinations, it was determined that the majority of patients with EVU were children aged 4 to 14 years ($79.3 \pm 3.3\%$). Uveitis of enterovirus etiology was detected in $54.7 \pm 4.1\%$ of children, viral-bacterial etiology in $28.0 \pm 3.7\%$ of children, and viral-allergic etiology in $17.3 \pm 3.1\%$ of children. The number of children with a first-time uveitis was only 78 people ($52.0 \pm 4.1\%$), with recurrent uveitis was 72 people ($48.0 \pm 4.1\%$).

2. The score-rating system allows developing the tactics of proper follow-up of the patient in the pre-hospital stage, predicting the course of the disease and its consequences. In this case, a system that detects quantitative criteria for assessing the severity of the disease is more effective as it allows characterizing the condition of the eyes during the exacerbation of uveitis, as well as the dynamics of symptoms over time.

3. For the first time in children, complex values of cytokines were determined during EVU. A strong direct correlation between IL-12 and INF- γ has been established, which is a manifestation of the inverse relationship between pre-inflammatory and regulatory cytokines. There is also a strong direct correlation between IL-6 and the clinical course of the disease, i.e. high levels of IL-6 are characteristic of severe uveitis and when all clinical symptoms are pronounced.

4. Detection of broad-spectrum changes in electrophysiological tests indicates damage to the optic nerve in the majority of children with EVU. A study of individual functional outcomes showed that 17.6% of children with EVU began to see poorly 2 years after the onset of the disease.

5. Due to the general anti-inflammatory, detoxification and antioxidant effects of the complex treatment, the reduction of the duration of the use of pharmaceutical drugs in the treatment process and the reduction of the drug load on the patient's body was observed. Recovery from viral uveitis occurred in $86.6 \pm 3.8\%$ of patients and improvement in 9.7% of patients. Recovery from viral-bacterial uveitis occurred in $61.9 \pm 7.5\%$ of patients, improvement – in $28.6 \pm 7.0\%$ of patients. Recovery from viral-allergic uveitis occurred in $69.2 \pm 9.1\%$ of patients, improvement – in $19.2 \pm 7.6\%$ of patients. The established regularities of the epidemic process of enterovirus infection have established a system of adequate anti-epidemic measures aimed at preventing the formation and spread of the epidemic variant of the causative agent.

Practical recommendations

1. The use of pre-hospital assessment of the severity of uveitis with a scoring-rating system (before immuno-laboratory tests) allows increasing the diagnostic effectiveness of the disease, which is considered an important factor in determining the patient's follow-up tactics and predicting the body's response to therapy.

2. Enterovirus uveitis (EU) is characterized by a significant increase in mean levels of TNF, IL-6 and IL-4 in the acute phase of the disease compared with similar indicators in the control group.

3. Higher levels of all cytokines are noted in uveitis of viral-bacterial and viral-allergic etiology, which indicates an active level of inflammatory response and a high level of immunization.

4. Prolonged course of uveitis, frequent relapses, complications, and autoimmune inflammation were observed in all patients with higher levels of pre-inflammatory cytokines.

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