7. Könönen E, Gursoy M, Gursoy UK. Periodontitis: A Multifaceted Disease of Tooth-Supporting Tissues. J Clin Med. 2019;8(8):1135. doi: 10.3390/jcm8081135.

8. Köse O, Arabacı T, Yemenoglu H, Ozkanlar S, Kurt N, Gumussoy I, et al. Influence of experimental periodontitis on cardiac oxidative stress in rats: a biochemical and histomorphometric study. J Periodontal Res. 2017;52(3):603–608. doi: 10.1111/jre.12428.

9. Susana FM, Paula P, Slobodianik N. Dietary modulation of thymic enzymes. Endocr Metab Immune Disord Drug Targets. 2014;14(4):309–12. doi: 10.2174/1871530314666140915125248.

10. Tomina DC, Petruțiu ȘA, Dinu CM, Crișan B, Cighi VS, Rațiu IA. Comparative Testing of Two Ligature-Induced Periodontitis Models in Rats: A Clinical, Histological and Biochemical Study. Biology (Basel). 2022;11(5):634. doi: 10.3390/biology11050634.

O.V. Zborovska, I.S. Horianova, V.O. Ulianov[1], O.E. Dorokhova, E.V. Maltsev, N.I. Molchaniuk
State Institution "Filatov Institute of Eye Diseases and Tissue Therapy
of NAMS of Ukraine", Odessa
[1]National University "Odesa Law Academy", Odessa

EFFECT OF NEUROPROTECTIVE THERAPY WITH CITICOLINE ON THE COURSE OF EXPERIMENTAL NON-INFECTIOUS ANTERIOR AND INTERMEDIATE UVEITIS

e-mail: li--na@ukr.net

Non-infectious anterior and middle uveitis is a significant uveitis group, leading to decreased visual acuity and often blindness. The purpose of the study was to determine the features of the clinical course and morphological changes of the choroid, retina, and optic nerve in the early and late stages of experimental non-infectious anterior and middle uveitis under the conditions of neuroprotective citicoline therapy. We studied the clinical course of the disease and morphological changes on the 10–13th, and 33rd days after the administration of the provocative dose. The use of citicoline led to a decrease in inflammation in uveitis. First of all, due to reduced swelling of the cornea and iris. It was confirmed by histomorphological examination. It reduced the violation of the retinal cytoarchitectonic disturbances and degenerative and destructive changes in its neurons. It also reduced the swelling of the retina and optic nerve cells. It activated intracellular compensatory processes in the retina, particularly in the pigment epithelium and optic nerve glial cells.

Key words: anterior uveitis, intermediate uveitis, experimental animal model, choroid, retina, optic nerve, citicoline.

О.В. Зборовська, І.С. Горянова, В.О. Ульянов, О.Е. Дорохова, Е.В. Мальцев, Н.І. Молчанюк

ВПЛИВ НЕЙРОПРОТЕКТОРНОЇ ТЕРАПІЇ ЦИТІКОЛІНОМ НА ПЕРЕБІГ ЕКСПЕРИМЕНТАЛЬНОГО НЕІНФЕКЦІЙНОГО ПЕРЕДНЬОГО ТА СЕРЕДНЬОГО УВЕЇТУ

Неінфекційні передні та середні увеїти – це значна група увеїтів, що призводить до зниження гостроти зору, а нерідко і до сліпоти. Метою дослідження було визначити особливості клінічного перебігу та мофрологічних змін хоріоідеї, сітківки і зорового нерву на ранніх та пізніх строках перебігу експериментального неінфекційного переднього і середнього увеїту за умов нейропротекторної терапії цитіколіном. Вивчався клінічний перебіг захворювання та мофрологічні зміни на 10–13 та 33 добу після введення провокуючої дози. Застосування цитіколіну призвело до зменшення виразності запалення при увеїті. В першу чергу за рахунок зменшення набряку рогівки та райдужної оболонки. Що підтверджується за допомогою гістоморфологічного дослідження. Це зменшення порушення цитоархітектоніки сітківки, дегенеративних та деструктивних змін її нейронів, зменшення набряку клітин сітківки і зорового нерва; активація внутрішньоклітинних компенсаторних процесів в сітківці, зокрема, в клітинах пігментного епітелію, а також в гліальних клітинах зорового нерву.

Ключові слова: передній увеїт, середній увеїт, експериментальна тваринна модель, судинна оболонка, сітківка, зоровий нерв, цитіколін.

Uveitis is a common, vision-threatening inflammatory eye disease with many clinical manifestations. The prevalence of different types of uveitis depends on many factors, such as age, sex, race, geographic distribution, environmental exposure, genetics, and social habits [11]. According to etiology, it is divided into infectious uveitis – more common (30–60 %) in developing countries, non-infectious – this is a significant group of uveitis arising from systemic diseases of the body (about 40 %) – more common in developed countries of the world [11].

Macular edema is the most common complication leading to vision impairment in 41 % of patients. It is most often found in chronic inflammation [1]. Macular edema can persist even when the inflammation is controlled or in remission, so treatment should also be aimed at eliminating this complication [3]. Swelling of the optic nerve in uveitis does not develop so often, but its threat to vision loss is also very high [6].

Modern treatment is based on corticosteroids and biological therapy aimed at reducing pain and preventing inflammation of eye tissues [12]. However, this treatment does not reduce the frequency of vision loss and blindness in patients.

Citicoline (cytidine 5"-diphosphocholine, or CDP-choline) is a neuroprotective substance or neuroprotector. Its primary function is to stimulate the biosynthesis of structural phospholipids in neuron membranes, which reduces swelling and improves nerve impulse conduction. It also inhibits apoptosis and stimulates acetylcholine synthesis, preserving neurons' energy reserves. Citicoline easily penetrates the blood-brain barrier [10]. Works have been done on its use in neurotoxic lesions of the optic nerve (ON) [8] and glaucomatous optic neuropathy [4].

Understanding the relationship between the clinical picture and morphological changes in uveitis will improve our understanding of the pathophysiological processes. The proposed experimental treatment can enhance therapy in the clinic in the future.

The purpose of the study was to determine the features of the clinical course and morphological changes of the choroid, retina, and optic nerve in the early and late stages of experimental non-infectious anterior and middle uveitis under the conditions of neuroprotective citicoline therapy.

Materials and methods. Experimental studies were performed on 48 Chinchilla rabbits kept in standard vivarium conditions. Work with experimental animals and their sacrificing was carried out in accordance with the rules of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) and according to the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty". The study was approved by the bioethical committee of the State Institution "Filatov Institute of Eye Diseases and Tissue Therapy of NAMS of Ukraine", Odesa, Protocol No. 2 of 11.10.21.

Experimental animals were divided into two groups: 1) non-infectious anterior and middle uveitis was modeled in 24 rabbits; 2) non-infectious anterior and middle uveitis was modeled in 24 rabbits, and citicoline therapy was carried out.

The clinical course of uveitis was assessed using ophthalmoscopy and biomicroscopy. The severity of the inflammatory process and the presence of the following symptoms were taken into account: lacrimation, photophobia, injection, corneal edema, precipitates, iris edema, iris vasodilation, cellular grading in the anterior chamber, hypopyon, fresh synechiae, inability to visualize the fundus (due to uveitis). In the presence of a symptom, 1 point was taken into account for the overall assessment of the expressiveness of the inflammatory process; in the absence – 0 points. In the presence of such symptoms as fibrin in the anterior chamber and the impossibility of visualizing the vitreous body (due to uveitis), 2 points were taken into account [2].

The animals were sacrificed after the disappearance of the symptoms of active uveitis on the 10th–13th day after the intravitreal injection of a provocative dose of sterile normal horse serum after the normalization of the temperature of the eyeball in the projection of the ciliary body, which indicates the disappearance of the inflammatory process, on the 33rd day [2].

After the previous administration of sodium thiopental at a dose of 50 mg/kg, animals were sacrificed by air embolism. Eyeballs were taken for histological studies, fixed in 10 % neutral formalin, and embedded in paraffin. The prepared sections with a thickness of 5 μm were stained with hematoxylin-eosin. The preparations were photographed using a microscope "Laboval 4, Carl Zeiss, Jena" and a digital camera "Canon Power Shot A 480" at the magnifications specified in the figure captions.

For research using the electron microscopic method, pieces of tissue were fixed in a 2.5 % glutaraldehyde solution in a phosphate buffer at a pH of 7.4, followed by fixation with a 1 % osmium acid solution at the same pH as the buffer solution. The samples were dehydrated in ascending alcohols. The impregnation of tissues and their polymerization was done in a mixture of Epon/Araldite epoxy resin. Ultrathin sections were contrasted according to the classic Reynolds method. Tissue samples were examined and photographed in an electron microscope PEM-100-01 (Ukraine). Histomorphological studies were performed in the pathomorphological and electron microscopic studies laboratory of the State Institution "Filatov Institute of Eye Diseases and Tissue Therapy of NAMS of Ukraine", Odesa.

Non-infectious anterior and middle uveitis was modeled according to the method described by O.E. Dorokhova with co-authors (2020). Rabbits were sensitized by daily intravenous injection of sterile normal

horse serum (BIOWEST SAS, France) in a volume of 1.0 ml for 5 days. Ten days after the start of sensitization, a provocative dose of 0.1 ml of normal horse serum was injected intravitreally into the right eye. The left eye remained intact. Anterior and middle uveitis developed a day after the administration of the provocative dose. In the second experimental group, when uveitis was modeled, neuroprotective therapy with citicoline was performed: daily intramuscular injections of 0.2 ml of the drug during the entire observation period from the first day after introducing a provocative dose of horse serum.

The temperature of the eyeball in the projection of the ciliary body was measured using a thermoelectric device, according to the method proposed by Dorokhova et al. [2].

Descriptive and variational statistics methods were used to analyze the obtained data. The variance distribution was tested for normality using the Shapiro-Wilk test. In the case of a normal distribution, variance analysis was performed to compare experimental groups according to the severity of inflammation; if the null hypothesis was rejected, the Newman-Keuls test was used for further study. The χ^2 test was used to compare groups based on the number of rabbits with various symptoms of uveitis.

Results of the study and their discussion. The studies characterized the clinical course of experimental non-infectious anterior and middle uveitis in rabbits and examined the effect of citicoline use on this course. In the first three days after the intravitreal injection of a provocative dose of horse serum, signs of the course of acute inflammation were observed in rabbits of both experimental groups. Lacrimation, photophobia, and sclera injection were found ophthalmoscopically and biomicroscopically in all animals of both groups. Vasodilation and edema of the iris and cornea were observed in more than 75 % of rabbits, cell grading in more than 71 %, and fibrin – in 58 % of animals. Hypopyon occurred less often in the first three days of the experiment – in 33–42 % of cases (Table 1). The level of inflammation on the first day of the experiment was 9.42±0.29 points in animals receiving citicoline and 9.29±0.27 points; on the third day, 9.83±0.57 and 9.88±0.55 points, respectively.

A gradual decrease in the inflammatory reaction was observed on the fifth day of uveitis. In both groups, the number of animals with lacrimation and photophobia decreased by half. In addition, compared to the previous observation period, the number of rabbits receiving citicoline decreased by 47.4 % and 34.8 %, respectively, in the number of animals with iris and corneal edema. On the fifth day of uveitis, there was no statistically significant difference between animals that received and did not receive citicoline. The level of inflammation in animals that did not receive citicoline averaged 8.38±0.58 points under conditions of neuroprotective therapy – 7.96±0.37 points.

Table 1

**Dynamics of detection and changes in symptoms
of experimental non-infectious anterior and middle uveitis (n – number of experimental animals)**

Clinical sign	Experimental uveitis, group without neuroprotector, day of follow-up, (n)					Experimental uveitis and the use of neuroprotective therapy, day of follow-up, (n)				
	1	3	5	7	10	1	3	5	7	10
Lacrimation	24	24	12* p<0.001	2* p=0.002	0	24	24	11* p<0.001	2* p=0.004	0
Photophobia	24	24	12* p<0.001	2* p=0.002	0	24	24	11* p<0.001	2* p=0.004	0
Injection	24	24	24	5* p<0.001	0	24	24	24	4* p<0.001	0
Corneal edema	20	22	18	5* p<0.001	0	19	23	15* p<0.001	0* p<0.001 ^{1}p=0.025	0
Precipitates	22	24	24	7p<0.001	3	19	24	24	5* p<0.001	2
Iris edema	16	18	14	6 * p=0.002	0	17	19	10* p<0.008	0 * p<0.001 *^{1}p =0.02	0
Iris varix	18	18	18	5* p<0.001	0	20	19	16	3* p<0.001	0
Anterior chamber cell grading	18	18	18	3* p<0.001	0	18	17	17	3* p<0.001	0
Fibrin in the anterior chamber	15	17	16	3* p<0.001	0	14	16	17	1* p<0.001	0
Hypopyon	10	10	9	2* p=0.017	0	8	9	9	1* p=0.005	0
Fresh synechiae	20	20	20	0	0	22	22	20	0	0

Notes: * – p<0.05 compared to the previous observation period; *1 – p<0.05 compared to animals that did not receive neuroprotective therapy.

On the seventh day of the experiment, the most significant differences in the clinical course of uveitis were found between animals that received and did not receive neuroprotective therapy. Thus, any animal with edema of the iris and cornea was found using citicoline. The mean level of inflammation in animals treated with citicoline was statistically significantly lower than in animals with uveitis without

treatment: 0.83±0.21 points versus 1.67±0.36 points (p=0.049). Finally, the clinical signs of inflammation disappeared on the 10th–13th day after administering the uveitis-inducing dose of horse serum. It should also be noted that in most animals of both groups, it was impossible to visualize the fundus from the first to the fifth day of the course of uveitis. The inability to visualize the fundus after the fifth day of uveitis was not associated with the course of the acute stage of the disease but with the development of its complications, particularly lens opacity.

Understanding the qualitative parameters of the structural changes in the eye membranes caused by the inflammatory process is essential for predicting the consequences of uveitis. Therefore, we investigated and compared the structural changes in the choroid, retina, and optic nerve at the end of the acute period of anterior and middle uveitis (10–13 days after the administration of a provocative dose of horse serum) and the remote period, starting from the 33rd day of the disease's initiation, when the temperature of the eyeball in the projection of the ciliary body reached physiological values.

It was established that the course of anterior and middle uveitis was accompanied by pronounced damage to the structure of the retina with swelling and dyscomplexation of its layers, the death of photoreceptor cells and cells of the pigment epithelium, and dystrophic changes in ganglion cells on the 13th day of disease reproduction.

At the beginning of the early distant period, the destructive processes in the retina progressed, evidenced by several pathological changes, including those that were previously absent. Among them, retinal traction in the vitreous body, the appearance of subatrophy and atrophy, and previously existing dyscomplexation of its layers can be noted. Fig. 1 shows the focus of destruction of the retina with dyscomplexation of its layers and death of neurons.
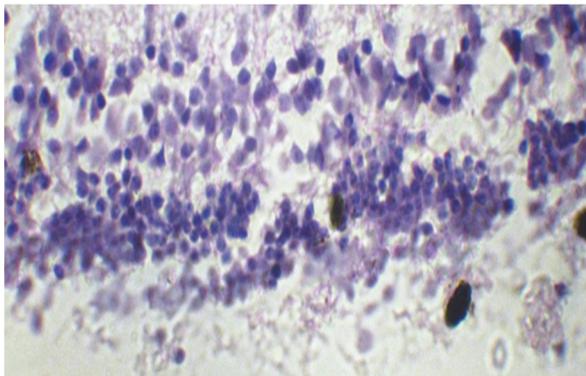

Fig. 1. Permanent histological preparation of the retina of a rabbit with non-infectious anterior and middle uveitis, 33rd day of observation. A focus on dyscomplexation of the layers of the retina. Staining: hematoxylin-eosin. Magnification 280×.

Neuroprotective therapy using citicoline from the first day of uveitis reproduction reduced the severity of the retinal layers' dyscomplexation, which became almost total focal. The differences between the animals that received the specified drug and those that did not increased on the 33rd day of the experiment.

At the ultrastructural level, in animals with uveitis without citicoline treatment, dystrophic changes in choriocapillaries of endothelial cells were found in the vascular membrane; dystrophic and destructive changes in the cells of the pigment epithelium in the retina, dystrophic and destructive changes in pigment epithelial cells, damage to photoreceptor cells on the 13th day of the experiment and replacement of dead neurons with glial cells – gliosis, on the 33rd; in the optic nerve – axoplasmic edema, damage to cytoskeletal components, dystrophic changes in glial cells, myelin deformity shells (fig. 2A, 2B).
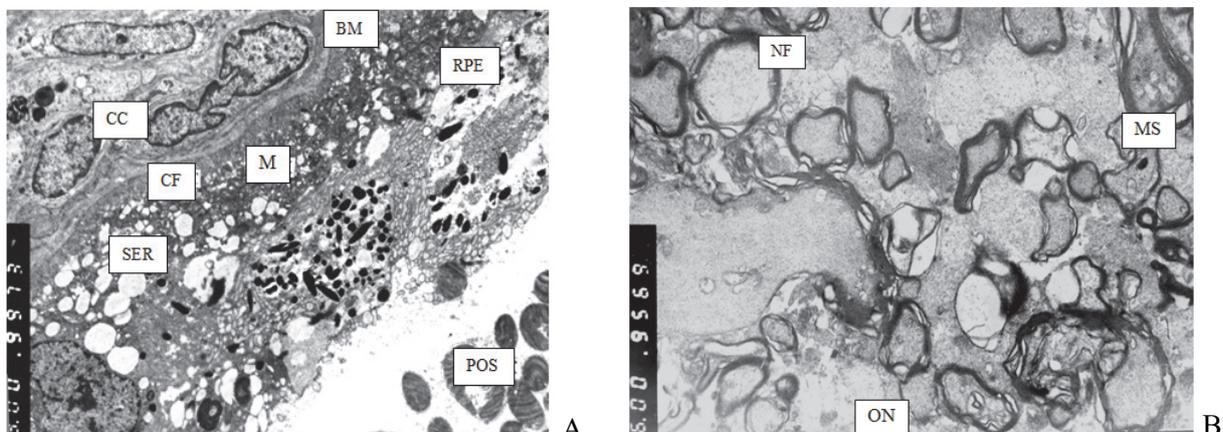

Fig. 2. Ultrastructure of the choroid and retina (A) and optic nerve (B) of a rabbit on day 13 after simulation of non-infectious anterior and middle uveitis without treatment with citicoline. A – Hydropic degeneration of pigment epithelium cells, X 3 000. B – Deformation of the myelin sheath with elements of separation into lamellae. Swelling of axoplasm in individual nerve fibers, X 6 000. Symbols: RPE – retinal pigment epithelium, SER – smooth endoplasmic reticulum, BM – Bruch's membrane, M – mitochondria, CC – choriocapillaris, POS – photoreceptor outer segments, CF – choroidal folds, ON – optic nerve, NF – nerve fibers, MS – myelin sheath.

Neuroprotective therapy with citicoline reduced the severity of negative ultrastructural changes in the membranes of the eyeball in experimental anterior and middle uveitis. First, interstitial edema decreased, compensatory and restorative processes in retinal neurons increased, and dystrophic changes in choriocapillaries of epithelial cells decreased (Fig. 3A).
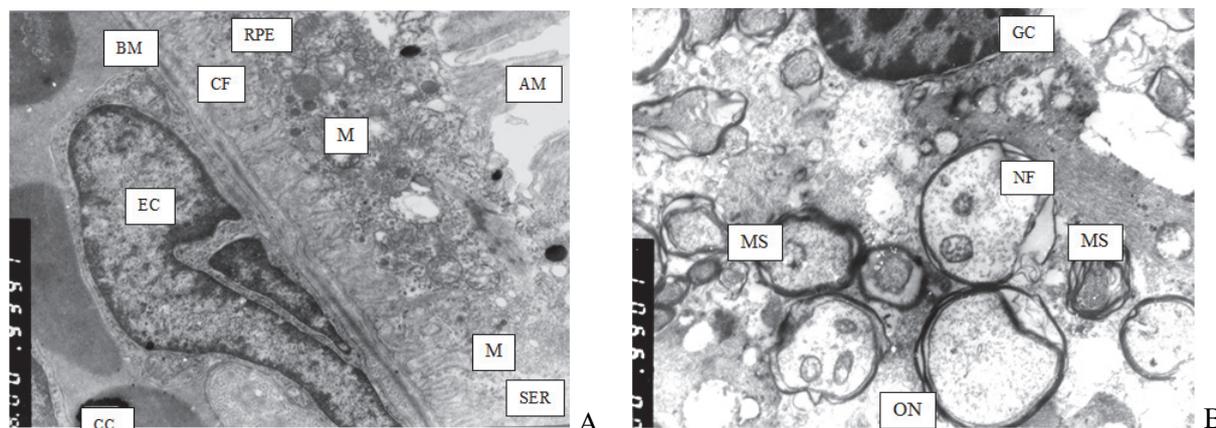

Fig. 3. Ultrastructure of rabbit retina on day 13 (A) and optic nerve on day 11 (B) after simulation of non-infectious anterior and middle uveitis with citicoline treatment. A – Signs of compensatory and restorative processes in the choriocapillaries of epithelial cells and the pigment epithelium cell. X 8 000. B – Hydropic changes in the axoplasm and focal stratification of axons of nerve fibers. X 8 000. Symbols: RPE – retinal pigment epithelium, BM – Bruch's membrane, CF – choroidal folds, POS – photoreceptor outer segments, P – polysomes, SER – smooth endoplasmic reticulum, AM – apical microvilli, M – mitochondria, EC – endothelial cell, CC – choriocapillaris, ON – optic nerve, GC – glial cell, MS – myelin sheath, NF – nerve fibers.

In the optic nerve, after the neuroprotector was used, the deformation of the myelin sheaths and swelling in the axoplasm occurred to a lesser extent and in a smaller number of NF. The majority of glial cells had signs of enhanced compensatory and restorative processes. (Fig. 3B).
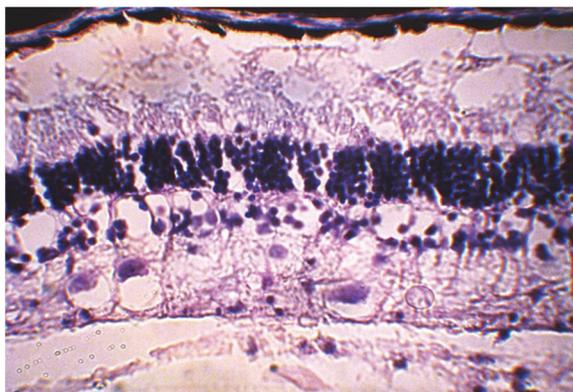

Fig. 4. Permanent histological preparation of the retina of a rabbit with non-infectious anterior and middle uveitis, treatment with citicoline, 33rd day of observation, relatively mild dystrophic changes, lymphocytes in the surface layers of the retina and vitreous body of the patient eye. Staining: hematoxylin-eosin. Magnification 280×.

In the long-term follow-up, neuroprotective therapy caused relatively minimal damage to the retina and optic nerve (Fig. 4). Although the cytoarchitectonics of the retina are preserved, there are degeneratively changed neurons of the inner nuclear layer and ganglion cells (Fig. 4).

We believe several pieces of information obtained through the research are essential for understanding the pathogenesis of non-infectious anterior and middle uveitis and improving its treatment methods. Namely, the inflammatory process of the choroid in anterior and middle uveitis is accompanied by pronounced dystrophic changes in the retina and optic nerve. One essential clinical manifestation of uveitis is swelling of the cornea, iris, choroid, retina, and optic nerve tissues at the light-optical and ultramicroscopic levels. Neuroprotective therapy with citicoline reduces retinal and optic nerve tissue damage.

As for edema, the hypothesis is that retinal tissue swelling can change its plastic properties and, when critical values are reached, cause irreversible local damage. Edema is not excluded as a significant factor in the occurrence of areas of dyscomplexation of the retinal layers detected during the modeling of uveitis. After all, one of the mechanisms of retinal alteration in uveitis is the effect of pro-inflammatory cytokines, particularly by contributing to cystic macular edema [9]. In this case, the proven ability of citicoline to reduce swelling of the retina and this method of exerting a neuroprotective effect will be extremely useful [5].

Citicoline's neuroprotective effect was revealed. It reduced retina dyscomplexation, neuron destruction, and gliosis due to increased Müller cells and their replacement of dead neurons, which we observed in animals that did not receive neuroprotective treatment. Microglial cells may interact with Müller cells during the reconstruction of the damaged retina. It is known that microglial cells can initiate the infiltration of immune cells into the retina during the development of autoimmune uveitis [7].

Similar mechanisms associated with edema may be responsible for the damage to the optic nerve we detected in modeling uveitis, particularly swelling of the axoplasm, deformation of myelin sheaths, and foci of their destruction in individual nerve fibers. The last assumption can be based on the mathematical

model of damage to retinal ganglion cell axons in glaucomatous optic neuropathy [14]. It should also be noted that the treatment of uveitis, in particular with corticosteroids, can cause an increase in intraocular pressure and additional damage to the optic nerve [13]. Therefore, citicoline's revealed effects can help treat uveitis in the acute period and as a neuroprotector during long-term anti-relapse treatment with corticosteroids.

Conclusions

1. Neuroprotective therapy (citicoline) changes the clinical course of experimental non-infectious anterior and middle uveitis. The expressiveness of the inflammatory reaction in animals that received citicoline on the seventh day of the disease was 0.83 ± 0.21 points, lower than in untreated animals by 50.3 % (p=0.049). The reduction of inflammation in uveitis was achieved primarily due to reduced edema of the cornea and iris in animals treated with citicoline compared to animals that did not receive neuroprotective therapy (p<0.05).

2. Using a neuroprotector (citicoline) from the first day of reproduction of non-infectious anterior and middle uveitis reduces retinal cytoarchitectonic disturbances and degenerative and destructive changes in its neurons. It also reduces swelling of cells of the retina and optic nerve. It activates intracellular compensatory processes in the retina, particularly in pigment epithelium cells and optic nerve glial cells.

References

1. Alvarez-Guzman C, Bustamante-Arias A, Colorado-Zavala MF, Rodriguez-Garcia A. The impact of central foveal thickness and integrity of the outer retinal layers in the visual outcome of uveitic macular edema. Int J Retina Vitreous. 2021 Apr 27;7(1):36. doi: 10.1186/s40942-021-00306-8.
2. Dorokhova O E, Zborovska OV, Guanjun Meng. Relationship of the ocular surface temperature with the clinical features of induced non-infectious anterior and intermediate uveitis in rabbits. J.ophthalmol.(Ukraine).2020;6:38–43. http://doi.org/10.31288/oftalmolzh202063843.
3. Fung S, Syed YY. Suprachoroidal Space Triamcinolone Acetonide: A Review in Uveitic Macular Edema. Drugs. 2022 Sep;82(13):1403–1410. doi: 10.1007/s40265-022-01763-7.
4. Jünemann AGM, Grieb P, Rejdak R. Bedeutung von Citicolin bei der Glaukomerkrankung [The role of citicoline in glaucoma]. Ophthalmologe. 2021 May;118(5):439–448. German. doi: 10.1007/s00347-021-01362-z. [in German]
5. Laksmita YA, Sidik M, Siregar NC, Nusanti S. Neuroprotective Effects of Citicoline on Methanol-Intoxicated Retina Model in Rats. J Ocul Pharmacol Ther. 2021 Nov;37(9):534–541. doi: 10.1089/jop.2021.0018.
6. Luceri S, Erba S, Casalino G. A Boy with Anterior Uveitis and Optic Disc Swelling. JAMA Ophthalmol. 2021 Dec 1;139(12):1313–1314. doi: 10.1001/jamaophthalmol.2021.1056.
7. Okunukia Y, Mukaia R, Nakaob T, Tabora SJ, Butovskyc O, Danab R et al. Retinal microglia initiate neuroinflammation inocular autoimmunity.PNAS. 2019;116(20):9989–9998.
8.Park CH, Kim YS, Cheon EW, Noh HS, Cho CH, Chung IY et al. Action of citicoline on rat retinal expression of extracellular-signal-regulated kinase (ERK1/2). Brain Res. 2006 Apr 7;1081(1):203–10. doi: 10.1016/j.brainres.2005.12.128.
9.Santina A, Bousquet E, Somisetty S, Fogel-Levin M, Tsui E, Freund KB et al. Recurrent anterior uveitis associated with major fluctuations in choroidal thickness in a patient with pachychoroid disorder. Retin Cases Brief Rep. 2024 Sep 1;18(5):562–565. doi: 10.1097/ICB.0000000000001437.
10. Secades JJ, Gareri P. Citicoline: pharmacological and clinical review, 2022 update. Rev Neurol. 2022 Nov 30;75(s05): S1–S89. doi: 10.33588/rn.75s05.2022311.
11. Tsirouki T, Dastiridou A, Symeonidis C, Tounakaki O, Brazitikou I, Kalogeropoulos C, et al. A Focus on the Epidemiology of Uveitis. Ocul Immunol Inflamm. 2018;26(1):2–16. doi: 10.1080/09273948.2016.1196713.
12. Valdes LM, Sobrin L. Uveitis Therapy: The Corticosteroid Options. Drugs. 2020 Jun;80(8):765–773. doi: 10.1007/s40265-020-01314-y.
13. Wu X, Tao M, Zhu L, Zhang T, Zhang M. Pathogenesis and current therapies for non-infectious uveitis. Clin Exp Med. 2023 Aug;23(4):1089–1106. doi: 10.1007/s10238-022-00954-6.
14. Yakymenko I, Ulyanova N, Shakun K. The development of glaucomous optic neuropathy prediction. Part I. Mathematical model of deformation of the lamina cribrosa and damage to nerve filaments in glaucoma. Oftalmologija. Vostochnaja Evropa. 2018;8(4):475–486.