NEURODEGENERATIVE DISEASES AND THEIR IMPACT ON THE OPTIC NERVE

Jalalova Dilfuza Zuhridinovna

Scientific supervisor.

Department of Ophthalmology, Samarkand State Medical University.

Eshimov Elbek

Samarkand State Medical University, Department of Ophthalmology,

1st year clinical Ordinator.

https://doi.org/10.5281/zenodo.15075139

Abstract. *Study of morphological changes in the central parts of the visual analyzer in glaucoma and identification of the role of mitochondrial dysfunction in the development of neurodegenerative changes. study of morphological changes in the central parts of the visual analyzer in glaucoma and identification of the role of mitochondrial dysfunction in the development of neurodegenerative changes. A post-mortem examination was conducted on two people who had glaucoma during their lives and whose deaths were not associated with diseases of the central nervous system. Immunohistochemical examination revealed astrogliosis and beta-amyloid deposits in the cerebral cortex and optic nerve. Structural and functional changes in mitochondria were detected.*

Degenerative changes in POAG affect both retinal ganglion cells and optic nerve fibers, as well as tissues of the visual analyzer pathways up to the cerebral cortex. Mitochondrial dysfunction may be one of the mechanisms of development and progression of neurodegeneration in primary open-angle glaucoma.

Keywords: *glaucoma, neurodegeneration, brain, mitochondria.*

Introduction: to study morphological changes in the central part of the visual analyzer in glaucoma and to determine the role of mitochondrial non-degenerative changes in its development.

Primary open-angle glaucoma (POAG) is an age-related disease characterized by a progressive course even against the background of normalized ophthalmotonus [1, 3]. As is known, as in all neurodegenerative diseases, the mechanism of death of retinal cells and optic nerve axons in glaucoma is physiologically programmed apoptosis [3, 4, 6, 12].

Neurodegeneration is characterized by damage to cells and intercellular substance, which leads to organ dysfunction. Neurodegeneration is based on a violation of trophism, that is, a set of mechanisms that ensure the metabolism and preservation of the structure of cells and tissues.

Neurodegenerative diseases are diseases that occur as a result of progressive degeneration and death of neurons that are part of certain structures of the central nervous system, leading to disruption of connections between parts of the central nervous system and an imbalance in the synthesis of relevant neurotransmitters, and as a result, a general deterioration in memory, coordination of movements, and thinking. In particular, most such diseases develop in older people. For example, the prevalence of neurodegenerative diseases in patients aged 70-75 years is approximately 5%, and in those over 80 years old it reaches 15%. Modern clinical and experimental research data show that the majority of neurodegenerative diseases are determined by hereditary factors (i.e., the disease is inherited or occurs as a result of pathological mutations of the corresponding genes during life). Common symptoms of neurodegenerative diseases include a long latent period (from 6 to 8-10 years).

The most famous of these diseases are Alzheimer's, Parkinson's, Huntington's and Pick's diseases. As the population continues to age in developed countries, the overall prevalence of neurodegenerative diseases shows a clear upward trend [5]. There are diseases that manifest themselves mainly as dementia, such as Alzheimer's disease (atrophy of the gray matter and cholinergic neurons of the brain, cognitive functions (memory, reasoning, etc.) suffer), Pick's disease - a malignant dementia in which the frontal and temporal lobes of the cortex atrophy occurs. There are also diseases with extrapyramidal syndromes, such as Parkinson's disease, in which neurodegeneration of gray matter and dopamine neurons occurs, manifested by movement disorders and tremors. The clinical presentation of Huntington's disease, in which the striatum and cortex atrophy, is characterized by hyperkinesia and mental retardation. Cerebellar degenerations and motor neuron lesions are distinguished, for example, amyotrophic lateral sclerosis, which occurs as a result of degeneration of the motor cortex and manifests itself in the form of paralysis and muscle atrophy.

Glaucoma is also one of the neurodegenerative diseases. The development of neurodegeneration in glaucoma combines many factors and pathways of ganglion cell apoptosis, but all of them are somehow related to mitochondria as the main unit responsible for energy processes and apoptosis in the cell. Identifying the role of mitochondrial dysfunction in the development of POAG provides the opportunity to develop neuroprotection on a pathogenetic basis.

Let's present facts that may link glaucoma to neurodegenerative diseases.

1.General mechanism of cell death: it is known that the death of retinal ganglion cells, as in all neurodegenerative diseases, is a physiologically programmed apoptosis. Apoptosis begins with the activation of special proteases - caspases, which enter the cell nucleus and destroy DNA.

In turn, the activation of caspases is directly related to mitochondrial dysfunction. In other neurodegenerative diseases, for example, Alzheimer's disease, they are also activated.

2.The death of a type of neuron, the disruption of synaptic connections, which leads to a disruption of central function: In Alzheimer's disease, the frontal lobes of the brain are affected, leading to a disruption of cognitive function, while in glaucoma, the optic nerve fibers die and visual function is impaired.

3.The "age-related" nature of the disease: neurodegenerative diseases develop with age and have a long-term chronic course. The prevalence of glaucoma increases with the age of the population, and the development of the disease occurs over several years.

There is a belief that glaucoma is a manifestation of a general neurodegenerative condition of the body [8-11].

The aim of the study is to study morphological changes in the central parts of the visual analyzer in glaucoma and to determine the role of mitochondrial dysfunction in the development of neurodegenerative changes.

Methods

Pathological examination was performed on 2 people whose deaths were not associated with diseases of the central nervous system. As indicated in the outpatient records, the duration of POAG was from 8 to 10 years and the diagnosis of advanced glaucoma was documented.

Morphological and pathological studies, including the description of the material and morphometry of the cells of the analyzed structures, were carried out at the Department of Pathological Anatomy of the North-Western State Medical University named after. II Mechnikov" Corresponding Member of the Russian Academy of Medical Sciences of the Ministry of Health of the Russian Federation, Honored Scientist of the Russian Federation, Doctor of Medical Sciences, Professor NM Anichkova.

Immunohistochemical research was carried out in the Laboratory of Functional Morphology of the Central and Peripheral Nervous System of the Federal State Budgetary Institution "Research Institute of Experimental Medicine" of the North-Western Branch of the Russian Academy of Medical Sciences under the leadership of the Head of the Department of General and Special Morphology, Doctor of Medical Sciences DE Korzhevsky.

Results

Macroscopic examination of preparations of the visual analyzer pathways revealed pronounced atrophy of the optic nerve with the loss of numerous axons, as well as the loss of a significant number of neurons in the lateral geniculate body. Microscopic examination revealed a decrease in the thickness of the cell layer of the visual cortex, a reduction in the radius of neurons and their nuclei, a fragmented, granular cytoplasm, and the presence of a large amount of lipofuscin, which indicates an atrophic process.

In both cases, neurodegenerative processes were detected in deceased patients who had POAG during their lifetime. All levels of the central part of the visual analyzer were involved in the degenerative process, but the most noticeable was the area of the visual cortex in the calcarine tubule. It should be noted that amyloid plaques and bodies were found in the optic nerve and in layers IV-V of the cerebral cortex (Fig. 1, 2).

Beta-amyloid is known to be a marker of neurodegenerative diseases, and its presence suggests a pathogenetic link between POAG and Alzheimer's disease. The neurodegenerative process in the cerebral cortex is also indicated by the tortuosity of individual arteries in the cortical region, which is a consequence of a decrease in the thickness of the cortex while maintaining the length of the vascular bed. In this case, the radial arteries of the cortex are tortuous and twisted in the vascular lumen. Signs of astrogliosis, detected under the microscope, can be considered as a result of neurodegeneration, the death of neurons and oligodendrocytes and their replacement by immature, functionally defective astrocytes.

With POAG, a neurodegenerative process develops, which involves not only the peripheral part of the visual analyzer, but also the conductive pathways and the central part, that is, the visual pathway as a whole.

Two cases require separate consideration. First, the presence of beta-amyloid, a generally recognized marker of neurodegeneration, a characteristic morphological sign of Alzheimer's disease, in the brain tissue of people with POAG. Second, the process of neurodegeneration is accompanied by astrogliosis, that is, the death of brain cells and their replacement by young, functionally immature astrocytes that are unable to perform supportive, protective, trophic, and other auxiliary functions.

Many neurodegenerative diseases are polyetiological, and at present it is very difficult to determine the trigger mechanism for each of them. However, there is convincing evidence that mitochondria play a central role in the processes of neuronal apoptosis [6]. Under various conditions (aging, "oxidative stress", accumulation of mutant mitochondrial DNA) and under the

influence of various substances (neurotoxic proteins, including beta-amyloid), the permeability of mitochondrial pores changes [7]. This process leads to the release of calcium ions and apoptosis activators from mitochondria, which determines the irreversible process of neurocyte death. In this regard, we investigated mitochondrial functions in patients with POAG.

Currently, clinical and biochemical (evaluating the level of pyruvate and lactate, antioxidant activity and blood lipid peroxidation products) research methods are used to determine the characteristics of mitochondrial functions. The essence of these studies is that when mitochondrial functions are impaired (oxidative aerobic phosphorylation), intracellular processes switch to catabolism. Most processes in the cell proceed anaerobically with the formation of lactic acid. In addition, mitochondrial dysfunction is accompanied by the formation of a large amount of ROS and the development of oxidative stress, which exacerbates mitochondrial dysfunction [2, 12]. The processes of lipid peroxidation and oxidation of thiol groups of membrane proteins are activated.

In our study, sulfhydryl (SH-) and disulfide (SS-) groups, as well as their ratio (normally not lower than 6.5), were studied in 30 patients with POAG. A decrease in the level of sulfhydryl SH groups and an increase in the level of disulfide SS groups, as well as a change in their ratio, which averaged 5.4, were found in the blood of patients. These results reflect a violation of the redox balance of tissues and its transition to catabolic processes (Fig. 3).

The participation of sulfhydryl groups in the processes of lipid peroxidation of membrane components, which leads to the development of degenerative changes in tissues, has also been established. Activation of free radical lipid peroxidation of cell membranes is one of the causes of accelerated aging. Changes in the membrane during aging lead to a different reaction of the cell to the processes of excitation and inhibition, intercellular relations, and the transport of substances in conditions of hyperfunction caused by age-related changes in metabolism. During biological aging, tissue oxygen consumption and the intensity of all basic metabolic processes decrease.

An increase in the level of lactate in the blood of patients may indicate a violation of redox processes and tissue respiration. We conducted a study of the content of lactic acid in the blood of patients with POAG, as well as patients in the control group. There were no statistically significant differences in gender and age between patients in the main and control groups (Fig. 4).

The normal blood lactate level is 1.33-1.80 mmol / L. In patients in the control group, the level of lactate in the blood was on average 2.78±0.15 mmol / L, while in patients in the main group (with POAG) the level of lactate in the blood was significantly higher than the norm and averaged 4.33±0.3 mmol / L.

A cell with damaged mitochondria cannot produce enough energy to sustain its life, cannot maintain the necessary amount of calcium, and produces large amounts of harmful oxidizing molecules.

Under normal conditions, all mitochondria in a cell have the same copy of DNA.

However, mutations can occur in the mitochondrial genome, as a result of which the function of mitochondria is impaired. In this case, normal DNA can compensate for the pathological effects of the mutation. Thanks to unchanged mitochondria, the cell can function for some time. If energy production in it falls below a certain threshold, compensatory proliferation of all mitochondria, including defective ones, occurs.

The minimum amount of altered DNA required to cause significant disruption and dysfunction in the energy metabolism of a particular organ or tissue is called the “kissing effect.”

When the threshold is exceeded, the functioning of the cell changes, which is accompanied by certain clinical diseases. The “threshold effect” is influenced by various factors, but the most important are the energy needs of certain tissues and organs, as well as their sensitivity to oxidative stress and age.

In connection with the above, the possibility of visual assessment of the state of mitochondria in the structures of the eyeball in POAG is of particular interest. The only material available for electron microscopy is a preparation of the anterior chamber angle obtained during penetration for deep sclerectomy using the block cutting method.

Electronograms showed endothelial cells of Schlemm's canal, as well as connective tissue fibroblasts, in which slightly enlarged mitochondria with an electron-dense matrix were found.

Mitochondrial crystals were reduced and shrunken. Degeneration and disruption were observed in individual mitochondria. All registered structural changes in mitochondria had varying degrees of severity.

Fibrocytes, surrounded by bundles of collagen fibers of various structures, predominate in the connective tissue. The contours of the mitochondria of fibroblast cells are wavy, their crystals are deformed (Fig. 5). The outer cavity of the mitochondria appears light and optically empty. A fine-grained substance with increased electron density is detected in the matrix (Fig. 6). In some fibroblasts with pronounced dystrophic changes, sharply swollen mitochondria are found. They show vacuoles and fragments of crystals located near the membrane. The matrix of the inner cavity is sharply illuminated.

Mitochondrial changes are less pronounced in the endothelium than in fibroblast cells.

Disintegration of mitochondrial crystals is noted. A fine-grained substance with increased electron density is also detected in the inner cavity of endothelial mitochondria.

Discussion: During morphological studies, in particular, electron microscopic studies of mitochondria in the trabecular zone of the eyeball, we identified clear changes in the structure of the organelles under study. Disorders in the structure of mitochondria can lead to a significant inhibition of their functions. With age, free radical lipid peroxidation of cell membranes is activated. A genetically determined decrease in mitochondrial function is also possible. Structural and functional changes in mitochondria lead to excessive production of reactive oxygen species. Mitochondria are the main source of superoxide anion production in cells.

During the transport of electrons to molecular oxygen, 1 to 5% of the electrons in the respiratory chain are lost in the formation of superoxide anion. Damage to the mitochondrial DNA genome occurs due to free radicals - using 90% of cellular oxygen, mitochondria are the main candidate for oxidative DNA damage. Decreased ATP production and impaired calcium homeostasis in mitochondrial dysfunction contribute to the development of neurodegeneration, which occurs through the mechanism of metabolic excitotoxicity. Mitochondrial swelling leads to the release of caspase activators (e.g., cytochrome C), which trigger the process of apoptosis - programmed cell death.

There is growing evidence that glaucoma has many similarities with other neurodegenerative diseases. The glaucoma process extends far beyond the eyeball, the pathogenesis of this disease goes beyond the scope of traditional ophthalmology, being at the intersection of ophthalmology and neurology. In this regard, it is necessary to look at the glaucoma process from a perspective that is not typical for us, ophthalmologists. The experience accumulated by neurologists involved in the development of neurodegeneration will help us to further study the pathogenesis, diagnosis and treatment of the glaucoma process.

Conclusion

In POAG, degenerative changes are detected at autopsy in both retinal ganglion cells and optic nerve fibers, as well as in the tissues of the visual analyzer pathways up to the cerebral cortex.

This indicates a clear neurodegenerative nature of POAG, which is confirmed by the generally accepted criteria of a neurodegenerative process, such as astrogliosis, and the presence of beta-amyloid deposits in the cerebral cortex and optic nerve.

REFERENCES

1. БЕЛКА, F. S. P. C. P. (2022). В ПАТОГЕНЕЗЕ СОСУДИСТЫХ ЗАБОЛЕВАНИЙ ОРГАНА ЗРЕНИЯ У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ.
2. Жалалова, Д. З., Кадирова, А. М., & Хамракулов, С. Б. (2021). Исходы герпетических кератоувеитов на фоне лечения препаратом «офтальмоферон» в зависимости от иммунного статуса пациентов. междисциплинарный подход по заболеваниям органов головы и шеи, 103.
3. ЖД, З., and А. БС. "РЕЗУЛЬТАТЫ ОЦЕНКИ УРОВНЯ ЭНДОТЕЛИНА-1 И Д-ДИМЕРОВ В СЛЕЗНОЙ ЖИДКОСТИ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ." SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES 3.3 (2024): 300-307.
4. Zhalalova, D. Z. OCT angiography in the assessment of retinal and choreoretinal microcirculation in patients with uncomplicated arterial hypertension International Ophthalmological Congress IOC Tashkent 2021.
5. Zhalalova, D. Z. Evaluation of markers of endothelial dysfunction in tear fluid in patients with arterial hypertension. Journal of Biomedicine in Amaliet. Tashkent-2022, Volume No., No. WITH.
6. Жалалова, Д. З. (2021). Эндотелин-1 ва гомоцистеин даражасини артериал гипертензия фонида тур пардв узгаришларида эндотелиал дисфункциянинг маркерлари сифатида текшириш. Биомедицина ва амалиет журнали, 6(5), 203-210.
7. Jalalova, D., Axmedov, A., Kuryazov, A., & Shernazarov, F. (2022). Combined dental and eye pathology. Science and innovation, 1(8), 91-100.
8. Zhalalova, D. Z. (2022). Pulatov US MICROCIRCULATORY DISORDERS IN THE VASCULAR SYSTEM OF THE BULBAR CONJUNCTIVA WITH INITIAL MANIFESTATIONS OF INSUFFICIENT BLOOD SUPPLY TO THE BRAIN. European journal of molecular medicine, 2(5).
9. Жалалова, Д. З. (2021). ОКТ-ангиография при оценке сосудистого русла сетчатки и хориоидеи. Биология ва тиббиет муаммолари, 6(130), 211-216.
10. Жалалова, Д. З. (2022). Классификационые критерии изменений сосудов сетчатки при артериальной гипертензии. In Международная научная конференция Университетская наука: взгляд в будущее (pp. 56-64).
11. Долиев, М. Н., Тулакова, Г. Э., Кадырова, А. М., Юсупов, З. А., & Жалалова, Д. З. (2016). Эффективность комбинированного лечения пациентов с центральной

серозной хориоретинопатией. Вестник Башкирского государственного медицинского университета, (2), 64-66.

12. Жалалова, Д. З. Оценка маркеров эндотелиальной дисфункции в слезной жидкости у пациентов с артериальной гипертензиейЖурнал «Биомедицина ва амалиет». Тошкент-2022, Том №, №. С.
13. Жалалова, Д. З. (2021). ОКТ-ангиография в оценке ретинальной и хореоретинальной микроциркуляции у пациентов с неосложненой артериальной гипертензией/I Международный офтальмологческий конгресс IOC Uzbekistan, 2021 г. Ташкент, с, 96.
14. Shernazarov, F., Jalalova, D., Azimov, A., & CAUSES, S. A. (2022). SYMPTOMS, APPEARANCE, TREATMENT OF VARICOSE VEINS.
15. Жалалова, Д. З. (2021). Эндотелин-1 ва гомоцистеин даражасини артериал гипертензия фонида тур пардв узгаришларида эндотелиал дисфункциянинг маркерлари сифатида текшириш. Биомедицина ва амалиет журнали, 6(5), 203-210.
16. Shernazarov, F., Tohirova, J., & Jalalova, D. (2022). Types of hemorrhagic diseases, changes in newboens, their early diagnosis. Science and innovation, 1(D5), 16-22.
17. Zhalalova, D. Z. (2022). The content of endothelin and homocysteine in blood and lacrimal fluid in patients with hypertensive retinopathy Web of Scientist: International Scientific Research Journal. ISSUE, 2, 958-963.
18. Shernazarov, F., & Zuhridinovna, J. D. (2022). Microcirculation disorders in the vascular system of the bulbar conjunctiva in the initial manifestations of cerebral blood supply deficiency. Science and innovation, 1(Special Issue 2), 515-522.
19. Zhalalova, D. Z. (2022). Modern aspects of neuroprotektive treatment in hypertensive retinopathy Web of Scientist: International Scientific Research JournalVolume 3. ISSUE, 2, 949-952.
20. Жалалова, Д. З. (2009). Метод комбинированного лечения диабетической ретинопатии. Врач-аспирант, 37(10), 864-868.
21. Жалалова, Д. З. (2023). Результаты оценки эффективности комплексного лечения у пациентов с 3-4 стадиями гипертонической ангиоретинопатии. Miasto Przyszłości, 41, 33-36.
22. ЖД, З., & ИЖ, Ж. (2024). КЛАССИФИКАЦИЯ ГИПЕРТОНИЧЕСКОЙ РЕТИНОПАТИИ НА ОСНОВЕ ДАННЫХ ОПТИЧЕСКОЙ КОГЕРЕНТНОЙ ТОМОГРАФИИ. SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES, 3(3), 336-342.

23. ЗЖД, Ж. (2024). КЛИНИКО-ФУНКЦИОНАЛЬНЫЕ ПОКАЗАТЕЛИ ОРГАНА ЗРЕНИЯ У ПАЦИЕНТОВ С ИШЕМИЧЕКИМИ ИЗМЕНЕНИЯМИ СОСУДОВ СЕТЧАТКИ. SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES, 3(3), 286-293.
24. ЖД, З. (2024). ОЦЕНКА КЛИНИЧЕСКИХ И ФУНКЦИОНАЛЬНЫХ ПОКАЗАТЕЛЕЙ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ В СЛЕЗНОЙ ЖИДКОСТИ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ. SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES, 3(3), 330-335.
25. Жалалова, Д. З. (2023). Актуальность проблемы изменений глазного дна при артериальной гипертензии. Miasto Przyszłości, 41, 37-40.