



Neurodegenerative Change of the Visual Analyzer in Glaucoma

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Abstract

The aim of the research was to explore structural changes in the central departments of the visual analyzer for glaucoma.

Materials and Methods: mortem examination was carried out in two people's death was not related to diseases of the central nervous system. Far-advanced glaucoma diagnosis was established and verified in life. There have been mortem, morphological and immunohistochemical studies, including a description of the material, morphometry of the optic nerve cells, optic chiasm, lateral geniculate body and visual cortex.

Results: Macroscopic examination revealed severe atrophy of the second cranial nerve with the loss of a considerable number of axons and neurons in the lateral geniculate nucleus. Micrography showed the reduction of the cell layer's thickness of the visual cortex, the puckering of the neurons' radius and their nuclei's radius. Examination also revealed grumose, granular cytoplasm, the presence of lipofuscin in vast numbers, which indicates an atrophic process.

In either case, neurodegeneration processes were revealed in deceased patients, who suffered from POAG. All levels of the visual analyzer's central division were involved in the degenerative process; however, the area of the visual cortex in the area of the calcarine fissure was most noticeable. It should be highlighted that in the optic nerve and IV-V layers cortical amyloid plaques were detected and calf.

Conclusion: It was established as a result of autopsy that with POAG degenerative changes occur in the retina ganglion cells, fibers of the second cranial nerve, and the tissue of the visual analyzer's pathways until visual cortex. This indicates a marked neurodegeneration character POAG, which is confirmed by the presence of the generally accepted criteria of neurodegenerative process as astrogliosis and the presence of beta-amyloid accumulation in the cortex and in the optic nerve. This pathology is similar to other neurodegenerative diseases such as Alzheimer's or Parkinson's.

Key Words: Open-angle Glaucoma, Neurodegeneration, The Optic Nerve, Chiasm, Lateral Geniculate Nucleus, Visual Cortex, Astrogliosis, Beta-amyloid, Alzheimer's Disease.

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Introduction

Primary open-angle glaucoma has been attributed to neurodegenerative diseases over recent years. Intolerant intraocular pressure is considered to be the main reason for the development of

neuroopticopathy in glaucoma. The disease develops with age and is defined by a progressive course even against the background of a normalized level of ophthalmotonus (Alekseev *et al.*, 2014; Abysheva *et al.*, 2015).

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The mechanism of death of retinal cells and axons of the optic nerve in glaucoma, as in all neurodegenerative disorders, is a physiologically programmed apoptosis (Egorov *et al.*, 2001, p.118; Egorov *et al.*, 2016; Elichev *et al.*, 2012; Izzotti *et al.*, 2010).

However, especially in foreign literature, increasingly frequently, works declare the connection between POAG and such neurodegenerative diseases as Alzheimer's and Parkinson's (Bayer *et al.*, 2002; Gupta *et al.*, 2008). Undoubtedly, there is much in common between them: an increase in the incidence rate with age, a selected lesion of one type of neuron, and the same mechanism of nerve cell death. It is possible that with POAG, pathological changes do not end in the optic nerve disk, but spread throughout the path of the visual analyzer (tractus opticus) (Bizrah *et al.*, 2011; Gupta *et al.*, 2006).

The aim of the research was to study the structural changes in the central departments of the visual analyzer for glaucoma.

Materials and Methods

The studies were carried out taking into account the provisions of the Helsinki Declaration of the World Medical Association (1996 - 2013). In the process, the requirements of the Federal Law of the Russian Federation No. 152 "On Personal Data" (Clause 3, Article 6) and the order of the Ministry of Health of the Russian Federation "On the Procedure for Anatomicopathological Autopsy" (No. 354 of 06/13/2013) were followed. The article strictly complied with international recommendations on work with material obtained from humans (International ethical guidelines for biomedical research involving human subject, CIOMS). Permission was received from the Ethics Committee of the 'North-West State Medical University named after I.I. Mechnikov' for all types of research.

Anatomicopathological examination was conducted for two people whose death was not related to diseases of the central nervous system. As indicated in the ambulatory medical record, they suffered from POAG for 8-10 years, and the diagnosis of advanced glaucoma was established with the targeted use of appropriate methods and documented. A morphological and pathoanatomical study, comprising the material's description and morphometry of the cells of the analyzed structures, was performed at the Department of Pathological Anatomy of 'North-West State Medical

University named after I.I. Mechnikov' of the Ministry of Health of Russia under the supervision of a corresponding member of the Russian Academy of Medical Sciences, Honored Scientist of the Russian Federation, Doctor of Medical Sciences, Professor N.M. Anichkova. An immunohistochemical study was undertaken at the Laboratory of Functional Morphology of the Central and Peripheral Nervous System of the Federal State Budgetary Institution 'Scientific Research Institute of Experimental Medicine' of the North-Western Branch of the Russian Academy of Medical Sciences. The study was performed under the supervision of the head of the department of general and private morphology, D.E. Korzhevsky.

Immunohistochemical Study

Paraffin sections of the brain with a thickness of 10 μm were made according to the generally accepted method on a rotational microtome RM2125RT (Leica, Switzerland). After dewaxing and rehydration in alcohols with descending concentration, the preparations were washed in distilled water for 2–5 min. Further, a number of cell type markers were detected by the immunohistochemical method: GFAP (glial fibrillary acidic protein) - an astroglia marker (antibodies from Dako, Denmark; Spring Bioscience and Biocare Medical, USA); NeuN - marker of the nucleus of mature neurons (Dako, Denmark); A β 1-42 - marker of beta amyloid protein (antibodies from Spring Bioscience, USA); vWF - von Willebrand factor - a marker of endotheliocytes of vessels (antibodies from Dako, Denmark). Identification of the NeuN marker was conducted according to a modified technique (Korzhevsky D.E. *et al.*, 2009). The remaining markers were detected according to the manufacturer's protocols. The preparations were studied using a Leica DM light microscope (Leica, Germany) and a confocal laser microscope (LSM 510 Meta (Zeiss, Germany). Image processing was performed using computer programs included in the LSM Image Browser package (Zeiss, Germany).

Results

A macroscopic examination revealed acute optic nerve's atrophy with the loss of a considerable number of axons and neurons in the lateral geniculate body. Micrography showed a decrease of the cell layer's thickness of the visual cortex, puckering of the radius of neurons and nuclei.



Moreover, it revealed grumose, granular cytoplasm, and the existence of lipofuscin in vast numbers, which indicated an atrophic process. In either case, neurodegeneration processes were revealed in deceased patients, who suffered from POAG. All levels of the central department of the visual analyzer were involved in the degenerative process; however, the area of the visual cortex in the area of the calcarine fissure was most noticeable. It should be stressed that amyloid plaques and bodies were found in the optic nerve and in the IV - V layers of the cerebral cortex (Figures 1, 2).

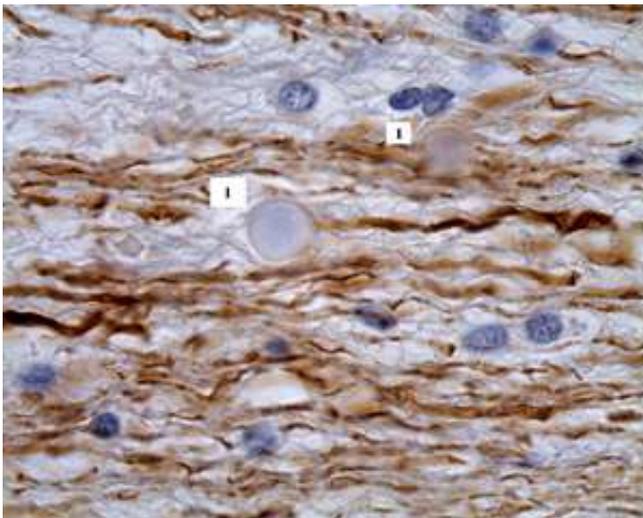


Figure 1. Autopsy. Amyloid Bodies (1) in the Optic Nerve in Glaucoma. Immunohistochemical Study

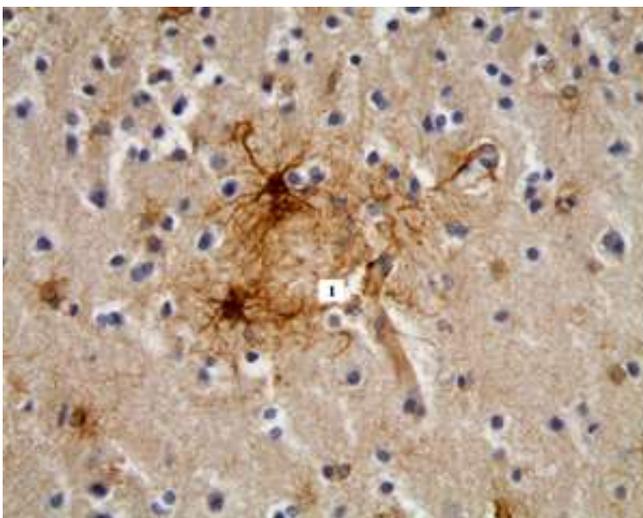


Figure 2. Autopsy. Amyloid plaque (1) in the cerebral cortex in glaucoma. Immunohistochemical Study

It is common knowledge that amyloid-beta is a marker of neurodegenerative diseases; its presence shows a pathogenetic relationship of POAG with Alzheimer's disease. The tortuosity of individual arteries of the j also indicates a neurodegenerative process in the cerebral cortex (Figure 3), which is a

consequence of a decrease in the thickness of the cortex while maintaining the blood stream's length. In that case, the radial arteries of the cortex are folded and twisted within the paravascular space. The signs of astrogliosis revealed by microscopy can be considered as a consequence of neurodegeneration, the death of neurons and oligodendrocytes, and their substitution by immature, functionally incomplete astrocytes.

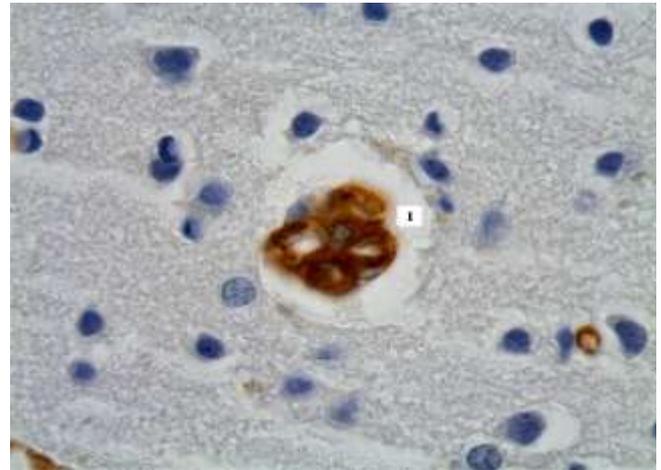


Figure 3. Autopsy. Twisted arteries (1) of the visual cortex in glaucoma. Immunohistochemical Study

Finally, the presence of astrogliosis should be noted (Fig. 3), which is detected during the death of neurons and oligodendrocytes and replacing them with immature astrocytes, which can slow down the process, but cannot solve the problem of degeneration.

Summarizing the data, it can be argued that with POAG there is a degenerative process that captures not only the retina and second cranial nerve, but also the entire optic pathway. Such pathology is similar to such neurodegenerative diseases as Alzheimer's or Parkinson's. And here it makes sense to mention two more significant aspects: the presence of β -amyloid in the nervous tissue. β -amyloid is a generally accepted marker of neurodegenerative diseases, which is also a recognized marker of degeneration in Alzheimer's disease.

Another aspect is astrogliosis. Degenerative changes in the nervous tissue lead to the death and disappearance of a large number of nerve cells. There is a kind of replacement of neurons and oligodendrocytes with young, immature astrocytes, which cannot fully conduct their supporting, protective and trophic function.

And finally, on the mechanisms of nerve tissue degeneration. Recently, many authors agree that the degeneration of the neural elements of the optic

pathway can with the process of secondary transsynaptic neurodegeneration. In other words, there is a direct transition of the degenerative process from damaged altered cells to intact ones (Bayer *et al.*, 2002).

This hypothesis is supported by numerous data on pathological changes in the conduction paths of the healthy eye in experimental models of unilateral glaucoma.

According to N. Gupta *et al.* (2008), the process of transsynaptic degeneration combines primary glaucoma with other neurodegenerative diseases, while axonopathy is a key element in their development.

An in-depth study of this issue led to a revision of the classical theory of neuronal death in which the degeneration of dendrites and axons occurs after damage to the body of cell. Distal processes of neurons and their synapses are the most vulnerable point in the development of a degenerative process, which also applies to primary open-angle glaucoma. Violation of axonal transport and degenerative changes progress in the proximal direction and spread from the lateral geniculate bodies to the retina. An indirect confirmation of this fact is our finding of β -amyloid bodies in the glaucomous optic nerve, while their clusters, estimated as β -amyloid plaques, were found in the cortical region.

It can be considered as established that a neurodegenerative process develops with POAG, in which not only the peripheral section of the visual analyzer is involved, but also the pathways and the central section, i.e. optic pathway in general.

It is required to consider 2 circumstances. First of all, the presence of amyloid beta in the brain tissue of people, who suffer from POAG. Amyloid beta is a recognized marker of neurodegeneration, a characteristic morphological sign of Alzheimer's disease. Secondly, the neurodegeneration process is accompanied by astrogliosis, i.e. by death and replacement of brain cells by young, functionally immature astrocytes, which are not able to achieve supporting, protective, trophic and other auxiliary functions.

Conclusion

In summary, it was established as a result of autopsy that with POAG degenerative changes occur in the retina ganglion cells, fibers of the second cranial nerve, and the tissue of the visual analyzer's pathways until visual cortex. This indicates the pronounced neurodegenerative

nature of POAG, which is confirmed by the presence of such generally recognized criteria for the neurodegenerative process as astrogliosis and the presence of accumulations of beta-amyloid in the cerebral cortex and in the second cranial nerve. Such pathology is similar to such neurodegenerative diseases as Alzheimer's or Parkinson's.

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