MORPHOLOGICAL CHARACTERISTICS OF TOXIC BRAIN DAMAGE

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The effects of various toxicants on the body tissues cause tissue abnormalities resulting in dystrophic changes and necrosis. The nervous system is the most vulnerable to the effects of exogenic substances, both chemical and biological, due to high metabolic activity and the cells' incapability of self-renewal. Neurotoxicants lead to disturbances of cellular nutrition and eventually to neurodegeneration. Neurons can die due to both apoptosis and necrosis.

Keywords: toxic damage, nervous system, dystrophy, apoptosis, neurodegeneration

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МОРФОЛОГИЧЕСКИЕ ХАРАКТЕРИСТИКИ ТОКСИЧЕСКОГО ПОРАЖЕНИЯ ГОЛОВНОГО МОЗГА

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Воздействие различных токсикантов на ткани организма вызывает в них патологические изменения, в итоге приводящие к дистрофическим и некротическим изменениям. Из-за высокой метаболической активности и неспособности клеток к самовозобновлению нервная система наиболее уязвима к влиянию экзогенных веществ как химической, так и биологической природы. Нейротоксиканты приводят к нарушению питания клеток и в итоге к нейродегенерации. Нейроны могут погибать как вследствие апоптоза, так и некроза.

Ключевые слова: токсическое поражение, нервная система, дистрофия, апоптоз, нейродегенерация.

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Normal brain functioning depends on the complex interactions between neurotransmitters, hormones, enzymes, and electrolytes. Many chemically complex substances can intervene in these interactions and disrupt them. Today, there are more than 100,000 chemical compounds, of those 25% can damage the brain [1]. Apparently, there are still many unrecognized neurotoxins in the environment. The central nervous system (CNS) is to some extent protected against toxic effects by the blood-brain barrier, however, some compounds can easily cross the barrier (for example, non-polar fat-soluble substances). Neurons are vulnerable to toxic effects due to high lipid content and high metabolism [2].

The neurotoxin exposure can cause a number of symptoms, all of which are non-specific. Acute toxic encephalopathies are often manifested by the symptoms of confusion, attention deficit, seizure, and coma. It is believed that most of these symptoms are associated with damage to the CNS capillaries, hypoxy, and cerebral edema. Neurological symptoms can vanish completely in case of correct and timely treatment. However, even a single toxic exposure can leave consequences. In cases if chronic negligible exposure to minor toxin doses, the symptoms can show up slowly and remain undetected for some time. The symptoms usually include mood changes, fatigue, memory problems, and congnitive impairment. The toxin elimination can be followed by improvement, but neurological deficit can persist over a long time in cases of severe encephalopathy or long-term exposure. Achieving the peak of recovery from chronic encephalopathy caused by toxins can take from months to years [3].

Toxic exposure is especially dangerous during the period of brain development. The available data suggest that the exposure to ubiquitous toxicants, such as fine particulate matter, manganese, and many phthalates, is associated with alterations of the development trajectory, physical and mental health throughout life [4]. Laboratory and clinical studies have shown that the developing brain demonstrates unique sensitivity to toxic agents [5].

Until recently, toxic neuropathy and brain damage were considered to be rare; these were caused mostly by alcohol intoxication or side effects of chemotherapy agents. These came to the fore due to the development of new treatment methods for neoplasms, improved diagnosis, and the increase in their share in the overall morbidity. Introduction of immunotherapy have led to the increase in the number of toxic

neuropathy cases and the need to develop the diagnosis and treatment methods for toxic neuropathy [6].

The other problem is the use of anesthesia. There is growing concern that the brain, both young and elderly, can be vulnerable to harmful effects of many modern anesthetics. Animal studies have yielded strong evidence of the fact that the exposure to sedatives and anesthesia causes morphological damage to the brain cells and neurocognitive impairment. However, these data can be hardly extrapolated to humans. Anesthetics can cause apoptosis of neurons and glial cells. The mechanisms underlying their toxic effects include excitatory neurotransmission, loss of calcium homeostasis, neuroinflammation induction, and trophic factor modulation [7].

Major characteristics of toxic damage to nervous system

Toxic damage to the nervous system, the same as that to the whole body, is characterized by activation of dystrophic and necrotic processes.

Due to the nervous system morphological features and high vulnerability to adverse factors, the disease processes in the nervous system, expecially in the brain, are significantly different from that observed in other human organs and systems. The body's exposure to new or poorly understood chemical compounds, as well as previously unknown infections, poses the challenges of the diagnosis and treatment of such disorders to pathologists, forensic experts, and occupational therapists. The development and use of the technology for diagnosis, treatment, and prevention of health problems associated with the adverse effects of hazardous chemical and biological factors is one of the challenges of state policy in the field of ensuring chemical and biological safety of the Russian Federation. The brain and nervous system in general represent the most vulnerable targets of both chemical and biological pathological agents. At the same time, even the general pathological processes that take place in the nervous tissue, i.e. the possibility to differentiate between normal and disease, are definitely underrepresented in the literature, especially domestic. Sporadic monographs are focused on specific issues of the diagnosis of nervous system tumors [8], vascular diseases [9, 10].

At the same time, the general pathological processes, such as damage, atrophy, circulation disorders, inflammation showing some specifics in the nervous system, are discussed only in sporadic monographs [11]. Neurohistologists pay attention only to certain components of brain tissue, most often to neurons [12], and they describe such types of pathology and in such a variety that can only confuse the pathologist. There is no detailed description of pathology of the other nervous system components: glial cells, neuropil, myelin, cerebral blood vessels.

Damage has various morphological manifestations at the cellular and tissue levels. Injuries can be superficial and reversible or deep and irreversible. One can distinguish damage to the single cell or tissue; this process can be represented by dystrophy or necrosis at the tissue level.

Among cellular dystrophies, pigment dystrophy manifested by the lipofuscin pigment buildup normally occurring with age and developing under exposure to toxicants, alcohol, and drugs, is considered to be the most common in the nervous system. In the majority of observations lipofuscin accumulates in neurons (Fig. 1), however, in drug addiction, its accumulation in the choroid plexus epithelium, where it does not occur either normally or in other disorders under the age of 30 years, is pathognomonic (Fig. 2). Furthermore, this pigment is sometimes detected in astrocytes, oligodendrocytes, and pericytes. Lipofuscin represents a glycolipoprotein found in the form of golden or brown granules, depending on the stain used. These graniles show different electron density when examined by electron microscopy [13, 14].

Lipofuscin consists of lipids, metals, and abnormally folded proteins; it has the property of autofluorescence. In addition to the nervous system, it can be found in cardiomyocytes and the skin. In the CNS, lipofuscin accumulates in the form of aggregates, shaping a specific ageing pattern associated with both physiological and pathological conditions, changing the neuronal cytoskeleton, cell transport and metabolism. It is also associated with the loss of neurons, proliferation and activation of glial cells. Historically, the lipofuscin buildup was

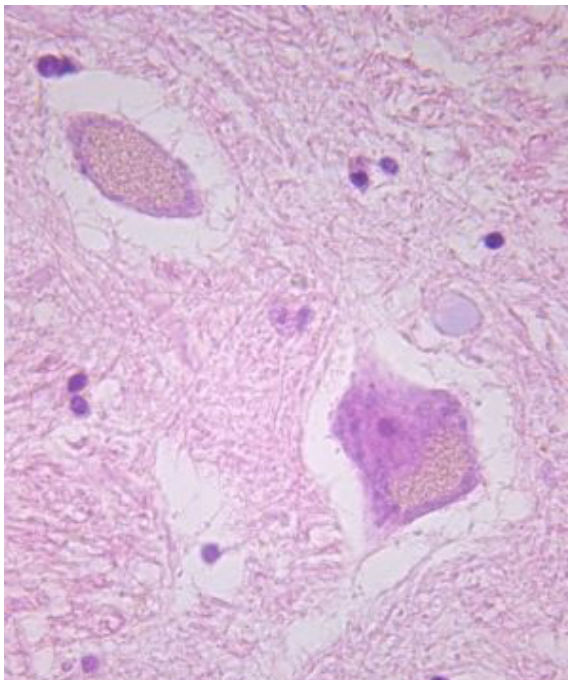

Fig. 1. Lipofuscin in the cytoplasm of neurons, multiple light-yellow granules, sectional material. Hematoxylin and eosin staining, ×630

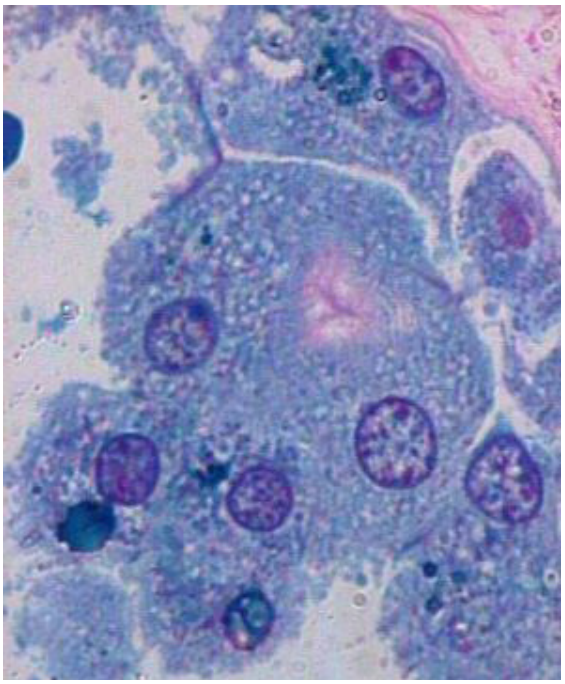

Fig. 2. Lipofuscin in the epithelium of the vascular plexus, blue-green granules in the cytoplasm, sectional material. Staining with alcian blue, ×1000

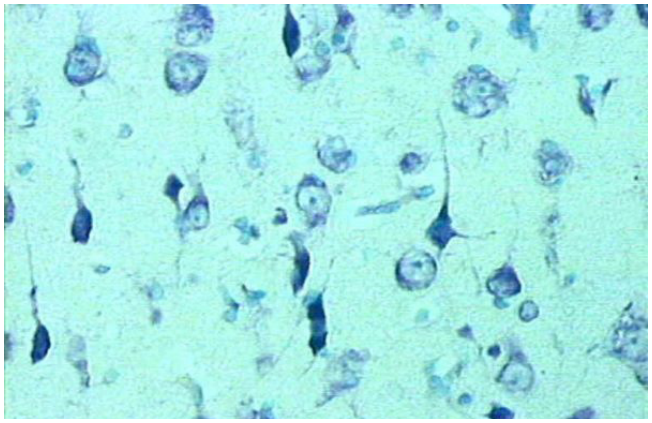

Fig. 3. Temporal lobe cortex acute swelling of neurons, shadow cells, dark, shriveled neurons, biopsy material. Nissl staining, ×400

considered to be secondary to ageing associated with various neurodegenerative disorders. However, the new data suggest that lipofuscin aggregates play an active role in ageing and neurodegeneration [15].

The other dystrophy type typical for the nervous system, hydropic dystrophy, is manifested by swelling of neurons in response to toxic damage. Acute swelling is reversible; it is associated with excess liquid accumulation in the cell. During this process the neuron becomes round, the cytoplasm and nucleus become lighter, and the tigroid is lost. Such dystrophy can be caused by hypoxy, intoxication, and other factors resulting in the cell damage and increased osmolality of the cytoplasm.

A rapid decrease in plasma osmolality causes rapid water absorption by astrocytes, but not neurons, while cells of both types swell due to ischemia. However, these abnormalities are fundamentally different at the cellular level. Astrocytes swell osmotically or shrink, since functional water channels, aquaporins, are expressed in these cells, while neurons have no functional aquaporins, so the volume of neurons is preserved. Nevertheless, both neurons and astrocytes swell slowly, when blood supply to the brain is impaired after the onset of stroke, sudden cardiac arrest or traumatic brain injury. In each situation swelling of neurons results directly from the spreading depolarization (SD) associated with the impaired function of the ATP-dependent sodium/potassium ATPase (Na^+/K^+ pump). Despite the fact that these mechanisms are poorly understood, they refute the dogma that states that swelling of neurons is associated with the absoption of water regulated by osmotic gradient with aquaporins as a vehicle [16].

When the toxicant effect is over, the neuron can return to normal again, taking a triangular shape. However, when damage is too severe and irreversible, the neuron transforms into the shadow cell. Such changes are typical for acute carbon monoxide poisoning [17, 18] and neurotoxic sequelae of poisoning with the substances exerting convulsive effects [19].

The emergence of dark neurons can represent one more variant of dystrophy. When examined by light microscopy, these seem to decrease in size and are usually rod-shaped, sharply stained with hematoxylin or thionin; it is almost impossible to see the nuclei of these neurons. These cells looking the same when examined by light microscopy can be divided into two types when examined with the electron microscope: the first represent precursors of necrosis followed by pyknosis and rhexis of the nucleus and cytoplasm, while the second (more common) represent the state of stress of the neuron, its increased activity with accumulation of organelles. Only one type of changes predominates in some cortical areas, most often acute swelling, however, the combination of acute swelling with the dark schriveled neurons can be found in some fields of view (Fig. 3).

Such neurons also do not necessarily die. In the experiments involving the rat model of septoplasty, the emergence of dark and p53-positive neurons in the hippocampus can be considered as the typical nervous system response to stress. The peak p53 protein expression growth in the cytoplasm of the neurons in the CA1 and CA2 fields was observed on days 2–4 after surgery; the number of such neurons decreased on day 6. Presumably p53 protein can not only trigger activation of damaged neurons in the hippocampus, but also plays a neuroprotective role [20].

Different dystrophic changes are typical for various cortical areas. However, these can be combined somewhere, and both swollen and dark schriveled cells are seen in the field of view.

The presence of myelin sheaths around the axonal processes of neurons, which are also prone to atrophy, is a characteristic feature of the nervous system. Little attention is paid to myelinopathy variants in the literarute, both domestic [11] and foreign [21, 22, 23]. Only demyelination processes are discussed, which are considered to result primarily from the death of oligodendrogliocytes [22, 24]. There are no detailed classifications of damage to myelin sheath, as well as no widely accepted classification. The same is typical for axonal pathology. Toxic peripheral neuropathies represent an important form of acquired polyneuropathy caused by various zenobiotics and toxicants. Primary damage occurs in the most distal parts of the nerves, particularly in the axons with the thickest myelin sheath and large diameter having the highest metabolism. Primary lesion is represented by edema and color change (pale or more intense color), which transform into fragmentation of the axon with time. The surrounding myelin sheath is disrupted due to secondary reaction. The main lesion is represented by segmental demyelination. The remains of the nerve fibers are decomposed by Schwann cells capable of functioning as phagocytes, or penetrating macrophages [25].

Among alterations of myelin sheaths at the microscopic level revealed by light and electron microscopy, the following are distinguished: dissociation, delamination, granular disintegration, homogenization, and demyelination. The axon that has lost myelin is prone to swelling and axial cylinder destruction.

Myelinopathy

1. Delamination — disrupted regularity of the myelin sheath layers fitted tightly around each other with the formation of dilated areas with significant hollows between individual lamellae.

2. Dissociation — disruption of the myelin sheath configuration — the type of myelin deformation associated with mismatch in the circle's circumference values of the axial cylinder and the covering myelin sheath, due to which protrusions of lamella folds, both outward and inward of the fiber, are formed.

3. Granular disintegration — type of myelin sheath local destruction, when the strict order of myelin layers is replaced with granular fragmentation of membranes.

4. Myelin homogenization — type of myelin sheath local or total destruction characterized by enzymatic degradation of membranes to the state of dispersion with varying electron density.

The combinations of the delamination and dissociation or granular disintegration and myelin homogenization are rather common (Fig. 4A, B).

5. Demyelination — myelin sheath thinning due to rapid decrease in the number of lamellae constituting it structure or total lack of myelin sheath.

6. Remyelination — restoration of the thinned myelin sheath.

7. Hypermyelination — excess increase in the number of

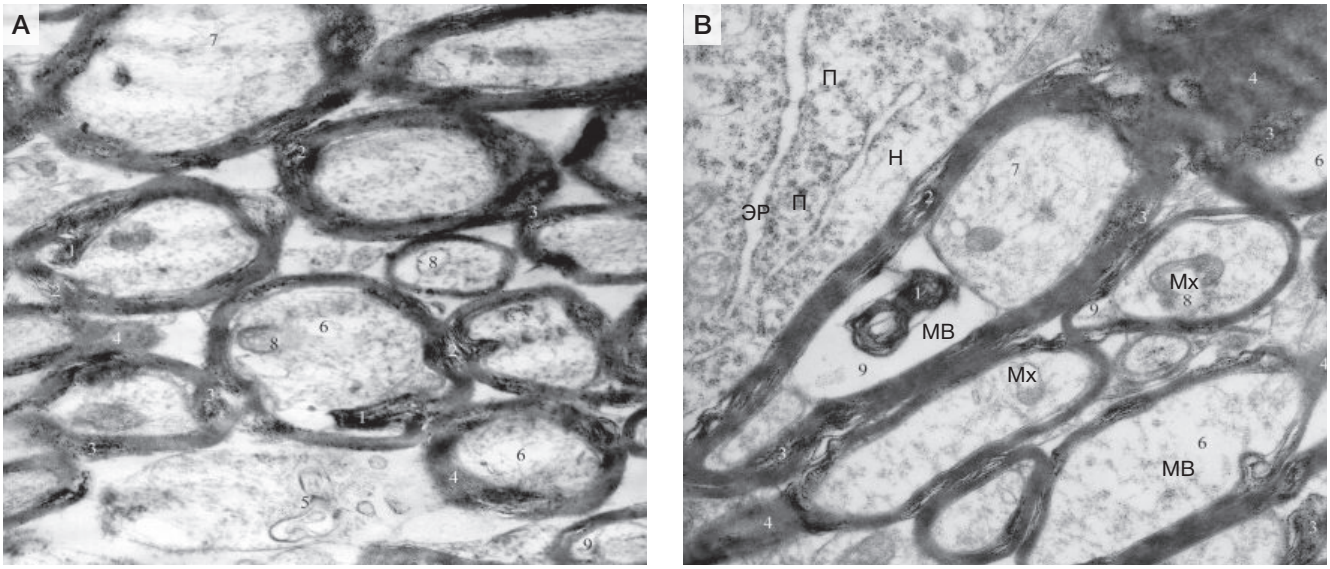

Fig. 4. Changes in myelinated fibers of the white matter Fig. 4A — ×20,000.; Fig. 4B — ×16000. MF — myelin fiber; N — neuron; ER — endoplasmic reticulum; P —polysomes; Mch — mitochondrion; 1 — Disruption of myelin sheath configuration; 2 — delamination; 3 — granular disintegration; 4 — homogenization; 5 — demyelination; 6 — brightening of the axial cylinder matrix; 7— disorientation of neurofilaments; 8 — destruction of mitochondria; 9 — periaxonal edema, experimental material (rats). Electronograms

lamellae in the myelin sheath resulting in significant constriction of the axial cylinder [11].

Demyelination is often found in many disorders. However, the role of demyelination is poorly understood and is not considered to be leading.

There is a term “leukoaraiosis” in radiation diagnosis. Comparison of postmortem MRI scans and morphological data has shown that neuropil rarefaction associated with demyelination is among visible equivalents of this MRI phenomenon.

Necrosis is the death of cells or tissues in the living organism. Single cells can die due to both necrosis and apoptosis (programmed cell death). Pathologists are familiar with the term “necrosis”, while the term “apoptosis” is rather new, and the diagnosis of apoptosis can cause some difficulties, since this is cell damage without inflammation or cell lysis.

Apoptosis

Light microscopy allows one to suspect apoptosis. Chromatin condensation in the cell nucleus that later becomes fragmented, is a typical sign of the apoptosis onset. Each fragment is surrounded by the cytoplasm, and the apoptotic body is formed that are ingested by macrophages. Electron microscopy, immunohistochemical methods, and the TUNEL apoptosis detection method are used to diagnose apoptosis. Programmed cell death was determined in the majority of chronic disorders and cases of toxic damage to the nervous system. Immunohistochemical studies of the human brain showed that cortical neurons responded positively to the p53 tumor suppressor controlling the state of DNA in the cell and triggering the cell death (apoptosis) program in case of DNA damage and impossibility of repair (Fig. 5, 6).

Necrosis of cells, particularly neurons, can go in two ways: through cytolysis and cytorhexis. For the neuron, cytolysis is a continuation of acute swelling, when it proceeds to the irreversible stage of the shadow cell, while cytorhexis is developed after shriveling of neurons with subsequent fragmentation of the nucleus.

Direct (traumatic and toxic damage) and indirect necrosis most often associated with circulation disorders represent the clinical and

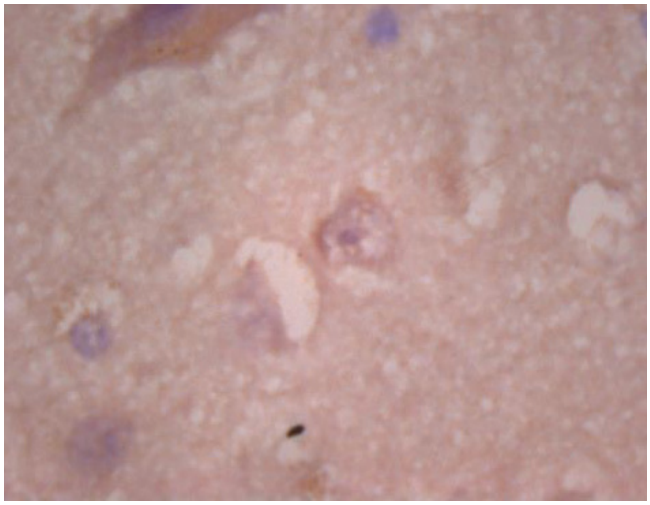

Fig. 5. Oncosuppressor gene is determined in the nucleus of the "dementia neuron". The cytoplasm of a large neuron of typical structure has a large amount of lipofuscin (sectional material). Immunohistochemical reaction of p53, ×1000

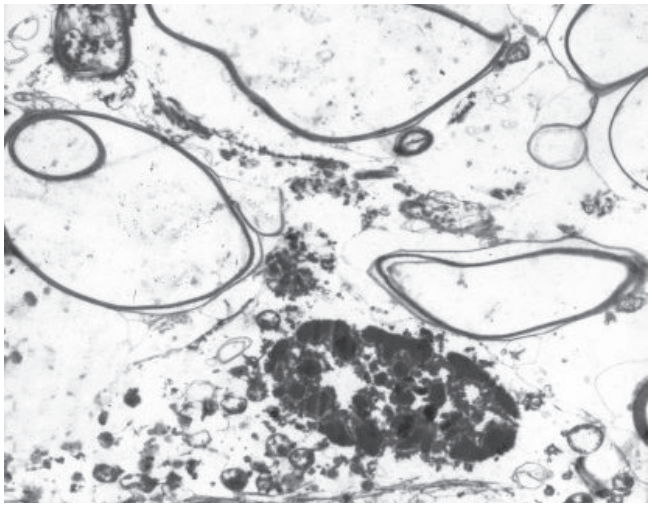

Fig. 6. Sections of white matter. Filamentous myelin fibers with transparent axial cylinders. Near oligodendrocyte with signs of apoptosis (sectional material). Electronogram, ×5000

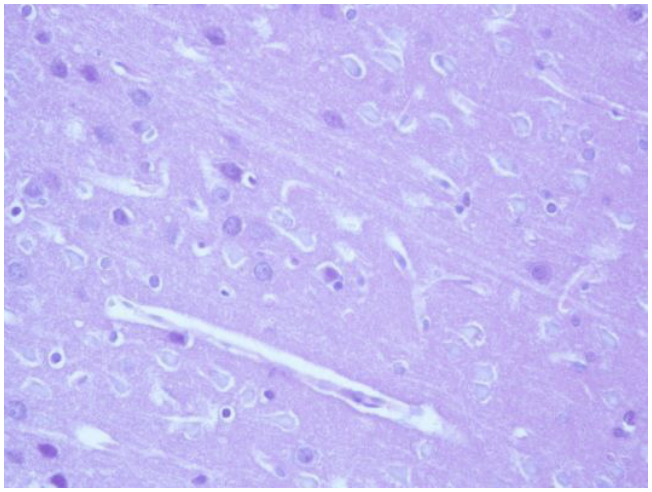

Fig. 7. Cerebral cortex. The perivascular spaces are dilated. Most neurons are "shadow cells", single neurons with neuronophagy phenomena. Foci of neuron loss, experimental material (rats). Hematoxylin and eosin staining, ×400

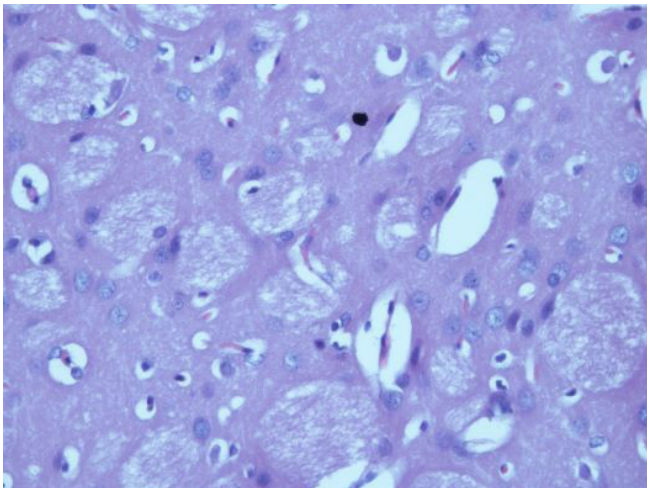

Fig. 8. Brain, subcortical nuclei. The perivascular spaces are significantly enlarged. Most neurons are unchanged, marked rarefaction of the neuropil of the conducting pathways, experimental material (rats). Hematoxylin and eosin staining, ×400

morphological forms of the brain necrosis. Small foci of necrosis that are often elective, where only some components of the tissue are damaged, while other components are preserved (Fig. 7, 8), are most typical for toxic brain tissue damage. Such foci show up as neuropil rarefaction and gliopenia [11].

CONCLUSION

Thus, common disease mechanisms, such as neuroinflammation, atrophy and dystrophy, damage to neurons and glial component that can result in the death of cells occurring in different ways, including apoptosis and necrosis, underlie toxic damage to the brain, regardless of the cause (toxic or medicinal substances, bacteria, protozoa or viruses, endogenous toxicants, drugs, alcohol, traumatic brain injury, etc.).

The changes in cell morphology can be both reversible and irreversible; these can to varying degrees and in different ways manifest themselves in the brain regions. Today, such changes are poorly understood due to non-specific nature, despite the fact that these data are essential for selection of optimal treatment and reduction of dangerous sequelae of the number of medical procedures.

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