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Morphological Signs of Dystrophy, Regeneration and Hypertrophy of Neurons

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ABSTRACT

Objective: Generalization and systematization of literature data on dystrophic, regeneration and hypertrophy changes in neurons in the rat cerebral cortex.

Methods: The basis of this study was a review of the literature on this topic.

Results: Dystrophic changes constitute an extensive group of neuronal disorders and are manifested at the morphological level by deformation of the perikarions and neuropil, wrinkling or swelling of the cell, and changes in the chromatophilia of the cytoplasm. At the electron microscopic level, disorganization of organelles is observed, reflecting gross violations of the vital processes of the neuron. There are several ways to regenerate neurons: intracellular regeneration, restoration of the neuropil, the formation of new neurons (in some parts of the nervous system - the hippocampus, the subventricular layer of the lateral ventricles and olfactory bulbs) and the formation of heterokaryons (fusion of a neuron with an oligodendrocyte). Hypertrophy of neurons may indicate both compensation and the development of a pathological process. To clarify the nature of this phenomenon, it is necessary to conduct an ultramicroscopic study of the organelles of the nerve cell.

Conclusion: Further study of dystrophic regeneration and hypertrophy changes in neurons at the histological, ultrastructural and molecular levels will serve as a fundamental basis for the search and improvement of new ways of preventing and correcting diseases of the nervous system.

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When studying the pathology of the central nervous system, the question arises about the interpretation of the revealed changes in nerve cells. When modeling brain damage, various size disorders, thieves of the perikarion of neurons, as well as changes in the degree of chromatophilia of their cytoplasm are revealed. It is important to establish the dependence of the severity and nature of damage to the nervous system as a whole on the structural changes of the neuron, as its morphofunctional unit.The purpose of this article is to analyze and systematize information about pathological changes in brain neurons in the experiment.

There are several classifications of pathological changes in neurons. So, Nissl, on the basis of the peculiarities of changes in the chromatophilic substance, distinguished: axonal reaction, swelling and wrinkling of neurons. A.I. Strukov and S.K. Lapin in 1956 formulated a classification that includes:

1. Age
2. Functional and reactive (easily reversible)
3. Dystrophic (difficult to reversible and irreversible)
4. Compensatory and adaptive changes in neurons.

The classification of N.E. Yarygin (1957) is similar to it. In his classification Yarygin distinguishes age-related, functional, dystrophic, regenerative and hypertrophic, changes in the structures of nervous tissue [1, 2].At the later stages of postnatal ontogenesis, destructive changes occur in neurons, manifested at the histological level by a decrease in the size and deformation of perikarions, hyperchromatosis, hypochromatosis and cell shrinkage [3].

Dystrophic Changes

It is customary to divide dystrophic periods into three phases.

In the first phase of dystrophy, metabolic molecular and ultrastructural changes occur. They can only be detected using biochemical, physicochemical, histochemical and electron microscopic methods. These changes are in many cases reversible.

In the second phase of tissue dystrophy, metabolic disorders are accompanied by the appearance of morphological changes in tissue structures, which are detected using conventional histological

methods (Nissl staining). These include a slight swelling of nerve cells with a diffuse arrangement in their cytoplasm of a chromatophilic substance or a thickening of the cytoplasm of neurons with moderate hyperchromatosis. On the neuropil side, dystrophic changes are manifested by the appearance of varicose thickenings along the axial cylinders with garnetting of neurofibrils, a change in the tinctorial properties of axoplasm and myelin, and swelling of the terminals.

In the third phase of the dystrophic process, irreversible changes occur. They are manifested by wrinkling or, conversely, swelling of nerve cells with dissolution of chromatophilic substances in them, disintegration of neurofibrils, disorganization of organelles. The neuropil is vacuolated and fragmented, undergoing granular-lumpy disintegration, and myelin dissolves, as a result of which lipid droplets begin to be detected along the nerve fibers. Synapses swell, collapse, and disappear.

The cytoplasm of some neurons is filled with vacuoles, both small and large, which is why the cell takes on a "foamed" or cellular appearance.Destructive forms of neurons with impaired metabolism are eliminated by microglial cells. In this case, on histological preparations, phenomena are often observed satellitosis, in which glial cells are located on the surface of a neuron and neuronophagy (penetration of glial cells into the body of a dying neuron), Figure 1 [1, 4, 5].

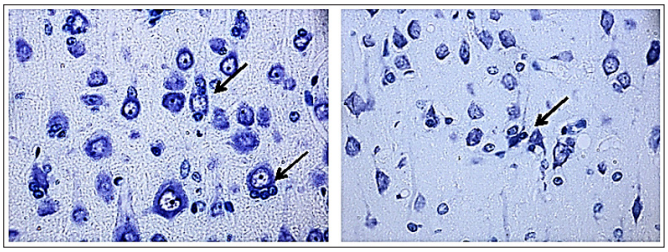

Figure 1: Satellite and neuronophagy of rat neocortex neurons. Indicated by arrows. Nissl staining. Digital micrograph. Magnification 400

Dystrophic changes in neurons are often accompanied by deformation of the perikarions and neuropil, most likely associated with a violation of the cytoskeleton (Figure 2) [6, 7].

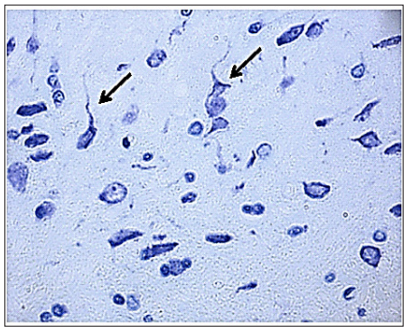

Figure 2: Deformation of the perikarions and neuropil of neurons in the rat neocortex. Indicated by arrows. Nissl staining. Digital micrograph. Magnification 400

In experimental pathology, shrunken, swollen neurons, as well as cells with pericellular edema, are often found among the neurons of the cerebral cortex. Hyperchromic shrunken neurons are very common in cerebral cortex damage. Their number, as a rule, significantly increases already at the 15th minute of the cessation of the oxygen supply. In hyperchromic shrunken neurons, deformation of the perikarions occurs, possibly under the influence of a violation of the water-electrolyte balance. Their sizes, in comparison with normochromic neurons, are significantly reduced, the cytoplasm is intensely stained with thionine according to the Nissl method [4, 5, 8-12] (Figure 3.4).

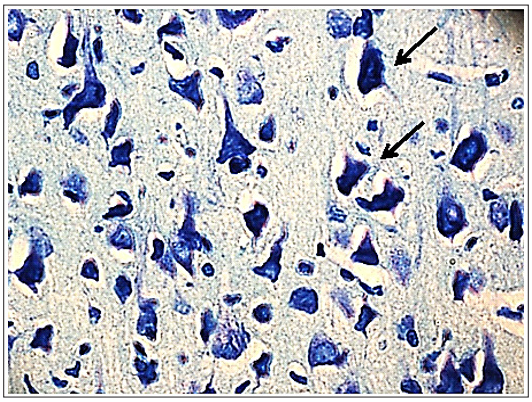

Figure 3: Hyperchromic shrunken neurons in the rat neocortex with 15-minute total cerebral ischemia. Indicated by arrows. Nissl staining. Digital micrograph. Magnification 400

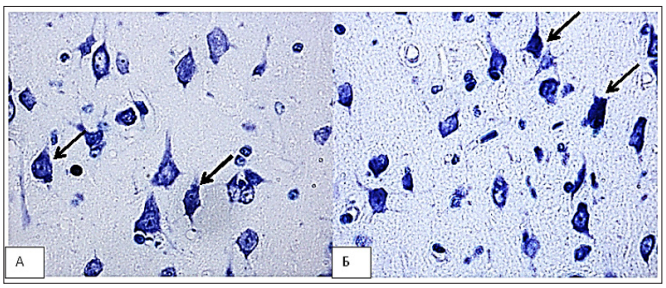

Figure 4: Hyperchromic shrunken neurons in the rat neocortex. Indicated by arrows. Nissl staining. Digital micrograph. Magnification 400

In addition to hyperchromic shrunken neurons, there are also hypochromic shrunken cells (Figure 5).

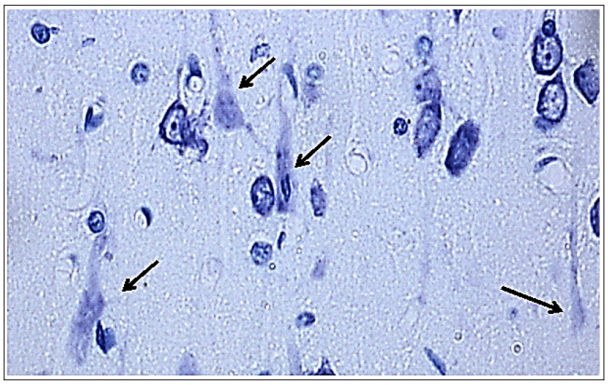

Figure 5: Hypochromic shrunken neurons of the parietal cortex of 2.5-year-old rats. Indicated by arrows. Nissl staining. Digital micrograph. Magnification 400

The pale staining of their cytoplasm with thionine according to the Nissl method is possibly associated with the disintegration of the cisterns of the granular endoplasmic reticulum. This type of neurons is formed either from hyperchromic shrunken neurons during their further involution, or from hypochromic cells. One of the forms of neuronal dystrophy is their acute swelling. At the same time, neurons increase in volume (sometimes 2-4 times). The nucleus also swells and takes on an eccentric arrangement. On histological preparations, the cytoplasm of swollen neurons is painted pale and has a fine-grained appearance. Acute swelling of

neurons is reversible, but some of them still undergo necrobiosis and die (Figure 6) [1, 12-14].

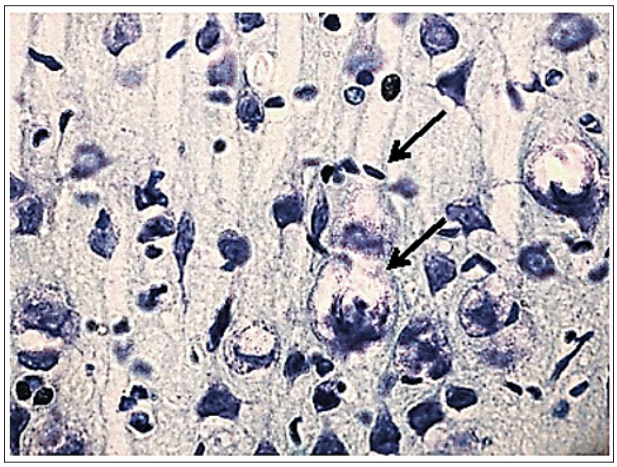

Figure 6: Swollen neurons in the rat neocortex during 30-minute total cerebral ischemia. Indicated by arrows. Nissl staining. Digital micrograph. Magnification 400

At the electron microscopic level, the destruction of organelles occurs. Thus, in the cytoplasm of dystrophically altered neurons, mitochondria devoid of cristae are observed. A decrease in the relative number of mitochondria, the number and length of their cristae, which is accompanied by a decrease in the cytoplasm of these neurons in the activity of the enzymes of aerobic oxidation of carbohydrates in the Krebs cycle and the enzyme involved in the transfer of electrons and which is an important link between the end products of the decay of the carbon skeleton and the respiratory chain. This indicates a progressively reduced functional activity of mitochondria and energy supply of neurons.

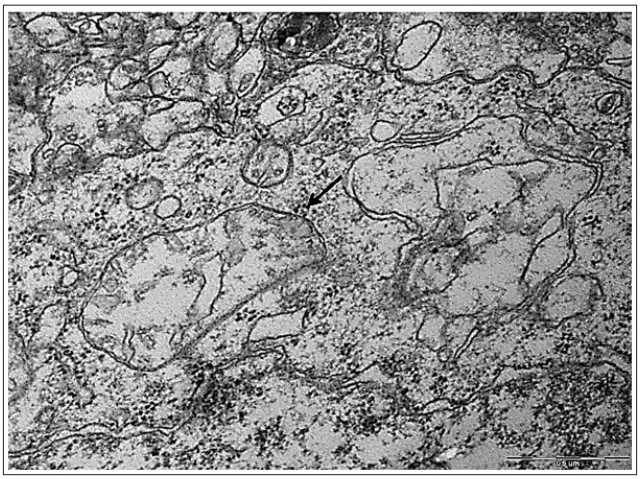

Figure 7: Fragments of the nucleus and cytoplasm of neurons of the inner pyramidal layer of the rat neocortex. The mitochondrion deprived of cristae is indicated by an arrow

Scale bar: 0.5 мм.
Electronogram. Magnification: 50,000

Disorganization of the endoplasmic reticulum and the Golgi complex is observed. Their cisterns expand significantly and can take the form of vacuoles (Figure 8).

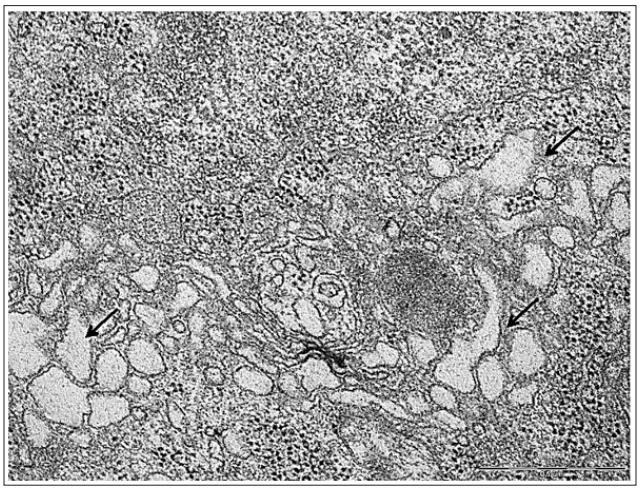

Figure 8: Fragments of the nucleus and cytoplasm of neurons of the inner pyramidal layer of the rat neocortex. Expanded tanks of the Golgi complex (indicated by an arrow).

Scale bar: 0.5 мм.
Electronogram. Magnification: 50,000

Due to the developing energy deficit, the ribosomes lose their connection with the cisterns of the endoplasmic reticulum and are located in the cytoplasm in the form of separate clusters (Figure 9).

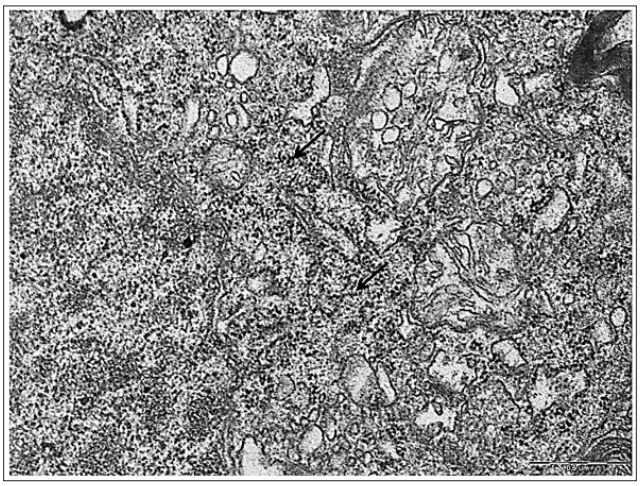

Figure 9: Fragments of the nucleus and cytoplasm of neurons of the inner pyramidal layer of the rat neocortex. Free ribosomes (indicated by arrows).
Scale bar: 0.5 мм.
Electronogram. Magnification: 50,000

The above changes indicate significant disturbances in neuronal metabolism accompanying morphological changes. The shrinking of neurons, as well as their swelling as a result of edema of the perikarions, can be associated with gross violations of the water-electrolyte balance caused by impaired permeability of the cytolemma to ions due to severe energy deficiency, which, in turn, is associated with the reduction of cristae in mitochondria. Lack of energy leads to deactivation of synthetic processes, which is reflected in the disorganization and vacuolization of the cisterns of the endoplasmic reticulum and the Golgi complex. Free ribosomes in the cytoplasm are incapable of protein synthesis for export. The proteins formed by their means are used by the cells for their own needs, and in the event of an aggravation of the energy deficit, they remain unclaimed at all. The accumulation of these proteins

in the cytoplasm of the neuron contributes to a further increase in acidosis and hypoxia, ultimately leading to the destruction of the cell [10, 12].

Regenerative Changes

Speaking about the regeneration of neurons, they usually mean the restoration of damaged processes of nerve cells, that is, the regeneration of nerve fibers and synapses. In the course of many years of morphological studies, it was found that the regenerative process in neurons is manifested by the restoration of damaged and the formation of new processes of the neuropil, as well as the appearance of additional collaterals on the existing processes. Neuropil neoplasms lead, in turn, to a complication of the structure of neuronal dendrites. These changes can occur not only in neurons with damaged processes, but also in normal neurons, with the death of other nerve cells. Most often, regenerative rearrangement is detected in the extra- and intramural ganglia of the intervertebral and cranial sensory nodes. This may be due to the fact that the neurons of the sensory ganglia have only one T-shaped process. Therefore, in the case of the appearance of regenerative changes in them, it is easier to detect new branches of the neuropil, often having a spiral shape with distal thickenings (microneuromas). Thus, if part of the neurons of one or another part of the nervous system die, then a regenerative process takes place in the remaining neurons, accompanied by hyperplasia of the neuropil and subsequent hypertrophy of the cell body itself. The degree of restoration of the function of the nervous system is determined not only by the volume and nature of its damage, but also by the localization of the process, since the plastic capabilities of neurons in different parts of the central and peripheral nervous system are far from the same.

So, in the central nervous system, the regeneration of the neuropil is slower and does not always complete successfully. At the same time, peripheral nerve fibers regenerate relatively well. The process, as a rule, begins with the formation of retraction balls on the proximal segments of the axons, with clavate influxes of neuroplasm, which then disappear. Normal regeneration of the neuropil is always accompanied by proliferation and hypertrophy of oligodendrocytes, which form the cords that guide axonal growth. Sometimes, during the growth of an axon, flask-like thickenings appear at its end, which indicates a violation of the normal course of regeneration, especially if new branches lose their connection with oligodendrocytes. This phenomenon is usually observed when there is an obstacle in the path of the growing neuropil. Regenerating axons first grow along the strands of oligodendrocytes, and then they are enveloped in folds of their cytolemma, which forms mesaxons. At the first stages of regeneration, part of the strands of oligodendrocytes may include several axons. However, in the future, only one is preserved and covered with myelin, the rest disappear. Regeneration is considered complete when the axon reaches the original innervated tissue and forms a synapse with the working organ. In the morphological study of histological specimens, it is sometimes difficult to distinguish between a normal nerve ending (the result of successful regeneration of the neuropil) from pathological branching with microneurium proliferation. The differences lie in the fact that microneuromas usually do not have a capsule and consist of randomly intertwining thin myelin-free nerve endings. These data indicate that neurons have rather high regenerative capabilities. The restoration of the structure of the nervous tissue after its damage in most departments is carried out not through the division of the preserved neurons, but due to the regeneration and hyperplasia of their neuropil, which leads not only to the restoration of the lost, but also to the establishment of new connections between the nerve cells and the innervated organ. In some cases, the regeneration of nerve fibers and end apparatus is disturbed and accompanied by the formation of neuromatous growths, which may be the cause of the appearance of pathological reflexes [15-22].

However, there are data in the literature on the division of neurons in the central nervous system of adult mammals and humans. In 1998, the fact of postnatal neurogenesis in the human hippocampus was established using the molecular marker bromodioxyuridine (BrdU). In addition, new neurons were integrated into the general neuropil network [23-25]. Also, postnatal neurogenesis was noted in the subventricular layer of the lateral ventricles and olfactory bulbs [26]. However, the presence of the formation of new neurons in adult mammals and humans remains controversial [27-33]. However, the process of studying neurogenesis is complicated and can give false results, since BrdU can also be turned on during reparative DNA synthesis in a neuron after its damage and can cause an erroneous determination of the fact of neuron division. It is believed that one of the forms of regeneration is the formation of nerve cell heterocarins. They are described in an electron microscopic level. In these structures, the fusion of the nuclei of neurons and oligodendrocytes was observed.

Gradually, in the heterokaryon, the nucleus of the oligodendrocyte is reprogrammed and it gradually becomes more and more similar to the nucleus of the neuron in size, shape, structure of chromatin. Upon completion of the reprogramming process, the kernels become indistinguishable. Heterokaryon turns into a cell with two identical nuclei – dikarion. Thus, as a result of fusion and reprogramming, a second nucleus is formed in the neuron, and the functionality of the neuron increases significantly. This is important to compensate for the loss of a certain number of neurons during damage. The presence of such dicarions has been described in the cerebral cortex in the area adjacent to the focus of postischemic necrosis [32, 34, 35].

Hypertrophic Changes in Neurons

Hypertrophy of neurons is observed most often due to either the death of a part of the nerve cells, while the remaining neurons take over their function and hypertrophy, or by the enhanced work of this part of the nervous system. Thus, neuronal hypertrophy can occur both on a pathological and physiological basis. As a rule, hypertrophic changes in the structures of nervous tissue are not always compensatory, since the functional concept of "compensation" is broader than the morphological concept of "hypertrophy". Hypertrophy of neurons is manifested mainly by an increase in the size of the perikarion, nucleus and nucleolus. There may be neurons with two or more nucleoli (Figure 10).

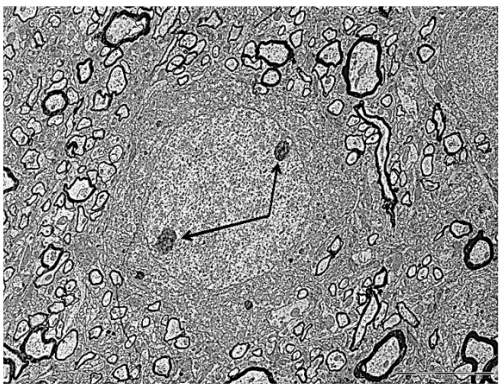

Figure 10: Neuron of the inner pyramidal layer of the parietal cortex of the brain of an adult rat. Fragment of the cytoplasm. The nucleus has two nucleoli (indicated by arrows). Digital micrograph. Electron microscopy.
Magnification: 25000.
Scale bar: - 5 microns.

An increase in the number and enlargement of lumps of chromatophilic substance is observed, that is, an increase in the length of the cisterns of the granular endoplasmic reticulum and the number of ribosomes associated with it, hyperplasia of neurofibrils, thickening of the neuropil. At the same time, the axons thicken somewhat and sometimes contain varicose enlargements along their course. However, an increase in the size of perikaryon neurons in itself cannot be a sign of hypertrophy, as it is often observed in dystrophic processes. To differentiate between these phenomena allows electron microscopic study of organelles. With neuronal dystrophy, destruction of the endoplasmic reticulum is noted, the loss of ribosomes by it, disorganization of the Golgi complex, swelling and destruction of cristae in mitochondria. At the same time, hypertrophied neurons carrying an increased load are functionally depleted over time and undergo dystrophic, necrobiotic and necrotic changes. One of the manifestations of neuronal hypertrophy is intense staining of their cytoplasm according to the Nissl method (hyperchromia). According to the shape of the perikarion, hyperchromic neurons are subdivided into non-shrunken and shrunken. Under normal conditions, in the brain of animals and humans, there are only single "dark" hyperchromic and hyperchromic shrunken neurons. Their number can increase significantly under experimental influences and pathological conditions [1, 4, 5, 14, 31].

Conclusion

Thus, dystrophic changes constitute an extensive group of neuronal disorders and are manifested at the morphological level by deformation of the perikarions and neuropil, wrinkling or swelling of the cell, and changes in the chromatophilia of the cytoplasm. At the electron microscopic level, disorganization of organelles is observed, reflecting gross violations of the vital processes of the neuron. There are several ways to regenerate neurons: intracellular regeneration, restoration of the neuropil, the formation of new neurons (in some parts of the nervous system - the hippocampus, the subventricular layer of the lateral ventricles and olfactory bulbs) and the formation of heterokaryons (fusion of a neuron with an oligodendrocyte). Neuronal hypertrophy may indicate both compensation and the development of a pathological process. To clarify the nature of this phenomenon, it is necessary to conduct an ultramicroscopic study of the organelles of the nerve cell. Further study of dystrophic regeneration and hypertrophy changes in neurons at the histological, ultrastructural and molecular levels will serve as a fundamental basis for the search and improvement of new ways of preventing and correcting diseases of the nervous system.

Conflict of interest statement

The authors declare no conflict of interest.

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