MORPHOLOGICAL CHANGES OF SYNAPTIC FORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN EXPERIMENTAL CHRONIC RADIATION SICKNESS

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MORPHOLOGICAL CHANGES OF SYNAPTIC FORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN EXPERIMENTAL CHRONIC RADIATION SICKNESS (1)

Following is the translation of an article by A. G. Khanin entitled "O Morfologicheskikh Izmeneniyakh Sinapticheskikh Obrazovaniy Tsentral'noy Nervnoy Systemy pri Eksperimental'noy Luchevoy Boleznii" (English version above) in Zhurnal Nevropatologii i Psikhiatrii Imeni S. S. Korsakova (Journal of Neuropathology and Psychiatry im S. S. Korsakov), Vol. 60, No. 5, Moscow 60, pages 522-528.7

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Studies were carried out on 14 dogs (nine experimental and five controls), two to four years of age, 14 to 18 kw in weight. The dogs were exposed daily (except on rest-days) to a total bilateral X-ray irradiation by means of two RUM-3 apparatus with a 15 r dose for two minutes at 120 cm focal distance and physical power of the two apparatus seven to eight r/min. The tube voltage was 180 kV, current strength -- 15 mA; filter -- 0.5 mm cuprum and one mm / aluminum.

A certain number of dogs were killed at various stages of chronic radiation sickness, others were subjected to an autopsy after death (terminal stage). Pieces of the brain and spinal cord were impregnated with silver by the Kakhal method with pyridine fixation, and paraffin sections were prepared. The cerebral tissue sections were also stained according to Nissl's method.

There were no microscopic changes noted in the brain in the first and second stages. In the third and fourth

stages there was an uneven plethora of brain tissue and its membranes, a smoothing-out of the cerebral convolutions and flabbiness of its substance. In two cases there were extensive subdural hemorrhages on the convex surface of the brain. There were no discernible macroscopic changes in the spinal cord.

Studies of the sections of the brain and spinal cord of five healthy dogs showed axosomatic and axodendritic synaptic formations of monotypic structure; the presynaptic fibrils were thin, of uniform thickness along their entire length, with even edges and no tortuosity; the synaptic Auerbach-Held plaques were represented by characteristic small rings and loops of round or oval form with a light center and even contours. Button-like endings were encountered among them. The size of the plaques varied; there were encountered only isolated synaptic loops, about twice as large in their diameter as that of the basic mass of rings, and somewhat darker impregnated. One could see in the cerebral tissue a considerable number of plaques without presynaptic fibrils. The polymorphism of terminal formations was negligible. The dendritic processes with smooth, even contours were not tortuous. The neurofibrillary apparatus was lightly stained, the striated structure well expressed.

The cerebrum and spinal cord of two dogs (total dose of ionizing radiation 225 r) were examined in the first stage (the stage of initial phenomena, according to the clinical hematological indices).

The histopathological changes in the interneural structures of the cerebral hemispheres, brain stem and spinal cord were of an irritation type against the background of unaltered synaptic formations. In the neural cells and their dendritic processes there could be observed a coarse staining of the neurofibrillary apparatus and the disappearance of its striated character. The protoplasmic processes not infrequently appeared tortuous. The axosomatic and axodendritic ringlets and knobs were more polymorphous than normal and more intensively stained with silver. A large quantity of synaptic rings, enlarged in size, could be seen. In the presynaptic fibrils there was swelling and argyrophilia, varicose thickenings, and a tortuous course.

In the cortex of the cerebral hemispheres there were analogous pathological changes in the interneural terminal apparatus -- in the frontal, precentral, postcentral, parietal, occipito-parietal, occipital and limbic areas. In the cortical preparation, Nissl stained, there were observed changes in the minute groups of neural cells, as well as in isolated cells scattered in various areas. These changes were manifested by the altered staining of the chromatophis substance.
and minute changes in the cellular structure. The protoplasm of a number of neural cells was slightly stained, the contours of the nucleus smoothed out. In the cortex there were encountered slightly swollen, lightly stained cells, as well as cells of irregular form. In the upper layers there were minute groups of pale, darkly stained neural cells (hyposthenic and hyperchromatic cells). Among the hyperchromatic cells of all layers there were isolated cells with slightly shrunken bodies and tortuous, somewhat thinned processes (phenomena of shriveling).

In the central and lateral nucleus and in the other nuclei of the thalamus opticus there was noted a certain irritation of the synaptic structures in the form of increased argyrophilia. Similar changes were also observed in the reticular substance of the diencephalon. In the subcortical notes, subthalamus and corne Ammonis the irritation phenomena were insignificant and consisted of a certain coarsening and swelling of the fibers.

In the motor, sensory, and vegetative nuclei of the cerebrocranial nerves (third to 12th pair) there was observed in a number of neurons an increased argyrophilia of the neurofibrillary apparatus, as well as neuroplasms. In addition, there were often encountered swollen (evenly or unevenly) and varicosely changed presynaptic fibers. The synaptic plaques on the bodies and dendrites of the cells were more polymorphous than normal, often hypertrophied and solidly stained. In the reticular substance the affections /pathological changes/ of the synaptic ends were more clearly manifested than in other nuclei of the stem area of the brain and involved a considerable number of neurons.

In the cerebellum there was observed swelling and impregnation of the basket-like apparatus of Purkinje's cells, as well as of the fibrils of the stellate cells along the course of the axis cylinders of purkinje's cells.

In the gray matter of the spinal cord, as well as in the cerebrum, there were detected changes in the axosomatic and axodendritic bonds, the neurofibrillary apparatus, and the neuroplasm of the body and processes. We did not observe the predominance of affection of Clark columns, as described in acute radiation sickness by A. D. Zurabashvili and B. P. Naneyshevili /1/. On the Nissl-stained preparations from the subcortical nodes, brain stem, and spinal cord, hyper- and hypo-chromatic neural cells were encountered at times. In comparing synaptic endings of the motor (motor neurons of the spinal cord, motor nuclei of cerebrocranial nerves, neural cells of the precentral area), sensory (neurons of the dorsal horns of the spinal column, nuclei of the thin and wedge-shaped bundles, the ventral and lateral thalamic nuclei, the
postcentral cortical area) and vegetative formations of the
cerebrum and spinal cord (dorsal nucleus of the vagus, supra-
optic nucleus, sympathetic nucleus), as well as the reticular
substance, in the control preparations from healthy animals
and in the preparations from experimental animals we could
not succeed in detecting any predominance in the affection
of the synapses of any of these structures. The synaptic ap-
paratus was better manifested in the motor cells and cells
of the reticular substance, in which it was easier to study
it.

In the second stage (stage of comparative clinical
welling) we examined the cerebellum, medulla oblongata
and various sections of the spinal cord of two dogs (total
doses of ionizing radiation -- 480r and 510 r, duration of
the experiment 38 and 40 days). Pathological changes of the
terminal interneuron apparatus of bonds in this stage was
manifested in approximately the same degree as in the first
stage. Possibly some of the synaptic structures were re-
stored, and at the same time certain still intact neuronal
synapses became involved in the pathological process, as a
result of which evidence of reactive changes was observed.
The neurofibrillary apparatus and the neuropil of the body
and processes of neural cells were often hyperimpregnated.
Pathological changes were found in the terminal formations
of the motor neurons, cells of Clarke and Schilling, in the
intermediate zone and the dorsal horns. The presynaptic fibr-
rils along the course of the dendritic processes, as well as
the fibrils approaching the neural cells, were swollen,
coarsened, and highly argyrophilic. The synaptic plaques in
a number of cells were not infrequently hypertrophied, argy-
rophilic and polymorphous. In addition, a polychromatic
staining of a considerable number of small loops, was also
observed i.e., various intensities of their staining with
silver. In the cerebellum an increased argyrophilia of the
basket apparatus of Purkinje's cells was observed.

Nissl staining of the cerebral tissue revealed hyper-
and hypo-chromatic, as well as shrunken cells.

We examined the brains of two dogs in the third stage
(stage of pronounced clinical manifestations); they had re-
ceived total doses of irradiation amounting to 1650r and 1785r
and had been subjected to the experiment for 130 and 140 days.
The medullae oblongatae and spinal cords were examined histo-
logically.

This stage was characterized by further development,
extension, and intensification of reactive reversible changes
of the terminal interneuronal structures, as well as the de-
velopment of non-reversible degenerative-necrobiosis changes
against this background. On the whole, however, the patho-
logical changes of the non-reversible type were much less in
evidence than the reactive reversible changes, and the axo-
somatic bonds were more easily affected than the axodendritic
ones. Together with the changed synapses there could also be
observed a considerable number of intact synaptic formations.
Compensation-adaptation processes were only slightly manifest-
ed.

The increased argyrophilia of the neurofibrillary ap-
paratus and neuroplasm of the neurons, their bodies and protop-
plasmic processes was observed in a larger number of neural
cells than in the second stage. The dendritic processes of a
number of cells were tortuous in various degrees.

Against the background of an increase and greater ex-
pansion of reactive changes in the preterminal fibers there
were manifested degenerative-necrobiotic changes in their
structure, as the result of which the histological picture
of affection of the fibers was very variegated.

Together with increased phenomena of swelling and
argyrophilia there were also an increased number of hyperim-
pregnated evenly and unevenly swollen fibers, fibers with
bead-like and varicose bulges and marked tortuosity (zigzag,
serpent-like, serpent-like and at the same time bow-shaped,
etc.) These changes involved the pericellular as well as
the peridendritic fibers. In many synaptic structures phen-
omena of fragmentation were observed. Besides, near the den-
drites fibers could be seen with lighter and interrupted seg-
ments (the fragmentation process). Most frequently the frag-
mented fibers were found in the pericellular zone and the
bodies of neurons (Fig. 1). The fragmentation forms varied
greatly: in the form of an elongated comma, rough rods, arc,
segments, zigzag or serpent-like curve, fork, horseshoe,
letter J; often the fragments had varicose or bead-like
bulges. Their arrangement in relation to the neuron had a
haphazard character. These changes in the preterminal fibers
were widely distributed in the reticular substance and ante-
rior horns of the medulla oblongata, in various horns of the
spinal cord, intermedial zone, Clarke's column and in its
reticular nucleus.

During the third stage a slightly manifested progress-
ive reaction of a hyperplastic regenerative type was observed
in the presynaptic fibers. Some presynaptic fibrils formed
collaterals (of normal or hypertrophied structure), which
created the impression of a synaptic little bush approaching,
with its fibrils, the cellular body (Fig. 2). Phenomena of
branching and collateralization of preterminal fibrils can
be related to the proliferative, compensatory-adaptation
changes, which contribute to the improvement of the innervat-
ion mechanism of the neurons under pathological conditions of
the synaptic structures. However, the collateralization pheno-
mena were observed only in a small number of cells, therefore
they apparently have a wide protective physiological impor-
tance, the more so in that the hyperplastic branches were not
infrequently pathologically altered (hypertrophied).

The reactive changes in the terminal synaptic plaques
of the cellular bodies and dendritic processes in the third
stage assumed an even more demonstrative and extensive char-
acter; in contrast to the first two stages, degenerative-
necrobiotic changes developed in them. The structural changes
in the terminal plaques were characterized by strikingly mani-
ifested signs of swelling, hyperimpregnation, polymorphism and
polychromia, deformation and disintegration (Figs. 1 and 2).
Such changes were observed in the somatic and dendritic termi-
nal plaques. The phenomena of marked deformation and break-
ing-up of synaptic plaques were first observed during the
third stage. A considerable number of terminal knobs were
deformed, and had angular, broken, scalloped contours. The
deformation phenomena were observed in the hypertrophied
plaques as well as in the small ones. They were widely dis-
tributed in all horns of the spinal cord and in the medulla
oblongata (reticular substance, anterior horns). In the peri-
cellular space and on the body of cells there were observed
clumps of disintegrated plaques, as well as separation (frac-
tion) of altered plaques from the presynaptic fibers.
In a number of neural cells there was observed a heap-like
arrangement of deformed, markedly argyrophilic plaques situ-
ated close to each other.

The extent of degenerative-necrobiotic changes in
the neuronal synapases after ionizing irradiation depended on
the resistance of the animal organism (the resistance was de-
termined mainly by the dynamics of clinico-hematological in-
dices). For instance, in a dog of average resistance with
clinical symptoms of third-stage radiation sickness, after a
total radiation dose of 1650 r and an experiment lasting 130
days, the degenerative-necrobiotic changes in the synaptic
apparatus were more pronounced than in a dog with higher re-
sistance and an analogous clinical symptom complex of radi-
tation sickness, which had developed under comparable irradia-
tion conditions (total dose 1785 r, duration of experiment 140
days).

Nissl staining of neural cells of the brain and spinal
cord, presented a variegated picture of different histopatho-
logical changes of a reactive and degenerative-necrobiotic
character. In the brain and spinal cord there were observed,
in a considerable number of cells, phenomena of chromatolysis
and vacuolation, acute swelling, cytolysis, and small areas of
disappearance of neural cells with a mild reaction of glia
Fig. 1. Posterior lateral nucleus of the anterior horn of the thoracic section of the spinal cord. Fragmentation of presynaptic fibers. Polymorphism and hypertrophy of terminal plaques. Magnification: 1740 times. Total ionizing radiation dose 1650 r. Third stage of chronic radiation sickness.
Fig. 2. Medio-lateral nucleus of the anterior horn of the thoracic section of the spinal cord. Marked polymorphism of synaptic endings. Fork-like branching of some presynaptic fibers.

Magnification: 1440 times. Total ionizing radiation dose 1785 r. Third stage of chronic radiation sickness.
cells. In addition, quite frequently small groups, or isolated hyperchromatic and shriveled (sclerotic) cells with corkscrew-like twisted processes were seen.

The spinal cords and medullae oblongatae of three dogs in the fourth stage (terminal), were subjected to study: two dogs had died after total doses of 1095 r and 2175 r, having endured the experiment 85 and 169 days, respectively. The third dog was killed following a total dose of 1545 r, the experiment lasting 120 days.

Against the background of reactive changes of the synaptic structures, degenerative-necrobiotic changes continued to increase (swelling, varicose state, bead-like character and tortuosity of the presynaptic fibers, their fragmentation, and disintegration of terminal plaques), involving an ever greater number of cells. A considerable number of fibers, situated along the dendrites and near neural cells, underwent fragmentation. The angyrophilic fragments had various abnormal shapes, or appeared in the form of swollen clumps and grains. In a number of fragments of fibers there were minute spheroid swellings. On the dendrites and neural cells there were often observed hypertrophied plaques with remnants of presynaptic fibers, and disintegration grains of synaptic knobs were encountered. Among markedly changed presynaptic fibers and terminal plaques slightly altered synaptic apparatus were also seen. In the cerebral tissue one could also see morphologically intact synaptic structures.

The changes described were observed in the neural cells of all horns of the spinal cord and in the medulla oblongata (ventral nucleus of the supplementary nerve, the nucleus of the cuneiform bundle, the reticular substance and Rolando's gelatinous substance).

Changes in the synaptic formations of different animals were not uniform, depending on their resistance, the total ionizing radiation dose, and the duration of irradiation. Thus, in a dog with high resistance who had received a total irradiation dose of 2175 r and had been under experimental observation for 169 days, there were observed grave affections of the synaptic apparatus. On the other hand, in dogs of average or lower resistance, at total doses of 1545 r and 1095 r, the experiment lasting 120 and 85 days, respectively, lesser pathological changes of the synaptic ends, approaching those of the third stage, were noted. These data indicate that, at a considerably higher total dose and longer duration of irradiation, the morphological changes of synapses in dogs with high resistance may be more markedly expressed than in dogs with average or lower resistance. In examining Nissl-stained preparations of the brain and spinal cord, we established that degenerative-necrobiotic changes extended to a
larger number of neural cells (chromatolysis, vacuolation, caryoplasticosis, caryocytolysis, hyperchromia and sclerosis of cells), and the number of areas in the cerebral tissue where neural cells had disappeared showed an increase.

The results of histopathological studies of interneuronal synaptic bonds in the central nervous system during the development of an experimental chronic radiation disease enabled us to characterize the pathology of the synaptic neuron apparatus as a toxicodystrophy which develops by stages. The gravity of the dystrophic phenomena depended on the resistance of the organism to ionizing radiation, the total dose, and the duration of irradiation.

Analogous toxicodystrophic destructive changes in the synaptic formations of the central nervous system were described by M. S. Tolgskaya in chronic intoxication with occupational poisons (lead, aniline, arsenic). This fact may serve as confirmation of the characterization of interneuron bonds pathology in experimental chronic radiation sickness as a toxicodystrophy.

These data show that the resistance of the synaptic apparatus to experimental chronic radiation sickness is relative. It depends on the stage of development of the disease, resistance of the animal, the total ionizing radiation dose, and the duration of irradiation. On the basis of their observations in acute radiation sickness, A. D. Zurabashvili and B. R. Naneysvilli, pointed out only the importance of the duration and strength of the effect of penetrating rays.

Pathological changes in the interneuronal structures during the first two stages are reversible. In the third and fourth stages, against the background of reactive, restorative changes, the non-reversible reaction component -- coarse necrobiotic changes -- can be easily observed.

In conclusion it is necessary to point out that in the literature devoted to morphological studies of acute radiation sickness, no attention has been paid to the dynamics of changes in the terminal interneuron structures; therefore there is a need to carry out investigations in this direction, as indicated by our data.

Bibliography


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