NEUROPAT. POL., 1988, 26, 2
PL ISSN 0028-3894

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REMOTE PATHOLOGICAL BRAIN CHANGES IN RATS FOLLOWING EXPERIMENTALLY INDUCED CLINICAL DEATH

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Experimental studies on the consequences of global ischemia of the central nervous system due to cardiac arrest and their complex pathogenic mechanisms are of special importance for a better understanding of thouse clinical cases in which resuscitation procedure results are not limited simply to restoration of basic life functions but allow the preservation of normal brain structure and function.

The experimental model of clinical death in rats, induced without thoracotomy and, therefore, allowing animal survival for the required periods of time after the experimental procedure, introduced by Korpaczev et al. (1982) creates particularly advantageous conditions for studying the evolution of postischemic encephalopathy. Morphological evaluation of cerebral abnormalities in this experimental model, performed by Mossakowski et al. (1986) concerned animals with 10 min cardiac arrest and subsequent survival for periods ranging from 24 h to 28 days. This period of time covers the appearance of neuropathological changes resulting both directly from the ischemic incident itself and from circulatory and metabolic disorders accompanying and following restoration of cerebral blood flow.

The present studies aimed at establishing whether the neuropathological picture observed in remote postresuscitation stages differs from that seen in the early phases of the pathological process. These differences may be indicative of further development and evolution of postischemic encephalopathy. In addition, tissue abnormalities were evaluated in the brains of rats, which survived 15 min long clinical death of their mother during pregnancy.

MATERIAL AND METHODS

The studies were carried out on adult female albino rats, weighing 160–170g in which global cerebral ischemia due to cardiac arrest was evoked according to the method of Korpaczev et al. (1982). Under light ether

anesthesia of animals, a specially constructed metal hook was inserted intrathoracically, which compressed the heart vascular bundle against the sternum. The procedure led in the course of 1.5–2 min to cardiac arrest followed by cessation of respiration. The cardiac arrest resulted in the course of 10–15 sec. in disappearance of the cerebral bioelectric activity, confirmed by its isoelectric electrocorticographic record (Mossakowski et al. 1986). Following 15 min of cardiac arrest resuscitation procedure was introduced. This consisted in external heart massage carried out till full recovery of spontaneous heart action, and controlled respiration with air of normal composition inhaled through a polyethylene tube inserted intratracheally and connected with a respirator for small laboratory animals. In the above presented experimental conditions spontaneous heart action was restored in 2–4 min (average 3 min), and the respiratory function within 10 to 17 min (average 14 min). The pain reflexes reappeared at the time from 38 to 45 min (average 42 min) and corneal reflexes between 55 and 75 min (average 65 min). Directly after resuscitation the animals were lying with maximally straightened extremities. Increased muscle tone and tautness of extremities were commonly observed. Gradually the condition of the animals improved, and 24 h following the ischemic incident it did not differ from that of animals not subjected to any experimental procedure. Six months after experimentally induced clinical death the animals were sacrificed by transcardiac perfusion with 10% neutral formalin solution. The brains removed from the skull were postfixed in the same formalin solution and then cut frontally into blocks. Tissue blocks from 3 levels of the cerebral hemispheres, midbrain, pons, cerebellum and medulla were processed routinely and embedded in paraffin. Paraffin sections were stained with hematoxylin-eosin, cresyl violet and according to Klüver-Barrera's method.

Brains of 10-week-old progeny of the female rat subjected on the 10th day of pregnancy to 15-min clinical death (pregnancy was not noticed during selection of animals for the experiment) were also examined. The material for histological studies was taken from the same brain areas as in adult animals. The same histological techniques were applied.

RESULTS

The animals, which survived 6 months following reanimation did not exhibit any neurological and somatic deficits during the whole period of observation, except two rats in which body weight was 10 percent lower as compared with the average for the whole group.

The progeny of the female rat subjected during pregnancy to experimental clinical death developed normally and showed no differences as compared with their age mates not subjected to any experimental procedure.

Brains in both experimental groups showed no macroscopic alterations.

Microscopic examination of brains from animals, which survived 6 months

following clinical death in all cases revealed tissue abnormalities. These varied considerably in their intensity and extension in individual animals. They appeared in grey matter structures and took the form of neuronal degeneration and/or loss, either accompanied by glial reaction or showing no glial response. In none of the examined animals were present foci of full tissue necrosis. Macrophage appearance was not a feature. Tissus abnormalities were not noted in the white matter, except some focal glial proliferation in the direct vicinity of more extensive areas of neuronal lose in the neighbouring grey matter structures.

Grey matter alterations consisted in the appearance of shrunken neurons and cells with changes resembling those typical for what is called chronic Nissl degeneration or ghost cells. Small holes in places of brokendown neurons, neuronal rarefaction and widespread areas of neuronal loss were seen. Most commonly neuronal changes showed no accompanying glial reaction, however, in some cases a certain astrocytic or astrocytic-microglial reaction

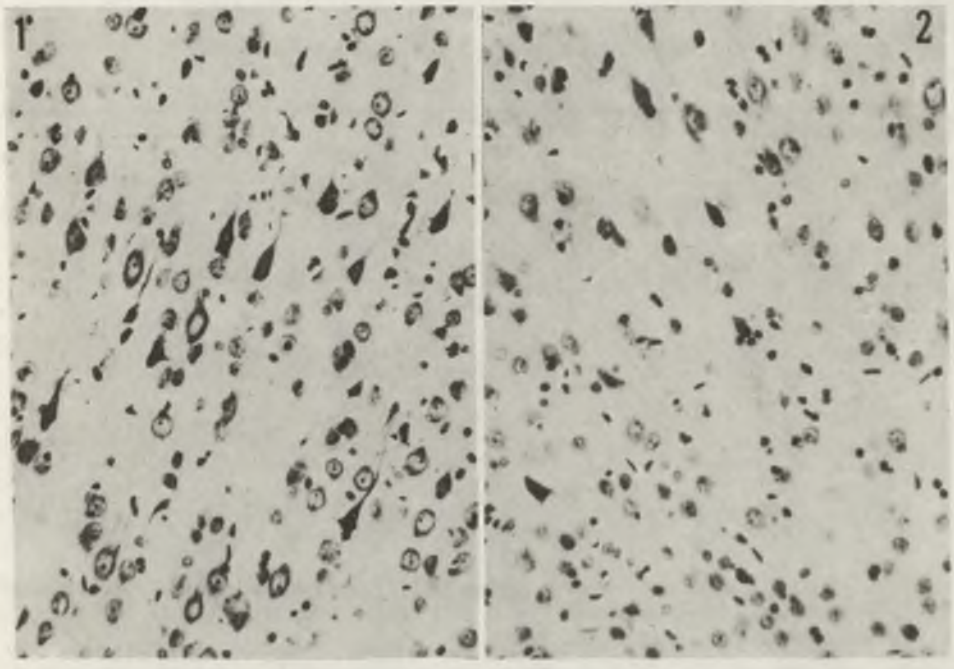

Fig. 1. Rat with 6 months survival after clinical death. Fronto-parietal cortex. Laminary rerefaction of nerve cells. Numerous neurons showing features of chronic degeneration. H – E. × 200

Ryc. 1. Szczur z 6 miesięcznym przeżyciem po reanimacji. Kora czołowo-ciemieniowa. Warstwowe przerzedzenie komórek nerwowych. Widoczne również dość liczne neurony o cechach schorzenia przewlekłego. H – E. Pow 200 ×

Fig. 2. Rat with 6 months survival after clinical death. Neuronal rarefaction in borderline zone between vascularization areas of anterior and middle cerebral arteries. Shrunken dark neurons. There is some glial proliferation. Cresyl violet. × 200

Ryc. 2. Zwierzę z 6 mies. przeżyciem po reanimacji. Przerzedzenie neuronów w obszarze pogranicza unaczynienia tętnicy mózgu przedniej i środkowej. Widoczne obkurczone, ciemne neurony. Zaznaczone pomnożenie komórek glejowych. Fiolet krezylu. Pow. 200 ×

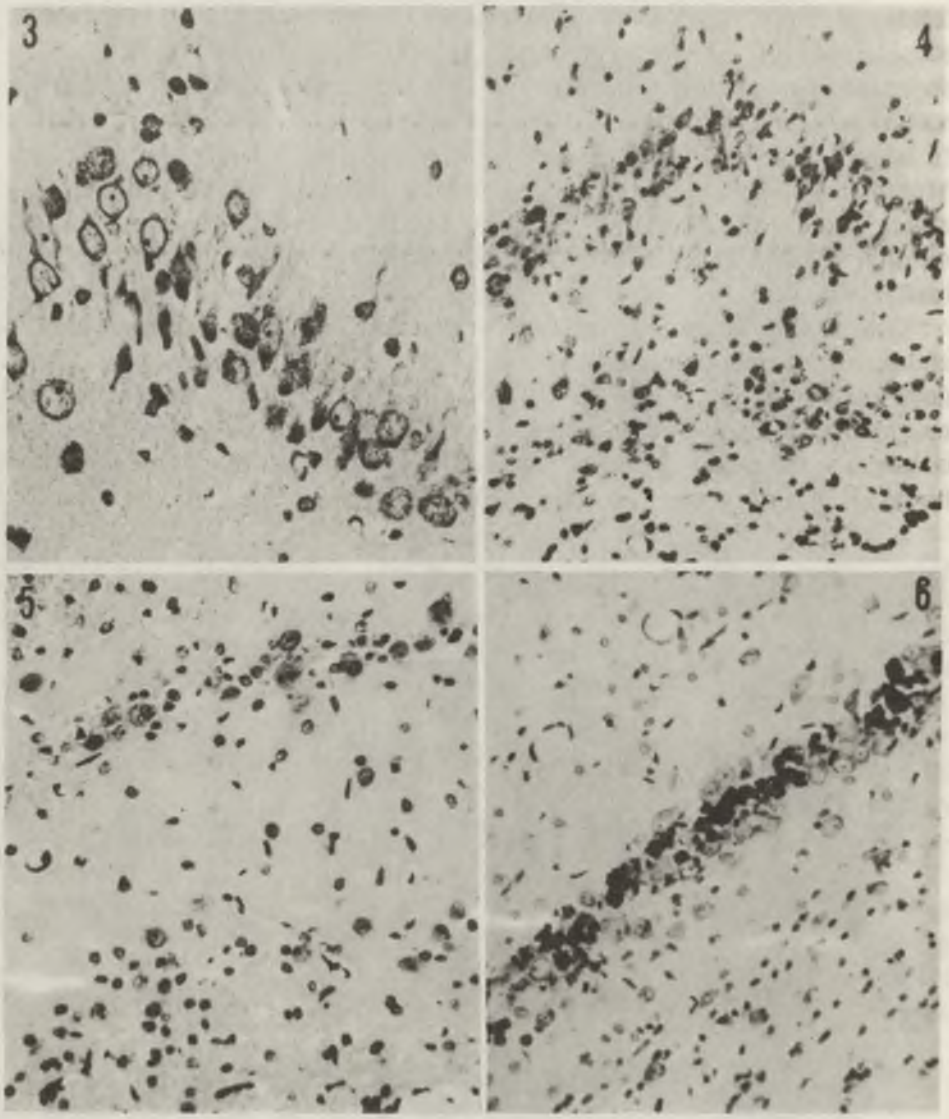

Fig. 3. Rat with 6 months survival after clinical death. Paramedial segment of CA_1 sector of Ammon's horn. Impairment and loss of pyramidal neurons. Cresyl violet. × 400

Ryc. 3. Zwierzę z 6 mies. przeżyciem po reanimacji. Przyśrodkowy odcinek sektora CA_1 rogu Amona. Widoczne zaniki i uszkodzenia neuronów piramidowych. Fiolet krezylu. Pow. 400 ×

Fig. 4. Rat with 6 months survival after clinical death. Paramedial segment of CA_1 sector of Ammon's horn. Severe damage of pyramidal cell layer taking the form of extensive neuronal loss and degeneration with profuse glial reaction (astrocytic-microglial proliferation and hypertrophy). H – E. × 200

Ryc. 4. Zwierzę z 6 mies. przeżyciem po reanimacji. Przyśrodkowy odcinek sektora CA_1 rogu Amona. Widoczne uszkodzenie warstwy komórek piramidowych w postaci rozległych ubytków i zmian neuronalnych z nasilonym odczynem glejowym (astrocytarno-mikroglejowym). H – E. Pow. 200 ×

Fig. 5. Rat with 6 months survival after clinical death. Sector CA_1 of Ammon's horn with profuse neuronal loss. Strong astrocytic-microglial reaction in the vicinity of dentate gyrus. H – E. × 100

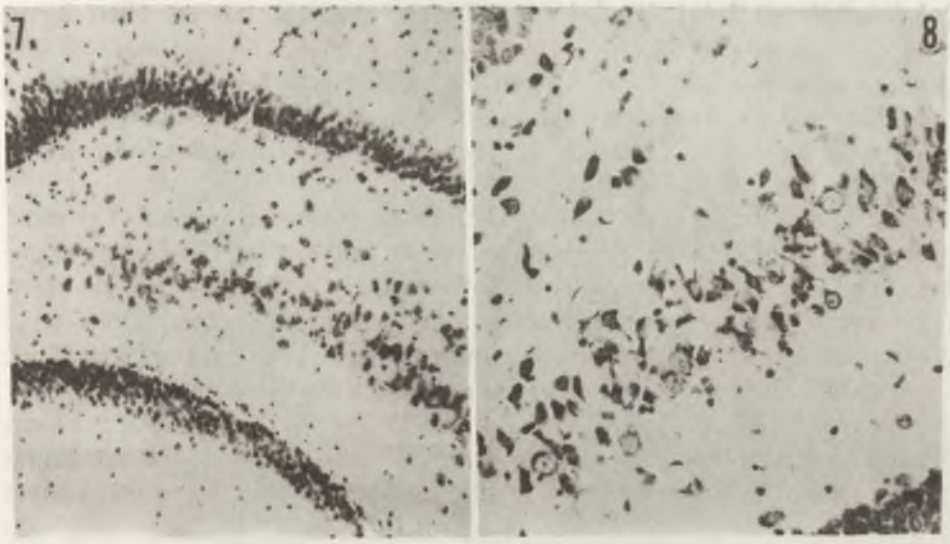

Fig. 7. Rat with 6 months survival after clinical death. Rarefaction of nerve cells and numerous degenerated neurons in sector CA_4 of Ammon's horn. Increased population of glial cells. H—E. × 100

Ryc. 7. Szczur z 6 mies. przeżyciem po reanimacji. Widoczne przerzedzenie komórek nerwowych oraz uszkodzone neurony w sektorze CA_4 rogu Amona. Komórki glejowe pomnożone. H—E. Pow. 100 ×

Ryc. 8. Szczur z 6 mies. przeżyciem po reanimacji. Ubytki i uszkodzenie neuronów w sektorze CA_4 Ammon's horn with presence of glial reaction. Cresyl violet. × 200

Ryc. 8. Szczur z 6 mies. przeżyciem po reanimacji. Ubytki i uszkodzenie neuronów w sektorze CA_4 rogu Amona z zaznaczonym odczynem glejowym. Fiolet krezylu. Pow. 200 ×

was present. Its nature and intensity varied, depending on the character and extensiveness of neuronal damage as well as on the brain structure involved.

In the fronto-parietal cortex, among the population of normal neurons more or less numerous nerve cells with features of chronic degeneration were dispersed (Fig. 1). These were concomitant with laminar neuronal rarefaction (Fig. 2). and perivascular neuronal loss. The latter were more common in the upper cortical layers (II—IV) and in borderline zones between vascularization areas of larger cerebral arteries. Sometimes, the periphery of those microfoci contained a greater number of altered neurons (Fig. 1). Impaired neurons, both shrunken and showing features of chronic degeneration, were seen also in the

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Ryc. 5. Szczur z 6 mies. przeżyciem po reanimacji. Sektor CA_1 rogu Amona z rozległymi ubytkami neuronów piramidowych. Wyraźny odczyn astrocytarno-mikroglejowy na pograniczu zakrętu zębatego. H—E. Pow. 100 ×

Fig. 6. Rat with 6 months survival after clinical death. Sector CA_1 of Ammon's horn. Numerous caclified neurons in the pyramidal layer. Increased population of glial cells and abundant light astrocytes are seen. H—E. × 200

Ryc. 6. Szczur z 6 mies. przeżyciem po reanimacji. Sektor CA_1 rogu Amona. Liczne zwapniałe neurony w warstwie komórek piramidowych. Widoczne pomnożenie komórek glejowych i liczne jasne komórki gwiaździste. H—E. Pow. 200 ×

entorrhinal cortex, however, they were present here not so often as in neocortical structures and did not accompany perivascular neuronal loss and laminar neuronal rarefaction. The cortical glial reaction was generally weak and expressed by small aggregations of cells around degenerated neurons, slight focal cellular proliferation, appearance of hypertrophied astrocytes and intensified perineuronal satellitosis.

The hippocampal gyrus was involved in all examined animals. The most common alterations were observed in the CA_1 sector of the dorsal hippocampus. They were usually limited to its initial portion, where they took the form of cell rarefaction with no glial reaction and/or neuronal degeneration (Fig. 3). Sometimes they were expressed as a more extensive loss of pyramidal neurons, accompanied by astro-microglial response present both in damaged areas and in their vicinity (Fig. 4). In one animal severe CA_1 sector damage took the form of advanced neuronal loss concomitant with calcification of the remaining nerve cells and intensive astro-microglial proliferation (Fig. 5 and 6). In some

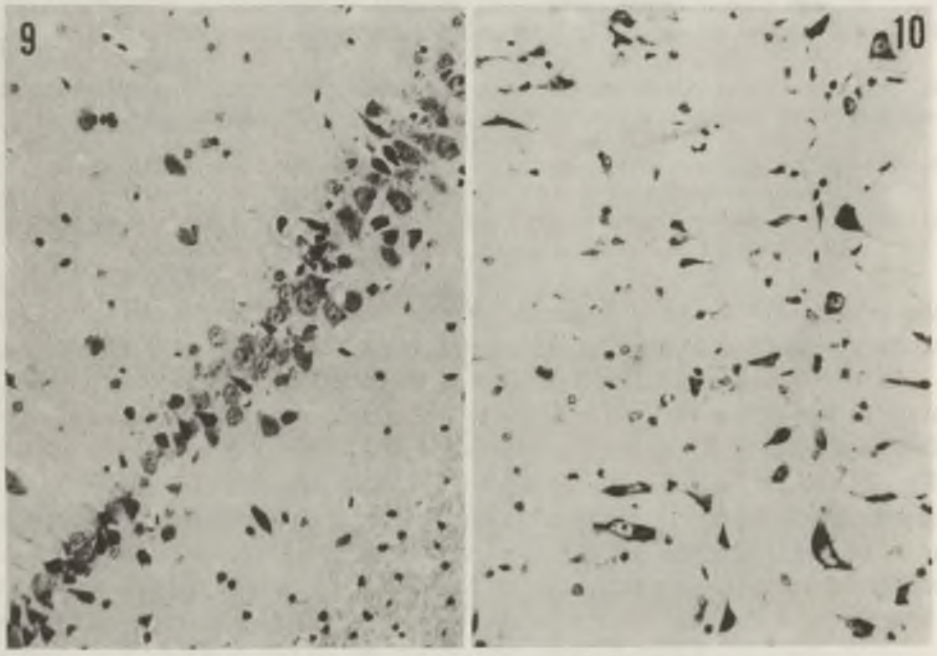

Fig. 9. Rat with 6 months survival after clinical death. Neuronal loss and chronic degeneration of nerve cells in sector CA_3 of Ammon's horn. H—E. × 200

Ryc. 9. Szczur z 6 mies. przeżyciem po reanimacji. Ubytki i przewlekłe zmiany neuronalne w sektorze CA_3 rogu Amona. H—E. Pow. 200 ×

Fig. 10. Rat with 6 months survival after clinical death. Sclerotic neurons in raphe structures. Increased glial population. Large "empty" astrocytic nuclei resembling naked nuclei. Cresyl violet. × 200

Ryc. 10. Szczur z 6 mies. przeżyciem po reanimacji. Sklerotyczne neurony w strukturach szwu. Komórki glejowe pomnożone, widoczne również komórki astrocytarne o pustych jądrach, przypominające nagie jądra. Fiolet krezylu. Pow. 200 ×

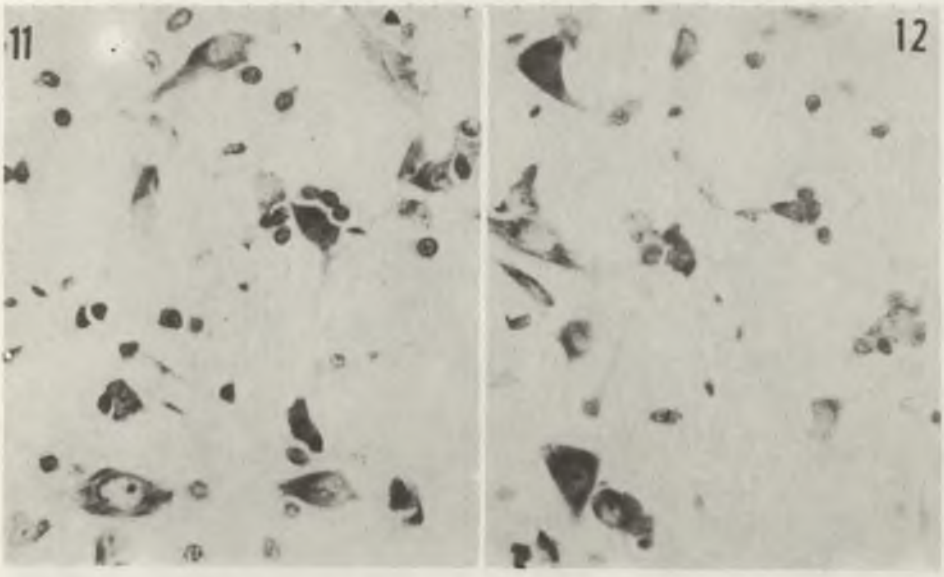

Fig. 11. Rat with 6 months survivale after clinical death. Brain stem. Degenerating nerve cells are visible, one of them surrounded by glial nuclei. Cresyl violet. × 400

Ryc. 11. Szczur z 6 mies. przeżyciem po reanimacji. Pień mózgu. Widoczne wyrodniejące komórki nerwowe. Jedna z nich otoczona komórkami glejowymi. Fiolet krezylu. Pow. 400 ×

Fig. 12. Rat with 6 months survival after clinical death. Degenerating nerve cells in the brain stem with glial proliferation surrounding damaged neurons. Cresyl violet. × 400

Ryc. 12. Szczur z 6 mies. przeżyciem po reanimacji. Wyrodniejące neurony w pniu mózgu z widocznym zagęszczeniem gleju wokół uszkodzonych komórek nerwowych. Fiolet krezylu. Pow. 400 ×

cases changes were strictly confined to the CA_1 sector while in others they occurred additionally in sector CA_4 (Figs 7 and 8) and sectors CA_2 and CA_3 (Fig. 9) or in the borderline between sectors CA_2 and CA_3. Usually they were expressed as disseminated or focal degeneration of pyramidal cells.

The striatum, as a rule, was devoid of larger nerve cells; the remaining ones showed features of chronic or "severe" degeneration. In some cases the pathological process involved also small striatal neurous, which were degenerated and their population seemed to be reduced. Similar changes were noted in the thalami.

In the midbrain, pons and medulla neuronal abnormalities were more pronounced that in the cerebral cortex and subcortical structures. Damaged neurons were seen practically in all structures of the brain stem. As a rule medium-size and small neurons were more often impaired than the large ones. The most advanced changes concerned raphe and pontine nuclei, substantia nigra and inferior olives. In structures of raphe, shrunken, sclerotic neurons prevailed (Fig. 10). In other nuclear formations there was preponderance of degeneration of nerve cells accompanied by proliferating glia (Fig. 11), gemistocytes and cells resembling Alzheimer's naked nuclei (Fig. 12). Glial cells were aggregated mostly around disintegrating and/or disintegrated neurons.

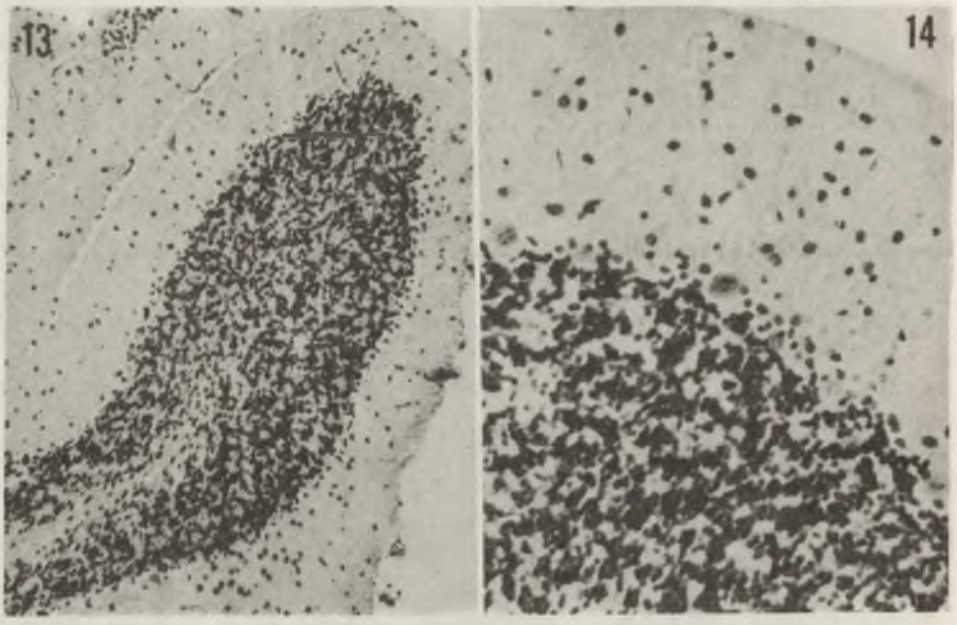

Fig. 13. Rat with 6 months survival after clinical death. Extensive loss of Purkinje cells in cerebellar lobulus with accompanying proliferation of Bergmann's glia. H—E. × 100

Ryc. 13. Szczur z 6. mies. przeżyciem po reanimacji. Rozległe ubytki komórek Purkinjego w w obrębie płacika móżdżku z towarzyszącym rozplemem gleju Bergmanna. H—E. Pow. 100 ×

Fig. 14. Rat with 6 months survival after clinical death. Widespread loss of Purkinje cells, remaining show features of severe impairment. Increased glial proliferation in the molecular layer of cerebellar cortex. Cresyl violet. × 200

Ryc. 14. Szczur z 6. mies. przeżyciem po reanimacji. Rozsiane ubytki komórek Purkinjego, zachowane — wykazują cechy uszkodzenia. W warstwie drobinowej kory móżdżku pomnożenie komórek glejowych. Fiolet krezylu. Pow. 200 ×

The cerebellar cortex revealed widespread or focal loss of Purkinje cells (Fig. 13), occurring more commonly on the convexite of gyri than in the sulci depths. Cerebellar hemispheres seemed more involved than the vermis. Purkinje cell loss was accompanied by proliferation of Bergmann's glia or increased glial population in the molecular layer (Fig. 14). Less often no glial reaction was observed. Degenerated Purkinje cells were widespread over the cerebellar cortex, they were more common in the vicinity of their extensive loss. Cerebellar deep nuclei, mostly the dentate nucleus, showed neuronal and glial changes similar to those described in brain stem structures.

Tissue abnormalities in brains of animals, which survived the ischemic incident during intrauterine life, were much less advanced. In the neocortex single or grouped degenerated neurons were relatively seldom seen (Fig. 15). The same concerned the hippocampal gyrus and subcortical structures. The most advanced abnormalities concerned brain stem structures. Most common was degeneration of neurons accompanied by some glia reaction (Fig. 16). Widespread degeneration and loss of Purkinje cells in the cerebellar cortex were relatively infrequent findings.

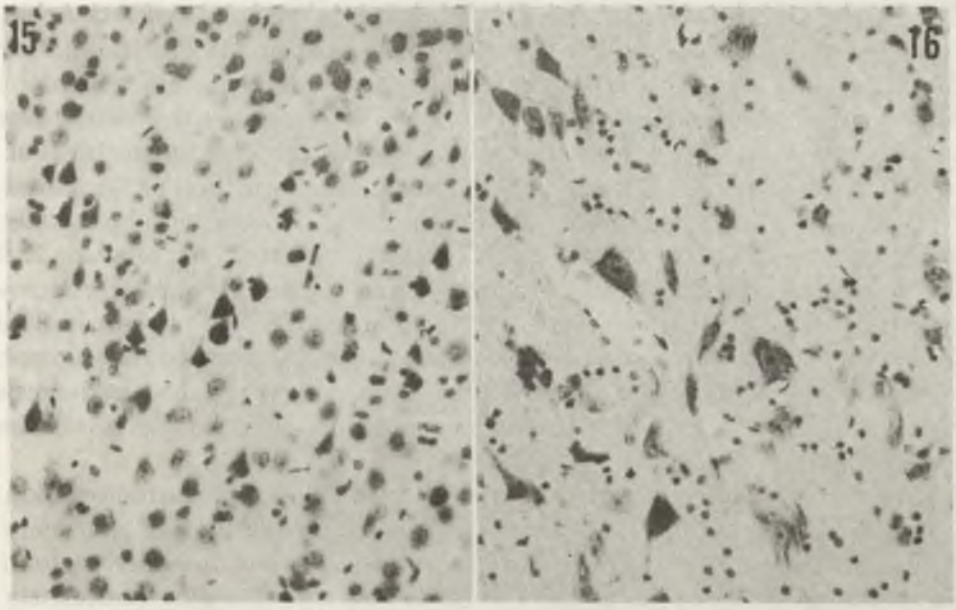

Fig. 15. Rat which survived 15-min clinical death of mother during intrauterine life. Hyperchromatic neurons with obliterated structure widespread single and in groups in fronto-parietal cortex. Cresyl violet. × 200

Ryc. 15. Szczur, który przeżył śmierć kliniczną matki w okresie płodowym. Nadbarwliwe neurony o zatartym obrazie strukturalnym, rozsiane pojedynczo oraz w niewielkich skupieniach w korze czołowo-ciemieniowej. Fiolet krezylu. Pow. 200 ×

Fig. 16. Rat which survived during intrauterine life 15-min clinical death of mother. Damaged neurons, proliferation of glial cells and their aggregation arround impaired nerve cells. Cresyl violet. × 400

Ryc. 16. Szczur urodzony przez samicę, która w okresie ciąży przeżyła 15 min śmierć kliniczną. Widoczne uszkodzone neurony, pomnożenie gleju komórkowego i skupienie się komórek glejowych wokół uszkodzonych neuronów. Fiolet krezylu. Pow. 400 ×

DISCUSSION

The above presented results indicate that rats which survived 6 months following experimentally induced clinical death, developed cerebral abnormalities which can be named postresuscitation encephalopathy. Despite of long duration of global brain ischemia, applied in our study, the intensity of cerebral lesions was relatively slight, for instance foci of full tissue necrosis were not a feature in any of the animals examined. This phenomenon can probably be connected with a relatively high resistance of the central nervous system in rats to the damaging influence of hypoxia and ischemia, this being known from numerous other experimental studies. This fact finds its confirmation in the relatively slight advancement of brain pathology in our material as compared with other animal models of global brain ischemia (Zaren et al. 1970; Snyder et al. 1975; Safar et al. 1976; Nemoto et al. 1977).

Evolution of cerebral structural lesions in the postresuscitation syndrome was biphasic in early stages of pathological process (Mossakowski et al. 1986).

The first phase was characterized by appearance of nonspecific neuronal changes spread throughout the central nervous system. Some of them were reversible with all probability. Reversible neuronal lesions were noticed in numerous experimental conditions. Klatzo (1985) pointed out the reversibility of ischemic neuronal changes in the „penumbra" areas. According to Ito et al. (1975) and Bubis et al. (1976) during ischemia in some structures of the central nervous system there appear characteristic neuronal changes, morphologically similar to axonal nerve cell degeneration, which are totally reversible. The occurrence of reversible neuronal alteration can explain the greater extensiveness of nerve cell changes observed in the early stage of postresuscitation encephalopathy as compared with its further phases characterized by neuronal loss and degeneration; the latter showing typical topographic selectiveness (Mossakowski et al. 1986) and dynamics dependent on the principles of what is called maturation phenomenon (Klatzo 1975).

In our material concerning brains of rats with long postresuscitation survival, tissue structural abnormalities showed an obvious lack of uniformity and simultaneity. Some of them can be considered as resulting directly from ischemia and both vascular and metabolic disturbances occurring immediately after restoration of the cerebral blood flow. This group of changes is represented by focal selective necroses in the neocortex and hippocampal gyrus, both lacking glial reaction and accompanied by astrocytic or astro-microglial response of varying intensity, perivascular neuronal loss in the cerebral cortex, rarefaction and neuronal loss in the borderline zones between vascularization areas of larger cerebral arteries, disintegration of larger striatal neurons and presence of atrophic nerve cells. Focal loss of Purkinje cells is also probably connected with this stage of the pathological process.

The second feature of the neuropathological picture consists in the presence of degenerating nerve cells widespread in the brain stem structures, cerebellar and cerebral cortex and in subcortical formations of brain hemispheres. The appearance of these changes concomitant with glial reaction is indicative of an active, slowly progressing pathological process. The mechanism of this phenomenon is unknown. Safar (1986) suggests that development of postresuscitation brain pathology is connected with functional insufficiency of internal body organs, with secondary additional damage to the central nervous system. The damaging influence may be exerted by toxic substances liberated from the abnormally functioning liver and/or kidneys as well as by endotoxins or aminoacids absorbed from ischemically altered intestinal walls. This hypothesis may find support in observations indicating that damage to the central nervous system in the case of experimentally induced cardiac arrest is more severe than that occurring under conditions of isolated brain global ischemia. Participation of immunopathological mechanisms in the development of postresuscitation brain pathology should also be taken into consideration. In the same experimental model, Mossakowski and Krajewski (1988) showed progressive accumulation of antineuronal antibodies

in the blood sera of resuscitated animals. These antibodies may be involved in the appearance of late degeneration of nerve cells in the central nervous system. Data concerning the immunopathological mechanism of neuronal loss in the ageing brain support this concept (Nandy 1982).

The brain abnormalities in rats, which survived during intrauterine life, clinical death of their mother, were very slight. The most advanced changes concerned brain stem formations. These observations confirm a well known fact concerning the relatively low sensitivity of the immature central nervous system to hypoxia. On the other hand, they are in agreement with data indicating the greatest intensity of hypoxic lesions in those structures of the central nervous system which at the time of action of the damaging factor(s) show the most advanced degree of development, and thus, the greatest sensitivity to the noxious influence (Myers 1977).

PÓŹNE ZMIANY PATOMORFOLOGICZNE W MÓZGACH SZCZURÓW PO PRZEBYTEJ ŚMIERCI KLINICZNEJ

Streszczenie

W badaniach patomorfologicznych mózgów zwierząt, które przeżyły okres 6 miesięcy po wywołanej doświadczalnie 15 min śmierci klinicznej stwierdzono, iż obok zmian, które można traktować jako bezpośrednie następstwo epizodu niedokrwiennego mimo ich ujawniania się ze zróżnicowaną latencją czasową, występują nieprawidłowości tkankowe świadczące o aktywnie postępującym procesie zwyrodnieniowym. Uzyskane wyniki wskazują, że encefalopatia poreanimacyjna ma charakter procesu, w którym na uszkodzenia związane z incydentem niedokrwiennym nakładają się zmiany wtórne, rozwijające się na podłożu zaburzeń zapoczątkowanych przez niedokrwienie, być może o charakterze immunopatologicznym.

Zmiany u zwierząt, które przeżyły incydent niedokrwienny w życiu płodowym były mniej nasilone i dotyczyły przede wszystkim struktur pnia mózgu. Potwierdza to mniejszą wrażliwość niedojrzałego układu nerwowego na niedotlenienie i lokalizację uszkodzeń w strukturach o najbardziej zaawansowanym dojrzewaniu w momencie zadziałania czynnika patogennego.

ПОЗДНИЕ ПАТОМОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В МОЗГАХ КРЫС ПОСЛЕ ПЕРЕНЕСЕННОЙ 15-МИНУТНОЙ КЛИНИЧЕСКОЙ СМЕРТИ

Резюме

В патоморфологических исследованиях мозгов животных, которые прожили 6 месячный период после 15-минутной клинической смерти обнаружено, что кроме изменений, которые можно обсуждать как непосредственное последствие ишемического эпизода, несмотря на их появление в разном периоде, выступают также тканевые напушения, свидетельствующие об активно прогрессирующем дегенерационном процессе. Полученные результаты показывают, что послереанимационная энцефалопатия является процессом, в котором на, связанные с инцидентом ишемии, повреждения накладываются вторичные изменения. Эти вторичные изменения, развиваются на основе нарушений, начатых ишемией и являются, вероятно, проявлением иммунопатологического процесса.

У животных, которые прожили эпизод ишемии внутриутробно, изменения были менее интенсивны и касались прежде всего структур мозгового ствола. Это подтверждает меньшую чувствительность незрелой нервной системы и локализацию повреждений в структурах, наиболее продвинутых в созревании во время действия повреждающего фактора.

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