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# ANTINEURAL ANTIBODIES IN BLOOD SERA OF RATS SUBJECTED TO GLOBAL CEREBRAL ISCHEMIA

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Appearance of antibrain antibodies or autoantibodies directed against specific cerebral antigens in the blood sera were described in quite a number of neurological diseases. The richest information concerns immunopathological processes accompanying brain ageing both in human subjects and in experimental animals (Ingram et al. 1974; Nandy 1975; Nandy et al. 1975; Makindan 1976; Redie et al. 1979; Cohen, Eisdorfer 1980; Goodwin et al. 1982). The increasing with age content of blood antineuronal antibodies underlies Nandy's concept on the immunopathological mechanism of brain ageing (Nandy 1982). In recent years a number of data have appeared concerning accumulation in blood of antineurofilament antibodies in those neurological diseases in which abundant neuronal breakdown in the central nervous system taken place (Bahmanyar et al. 1984, 1985; Stefansson et al. 1985; Toh et al. 1985). Karcher et al. (1986) in their rich clinical meterial found an enhanced level of antineurofilament antibodies in 24 percent of cases with cerebrovascular accidents. The same phenomenon was observed in cerebral trauma. Recently Ganushkina and Lebiedieva (1987) described immunological abnormalities, accompanying chronic hypertonic encephalopathy.

This inclined us to perform some experimental studies on the immunopathological reaction resulting from severe cerebral ischemia. It seemed even more justified as there exist some suggestions concerning the possible participation of immunological mechanisms in the pathogenesis of post-ischemic encephalopathy. The prerequisite for these studies was an appropriate experimental model ensuring severe enough cerebral ischemia and sufficiently long subsequent survival of animals.

## MATERIAL AND METHODS

The experiments were performed on adult, male albino rats weighing ca 180 g, in which clinical death was induced according to the method described by Korpaczev et al. (1982). Compression of the heart vascular bundle by a special

hook, inserted into the thorax, led in the course of 1.5 to 2 min to complete cardiac arrest and cessation of respiratory function, lasting till resuscitatory management was undertaken. In the case of our experiments this was done after either 10 or 15 min of complete cessation of brain bioelectric activity. Following resuscitation, which included external heart massage and controlled respiration, the experimental animals survived for 6 and 24 hrs, 3, 7, 14 and 28 days as well as 6 months. Their age mates, not subjected to any experimental precedures formed the control group.

The brains of control and experimental animals were examined histologically and immunomorphologically. Histology was done on paraffin sections stained with hematoxiline-eosine and according to the Klüver–Barrera's method. Immunomorphology included immunoreactions for host blood proteins, albumins and IgG performed by the peroxidase-anntiperoxidase technique as indicators of the blood-brain-barrier state and immunostaining of glial fibrillary acidic protein (GFAP) – to reveal the astrocytic response.

The blood sera of control and experimental animals, sacrificed at the end of the previously mentioned survival periods were collected and characterized by the immunofluorescent technique. Cryostat sections of normal rat brains, liver and kidney after 1 hour of PBS elution were fixed in cold acetone and then preincubated with goat antibodies against rat immunoglobulins in order to block the remainig host immunoglobulin reactivity. Then sera of experimental and control rats dilluted within the range 1:4 to 1:40, and occasionally 1:80, were put on the appropriate organ section. The immune reactions were visualized by subsequent incubation first with rabbit anti-rat IgG and then sheep antirabbit-immunoglobulins-FITC. Absorption of the examined sera with lyophilised brain and powdered liver tissues were run in order to check the organ-specificity of the reaction. Immunohistochemistry with mouse and gerbil brain cryostat sections controlled its species-specificity.

## RESULTS

Histological examination* revealed in the early postischemic period widespread moderate neuronal degeneration, appearing in various structures of the central nervous system prevailing especially in the cerebral and cerebellar cortex and basal ganglia. However, degeneration was also present in areas relatively resistant to ischemic damage, such for instance as substantia nigra, some nuclei of reticular formation and cranial nerves. Degeneration appeared either in the form of tigrolysis, leading to the pictures described in classical neuropathology as acute neuronal swelling or as typical ischemic neuronal changes (Fig. 1). Purkinje cells showed characteristic homogeneous degeneration. Features of neuronal loss appeared starting from the third postischemic

*Detailed histopathological data have been previously described in papers by Mossakowski et al. (1986) and Zelman and Mossakowski (1988).

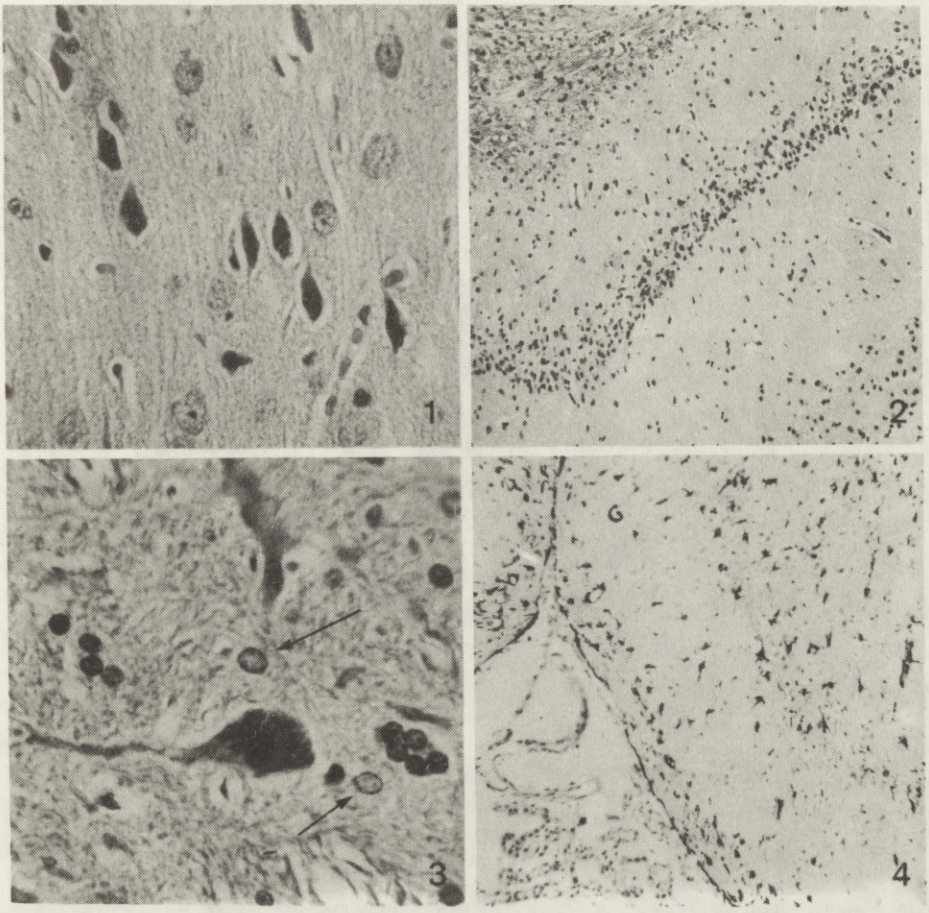


*Fig. 1.* Experimental animal. 10-min clinical death with 24-h survival. Ischemic dark neurons in the cerebral cortex. H–E. × 400

*Ryc. 1.* Zwierzę doświadczalne. 24 godz. przeżycia po 10 min śmierci klinicznej. Typowe zmiany niedokrwienne neuronów kory mózgu. H–E. Pow. 400 ×

*Fig. 2.* Experimental animal with 10-min clinical death and 7-day survival. Neuronal loss with accompanying glial proliferation in dorsal hippocampus (Ammon's horn sector $CA_1$). H–E. × 60

*Ryc. 2.* Zwierzę doświadczalne. 7 dni przeżycia po 10-min śmierci klinicznej. Rozległy ubytek neuronów z towarzyszącą proliferacją gleju w grzebietowej części zakrętu hipokampa (sektor $CA_1$ rogu Amona). H–E. Pow. 60 ×

*Fig. 3.* Experimental animal with 15-min clinical death followed by 6-month survival. Enlarged astrocytic nuclei (arrows) resembling Alzheimer cells type II and small groups of glial nuclei, probably replacing neuronal perikarya. H–E. × 900

*Ryc. 3.* Zwierzę doświadczalne. 6 miesięcy po przeżyciu 15 min śmierci klinicznej. Pojedyncze powiększone jądra astrocytarne (strzałki) przypominające komórki Alzheimera typu II oraz drobne skupienia jąder glejowych prawdopodobnie w miejscach zanikłych komórek nerwowych. H–E. Pow. 900 ×

*Fig. 4.* Experimental animal with 10-min clinical death followed by 28-day survival. Astrocytic proliferation and hypertrophy localized subependymally and in the area of brokendown pyramidal neurons of Ammon's horn. GFAP. × 100

*Ryc. 4.* Zwierzę doświadczalne. 28 dni przeżycia po 10-min śmierci klinicznej. Rozplem i przerost astrocytów w warstwie podwyściółkowej oraz w warstwie rozpadłych komórek piramidowych rogu Amona. GFAP. Pow. 100 ×

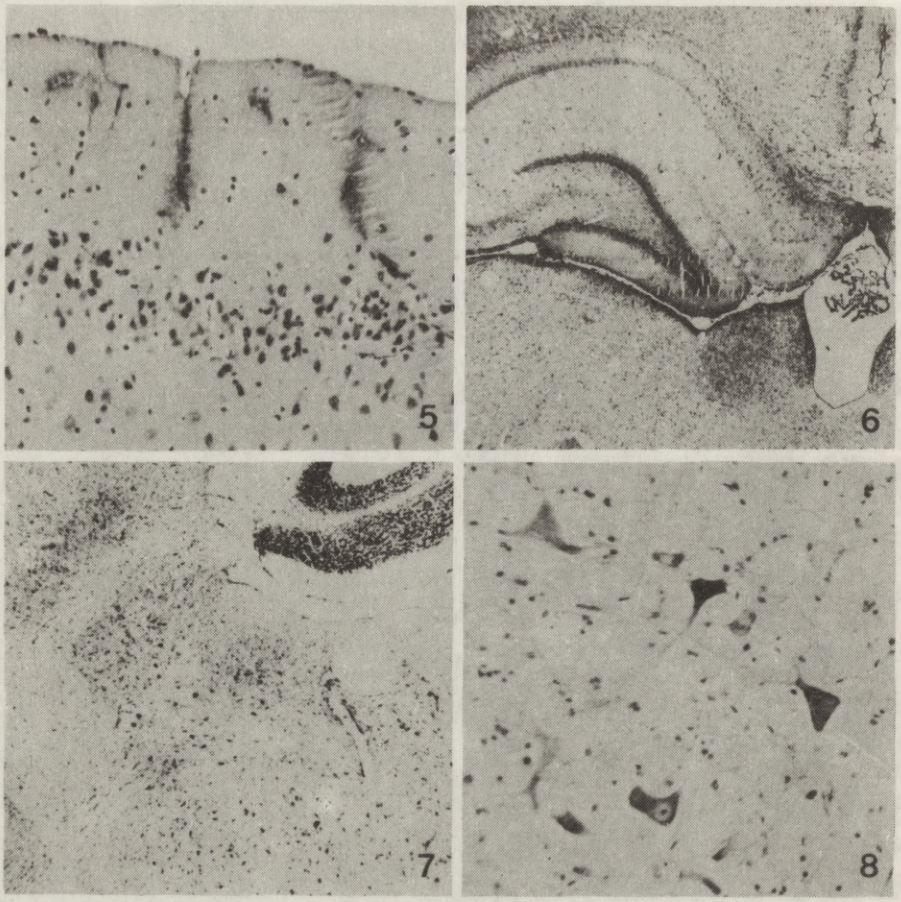


*Fig. 5.* Experimental animal with 10-min clinical death followed by 24-h survival. Perivascular accumulation of blood albumin in the molecular layer of hippocampal gyrus. PAP reaction. × 100

*Ryc. 5.* Zwierzę doświadczalne. 24 godz. przeżycia po 10-min śmierci klinicznej. Okołonaczyniowe nagromadzenie albumin surowicy krwi w warstwie drobinowej zakrętu hipokampa. PAP. Pow. 100 ×

*Fig. 6.* Experimental animal with 10-min clinical death followed by 24-h survival. Diffuse inbibition of periventricular structures, most pronounced in hippocampal formation, with blood serum albumin. PAP. Magnif. glass

*Ryc. 6.* Zwierzę doświadczalne. 24 godz. przeżycia po 10-min śmierci klinicznej. Rozlana inbibicja struktur okołokomorowych, najsilniejsza w rogu Amona, albuminami surowicy krwi. PAP. Pow. lupowe

*Fig. 7.* Experimental animal with 10-min clinical death followed by 3-day survival. Diffuse infiltration of the brain stem grey structures with blood serum proteins. PAP. × 10

*Ryc. 7.* Zwierzę doświadczalne. 3 dni przeżycia po 10-minutowej śmierci klinicznej. Rozlana inbibicja szarych formacji pnia mózgu białkami surowicy krwi. PAP. Pow. 10 ×

*Fig. 8.* Experimental animal with 10-min clinical death followed by 24-h survival. Large neurons of reticular formation revealing positive immunochemical reaction for blood serum proteins. PAP. × 200

*Ryc. 8.* Zwierzę doświadczalne. 24 godz. przeżycia po 10-min śmierci klinicznej. Duże neurony formacji siatkowatej pnia mózgu wykazujące dodatni odczyn na białka surowicy krwi. PAP. Pow. 200 ×

day and were localized first of all in typical selectively vulnerable areas such as the hippocampus (Fig. 2), ganglion cell layer of cerebellar cortex, 3rd neocortical layer and striatum. Borderline zones of the cerebral cortex were also the sites of severe changes. The intensity of neuronal loss increased remarkably with time in the whole postischemic period. It was much more severe in animals sacrificed 6 months after clinical death than in those killed 4 weeks afterwards. It involved also much greater areas than those of neuronal degeneration observed in early postischemic stages. Early postischemic stages were also characterized by severe rarefaction of the cerebral white matter; this was accompanied by features of acute swelling of oligodendrocytes.

The glial reaction consisted in the appearance of naked astrocytic nuclei, resembling those of the Alzheimer cells, type II; this being a rather early feature (Fig. 3). Intensive proliferation and hypertrophy of astrocytes localized mostly, but not exclusively, in areas of severe neuronal loss (Fig. 3 and 4) appeared later. In some cases mixed astrocytic-microglial nodules were present. Hematogenous cellular reaction was not a feature at any period of postischemic pathology.

Immunohistochemical reactions, for characterising brain barrier systems revealed perivascular tissue infiltration with serum proteins. This was particularly significant in the hippocampal gyrus (Fig. 5), molecular layer of cerebellar cortex and in extensive areas of the brain stem structures. Here, and particularly in the direct vicinity of the ventricular walls, the brain parenchyma was diffusely infiltrated with substances giving a positive reaction for whole serum proteins as well as for albumin and IgG (Figs 6 and 7). The above changes were present exclusively in the early postischemic period, that is they occurred in animals sacrificed 6 and 24 hrs 3 days following clinical death. They disappeared thereafter. In addition pyramidal cells of Ammon's horn, some of Purkinje cells and numerous neurons of the brain stem accumulated blood proteins in their cytoplasm (Fig. 8).

*Table 1.* Immunofluorescent test: affinity of sera to different organs (in brackets number of animals examined)

*Tabela 1.* Test immunofluorescencyjny: powinowactwo surowic do różnych narządów (w nawiasach liczba badanych zwierząt)

| Organ<br>Narząd | Control animals<br>Zwierzęta kontrolne | Experimental animals – Survival groups<br>Zwierzęta doświadczalne – Czas przeżycia | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 6h<br>godz | 24h<br>godz | 3 days<br>dni | 7 days<br>dni | 14 days<br>dni | 28 days<br>dni | 6 months<br>miesięcy |
| Brain<br>Mózg | 0 (4) | 0 (3) | 0 (3) | 0 (3) | 3 (3) | 2 (3) | 2 (4) | 4 (6) |
| Liver<br>Wątroba | 2 (4) | 1 (3) | 2 (3) | 1 (3) | 3 (3) | 2 (3) | 1 (3) | 2 (6) |
| Kidney<br>Nerki | 1 (4) | 0 (3) | 1 (3) | 1 (3) | 2 (3) | 1 (3) | 1 (3) | 1 (6) |

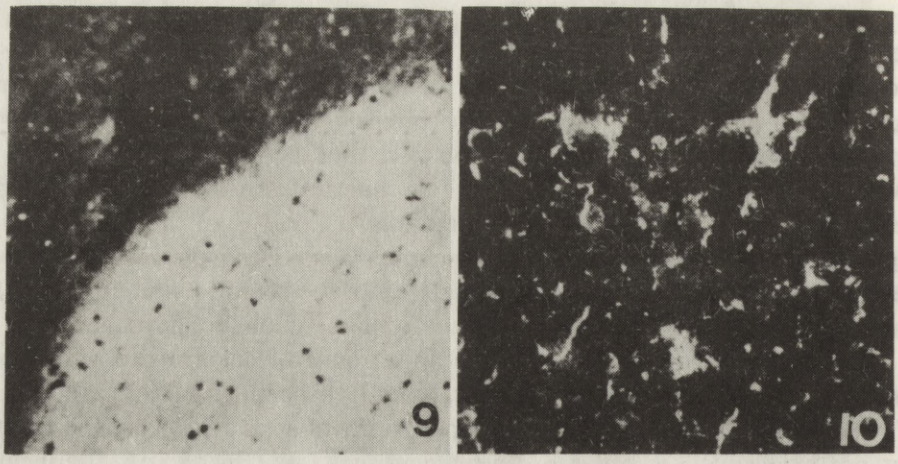


*Fig. 9.* Strong immunofluorescence of myelin sheaths in normal rat white matter with blood serum of experimental animal, which survived for 6 months clinical death of 15 min duration. Serum dilution 1:40. × 150

*Ryc. 9.* Silna immunofluorescencja osłonek mielinowych istoty białej szczura w reakcji z surowicą zwierzęcia doświadczalnego, które przeżyło 6 miesięcy po 15 min śmierci klinicznej. Miano surowicy 1:40. Pow. 150 ×

*Fig. 10.* Strong immunofluorescence of glial cells of Ammon's horn in rat with blood serum of experimental animal which survived for 28 days clinical death of 10 min duration. Serum dilution 1:40. × 500

*Ryc. 10.* Silna immunofluorescencja komórek glejowych w rogu Amona szczura z surowicą zwierzęcia doświadczalnego, które przeżyło 28 dni po 10 min śmierci klinicznej. Miano surowicy 1:40. Pow. 500 ×

Sera of control animals and those of experimental ones up to the 7th postischemic day were negative as far as the immunofluorescent reaction with brain tissue was concerned, although there their reaction was positive with liver and/or kidney (Tab. 1). The earliest immunological reaction with brain was observed in the case of sera, obtained from animals sacrificed on the 7th postischemic day. Positive immunofluorescence concerned different components of brain tissue. Alongside with neuronal reaction, immunofluorescence involved myelin and glial cells, mostly astrocytes (Figs 9, 10). In some, rare cases the diffuse immunofluorescence reaction concerned the brain tissue as a whole, without possibility to distinguish its particular structural elements. It is worth mentioning that this reaction was usually accompanied by strong positive immunofluorescence in hepatocytes and in epithelium or basement membrane of renal canaliculi.

The intensity of immunological reaction with structural components of the brain tissue, in particular that with neurons increased steadily in subsequent postischemic time intervals, reaching its highest degree in sera of animals sacrificed 6 months following clinical death (Tab. 2). In that group in 4 of 6 animals strong neuronal immunofluorencence, indicating the presence of antineuronal antibodies, was observed when serum dilution was 1:80 and higher.

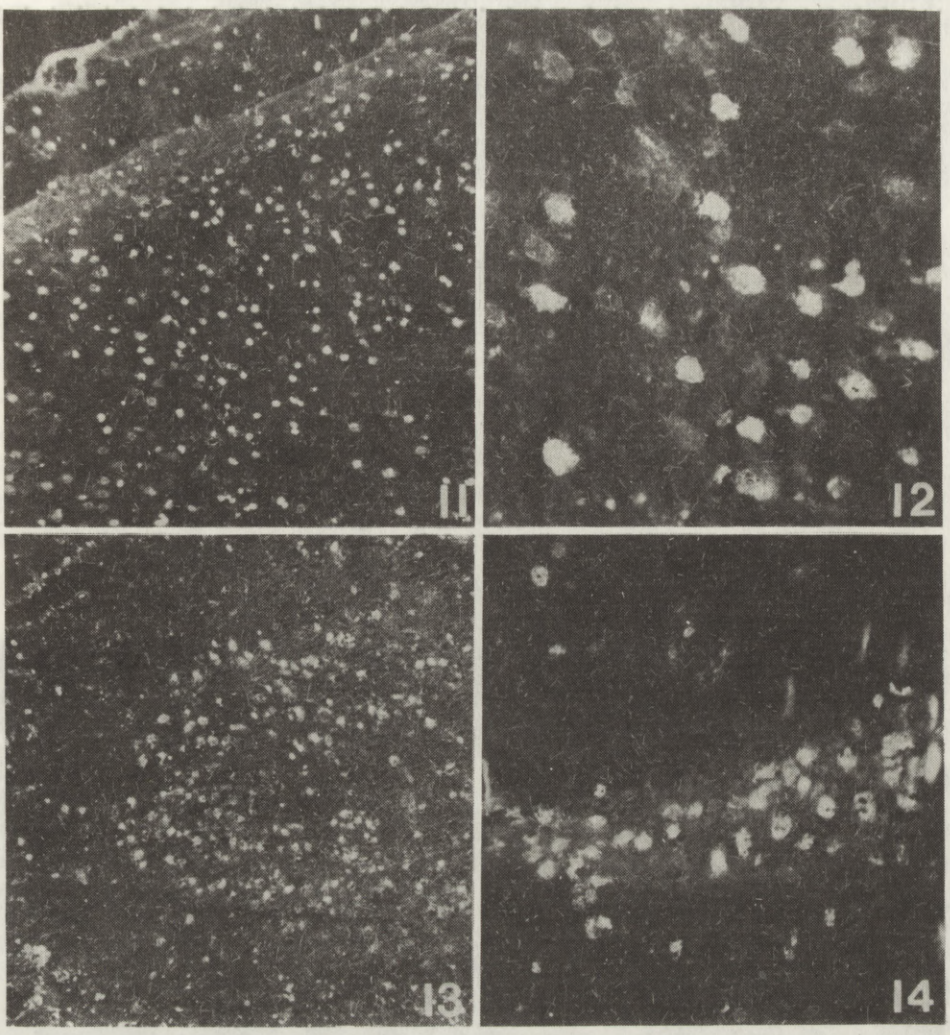


*Fig. 11.* Immunofluorescence of rat cerebral certex with blood serum of the experimental animal which survived for 6 months clinical death of 15 min duration. Serum dilution 1:80. × 100

*Ryc. 11.* Dodatni odczyn immunofluorescencyjny komórek kory mózgu szczura z surowicą zwierzęcia doświadczalnego, które przeżyło 6 miesięcy po 15 min śmierci klinicznej. Miano surowicy 1:80. Pow. 100 ×

*Fig. 12.* Higher magnification of picture shown in Fig. 11. Immunofluorescence restricted to neuronal cytoplasm. × 400

*Ryc. 12.* Większe powiększenie fragmentu ryc. 11. Zwraca uwagę ograniczenie odczynu immunofluorescencyjnego do cytoplazmy komórek nerwowych. Pow. 400 ×

*Fig. 13.* Immunofluorescence reaction in hippocampal structures with blood serum of experimental animal which survived for 6 months clinical death of 15 min duration. × 60

*Ryc. 13.* Dodatni odczyn immunofluorescencyjnej formacji hipokampa z surowicą zwierzęcia doświadczalnego, które przeżyło 6 miesięcy po 15-min śmierci klinicznej. Pow. 60 ×

*Fig. 14.* Higher magnification of a fragment from Fig. 13. revealing strong immunofluorescence of Ammon's horn pyramidal neurons. Serum dilution 1:80. × 400

*Ryc. 14.* Większe powiększenie fragmentu ryciny 13. Widoczny żywy odczyn immunofluorescencyjny w neuronach piramidowych rogu Amona. Miano surowicy 1:80. Pow. 400 ×

*Table. 2.* Immunofluorescent test: reaction with different structural elements of the central nervous system (in brackets – number of animals)

*Tabela 2.* Test immunofluorescencyjny: odczyn z różnymi elementami strukturalnymi ośrodkowego układu nerwowego (w nawiasach – liczba zwierząt)

| Tissue element Struktura tkankowa | Control animals Zwierzęta kontrolne (4) | Experimental animals – Survival groups Zwierzęta doświadczalne – Czas przeżycia | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 6 h godz (3) | 24 h godz (3) | 3 days dni (3) | 7 days dni (3) | 14 days dni (3) | 28 days dni (4) | 6 months miesięcy (6) |
| Myelin Mielina | – | – | – | – | ++ (1) | + (1) | – | ++ (2) |
| Astrocytes Astrocyty | – | – | – | – | ++ (1) | – | ++ (1) | – |
| Neurons Neurony | – | – | – | – | + (2) | ++ (1) | ++ (1) | +++ (4) |



*Fig. 15.* Immunofluorescence reaction in the cerebellar cortex with blood serum of an experimental animal, which survived 15-min clinical death for 6 months. Note positive reaction in a narrow rim of granular neurons cytoplasm and in Purkinje cells. Serum dilution 1:80. × 200

*Ryc. 15.* Dodatni odczyn immunofluorescencyjny w strukturach kory móżdżku z surowicą zwierząt doświadczalnych, które przeżyły 6 miesięcy po 15-min śmierci klinicznej. Fluorescencja występuje w cytoplazmie ziarnistych neuronów i komórek Purkinjego. Miano surowicy 1:80. Pow. 200 ×

*Fig. 16.* Immunofluorescence reaction in the cytoplasm of giant neurons from brain stem reticular formation. Experimental conditions as above. × 800

*Ryc. 16.* Dodatni odczyn immunofluorescencyjny olbrzymich neuronów tworu siatkowatego pnia mózgu. Warunki doświadczalne jak wyżej. Pow. 800 ×

The topographic distribution of neuronal immunofluorescence was relatively constant in all experimental groups. The intensive specific IF was seen first of all in neocortical neurons (Fig. 11) mostly those of pyramidal type (Fig. 12). Basal ganglia, in particular striatum, were the permanent site of strong neuronal immunofluorescence. So were pyramidal cells of Ammon's horn (Fig. 13). Here, at higher magnification, one could easily see the glial cells remained totally negative (Fig. 14). In the cerebellum the strongest IF reaction was present in the granular cell layer, it was somewhat weaker in Purkinje cells (Fig. 15). In the brain stem the immunohistochemical reaction was less intense than in cortical structures, although it was present in large neurons of the reticular formation (Fig. 16).

The absorption test performed with lyophilized rat brain tissue abolished totally the neuronal IF reaction and partially reduced that of the whole brain, showing no noticeable influence on the immunoreaction of the examined internal body organs. Contrary to that, absorption with powdered rat liver left neuronal IF unchanged, slightly reducing only that of the whole brain and significantly or totally abolishing immunofluorescence of both liver and kidney.

The immunofluorescence reaction of the sera from experimental animals was also positive with neurons of mouse and gerbil brains.

## DISCUSSION

The results presented above indicate that experimentally induced clinical death, accompanied by subsequent, progressive widespread breakdown of neurons of the central nervous system evokes an immunological reaction appearing in the postresuscitation period. This taken the form of production of antibodies directed against structural elements of the nerve tissue and those of the internal body organs.

With all probability the immunological response concerns different types of brain antigens, as indicated by the appearance of immunoreaction with a number of structural components of the central nervous system such as neurons, astrocytes and meylin. However, the frequency and intensity of the neuronal immunofluorescence reaction suggest prevalence of response to neuronal antigen or antigens, the nature of which remains to be elucidated. In the light of recent literature data (Bahmanyar et al. 1984; 1985; Stefansson et al. 1985; Karcher et al. 1986) confronted with the neuropathology of our material, concerning mostly neuronal damage, it seems justified to suppose that protein components of neurofilaments are the most probable antigens involved. The appearance of antibodies directed against other neural and/or glial components of the brain seems natural. However, it is worth mentioning that their presence was less common and constant than that of antineuronal ones, as less frequent were histologically dedectable abnormalities of myelin or glial cells, mostly oligodendrocytes. Anticerebral autoantibody appearance was preceded

and accompanied by formation of antibodies directed against internal body organs such as liver and kidneys, what seems understandable in the case of generalized severe ischemia resulting from cardiac arrest. These antibodies might be common with some of the anticerebral ones, especially those expressed by generalized diffuse immunoreaction with brain tissue with no clear cellular connections. This type of reaction was reduced both by absorption with lyophilized brain tissue and acetone-powder of rat liver. However, the time sequence of antineuronal antibodies appearance and results of absorption tests speak strongly in favour of their full organ-specificity. On the other hand the positive immunoreaction of experimental sera with normal brain neurons of mice and Mongolian gerbils indicates their species non-specificity. This might be a supportive argument for neurofilaments or their components as being the main antigen evoking the observed immunological response (Stefansson et al. 1985; Toh et al. 1985).

There exist two factors making possible contact of brain tissue antigens with the immunological system, resulting in specific antibodies formation. The first is widespread neuronal damage in the central nervous system, although less severe than in other animals in analogous or similar circulatory abnormalities (Pluta 1982; Kapuściński, Mossakowski 1983). The tissue abnormalities observed in our material in the early postresuscitation period took the form of nerve cell degeneration, of various nature, while starting from the third postischemic day destruction of the cerebral neurons was obviously prevailing. One has to point out, however, the great individual variation in the intensity and extension of neuronal alterations (Mossakowski et al. 1986), this, among other things may be reflected in the differences in antibody production observed in the material under study. The second factor involved in the discussed phenomena was damage of the encephalic barrier systems, as indicated by the leakage of serum proteins, and their particular components such as albumins and IgG into the cerebral parenchyma. The pathological features observed suggested that in addition to the damaged permeability of the cerebral blood vessels, manifested by extravasation of proteins into their direct surroundings, we were dealing with alterations of other barrier systems such as the blood-cerebrospinal fluid barrier, the function of which is connected with the choroid plexus. Their impairment is suggested by diffuse tissue imbibition with serum proteins along the ventricular walls. The latter phenomenon indicates moreover an increased penetration of proteins from the cerebrospinal fluid through the ventricular walls. All the above presented features are rather early events, occurring within the range between 6 h and 7 days of the postischemic period. Despite their relatively short duration, they cover the time of nerve cell degeneration and the early stages breakdown. It is worth mentioning that at that time marked changes in the permeability of cell membranes of morphologically unchanged neurons appeared. This was documented by accumulation of serum proteins in their cytoplasm.

The other problem requires a short discussion. It is the progressive nature

of nerve cell damage occurring during the whole postresuscitation period (Mossakowski et al. 1986). The intensity of neuronal loss observed in animals sacrificed 6 months after clinical death was much more advanced, as compared with that in animals with shorter survival periods. So was extension and distribution of tissue alterations (Zelman, Mossakowski 1988). The question arises, what is the pathogenetic mechanism of those protracted and progressive pathological events. One of a number possibilities is that the immunopathological processes, connected with the appearance of circulating antineural antibodies may be involved in the development of postresuscitation encephalopathy. Such a mechanism has been suggested for neuronal loss connected with brain ageing (Makinodan 1976; Redei et al. 1979; Cohen, Eisdorfer 1980; Goodwin et al. 1982; Nandy 1982). Acceptance or rejection of such a patogenic mechanism for the progressive in nature postischemic encephalopathy thy requires numerous further studies.

## PRZECIWCIAŁA ANTYNEURONALNE W SUROWICY KRWI SZCZURÓW PODDANYCH CAŁKOWITEMU NIEDOKRWIENIU MÓZGOWIA


### Streszczenie

Stwierdzono, że w surowicy krwi zwierząt, które przeżyły 10 lub 15 minutową doświadczalną śmierć kliniczną, pojawiają się przeciwciała dające dodatni odczyn immunologiczny z elementami strukturalnymi tkanki nerwowej takimi jak astrocyty, mielina oraz komórki nerwowe. Pojawiały się one od 7 dnia po niedokrwieniu, a ich miano, w szczególności przeciwciał antyneuronalnych, narastało do 6 miesięcy po niedokrwieniu. Obecność przeciwciał antyneuronalnych była zjawiskiem najbardziej stałym, a dodatnia reakcja immunologiczna dotyczyła neuronów kory mózgu, rogu Amona, kory móżdżku i jąder pnia mózgu. Odczyn miał charakter narządowo-swoisty przy braku swoistości gatunkowej. Kontaktowi antygenów tkanki nerwowej z układem immunologicznym sprzyjał rozpad komórek nerwowych OUN współprzebiegający z uszkodzeniami bariery krew–mózg, stwierdzonymi metodami immunochemicznymi.


## ПРОТИВОНЕВРОНАЛЬНЫЕ АНТИТЕЛА В СЫВОРОТКЕ КРОВИ КРЫС, ПОДВЕРГНУТЫХ ОБЩЕЙ МОЗГОВОЙ ИШЕМИИ


### Резюме

Обнаружено, что у животных, которые прожили 10-ти или 15-ти минутную экспериментальную клиническую смерть, появляются в сыворотке крови антитела, вызывающие положительную иммунологическую реакцию со структурными элементами нервной ткани – астроцитами, миелиной и нервными клетками. Они появлялись с 7 дня после ишемии, а их титр, особенно противоневрональных антител, увеличивался до 6 месяцев после ишемии. Присутствие противоневрональных антител было наиболее постоянным феноменом, а положительная иммунологическая реакция выступала в невронах мозговой коры, аммониева рога, коры мозжечка и в ядрах мозгового ствола. Реакция была органо-специфическая, не было видовой специфичности. Контакты антигенов нервной ткани с

иммунологической системой способствовало разрушение нервных клеток центральной нервной системы, сопутствующее с повреждением барьеры кровь-мозг, обнаруженным иммунохимическими методами.

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