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The Pathomorphology of Far Eastern Tick-Borne Encephalitis

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1. Introduction

In the 1990s, both in the Far East and other regions of Russia, has intensified the incidence of tick-borne encephalitis (TBE), which reached the 1940-1950s, with widespread worsening of clinical signs of infection (Mamunts, 1993, Zlobin & Gorin, 1996; Leonova, 1997; Erman et al., 1999, etc.). The Far Eastern version of the tick-borne encephalitis has long been known as a heavy neuroinfection clinically flows mainly in the focal paralytic forms with residual symptoms, high mortality rate reaching 30-35%, and sometimes a progressive transition to a chronic form.

Well-known in the literature, the classical data on the pathological anatomy and pathogenesis of human tick-borne encephalitis, date back to the early period of the study of this infection on Far East in 1940 - 1950's, given the generalized idea of the nature and location of the morphological changes in the central nervous system (Robinson & Sergeeva, 1939, 1940; Kastner, 1941; Panov, 1956; Shapoval, 1961; Belman, 1960).

In 1960 - 1990-s the study of pathology of tick-borne encephalitis occurred mainly in the experimental-morphological terms, and was aimed to clarify issues of pathogenesis and immunogenesis, the study of viral neurovirulence strains, and their differentiation to find high-performance candidates for the preparation of vaccine against tick-borne encephalitis (Rozina, 1972; Frolova, 1965, 1967, 1973, 1975; Konev, 1982, 1995; Kvetkova, 1984; Erman et al., 1999, etc.).

The experience 75- years of the study showed that the tick-borne encephalitis is not monolithic and heterogeneous infection, including several subspecies: the Far-Eastern, the Sibe-

rian and other variants, which differ in the clinic, the severity and outcome of disease, as well as antigenic and genetic structure of pathogens, habitats and mechanisms of transmission (V.I. Votyakov et al., 1978; A.A. Smorodintsev, A. Dubov, 1986; V.I. Zlobin et al., 1996; M.P. Isaeva, 1998; Y.P.Dzhioev, 2000, G.N. Leonova, 2009; H. Holzmann et al., 1991; G.N. Leonova et al, 1999).

It is shown that the disease is characterized by polymorphism of clinical manifestations from inapparent to severe fever and focal forms, from the acute to progressive chronic course, from the complete recovery to the serious residual effects and death.

Characteristic features of the pathogenesis of tick-borne encephalitis are: the presence of two phases of infection - visceral and neural; hematogenous, lymphogenous, and neural pathes the generalization of infection and penetration of the pathogen in the central nervous system (CNS); the marked tropism of the virus to lymphoid tissue, an early and active involvement of the immune system in the process of reproduction of the virus and the patholigical process; the pronounced neurotropizm and the diffuse spread of the virus in the CNS. The incubation period for TBE is an average of 7-14 days.

The well-known in the literature, the classical description of the pathomorphology of acute TBE in human is mainly characterized by the stage of maximum expression of the pathological process in the CNS. The evaluation of encephalitic changes carried out in accordance with general pathological knowledge that existed in the mid-twentieth century and up until the last decade (Erman et al, 1999; Ierusalimsky, 2001) did not undergo correction in terms of immunopathogenesis.

On examination of the dead peoples they often have a strong constitution and good physical development (Shapoval, 1980). Macroscopic changes appear only hyperemia and edema of the meninges and brain substance. There are a small subarachnoid and subpial hemorrhages. The figure matter of the spinal cord is blurred, especially in the neck and shoulder level. In the anterior horns of the spinal cord revealed small foci of hemorrhage, and softening. In the internal organs is determined the congestive hyperemia and degenerative changes. The serous and mucous membranes often have pinpoint hemorrhages. The spleen is usually hyperplasive. Some of the dead people have the thinning of the cortical layer of the adrenal glands.

The histopathological picture of acute tick-borne encephalitis is characterized by diffusely distributed in the central nervous system inflammatory changes that are made up of alterative, exudative and proliferative effects. The most severe changes with necrosis and massive deposition of motor nerve cells observed in the indicator areas (Nathanson et al., 1966): in anterior horns of the cervical and thoracic spinal cord, the nucleus of the hypoglossal and the vagus nerves, the reticular formation and inferior olive of the medulla oblongata as well as its own nucleus Varoliy pons, red nucleus and substantia nigra of the brain legs and in the cortex and nuclei of cerebellum (Robinson & Sergeeva, 1940). The pathological process with necrobiosis of nerve cells is also observed in the thalamus, caudate and lenticular nuclei, and diffusely in the cerebral cortex of the brain. The degree of severity of the process decreases in the oral direction of CNS. Alterative changes in the nerve cells are combined

with severe exudative phenomena with the formation of perivascular infiltrates consisting of lymphocytes, monocytes, plasma cells, histiocytes, as well as with diffuse proliferative glial response. As pointed out by Kestner (1941), the pathological process can be described as an acute non-purulent meningo-polioencephalomyelitis involving all sections of the central and peripheral nervous system. Pathological changes are found in sensory and vegetative nodes, as well as in peripheral nerves (Semenov-Tien Shansky & Shapoval, 1949; Dekonenko et al., 1994).

In the pia mater and vascular plexuses of brain ventricles observed redness, swelling, and stratificatione, perivascular infiltrates of lymphocytes and histiocytes, to a lesser extent – leukocytes and plasma cells. Revealed the destruction and proliferation of ependyma cells of the ventricles, subependimar glia cells, as well as the central gray matter of the Sylvius aqueduct.

The permanent feature of TBE pathomorphology are the vasomotor disturbances. There has been a dramatic expansion and vascular hyperemia until capillary stasis, diapedetic hemorrhages, coagulation thrombi, sometimes fibrinoid necrosis of vessel walls.

Nerve cells in the affected area are in a state of acute swelling, vacuolization, the perinuclear or the total chromatolysis, kariocytolisis, cytolisis elting, neuronophagia. It is characteristic of the TBE the piknomorfic (hyperchromic) changes of nerve cells.

The destructive changes occur in hematogenous cells of inflammatory infiltrates and in proliferating glial cells with the expressed klasmatodendrosis. In the subsequent formation of multiple foci of softening, localized in the varoliav pons, medulla oblongata, bain legs, hypothalamic area, basal ganglia and spinal cord. The deep destructive changes also occur in the vascular wall and in the white matter of the brain with signs of myelin and axons disintegration.

The most mobile part of the pathological process are inflammatory changes that already in the acute stage are not always identical. In most cases, there is an abundant infiltration of vessels wall, perivascular infiltration of lymphocytes and histiocytes with an admixture of polymorphonuclear leukocytes and a small amount of plasma cells. With the prolongation of infection the infiltration of lymphocytes and plasma cells increases, the massive perivascular infiltrates as a muffs appeared.

There is the focal and diffuse proliferation of microglia, astrocytes and oligodendroglia (Shapoval, 1961; Zlotnik, 1968; Zlotnik et al., 1976). There are formed numerous glial nodules, granulomas in place the dead nerve cells and around capillaries.

Thus, the preferential injury of Varoliy pons, medulla oblongata nuclei and the motor neurons of the anterior horn of the cervical spinal cord is the main feature of the topography of the histo-pathological changes typical for TBE.

Sometimes the inflammation in the brain at TBE passes in atypical with little or no productive and exudative changes. The perivascular infiltration is isinsignificant, the inflammatory response is expressed in the form of microglial nodules. In these cases, you should emphasize the discrepancy between the severity of the clinical course and low severity of inflam-

mation in the presence of the intensive dystrophic and destructive changes in neurons (Robinson & Sergeeva, 1939; Kastner, 1941; Belman, 1960; Somova, 2010). In the early occurrence of deep disturbances of consciousness (coma) in the cerebral cortex and other parts of the brain observed the common hyperchromatosis of neurons with a peculiar dark staining and wrinkling their (Shapoval, 1980).

The lack of etiotropic treatment of TBE dictated the need to further develop the issues on pathogenesis and morphogenesis of infection with the calculation of the especial feature of regional TBE strains, in order to support more efficient methods of pathogenetic therapy.

In the 1980-1990-s there is evidence of the involvement of lymphoid organs (thymus, spleen, lymph nodes) in the TBE virus reproduction, which greatly complement the information on the pathogenesis of acute and chronic processes during this infection (Pogodina et al., 1986; Rychkov et al., 1989, 1990; Karmysheva & Pogodina, 1990, 1991; Leonova &. Isachkova, 1995; Malkova & Frankova, 1959; Malkova & Smetana, 1966; Kopecky, 1987).

Using highly specific method of molecular hybridization of nucleic acids in cryostat sections of lymph nodes, spleen and brain of experimental animals (Zinoviev et al., 1990; Konev et al., 1991; Rychkov, 1992) it is found that on acute and chronic TBE is resettlement and virus replication in cells of the sinuses and T-dependent areas of lymphoid organs at the same time with the development of these reactions, reflecting the formation of an immune response. In the dynamics of the incubation period the TBE virus is accumulated in the lymphoid organs, especially the regional to the site of infection lymph nodes, and subsequently recorded in the area of vascular lesions of the brain, where the beginning of clinical manifestations of the disease the virus is detected by IFA and electron microscopy.

It is determined that the damage of the lymphoid organs with subsequent development of the immune deficiency leads to the development of inflammation in the brain with a quick invasion of his virus, and the degree of damage of lymphoid organs is an important criterion for prediction of viral infection (Konev, 1994, 1995). According to the author, in an experiment on animals the dependence of TBE morphogenesis and relationships in the "brain - lymphoid organs" from the degree of susceptibility of the host to the virus, the causative agent, take a place. In a susceptible animal the necrotic reaction develops in the lymphoid organs with subsequent formation of encephalitis in the background of secondary immunodeficiency, and in insensitive animal the damage of lymphoid organs and, accordingly, the immunodeficiency are absent, and encephalomyelitis does not develop.

Karmysheva and Pogodina (1991) in experiments on hamsters received the evidence about the active involvement of the thymus in the infectious process in the tick-borne encephalitis, with nature and extent of lesions of the thymus is heavier under the introduction of highly virulent strains than for infection caused fainly virulent strains. Immunological methods is shown that a severe course of TBE is associated with the expressive delay hypersensitivity (DH) under a weak antibody production, and asymptomatic infection – with a weak sensitization, an early and strong reaction of antibody-forming cells and increased nonspecific resistance (Perehodova et al., 1976; Pogodina et al., 1984). A more favorable prognosis when infected by fainly virulent strains, apparently, to a large extent dependent on the less affect-

ed of immune system organs and the development in these proliferative processes. A number of authors (Spindles, 1969; Vargin & Semenov, 1980; Konev, 1982; Alexandrov & Kislitsyna, 1982; Kvetkova & Shmatko, 1983; Webb & Smith, 1966) suggest that the failure of the immune system is an important factor in the pathogenesis of TBE.

For tick-borne encephalitis has been shown experimentally that the virus from the primary foci of multiplication in the skin and subcutaneous fat is distributed in the body with lymphogenous and hematogenous routes (Pogodina et al., 1986; Albrecht, 1968). The penetration of the virus in the brain associated with overcoming the blood-brain barrier through the wall of blood capillaries located in the parenchyma of the nervous tissue. This barrier is a complex system of defense mechanisms, including vascular plexus, the meninges, the wall of blood vessels and glial elements.

Pogodina et al. (1986), summarizing data on the immunopathogenesis of the disease, indicates that the TBE holds a pronounced immune response, characterized by a deficiency of T-lymphocytes, B-lymphocyte proliferation, macrophage reaction, the appearance of antibodies in the blood and cerebrospinal fluid, cellular immune responses in brain tissue, which in general have both protective and pathologic effects.

Thus, by the early 2000s, the accumulated extensive experimental material has prepared the basis for the specification of views on the nature of the pathological process in the CNS in human tick-borne encephalitis. On the basis of modern ideas that the inflammatory response, which is realized hematogenous elements, provides a basal level of immunity, we saw fit to approach the study of the pathology of tick-borne encephalitis in terms of immunopathological nature of central nervous system damage.

The main goal of our research was focused on an integrated assessment of the nature of the pathological process in the central nervous system in tick-borne encephalitis and identification of clinical and morphological variants of the disease caused her immunopathogenetic mechanisms. An important aspect of the study, in our opinion, was the distinction, on the one hand, the primary damage to tissue-structural elements of the CNS, directly related to the cytopathic effect and intracellular reproduction of the TBE virus, on the other hand, reactive and immunopathological changes with the definition of pathogenetic importance of the last in the development of various clinical and morphological forms of encephalitis. The study was based on the autopsy material from 35 patients aged 4 to 68 years old, ill tick-borne encephalitis in different parts of the Primorye Territory in the 1990s and died in different periods from the onset.

Date of death from the disease ranged from 3 to 28 days. The duration of hospital stay ranged from 1 hour to 25 days. The incubation period from the time of tick suction on bite before the first symptoms of the disease lasted from 7 to 23 days, an average of 15 days. In 6 cases there were multiple bites of ticks, so specify the duration of the incubation period was impossible. In two cases, infection occurred in the crushing ticks with the aid of arms.

For pathohistological study samples from different parts of the central nervous system were dissected: the anterior central gyrus, stem sections at the levels of the brain legs, Varolii pons and medulla, as well as the cortex and the vermis of cerebellum, cervical spinal cord.

2. The overall clinical and anatomical characteristics of tick-borne encephalitis

For the duration of the disease, all patients were divided into four groups in which the death occurred respectively in the first, second, third and fourth week of the onset of clinical symptoms. In all cases there was an acute onset of temperature increase to high numbers 38 º - 39 º C, quickly joined the general brain symptoms as headache, nausea, vomiting, stupor, and disorders of consciousness and sometimes convulsions. In the early days of the onset of the disease appeared meningeal syndrome and focal symptoms of central nervous system involvement: paresis and paralysis of the limbs, neck, bulbar disorders, due to which almost all patients at different times transferred to a ventilator.

From the brain of all died patients was isolated tick-borne encephalitis virus, and sera were determined by specific antibodies in diagnostic titers. At autopsy, macroscopic changes in the CNS manifested by edema and vascular injection of the meninges and brain substance, sometimes point hemorrhages scattered in different parts of the brain. The boundary of gray and white matter was somewhat effaced, especially in the cervical spinal cord and parts of the brain stem. There were congestion and degenerative changes in parenchymal organs (heart, kidney, liver), hyperemia of spleen. According to our observations, pathoanatomical diagnosis of tick-borne encephalitis should continue to be based on microscopic examination of brain and spinal cord. At the same time the crucial importance to the diagnosis has an analysis of pathological changes in the so-called indicator areas of the brain.

3. Morphogenesis of changes in the central nervous system

In the study of morphogenesis of tick-borne encephalitis in humans the main attention was paid to the sequence of the individual components of the inflammatory process, an assessment of their importance in the formation of various clinical manifestations of disease. In the first week of the disease (*the first group* - 5 cases) all deaths revealed an acute microvascular response in the central nervous system - congestion of vessels up to the capillaries, stasis, endothelial vacuolation. There were plasma soaking, stratification and focal fibrinoid necrosis of vessel walls. Frequently observed diapedetic hemorrhages, pronounced the virhov expansion space around the vessels due to edema (Fig. 1a).

In the pia mater were observed the stratification, the mucoid and fibrinoid swelling, the proliferation arahnoidendoteliya places, some parts of it were infiltrated with lymphocytes and histiocytes, to a lesser extent, erythrocytes and polimorphonuclear leukocytes. In the matter of the brain and spinal cord were determined the severe dystrophic and destructive changes of neurons - perinuclear and diffuse chromatolysis, in the part of neurons - the ectopic nucleus and kariolizis with the formation of cell-shading. There were also hyperchromatic cells. Alterative changes in the increasingly covered the neurons of the indicator brain areas: pyramidal cells of the motor cortex, nuclei of the substantia nigra, red and vestibular nuclei, inferior olive, nuclei of the caudal cranial nerves, cortex and nuclei of cerebellum, the anteri-

or horn of the spinal cord, mainly in the cervical region (Fig. 1b, d). In the cerebellar cortex is constantly met the degeneration and loss of Purkinje cells. At the nucleus of Semmering black substance the part of neurons was reduced the content of the pigment melanin.

The attention is drawn to the distinct focal reaction of microglia and oligodendroglia with neuronophagia and the formation of glial nodules on the site of dead nerve cells. In areas of inflammation was observed a significant admixture of polymorphonuclear leukocytes. There was also a diffuse infiltration of the brain substance by lymphocytes, polymorphonuclear leukocytes and glial cells. In the white matter of the brain and spinal cord was detected fragmentation of nerve fibers, were seen clusters of large, basophilic-stained cells. The inflammation around blood vessels of the brain substance were not common, however, in some places were found loose histiocytic and lymphocytic perivascular infiltrates, in which there was an admixture of neutrophils (Fig. 1 c).

In general, the pathological process in the CNS of patients with the first group can be characterized as meningo-polioencephalomielitis with a predominance of exudative phenomena and alterative changes in the nerve cells. The severe damage to the wall of blood vessels, edematous hemorrhagic component of inflammation with exudation of polymorphonuclear leukocytes showed marked sensitization of the organism in response to the introduction of the virus in the CNS with the presence of morphological reactions of immediate hypersensitivity (IH).

The second group of deaths was the most numerous (17 cases) and was 48.5% of cases. All died patients in the second week of the disease were observed in the brain the pronounced breach of hemocirclulation: eritrostasis, the presence of fibrin in the lumen of blood vessels, the expressive swelling of the brain tissue of spongy type. Vascular endothelium was in a state of proliferation, there was damage to the endothelial layer, porosity of the wall of blood vessels, often identified microhemorragii in different parts of the brain (Fig. 2 a). The elastic membrane of blood vessels had the irregular thickness, stratification, and sometimes not detected. There were the mucoid and fibrinoid swelling, the fibrinoid necrosis and aneurysmal expansion of vessels wall.

In the meninges, in addition to plethora, revealed swelling, stratification, proliferation of arahnoidendotelium, loose perivascular infiltrates of lymphocytes, histiocytes, with a small admixture of plasma cells.

In the vascular plexus of the brain ventricles were observed the rough swelling of the villi, the plethora and the homogenization of capillary wall, the degeneration, and in some places proliferation of the epithelium lining the villi. Ependyma cells were able to hyperplasia with areas of proliferation.

As in the previous period, the neuronal pathology was significantly expressed at different stages of damage. There were the diffuse chromatolysis, cell death and neuronophagia, focal loss of neurons with microglial reaction in these areas (Fig. 2b). Processes of nerve cells are often not reviewed, observed their destruction - klazmatodendrosis. Often hyperchromic cells were seen.
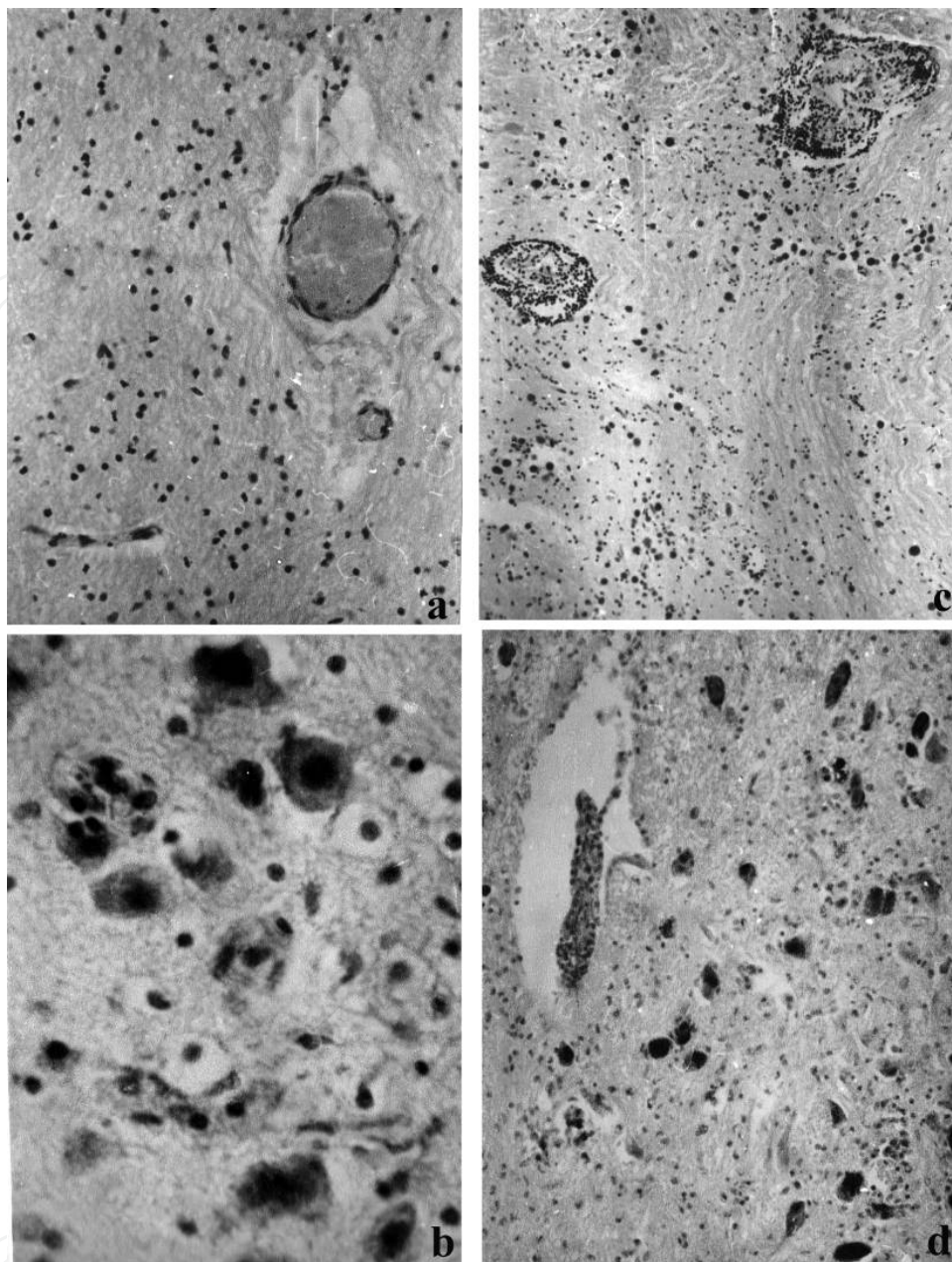
Figure 1. Pathological changes in the human brain with tick-borne encephalitis, 1st week of illness. a - hyperemia of blood vessels, diapedetic hemorrhage, intensive perivascular edema, diffuse glial reaction in the subcortical regions, x 100, b - alterative changes of neurons in the nucleus of the pons: chromatolysis, ectopia, hyperhromatosis, kariolisis, nodular glial reaction, x 200; c - plethora of vessels, leukocytosis and loose perivascular infiltration, accumulation of basophilic cells in the subcortical region, x 80, d - dystrophic changes in neurons of the black substance in the mid-brain, small glial nodules, vasculitis, a dramatic expansion of perivascular spaces, x 125. Stained with hematoxylin and eosin (a, c, d) and cresyl violet by Nissl (b).

The most severe damage of neurons were located in the III-V layers of the cortex of the anterior central gyrus, brain legs, Varolii pons and medulla oblongata, and especially significant - in the anterior horns of the cervical spinal cord (Fig. 2 b, d). In the pathological process are constantly involved neurons of red nuclei, substantia nigra, vestibular nuclei, nuclei of the bulbar cranial nerves and the cerebellar vermis. In the cerebellum, in all cases revealed com-

mon areas of loss of Purkinje cells, swelling and lysis of surviving ganglion cells, focal thinning of the granular layer cells (Fig. 2 c). In the field of loss of Purkinje cells was observed the expressive proliferation of Bergman glia in the spread of the molecular layer. Nerve fibers of the white matter of the brain and spinal cord were able to disorganization, fragmentation, and in some places granular disintegration.
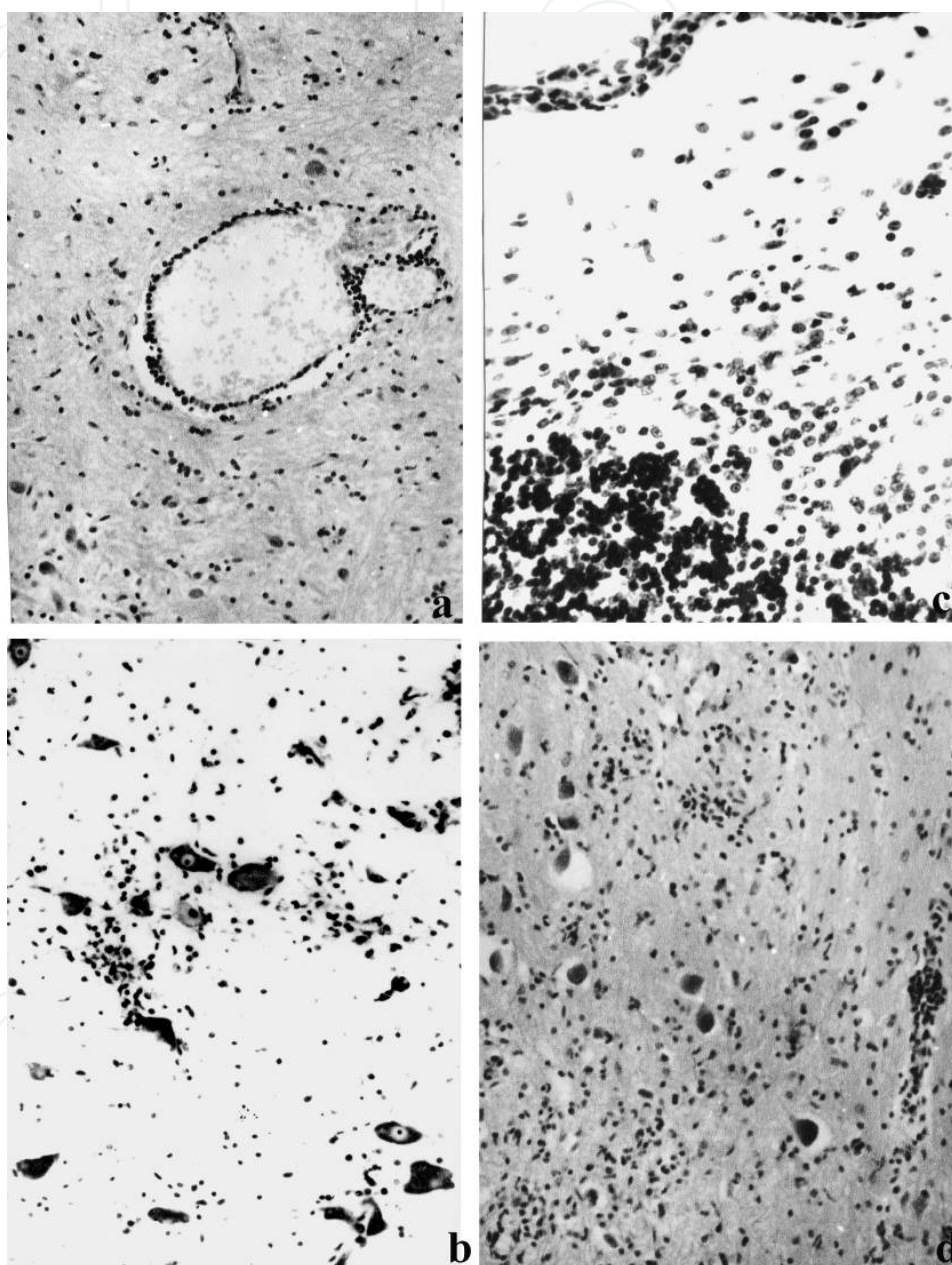

Figure 2. Pathological changes in the brain of human with tick-borne encephalitis, 2nd week of illness. a-porosity of the vascular wall, eritrodiapedesis, damage to neurons in the type of lysis in the medulla, x 125, b - diffuse chromatolysis and loss of neurons, kariolisis, neuronophagia, x 200; c - loss of Purkinje cells in the ganglionic layer of cerebellar cortex, the proliferation of Bergman glia, inflammatory infiltration of the pia mater, x 200; d - heavy damage and loss of neurons in the medulla, diffuse and nodular glial reaction, productive vasculitis, x 125. Stained with hematoxylin and eosin (a, d) and by Nissl (b, c).

Inflammatory - infiltrative changes in the second week of the disease were different in intensity at different dead patients. In 23.5% of cases the marked perivascular infiltration mainly by lymphocytes and histiocytes with an admixture of plasma cells were detected. The response of polymorphonuclear leukocytes in this period was negligible. Perivascular infiltrates were located in the meninges, and very often in the gray matter of the brain in the indicator areas. In the vessels the leukocytosis was observed, met perivascular "muffs."

Thus, in the second week of tick-borne encephalitis in the pathological picture in the background of alterative-proliferative changes in some of the dead patients, compared with the first group, detected the increased infiltrative reaction with the predominance of mononuclear cells in inflammatory foci.

In the next two weeks from the start of tick-borne encephalitis died 37.2% of patients.The pathological study of the central nervous system revealed that during this period changed the ratio of expression of various components of the inflammatory process. This is manifested by the increased intensity of infiltrative changes around the vessel in the meninges, and especially in the brain matter with a predominance of them in the indicator areas of the CNS.

In the third group of died patients (4 cases) the moderate hemo- and moderate liquorodynamic disorders were determined. In the brain, the stasis, sludge, diapedetic hemorrhages were found. In the lumen of blood vessels fibrinopurulent leukocyte thrombi often revealed. Perivascular spaces were greatly widened, areas by dilution (lysis) of the brain substance near the vessels were determined. On the background of the diffuse glial proliferation, glial nodules were also seen on the site of dead neurons. Along with the progressive (hyperplasia) changes in glial cells, the regressive (dystrophic-destructive) changes are found related to microglia and astrocytes.

For the objectification of the expression of alterative component of the inflammatory process in the dynamics of tick-borne encephalitis, the calculation of glial index was carried out, ie ratio of total number of glial cells to the number of neurons in the same area of brain tissue. It is established that the destruction and loss of neurons in the most damaged structural formations of the central nervous system were accompanied by an increase of glial index (Table 1).

The term bark disease	Anterior central gyrus	Midbrain (substantia nigra nucleus)	Medulla oblongata (nucleus of the vagus nerve)	Cerebellum (Purkinje cell layer)	Spinal cord (anterior horn motor neurons)
Control	7.26±0.06	2.82±0.03	2.67±0.04	3.45±0.06	3.12±0.04
The first week	8.15±0.04*	3.15±0.04*	5.13±0.03*	6.38±0.05*	7.26±0.04*
The second week	9.36±0.04*	3.85±0.03*	6.26±0.03*	10.26±0.04*	11.15±0.02*
The third week	10.28±0.06*	4.05±0.02*	6.36±0.03*	10.87±0.06*	12.05±0.03*
The fourth week	10.15±0.03*	4.17±0.04*	6.27±0.05*	11.25±0.04*	12.54±0.05*

Note: * - P <0.05 compared with control

Table 1. The glial index in the indicator areas of the brain at different times of acute tick-borne encephalitis (M ± m)

As the table shows, the significant increase in glial index occurred in the first - the second week of illness, and further significant change in performance was not found. This indicates that from the third week of tick-borne encephalitis is not going the increase in severity of alterative component of the inflammatory process, with the deepening of neuronal damage in the indicator areas of the central nervous system.

In the third group of died patients the mesenchymal inflammatory reaction around the blood vessels was greater than in the previous period, with the significant ($p < 0.05$) increase in the number and density of perivascular infiltrates (Table 2).

The evidence of inflammation intensity	Ratios of inflammation per unit area (M ± m)			
	The first week	The second week	The third week	The fourth week
The number of perivascular infiltrates (in sight)	1.8±0.01	2.8±0.01	4.6±0.02	4.8±0.02
The density of perivascular infiltrates (mm^2)	6.7±2.1	12.2±4.3	18.7±5.4	19.1±6.1

Table 2. The intensity of infiltrative changes in the brain at different times of acute tick-borne encephalitis

The perivascular infiltration with the formation of "muffs", consisting of mononuclear cells, was detected in various parts of the brain, the gray matter of spinal cord, mainly in the anterior horns of the cervical spine and a moderate degree in some areas of the meninges (Fig. 3 a, b). By the third week of the disease, compared with the initial period, in the inflammatory infiltrates the percentage of lymphocytes and plasma cells significantly increased. Using the method of fluorescent antibody (IFA), the specific emission of immunoglobulins is detected in the inflammatory infiltrates, which is consistent with the reaction of plasmocytes. For histochemical study in the foci of inflammatory cells, giving a positive reaction for acid phosphatase and α-naftilatsetatesterase, were observed, indicating that they belong to the T-lymphocytes (Fig. 3 c, d).

The attention is drawn to the expressive damage of blood vessels wall: thinning, vacuolization, blurring the structures of the vascular wall, breaking-stost endothelium, the deformation of the vessels lumen with the formation of aneurysmal extension, damage to elastic fibers. It should be noted that the penetration of cells of perivascular infiltrates into the surrounding brain tissue observed in the initial stages of the disease (first - second weeks), was limited in the third week of increasing the density of infiltrates, suggesting a decrease in diffuse lesions of the brain during the development of local (tissue) immune.

Thus, in dead patients on the third week of tick-borne encephalitis in the histopathological picture of the central nervous system the perivascular infiltrative changes were predominant, characterizing immunopathological process with expressive cell reactions of the immediate hypersensitivity type.

In the group who died on *the fourth week* of tick-borne encephalitis on *in the fourth group* of died patients (9 cases) revealed the pathological picture in general analogous to that in the third group. All patients of the fourth group in a long time (25 days) were unconscious, with severe focal disorders of the central nervous system, disorders of vital functions and connection to a ventilator.
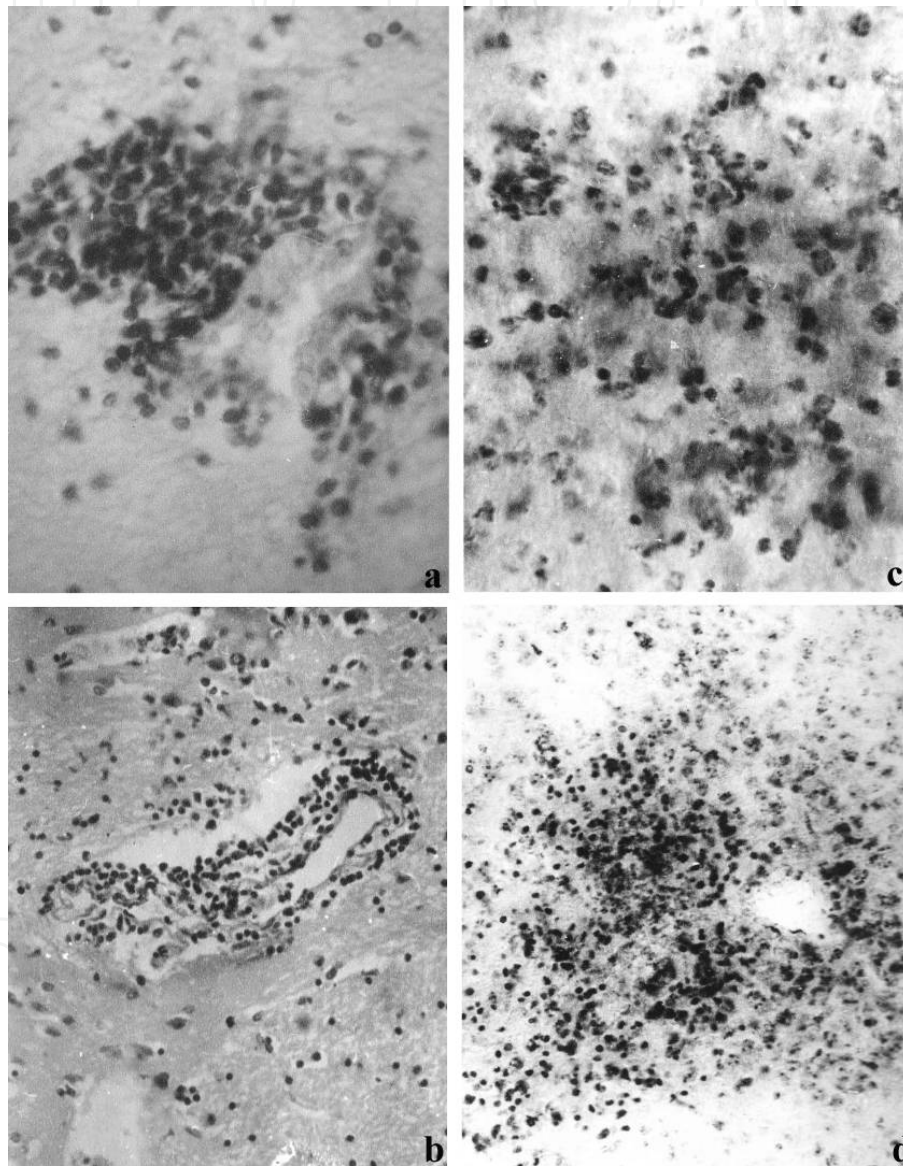

Figure 3. Pathological changes in the brain of human with tick-borne encephalitis. 3-d week of illness. a – destructive-productive vasculitis with the formation of perivascular "muff" in the pons, x 400, b - the venule with thinned wall and deformation of lumen, perivascular infiltration of lymphocytes, hystiosytes and plasma cells in the caudal brain stem, x 200; Stained with hematoxylin and eosin (a, b); a positive reaction to acid phosphatase in the cells of the perivascular infiltrate by Gomori (c), × 200, d-α-naftilatsetatesterase in cells of the inflammatory foci, the color by Pigarevsky - Zeltser, x 400.

In the indicator areas of the brain, in areas with destructive changes of nerve cells, the focal proliferation of microglial, oligodendroglial and astrocytic cells was observed with the formation of large glial nodes (Fig. 4 a). The surviving neurons were generally able to diffuse chromatolysis with the conversion of some of them in a cell-shade. In the cerebellar cortex of all the dead patients the total and subtotal loss of Purkinje cells, the focal thinning of the granular layer cells were discovered (Fig. 4 c). In the anterior horns of the cervical spinal cord single hyperchromic neurons were retained. In the brain stem marked neuronal lipofuscinosis of large neurons were observed.

There were the abrupt disruption of the gray and white matter of the brain through the spongy edema, widespread dystrophic and destructive changes of vessels with thinning and loosening of theirs wall, the mucoid and fibrinoid swelling, vacuolation of it. The lumen of many vessels contained fibrin threads, a few blood cells, in small vessels - hyaline thrombi. In some vessels were found clusters of white blood cells, in which there was a distinct part of the fragmentation of the nucleus with the location of its fragments on the periphery of the cytoplasm, which was similar to apoptosis (Fig. 4 b). Quite often diapedetic hemorrhages met around the vessels.

The expression of the infiltrative component of inflammation in the brain varied in different cases and manifested in the presence of vasculitis, and perivascular infiltrates, and in some cases the formation of "muffs" (Fig. 4). Inflammatory infiltrates composed of lymphocytes, histiocytes and plasma cells, they were detected histochemically cells with positive reaction to acid phosphatase (T-lymphocytes).

In general, in the fourth group of died patients, compared with the third group, the significant increase of the severity of infiltrative and proliferative changes in the brain and spinal cord, as well as significant changes in the percentage of cells of inflammatory infiltrates were not observed.

Thus, in died pations in the fourth week of tick-borne encephalitis the pathological process in the central nervous system should be characterized as meningoencephalomielitis, which clearly expressed alterative component of inflammation with widespread heavy damage and loss of nerve cells in the indicator areas of the brain, as well as the effects of spongiosis and focal gliosis of cerebral matter with the increase in morphological manifestations of immunodeficiency. In our observations, the absence of the clear increase of the severity of inflammation in the CNS of died patients in the later stages of the disease may be associated with significant virus-induced suppression of the immune system and profound disturbances of metabolic processes in the body.

Summary of results of morphological studies our observed fatal encephalitis cases in humans gives an idea of the features of the morphogenesis of the Far Eastern varient of this neuroinfection flowing with focal lesions of the nervous system, as well as to determine the value of the main components of the inflammatory process at different stages of the disease. The obtained data showed that the focal forms of tick-borne encephalitis in the initiation stage the leading importance belongs to the primary damage of the structures of the blood-brain barrier and neurons of the brain and spinal cord. There is the rapid development of

CNS pathology, morphological manifestations of which indicate the nature of hyperergic in‐
flammation. A change in the morphogenesis of the CNS in tick-borne encephalitis reflects
the basic laws of development of the inflammation in the immune basis with the presence of
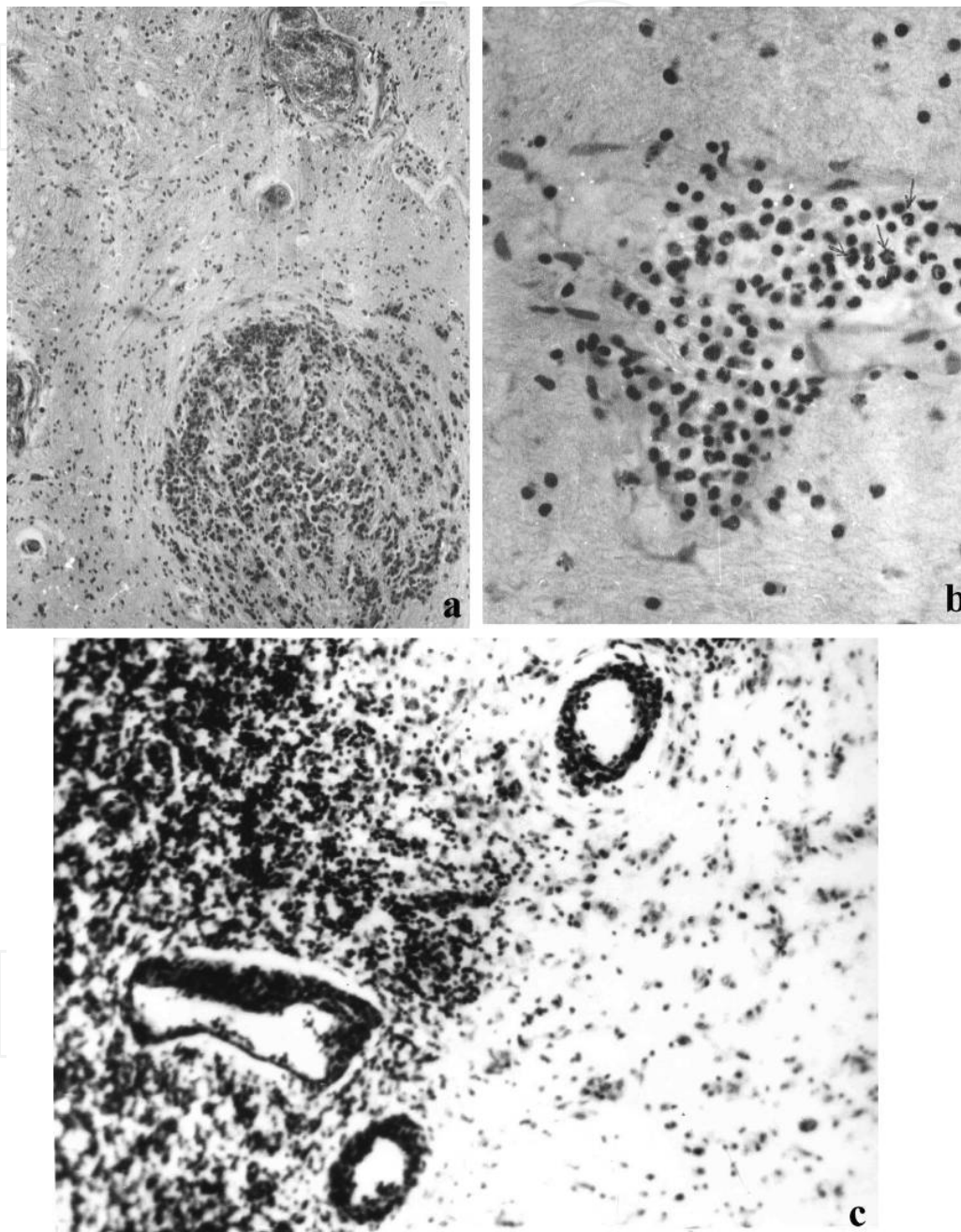tissue-specific features of its various components.

Figure 4. Pathological changes in the brain of human with tick-borne encephalitis. 4th week of illness. a - a major inflammatory infiltrate around the central canal in the spinal cord, to the right - a vessel with the wall stratification and eritrostasis, x 80, b - a destructive vasculitis, fibrin and leucocytes in the lumen of the vessel, fragments of the nu‐ cleus in some cells (arrows), x 320; c - numerous perivaskular "muffs", pronounced glial reaction in the area adjacent to the cerebellar cortex, x 100. Stained with hematoxylin and eosin (a,b) and by Nissl (c).

Thus, the histopathological study of material taken from patients who died during the first, second, third and fourth weeks of the first clinical manifestation of symptoms, possible to trace the morphogenesis of tick-borne encephalitis, and select the individual components of the pathological process. The feature of the pathological process in the first week of the disease is the low intensity of inflammatory changes around the vessels of the meninges and matter brain in the presence of infiltrates of neutrophils, lymphocytes and histiocytes.

The profound degenerative changes of the brain vascular lesions with accumulation of mucopolysaccharides, as well as neurons in conjunction with the exudation of polymorphonuclear leukocytes into the brain, on the background to identify with the IAF-specific antigen in the brain cells, suggest that these changes are due to a direct damaging effect of tick-borne encephalitis virus, over-coming the blood-brain barrier in the pathogenesis of neural phase of infection.

In addition, the proof of this fact is the data on the distribution of viral RNA in the brain and blood cells of died patients, as well as white mice infected subcutaneously with a prototype Sofjin strain of TBE virus (Demenev et al., 1990; Konev et al., 1990; Konev, 1996). Using a highly specific method of nucleic acid hybridization in situ were identified by the authors RFID viral RNA during the first week of the disease over the cytoplasm of morphologically intact and exposed to destruction of neurons, over the endothelial cells of capillaries and choroid plexus. Polischuk (1999) in experiments on white mice found that the RFID virus RNA appear in the vascular structures of the brain and spinal cord in the incubation period from 12 to 48 hours after infection.

In addition to the direct damaging effects of tick-borne encephalitis virus in the mechanism of pathological changes in neurons and other cells of the brain, apparently, to consider the possibility of cytolytic activities of specific antibodies determined already in the early acute stage of the disease, Semenov & Gavrilov (1976) suggested that the reaction of antibodies with virus-induced antigens (autoantigens - in Kanchurin, 1964), lead to the immunolisis of cells and are one of the launchers mechanisms of inflammation in viral infections, as well as the autoimmune process. The latter is known to regard the cells of the central nervous system (Strukov et al., 1982). This is consistent with the data Nathanson & Panitch (1978), Morishima et al. (1984).

The expressed alterative and exudative components of inflammation in the first or second week of illness, in our opinion, points to the hyperergic nature of the initial changes in tick-borne encephalitis, with symptoms of immediate hypersensitivity (ITH). Such changes in the weak expression of the cellular reactions in the most severe cases of TBE previously attributed to the atypical (Robinzon & Sergeeva, 1940; Robinzon, 1975).

If we consider that in endemic foci of the Far East, people often have the multiple, repeated sucking ticks, it is logical to assume the sensitization, previous the acute symptomatic infection of tick-borne encephalitis. Here the analogy with hemorrhagic dengue fever are reviewed (Halstead, 1973; Russell et al., 1969; Barnes & Rosen, 1974), in which the immunopathological mechanism of acute vascular reaction was determined, occurring in re-

sponse to the release of histamine from cells under the influence of excessive amounts of specific immune complexes in the presence of C3A, C5a complement components.

Along with the deep alterative and proliferative changes, the characteristic of pathological changes found in the died patients in the second week of tick-borne encephalitis should be considered more pronounced, than in the previous period, the cellular infiltration in the pia mater, choroidal plexus and around the cerebral vessels with the appearance of perivascular "muffs". In the composition of inflammatory infiltrates dominated by lymphocytes and histiocytes with the admixture of plasma cells. Neutrophil response in this period was minimal. In the 1/3 cases histiocytic and lymphocytic infiltration was significant.

The identification in cells of the inflammatory infiltrate as a specific antigen, and antitick-borne immunoglobulins, as well as the intense reaction to ribonucleoproteins, acid phosphatase (EC) and α-naftilatsetatesterase indicate the strengthening of immunopathological component of inflammation with a predominance of delayed-type hypersensitivity (DTH).

In recent years, began to pay attention to the value of immunological reactions in the pathogenesis of viral infections, including tick-borne encephalitis (Erman et al., 1996; Konev, 1989; Kvetkova, 1984; Pogodina et al., 1984; Barnshteyn, 1989.). Based mainly on experimental data, the pathology of central nervous system was seen in the close relationship with virus-induced damage of the immune system, coming back in the visceral phase of the TBE pathogenesis (Karmysheva & Pogodina, 1991; Rychkov, 1992; Tulakina et al., 1994). In the analysis of relationships in the "brain - lymphoid organs"system was found the strong direct correlation between the vascular and inflammatory changes and the state of the T-dependent areas of lymphoid organs (Konev et al., 1991; Polischuk et al., 1990).

Our studies with human tick-borne encephalitis confirm that the infiltrative component of inflammation in the form of a perivascular "muffs", local and diffuse cellular infiltrates, consisting mainly of T-lymphocytes, histiocytes and macrophages, should be seen as manifestations of the reactions of the cell (tissue) immunity. To this phenomenon it is also concerned the neuronophagia actively carried out mainly of microgliacytes related to the macrophage system. Using the MFA we found in the brain tissue the components of specific immune complexes (antibody-containing and antigen-containing cells) are yet another confirmation of the immune basis of inflammation in tick-borne encephalitis.

It should be noted that during the first - the second week of the onset of clinical symptoms of tick-borne encephalitis died most of the patients - 22 of 35 people, representing 62.9% of cases, in spite of all the patients carried out by the intensive therapy with the mechanical ventilation. This is the indirect proof of the predominant importance of destructive changes in the structure of the pathological process with the irreversible damage to cells of the vital areas central nervous system.

On the third or fourth week of the disease in inflammatory infiltrates increased the content of acid-phosphate-positive cells, indicating that they belong to the T-lymphocytes and macrophages, and plasma (antibody-containing) cells. In the indicator areas of the brain and spinal cord revealed extensive glial foci and nodules on the site of dead nerve cells. The expression of inflammatory cellular changes differed in each case, but generally on the third

- the fourth week of the disease in the brain infiltrative and proliferative components of inflammation dominated.

Thus, the study of morphogenesis of focal forms of tick-borne encephalitis, observed in the Primorye Territory, found that the pathological process in the central nervous system is a multi-component and, in all morphological characters, from the very beginning of its development is immunopathological in nature. In this case there is a consistent deployment of cell-tissue reactions immediate and delayed types. The trigger of the encephalitic process is certainly damage to mesenchymal structures of blood-brain barrier and nerve cells caused by the direct action of tick-borne encephalitis virus in its penetration and intracellular replication in the CNS, which immediately leads to the sensitization of immunologically isolated brain tissue. The immunological basis of inflammation in the brain at the tick-borne encephalitis, and assumed Robinzon and Frolova (1964), Girs (1976), Yaroslavsky et al. (1977).

On our data, the observed variations of the intensity of alterative-exudative and infiltrative-proliferative changes in the brain at tick-borne encephalitis depend, on the one hand, from the stage of inflammation, but on the other hand, from the type of immune responses in individual patients. This data confirms that high levels of specific antibodies in the blood and cerebrospinal fluid, and a more pronounced imbalance of immune responses observed in patients with severe focal forms of TBE than in patients with fever, meningeal, and blurred forms (Kvetkova et al., 1981; Leonova, 1989, 1997; Vereta et al., 1990; Sysolyatin et al., 1990; Shien et al., 1996).

To emphasize the importance of immunoreactivity in the development of inflammatory cell response in the brain at tick-borne encephalitis, it is necessary to refer to the work Pogodina and Frolova(1962, 1965, 1984), performed on a large number of monkeys. These data show that intracerebral infection of animal by neurovirulent TBE virus strains, when the infection was reproduced, bypassing the visceral stage of the pathogenesis without the severe damage to the lymphoid organs, morphological changes in the central nervous system are more pronounced the infiltrative-proliferative component of inflammation, with the domination of DTH reactions than in cases of fatal encephalitis in humans.

One of the factors, the lack of the full symptom- complex of inflammation in viral infections can be the possibility of virus to suppress the inflammatory cell reaction (Avtsyn, 1983). Our morphological data confirm that the tick-borne encephalitis is associated with the known immunosuppressive action of the virus and the resulting state of immunodeficiency (Ryabov et al., 1990; Konev, 1995; Leonova, 1997).

It is known that the severity of the inflammatory process depends not only on the immunological reactivity of the organism, but also on the degree of virulence of the pathogen. The data on the comparative pathology of tick-borne encephalitis, caused by virus strains of high and reduced neurovirulence, based almost solely on the experimental data using to infect animals with different sensitivity to TBE virus (Robinzon & Popova, 1949; Levkovich et al., 1967; Rozina, 1972; Frolova, 1964, 1967; Zinovev et al., 1978a, 1978b, etc.). It should be noted that these studies were mainly focused on characterization of pathogenicity of attenuated tick-borne encephalitis virus strains and the clarification of the pathogenesis of infection in

order to find variants of the virus that are suitable for the development of an effective vaccine for the prevention of TBE.

Our experimental studies have focused on the establishment of the morphological basis of different clinical manifestations of the Far Eastern tick-borne encephalitis, referred Shapoval (1980) to the main nozogeografic version of tick-borne encephalitis (Somova et al, 2001). To address this issue we have studied the morphology of experimental encephalitis on the model of golden hamsters induced by subcutaneous (analogical flowing natural infection process) infection of the virus strains isolated from patients with different clinical forms of infection. This model allows us to differentiate between virulent and attenuated strains of TBE virus (Pogodina et al., 1984). Morphological changes were compared in four groups of animals, ranging from the first up to 21 days after infection.

The histopathological study of animals in Group 1, infected with TBE virus strain 582, isolated from human white blood cells with the inapparent form infection, showed that this strain has a reduced neurovirulence and cause minor inflammatory changes in the brain (Fig. 5 a) and reversible changes in neurons in the form of the swelling and the perinuclear chromatolysis. The appearance of the brain to the 11-14th days after infection the lymphocytic-histiocytic infiltrates with the presence of plasma cells indicating the nature of the immune inflammatory response in the CNS (Fig. 5 b, c). The inflammatory changes concerned mainly the pia mater and the choroid plexus of the brain ventricles. We can assume that the asymptomatic form of the infectious process is limited to the visceral phase of the pathogenesis of TBE, when an adequate immune response flowing spread of the virus in the CNS is limited due to the development of protective immunomorphological changes in the structures of the blood-brain barrier. It is assumed that the asymptomatic form of tick-borne encephalitis is quite common in endemic areas (Shapoval, 1961; Levkovich et al., 1967). In the seropositive cases of TBE the low levels of specific antibodies are determined (Leonova, 1997).

The animals in Group 2, infected with TBE virus strain 208, isolated from a patient's white blood cells with the febrile form infection, the pathological process in the central nervous system characterized by a predominance of infiltrative and proliferative changes (Fig. 6 a, b). Distinct vascular and inflammatory reactions in the pia mater and substance of the brain were detected at an earlier date than the animals in Group 1. Perivascular infiltrates were distributed along the vessels from the pia mater to the deep brain substance. The response of nerve cells to viral infection manifested degenerative changes, the vacuolation of nuclei of individual neurons, the loss of small groups of Purkinje cells in the ganglionic layer of the cerebellum. In general, pathological changes in the central nervous system caused by the TBE virus strain 208, were identified as meningoencephalitis, and in some cases animals with paresis of the extremities and eyelids were observed a more widespread phenomenon of inflammation.

The conduct clinical and morphological parallels in experimental animals and humans can suggest that the absence of neurologic symptoms in patients with febrile form of tick-borne encephalitis does not exclude the involvement of the CNS in the pathological process. Most likely, reactive cellular changes in the arahnoidendotelium, choroidal plexus and ependyma of ventricles inhibit the penetration of the virus in nerve cells during infection of strains with

reduced neurovirulence. In this regard, the data from V.P. Konev (1995) are of interest, which in inapparent infection in hamsters infected subcutaneously with TBE virus, through MGNA in situ, detected the virus components in the structures of the microvasculature, although the alteration and signs of inflammation in the brain is almost absent. At the same reactions in the lymphoid organs reflect the active formation of cellular and humoral immune response.
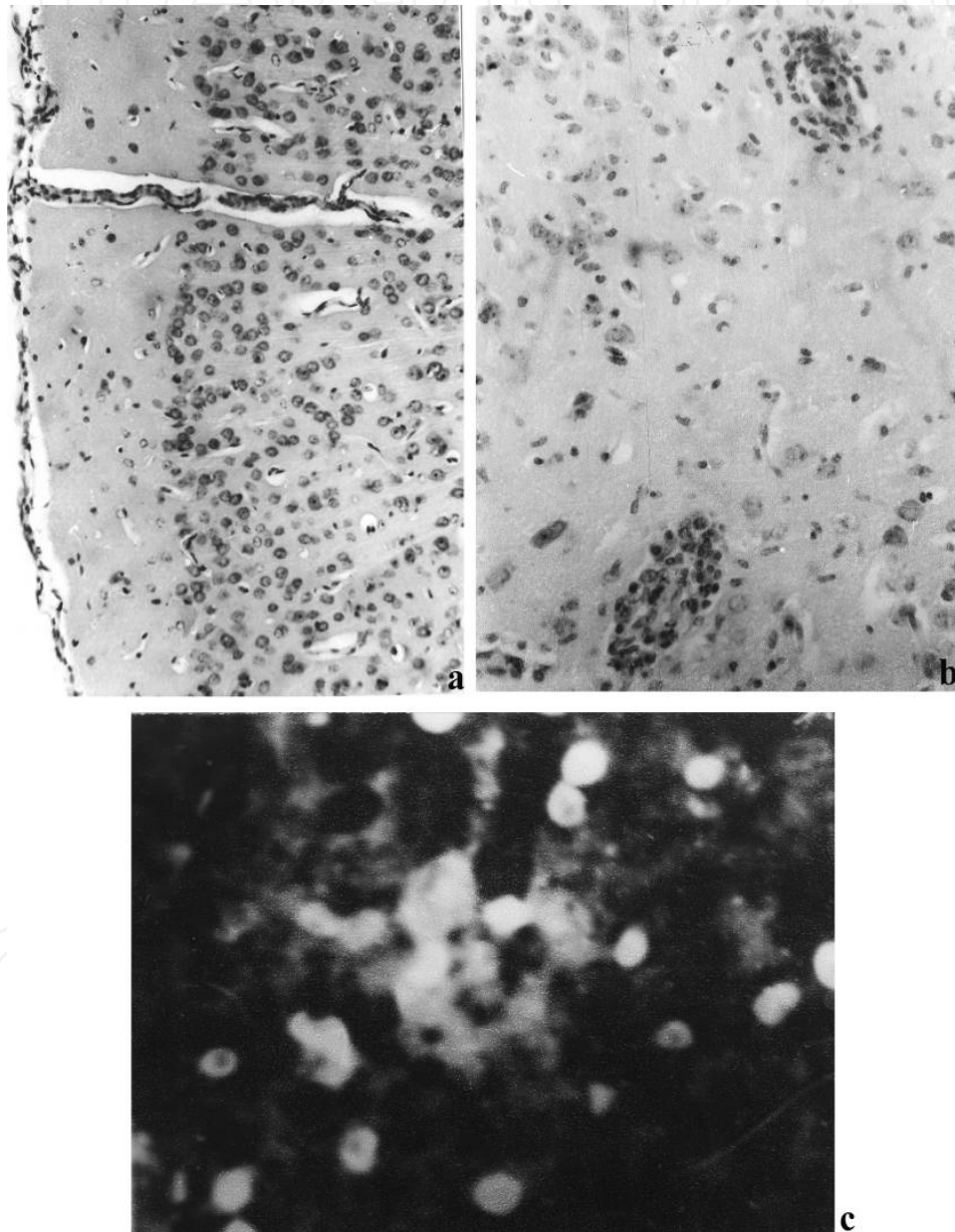

Figure 5. Pathological changes in the brain of hamsters infected with 582 strain of tick-borne encephalitis virus, isolated from human blood with inapparent form of infection, 11 days postinfection. a – the slight lymphocytic- histiocytic infiltration of pia mater in the spread of the brain substance, x 80, b – perivascular mononuclear infiltration in subcortex, x 200, stained with hematoxylin and eosin (a, b); c - specific immunoglobulin in the cells of perivascular infiltrate, x 200, the indirect IFA (c).
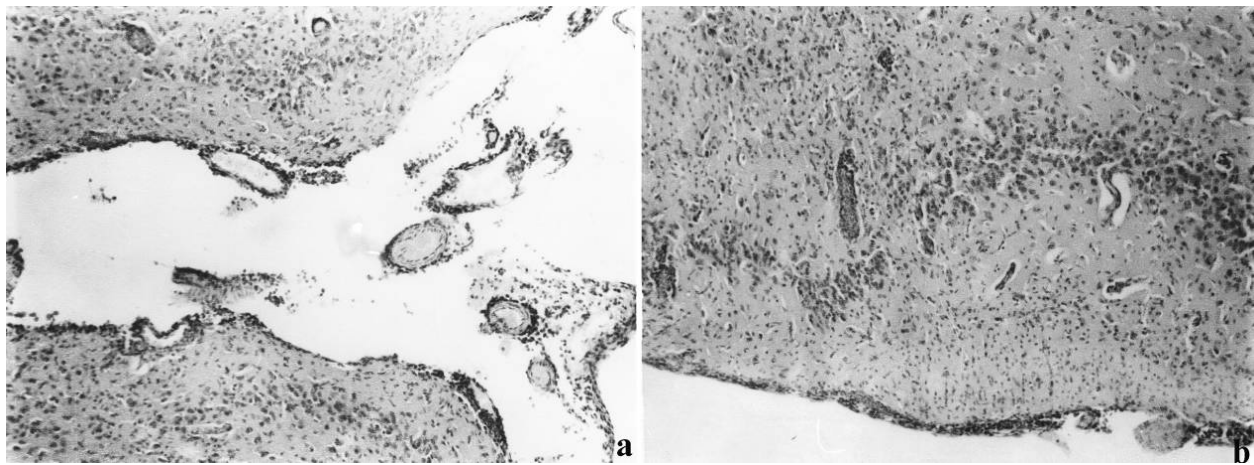
Figure 6. Pathological changes in the brains of hamsters infected with 208 strain of tick-borne encephalitis virus, isolated from the blood of patients with febrile form of infection, 11 days postinfection. a-plethora, edema and inflammation of pia mater in the sagittal sulcus of the brain, perivascular infiltration, x 80; b – the infiltrative and proliferative changes in the pia mater and the cerebral cortex, x 80. Stained with hematoxylin and eosin.

On the basis of morphological data can be assumed that the clinical differentiation of feverish, worn and meningeal forms of encephalitis, apparently, is conditional. In this regard, it should also pay attention to the experimental data (Frolova, 1967; Rozina, 1972) that even the attenuated and vaccine strains of tick-borne encephalitis virus can cause meningoencephalitis asymptomatic lesions without large foci neurons damage, with the formation of perivascular "muffs", glial reaction, as well as events of ependimitis and horioplexitis as indicators of immunomorphological reactions.

The experimental infection in animals infected with tick-borne encephalitis virus strains, isolated from patients with focal forms of the disease, manifested in the brain the development of the microscopic changes characteristic of a typical meningoencephalomielitis. Some animals were observed limb paresis, weakness. Thus, in the third group of animals, infected with strain 336, isolated from a patient's white blood cells with non-fatal, focal form TBE, the exudative and alterative component of the pathological process was pronounced (Fig. 7 a, b). Dystrophic and destructive changes in the nerve cells predominated in the brain areas adjacent to the ventricular system - Ammon's horn, subcortical layer of the cortex, around the Sylvius aqueduct. In hamsters, in addition to acute swelling of nerve cells in the cortical layer of the hippocampus is often observed oxyphilic foci of degeneration of neurons with their nuclei hyperchromatosis.

The infiltrative and proliferative component of the inflammation has been clearly expressed in the period from the 7th to the 14th days after infection, and manifested the moderate lymphocytic-histiocytic infiltration of the meninges, the choroidal plexus, the formation of glial "pillows" in the subependimal layer of the lateral ventricles. By 21 days the intensity of inflammatory changes decreases.

In the 4th group of animals infected with the "Walecki" strain of tick-borne encephalitis virus, isolated from the brain of the died patient with the focal form of the disease, the phenomenon meningoencephalomielis determined at an earlier date and were more expressive

pronounced in comparison with the animals of group 3 (Fig. 8). The dynamics of the pathological process was similar among patients who died of the tick-borne encephalitis.

There were severe degenerative and destructive changes in the nerve cells in the indicator areas of the brain, which combined with severe exudative and infiltrative changes around the pial vessels and in the brain substance with the formation of perivascular "muffs". As in patients with tick-borne encephalitis in the animals of the fourth group in the morphogenesis of inflammation discernible the change in the cellular composition of infiltrates with an increase in the percentage of lymphocytes and plasma cells with the growth of the duration of the infection.

The poor demarcation of inflammatory lesions with the penetration of hematogenous elements into the surrounding brain tissue, the expressed neuronal damage with loss of cell groups, as well as the active glial proliferation indicated on the high neurovirulence of the "Walecki" strain and on the severity of encephalitic process with immunopathological in nature.

In the study, from 5-th to 21-th day after infection in sera of animals antibodies to tick-borne encephalitis were determined in the HAI with an increase in their titers. However, in animals of group 4 showed the inhibition of the immunogenesis. This is consistent with the data of morphological studies of lymphoid organs, showed a significant degree of depletion of cellular responses in the spleen (delimphatization) and the accidental transformation of the thymus in animals infected with the "Walecki" strain. The phenomenon of the virus-induced immunodeficiency is also confirmed the redaction in the thymic index in animals of all four groups in proportion to the degree of neurovirulence of tick-borne encephalitis virus strains, taken for infection.
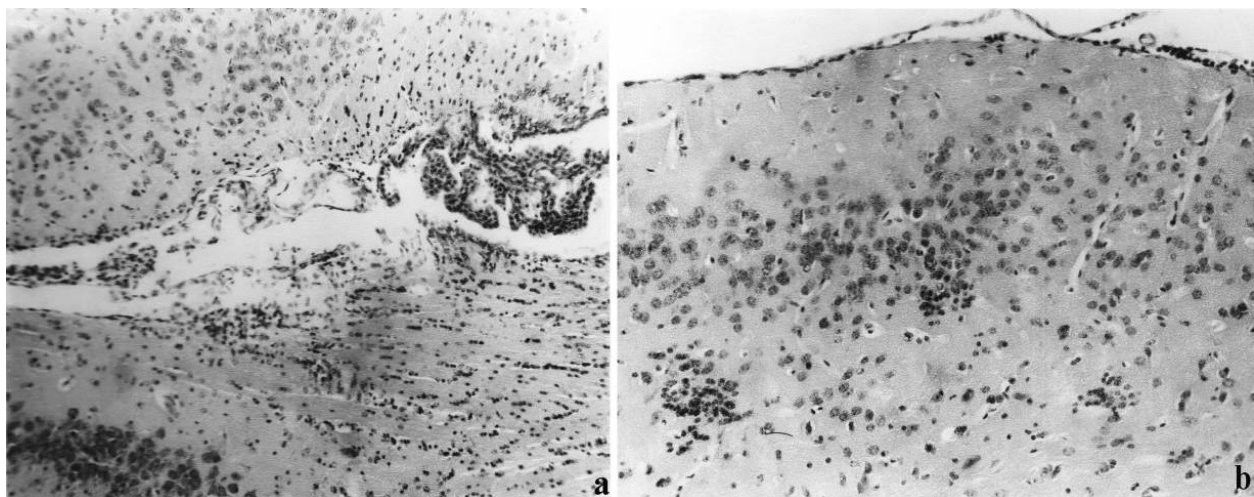

Figure 7. Pathological changes in the brain of hamsters infected with 336 strain of tick-borne encephalitis virus, isolated from the blood of patients with focal form of infection, 1 day postinfection. a – a part of the hippocampus, adjacent to the lateral ventricle of brain, inflammatory changes of the choroidal plexus, the focus of destruction under the ependyma with glial reaction, x 80; b - glial nodules in the cortical layers of the cerebral hemispheres, lymphoid infiltration of the pia mater, x 125. Stained with hematoxylin and eosin.
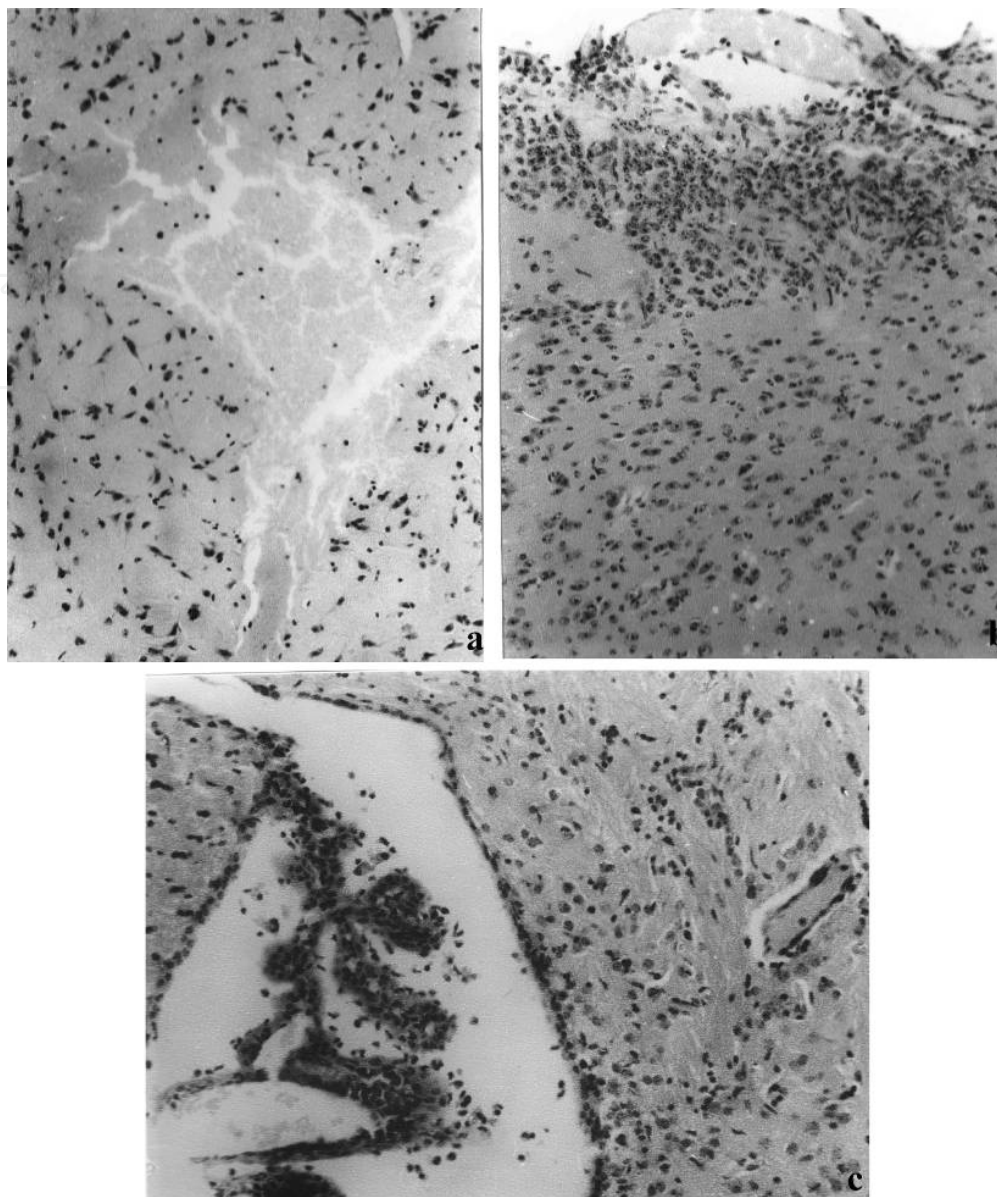
Figure 8. Pathological changes in the brain of hamsters infected with the "Walecki" strain of tick-borne encephalitis virus isolated from brain the died patient with the focal form of infection, 5 days postinfection. a – a hemorrhage around the necrotic vessel in the brain stem, glial reaction, x 125; b – the abundant infiltration of the pia mater and cortical brain regions by hematogenous elements, x 125; c –the expressive proliferation of ependyma of lateral ventricle, infiltrative-proliferative changes in the brain substance, x 125. Stained with hematoxylin and eosin.

Thus, our experimental studies were evidence the dependence of morphogenesis of tickborne encephalitis from the characterictic of infecting virus strains. The direct evidences for virus-induced immunodeficiency in TBE received Konev (1995), who showed in experiments using in situ MGNK the selective accumulation of the virus in lymphoid organs from the first day of infection in macrophages and lymphocytes of the T-dependent zones. According to the author, who used to infect animals Sofjin Far East neurovirulence strain, the nature of brain damage, the dynamics of the immune response with the morphological

equivalents in the lymphoid organs also depend on the specific susceptibility of animal models (mice, hamsters).

Our materials are allowed to evaluate the pathology of tick-borne encephalitis, caused by a heterogeneous viral population, in terms of a common mechanism underlying the protective and damaging effects of immunomorphological reactions. Based on the analysis of own and literature data were divided into three clinical-morphological variants of tick-borne encephalitis (table 3).

The first variant of the acute TBE is characterized by pronounced cerebral disorders, the high mortality during the first week of the disease, the prevalence of exudative and alterative components of inflammation and haemocirculating disorders in the CNS. The heavy damage to neurons has the direct connection to the intracellular reproduction of the virus. The development of this version of the tick-borne encephalitis is caused by highly virulent strains of TBE virus, as well as the specific sensitization of the organism dominated by immediate hypersensitivity reactions.

The second variant, the most typical of the acute TBE, is characterized by a slow rate in the development of changes in the CNS, focal symptoms, fatalities on 2 - 4th week of the disease. In the pathological pattern prevails the infiltrative-proliferative component of the inflammation with the presence of perivascular "muffs" as well as the severe nodular and diffuse glial reaction. These changes are the consequence of immunopathological process inherent in delayed-type hypersensitivity.

The third variant is characterized feverish, worn and inapparent forms of tick-borne encephalitis. The selecting this variant was possible on the basis of experimental elaboration during infection caused by attenuated strains of TBE virus, including those in the literature (Rozina, 1972), with the vaccination and the passive immunization of specific gamma globulin. In the pathological picture there are reactive changes in the structures of the blood-brain barrier in the form of the productive arachnoiditis, horioplexitis and ependimitis that protect nerve cells from the virus.

In parallel with our research, a lot of attention to the modern pathomorphosis of tick-borne encephalitis drew scientists of the Ural region (Erman et al, 1999), where by the end of the 1990s saw the significant increase in the incidence of tick-borne encephalitis, weighting the clinical course and outcome of disease. Based on analysis of 32 fatal cases of acute encephalitis authors, along with the general features characteristic of the disease, identified three types of pathological changes in the nature of the inflammatory response: the alterative-productive inflammation, the alterative-exudative inflammation and the alterative inflammation. The differences of these types of inflammation, according to the authors, was relative.

Based on our own research results of the Far Eastern tick-borne encephalitis cases, we believe that the differentiation of the pathological process, carried out by Yerman et al. (1999) without delay the onset of fatal diseases, caused by the morphogenesis of changes in the central nervous system during development of infection and in general similar to that described by us pathological picture of tick-borne encephalitis. In our opinion, the authors made a logical conclusion that the unstable cellular inflammatory response, from the intense

diffuse and focal perivascular infiltrates and proliferates to a small or virtually absent cellular inflammation is associated with the virulence of the virus strains and to a large extent with the immunological reactivity of the organism to infection. In assessing the nature of the pathological process, we stand in solidarity with Yerman, concluding that the immunopathology of tick-borne encephalitis includes both immediate type hypersevsitivity, and delayed-type hypersevsitivity, a different combination of which creates the impression of different types of inflammatory reaction.

Indexes	Clinical and morphological variants of the disease		
	The first	The second	The third
The clinical picture			
Cerebral symptoms	+++	+/++	-
Focal neurological symptoms	++	+++	-
The current of disease	heavy	heavy / moderate	light, with or without clinical picture
The during the onset of death, week	the first week	2-3-4 weeks	Till one week
Mortality	100 %	2 weeks. -56.6% 3 weeks. - 13.4% 4 weeks. - 30%	no
The morphological picture			
Alteration of neurons	+++	++/+++	+/±
Gemocirculating disorders	+++	++/+++	±/-
Infiltration due to:			
neutrophils	++	+	±/-
lymphocytes/ histiocytes	+/++	++/+++	++
Proliferation of glia:			
focal	++	++/+++	+/±
diffuse	++	++/+++	-
Reactions of ITH	+++	±/+	-
Reactions of DTH	±/+	++/+++	+/±

Note: + + + pronounced, + + moderate severity, + weak expression, ± low intensity, - the lack of symptom/sign.

Table 3. Clinical and morphological variants of tick-borne encephalitis

4. Conclusion

On the basis of their own and literature data is given the modern interpretation of the patho-morphology of tick-borne encephalitis (TBE) in terms of immunopathological nature of the inflammation. It is shown that the pathological picture of central nervous system reflects the hyperergic nature of inflammation with TBE. In the morphogenesis of the pathological process traced the consistent development of immediate type hypersensitivity reactions, initiated by the damaging effect of the virus in brain tissue, and delayed type hypersensitivity reactions to ensure the formation of local (tissue) immunity. For a comprehensive assessment of pathology of tick-borne encephalitis in humans and experimental animals set the variability of its manifestations, this depends on the properties of the infecting virus strain, such as the virus-induced immune response and the stage of disease morphogenesis. On this basis, divided into three clinical and morphological variant manifestations of infection with TBEV.

Acknowledgment

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