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POINT OF VIEW

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VILIUISK ENCEPHALOMYELITIS AS PRIMARY CHRONIC NEURODEGENERATIVE DISORDER

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The paper presents a new concept of the nature of Viliuisk encephalomyelitis – the unique disease of the Sakha ethnic group as primary chronic neurodegenerative disorder. It is based on an analysis of the participation of TNF superfamily members in the pathogenesis of the disease.

The ligands and receptors of TNF superfamily are key players of important biological processes, including the maintenance of tissue cell homeostasis using immunity mechanisms. It is suggested that sTRAIL ligand induce the loss of neurons in the cases of a primary chronic degenerative process. The sTNFα ligand is associated with an inflammatory complication of this disease under conditions of stress and perhaps participates in the neuronal necrosis in the acute stage. Elevated levels of sCD40L, detected in the plasma of patients, may act as a factor of the development of microvascular pathology, the cause of chronic hypoxia, inducing and supporting chronic processes of brain tissue atrophy.

Keywords: Viliuisk encephalomyelitis, Bokhooror, neurodegeneration, TNF superfamily, sTRAIL, sTNFα, sCD40L.

Introduction. "Bokhooror" is the native name for a rare primary chronic degenerative disease of the human central nervous system, observed among the Yakut population in Yakutia and known to medical science for more than 80 years. Phenotypic manifestations of this disease are associated with paresis of the muscles of the laryngeal area and motor functions caused by damage to the pyramidal, extrapyramidal tracts and the cerebellum. Patients experience difficulties in the initiation of movement, show emotional immobility and loss of socially significant features of the relationship in combination with the problems of reproductive memory. The disease is endemic and sporadic. Group cases of the disease is not observed, but can be traced generic ties [9, 14, 17].

One of the main features of the pathology is brain atrophy (in 83% of patients) and significant decrease of a brain mass, which correlates with the duration of the disease [1, 8]. Pathological findings indicate diffuse atrophy, predominantly of the cerebral cortex, cerebellum, and upper spinal cord, associated with loss of neurons. On the other hand, patients may have an inflammatory episode (about 30% of patients experienced acute encephalitis), which clinically manifests itself as neuroinfectious diseases. The clinic of inflammation that gave the name of the disease - Viliuisk encephalomyelitis (VE), is described and studied in detail by P.A. Petrov, A.P. Shapoval, L.G. Goldfarb, R.S. Tazlova and A.I. Vladimirtsev [2, 3, 6, 7, 9]. In the pathological picture of these patients, on the background of neuronal loss, scattered necrosis foci with an inflammatory reaction in the form of infiltrate in the fibrous membrane of small vessels in the brain parenchyma are added [33]. The infectious nature of this inflammation, despite many years of attempts, did not receive its confirmation, which suggests the idea of its aseptic nature associated with congenital abnormalities of the immune system in patients.

The potential possibility of self-limiting the inflammatory process (indicating a controlled process) and the transition to the chronic degenerative form is a characteristic feature of the acute forms of VE. In recent years, with the improvement of social and living conditions, the inflammatory episodes in patients gradually disappear and the primary chronic form of the disease is widespread. This form develops gradually with age and has the character of a neurodegenerative disease of the brain and spinal cord with a clinical picture according definition "Bokhooror". Another feature of the chronic form of this disease is immunosuppression (immune tolerance) of the pathogenic brain. Patients show pronounced and sustained suppression of the immune system [2, 4].

The causes and mechanisms of atrophy of the brain tissue and induction of a controlled inflammatory process (encephalitis) are main issues, which will allow reveal the pathogenesis and develop the treatment of the disease. The article presents a review of clinical, pathological data, as well as our own research on the immunology of Viliuisk encephalomyelitis, on the basis of which the hypothesis of the pathogenesis of the disease is proposed.

The primary chronic brain degeneration is the basis of the VE disease. In this section, we consider a typical clinical picture and pathological changes in the brain tissue in patients with primary chronic disease, which is more consistent with the native definition of the disease "Bokhooror". It is assumed that this state of encephalopathy is the basis of the disease, which may be complicated by an acute inflammatory episode.

The initial symptoms of encephalopathy manifest as stem symptoms. The most frequent complaints are headaches, fatigue and body aches. This state occurs, when the balance of functions of the excitatory and inhibitory neural

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pathways fails, excitement disinhibited and control of the spinal cord reflexes by the cortical structures is disturbed. The chronic disinhibition of excitability of the neurons leads to the depletion of this neural circuit (dystrophy of neurons) and irreversible organic neurological changes. The first researcher of this disease, A.N. Shapoval notes the same complaints and their resistance in patients with a developed clinical picture, which indicates the general nature of encephalopathy and the chronic form of the disease [9]. Astheno-depressive conditions are characteristic of these patients. Early disability of patients is associated with the aggravation of the symptoms of spastic paresis and speech disorder. Neuroimaging of the patient's brain reveals diffuse atrophy, more pronounced in the upper and temporal lobes and spongiosis of the cerebral cortex.

The pathology of the brain after a patient's lethal outcome shows far-gone morphological changes in the brain tissue — the result of secondary destructive processes, and therefore the analysis of these changes has no informational value for identifying the initial causes of pathogenesis. The primary morphological signs of damage to the brain tissue, adopted by the consensus of researchers, are neuron death by apoptosis without inflammation and neuron necrosis (destruction and release of cell contents), inducing an acute immune response toxic to neighboring healthy cells.

In patients with the chronic form, without acute inflammatory onset, it is registered mainly dystrophic changes of cortical neurons and their lysis. Despite the absence of pronounced inflammation of the brain tissue, isolated foci of micronecrosis are found surrounded by hypertrophic astrocytes, which subsequently initiate cortical foci of spongiosis [2, 20, 33]. The inflammation of the nervous parenchyma in these patients occurs in a subclinical form. In these cases unstable state of the brain is stabilized by the protective mechanisms of the brain.

In contrast, the patients with acute inflammatory onset (encephalitis) show a pronounced rash of numerous micronecrosis, mainly in the gray matter of the cerebral cortex with an active immune response. At the same time, the degenerative processes of the brain parenchyma outside the inflammatory focus are very pronounced and occur in the form of severe dystrophic changes of neurons, their lysis and the formation of cavities in the brain tissue. The extreme stress in the patients with an astheno-depressive state may cause acute encephalitis, which exacerbates the primary degenerative course of the disease.

The pathophysiological role of the superfamily of TNF receptors and ligands. The superfamily of TNF receptors and their ligands is one of the important systems in maintaining homeostasis of healthy tissue and the formation of a protective immune response [10, 15, 18]. The members of the TNF family are mainly expressed on the immune cells that monitor tissue cells and specifically detect pathogenic cells (immune and other non-hematopoietic tissue cells). The implementation of the three phenotypic manifestations of the target cell: cell survival, apoptosis or necroptosis is the result of the induction of biochemical signals by the interaction of the ligand and the receptor [12]. Survival of the target cell is supported by the expression of apoptosis protection and anti-inflammatory cytokines genes. The mechanism of cell destruction is initiated by the interaction of receptors (R) and ligands (L) of the TNF family. The most well-known L-R systems from the TNF family involved in these processes are TNFα, Fas, TRAIL, CD40.

The protein receptors of the members of TNF family, besides CD40, have a domain inducing activation of the cell apoptosis mechanism. The CD40 receptor is able to activate the generation of toxic T cells (CD8 +) and also induce apoptosis [13]. If the target cell has irreversible destructive changes, the TNFα ligand induces the formation of a toxic protein complex in the cytoplasm that performs apoptosis. The shock stress induces the intracellular activation of an alternative mechanism of cell destruction — programmed necroptosis. The triggering of these mechanisms depends on the state of another important system, including the p53 gene protein, which controls the health of tissue cells and its genome [25]. Numerous signaling pathways (outside and intracellular) monitor the state of the cells, and in the event of a pathophysiological cell crisis (genomic instability or dangerous metabolic changes occurring under stress), activate p53 protein, which induces the activity of the described cell death mechanisms.

Membrane-bound ligands or their receptors can split off and, in a soluble form, participate in nonspecific immune response reactions [32] with the development of the pathophysiological process of the body. Elevated concentrations in the circulating blood of soluble forms of L, R (sTNFα, sFas, sTRAIL, sCD40L, sCD40) can be an indicator of the development of this process.

Laboratory studies of sTNFα, sFas, sTRAIL, CD40L in the VE patients. In our study the levels of sTNFα, sFas, sTRAIL in peripheral blood of patients with chronic VE did not differ from healthy controls. The involvement of sTNFα in the development of an inflammatory episode (encephalitis) among patients (the indicator is an intrathecal synthesis of IgG) was revealed. Patients without inflammation show a twofold low level of sTNFα in the blood, which indicates their lack of an immune response with the participation of sTNFα. It is shown, that after immunosuppression of inflammation, the level of sTNFα in the blood decreases with the duration of the chronic course of the disease. Residual activity of sTNFα can also be traced in the cerebrospinal fluid (CSF).

In contrast to the above ligands, the level of sCD40 and sCD40L increased in peripheral blood of the patients with the chronic form. At the same time, the sCD40L ligand is several orders higher than the content of the sCD40 receptor of both blood and CSF. A high level of sCD40L, unbalanced with soluble CD40 receptor in the circulating blood, is able to induce pathophysiological processes.

The content of sTNFα, sFas in CSF samples of the patients was low. In contrast, the level of sTRAIL in patients CSF can be increased. Analysis of the role of these ligands in the pathogenesis reveals the participation of only the sTNFα and sTRAIL. As shown, the sTNFα ligand is a factor of the induction of neuron necrosis with the development of inflammation (encephalitis) and a participant in an inflammatory episode. The sTRAIL ligand seems to be considered as a factor inducing apoptosis of neurons in the primary chronic degenerative process [16, 31].

The self-limiting nature of inflammation in a disease indicates the immunosuppression and mechanism of regulated necrosis. What is this mechanism? One possible explanation is based on the involvement of the sCD40L ligand. The involvement of sCD40L in immunosuppression of circulating peripheral blood immune cells was shown. The sCD40L ligand induces proliferation of suppressor cells (Treg) and myeloid-derived cells (MDSC), and inhibition of the activation of monocyte and T-cells [27]. Perhaps the sCD40L ligand is a factor inducing the self-limiting

process of an inflammatory episode. In episodes of acute inflammation of the brain, the activity of immune T cells can also be blocked by an inflammatory reflex through the hypothalamic-pituitary-adrenal axis by glucocorticoid secretion [30]. These facts explain the immune tolerance of the pathogenic brain of a patient with disease chronic form, described previously.

It is known that platelet cells are the main producer of sCD40L in peripheral blood [22, 28]. Platelets control intravascular immunity, being active participants of the immune response. The secretion of sCD40L and inflammatory cytokines by platelets induces the expression of membrane receptors (integrins) of immune and endothelial cells, binding of the immunoactive cells with extracellular matrix and endothelial cells and provoke microvascular pathology. It has been shown that the blood of patients with chronic VE is characterized by a high content of platelets [5], which can be a source of high levels of sCD40L. The involvement of sCD40L in the blood-brain barrier disruption has been shown [24]. The small size of the sCD40 molecule contributes to their infiltration into the brain parenchyma, induction of astrocyte hypertrophy, which limits the necrotic focus of inflammation, gliolysis and, in general, disruption of trophic function. Developing microvascular pathology can be the cause of chronic hypoxia, inducing and supporting chronic apoptosis of brain tissue. It is possible that platelets chronically secreting sCD40L into the circulating blood may be a major factor in the pathogenesis of primary chronic VE.

Other diseases with high levels of sCD40L in blood are atherosclerosis, type 2 diabetes, metabolic syndrome, lupus erythematosus and others [19, 26]. It is known neurological diseases with elevated levels of sCD40L (multiple sclerosis, Alzheimer's) [24, 29]. Different nosologies can be associated with different sensitivity of organs to circulating sCD40L. In our case, the congenital high sensitivity of the microcirculatory system of the brain parenchyma to elevated levels of sCD40L may predispose to the brain pathology. The role of heredity in this disease is indicated by the tracing of generic connections, its endemicity and the sporadic nature of the onset of the disease. Sensitivity to sCD40L in VE may be associated with selective constant expression and / or higher receptor density in the endothelial cells of the brain microvascular system of the patients. The molecular nature of this sensitivity of the brain parenchyma in this disease remains uncovered.

Therapy issues. The ligands of the TNFα superfamily are currently the subject of much attention as promising tools for the destruction of pathogenic and toxic cells, including oncogenic ones. The innovative methods of therapy using these ligands are being developed. For example, the ways to reduce or block the action of sCD40L ligand in circulating blood in animal models at atherosclerosis, systemic lupus erythematosus and other diseases [11, 21, 23]. The use of these methods in the pharmacotherapy of this disease can be one of the promising approaches to the treatment of the disease.

Conclusion. The analysis of the participation of members of the TNF superfamily in the VE pathogenesis allow to us to re-examine the nature of this unique disease of the Sakha ethnos. Members of this family are key players in important biological processes of cell life, including maintaining homeostasis of tissue cells through immune mechanisms. In our case, brain tissue atrophy processes are associated with the participation of the sTRAIL and sTNFα ligands. In the case of a primary chronic degenerative process that occurs most often in a subclinical form, the loss of neurons appears to be induced with the participation of the sTRAIL ligand. In conditions of stress (severe hypothermia, excessive physical and psychological stress), patients with primary chronic degeneration may undergo acute inflammation, clinically manifested as an acute form of Viliuisk encephalomyelitis with prolonged fever, severe headache, impaired consciousness, inflammatory manifestations in the liquor. In this case, the ligand sTNFα is involved in the development of inflammation in the brain and induce neuron necrosis. In patients with a chronic form who survived after an acute period, the level of this ligand decreases over time.

The level of sCD40L is statistically significantly increased in the blood of patients. It is assumed that it can be a factor in the development of microvascular pathology, the cause of chronic hypoxia, inducing and supporting chronic processes of brain tissue atrophy. Earlier, researchers A.N. Shapoval [9], A.P. Savinov [8], S.A. McLean [33] adhered to the hypothesis of the primacy of neuronal damage based on the absence of inflammation of the brain parenchyma in primary chronic patients, as well as topographic dissociation of necrosis foci and infiltrates of the vascular fibrosis of patients with inflammatory episodes of the brain. Other authors A.P. Avtsyn and A.A. Zhavoronkov pointed out the important role of angiopathy in the slowly developing reduction of the microcirculatory bed in the chronic form of the disease [1]. Based on his own research on the pathology of the disease, F. Ikuta considered primacy of angiopathy [20]. The results of recent studies are most consistent with the last position.

Further study of the molecular mechanisms of the immunological disturbances in the brain can help in disclosing the etiology and pathogenesis of this unique disease, as well as in developing new approaches to the treatment of neurodegenerative diseases.

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