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NEUROIMMUNOLOGICAL CHANGES IN EARLY DIAGNOSTICS OF HIV INFECTION

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The aim of the study *– analysis of the influence of neurospecific proteins on the development of neuroAIDS, their role in the pathogenesis, determining the prospects of involvement in the early diagnosis of HIV infection.*

The study used theoretical methods that included analysis and synthesis of the study of modern world research, clinical observations, deductive-inductive methods.

Conclusions. *There is an active spread and late detection of HIV infection in Ukraine. Standard methods of laboratory diagnosis are unable to provide quality early diagnosis of HIV infection.*

The rapid penetration of the virus into the CNS creates difficulties for differential diagnosis with the subsequent formation of resistance to ART. As long as HIV in the blood remains in a long latent period, the pathogen is actively functioning in brain cells.

The connections and features of accumulation of matrix HIV-protein p-17 in the CNS, activity of transcriptional transactivator, regulatory protein Vpr remain poorly studied. Neurospecific proteins as markers of viral pathological process in the human nervous system need special attention and study.

Review of the basics of early diagnosis of HIV will provide opportunities to strengthen epidemiological control and prevent new cases of the disease, which will ultimately lead to a reduction in government funding of this problem not only in Ukraine but also in many countries.

Key words: *diagnosis; neuroAIDS; neurospecific proteins.*

HIV infection is a lentiviral anthroponous disease with the highest degree of development of the epidemic process, which covers all countries of the world [1, 2]. At the beginning of 2021, there were 42 million patients in the world, every fifth of whom did not know their status. Despite the improvement of prevention measures, the development of new treatment regimens, the disease continues to progress today [3, 4].

HIV infection has various variants of the clinical picture, which can be disguised as a large number of pathologies of other etiologies. This is due to the fact that among all HIV-infected people more than 50 % have signs of neurocognitive and psychosomatic disorders from mild and moderate to severe [5, 6]. There are problems with the identification of the disease and, accordingly, with the timely treatment. The issue of immediate revision of approaches to the study of the disease and the development and improvement of reliable early diagnosis is becoming relevant [7].

The aim of the study – analysis of the influence of neurospecific proteins on the development of neuroAIDS, their role in the pathogenesis, determining the prospects of involvement in the early diagnosis of HIV infection.

The study used theoretical methods that included analysis and synthesis of the study of modern world research, clinical observations, deductive-inductive methods.

From January to December 2020, 15 659 cases of HIV infection, 4 131 cases of AIDS and 2 112 deaths caused by AIDS were officially registered in Ukraine [8]. The disease in Ukraine is accompanied by a predominant lesion of people of working age with the growth of the age group over 50 years among the newly diagnosed disease. In general, there is a late detection of HIV-positive people, which confirms the data obtained from studies over the past 5 years, when the number of CD4 <350 cells/mm^3 is detected in 53 % of people, which is the highest rate among most European countries [9].

In the early stages, most often, the infection has a latent course with the presence of a period of seronegative window. It impedes the reliability of laboratory diagnostics and poses a great danger in the field of donation, newborns, as well as a significant spread of HIV infection [5-7].

The state spends an average 1.3 billion UAH a year on program measures to help and treat patients, about 57 % of which go to the treatment and care of AIDS patients. Over the last 5 years, the total amount of funding was 6.6 billion UAH [5, 9, 10].

We consider it necessary to pay attention to the pathophysiological features of HIV and the system of organs on which it has a direct impact for the successful formulation of the necessary questions and their perfect solution for early diagnosis.

HIV is associated with the CNS through its ability to penetrate the nervous system in the first days after the virus enters the human body, with subsequent replication in the brain and the formation of reservoirs of the pathogen. This creates the conditions for a rather complex mechanism of drugs functioning and influence on the pathogenic factor through physical barriers and functions of outflow from the brain. The above statements create the conditions for the preservation of isolated viral RNA in the brain [11]. The virus avoids active interaction with antiretroviral drugs, for some time, increases the likelihood of drug resistance [12, 13]. Because of this, about 40–60 % of cases progress to neuroAIDS, despite active ART [14-16].

The immune system monitors the level of viral RNA in the cerebrospinal fluid for the first months, keeping it very low, which cannot be detected in the laboratory, while the cellular reservoir of the virus is macrophages and microglia cells [10, 11].

There is often controversy among scientists about HIV infection of brain astrocytes. Recent studies have shown that the virus is able to form latent reservoirs of the virus in these cells [12].

By overcoming the blood-brain barrier, possibly with infected CD4 lymphocytes, the virus not only infects lymphocyte-type cells but also involves vascular endothelial cells and astrocytes. Due to further circulatory disorders, progression and release of toxic substances, it becomes possible for HIV to replicate in the CNS, thanks to the brain's own immune system, which provides a separate autonomous synthesis of the virus. The primary penetration of the pathogen provides its primary effect on the nervous system with the addition of autoimmune reactions with multiple formation of autoantibodies to the structural units of the brain [10, 11].

The death of neurons causes a toxic load on other CNS cells, thus forming a complex lesion. The above is justified by the neurotoxic effects of the virus itself and viral proteins gp120, the effects of damaged brain structures, autoimmune cytokine imbalance. Thus, it creates a powerful oxidative stress to neurons that are too sensitive to changes in pH, circulatory disorders of the brain by affecting the endothelial cells of small capillaries. All this creates conditions for a decrease in the interaction between neurons and other brain cells, disruption of the transport of electrolytes, metabolites, closing the pathogenic circle with interstitial edema and even greater disintegration of the blood-brain barrier. These factors confirm the multicomponent, constant effect of HIV on the nervous system with damage to many different structural units of the nervous system [10, 16].

It is proved that different classes of HIV viral protein enter the brain through damaged BBB, accumulate in brain structures causing progressive disturbances of neuronal activity. Accumulation of p-17 matrix HIV protein in the brain leads to behavioral and cognitive impairments. Loss of integral occludin proteins, due to the influence of viral substances on the CNS, also leads to a violation of the BBB, the launch of cascades of reactions of toxic and autoimmune genesis [17-19].

Transcriptional transactivator (Tat) is secreted by already infected microglia cells and astrocytes [20], creating a toxic environment for neurons and other CNS cells that are able to absorb this pathological protein [21]. The neurotoxicity of this substance is justified by an increase in intracellular calcium with a subsequent increase in reactive oxygen species, which causes the activation of caspases leading to cell apoptosis [22]. Tat can alter the distribution of proteins' expression Claudin-1 and Claudin-5 in endothelial cells of brain microvessels [23], increasing the probability of destruction of the hematoencephalic barrier. The substance is able to change the homeostasis and integrity of neurons, their neuro excitability and oxidative state of cells [24]. Accumulation and prolonged interaction of CNS cells with this protein impairs short-term and long-term memory, reduces motor activity and coordination [5, 25]. Cerebellar astrocytes have been shown to secrete significantly fewer cytokines than astrocytes from other parts of the nervous system under the influence of Tat. We can assume that more limited glial inflammatory responses in the cerebellum are able to protect this area from damage caused by various HIV proteins [26].

Along with the transcriptional transactivator, an important place in the pathogenesis of neuroAIDS is occupied by the regulatory protein Vpr. It can damage mitochondria, leading to the release of cytochrome C and cell apoptosis [27].

The neurological picture associated with the HIV infection process in the CNS has the following pathological features, characterized by: astrocytosis, decreased synaptic and dendritic density, pallor of myelin, macrophage infiltration, increased number of resident microglia cells, multinucleated giant cells and loss of neurons [28, 29] – what are the signs closely related to HIV-associated neurocognitive disorders and HIV-associated dementia.

The death of neuronal and other cells of the human nervous system remains a problem that is common in HIV-infected patients. Neurological disorders correlate with the presence of activated neurospecific proteins in the cerebrospinal fluid and blood. Therefore, in addition to the above information, the question of their study as early

markers of pathological lesions of the human nervous system by HIV becomes relevant [5, 29].

Neurospecific proteins (NSPs) are neurobiologically active molecules that can perform many functions of the nervous system. Due to their indicator ability to report active pathological changes that cannot be detected by instrumental diagnostic methods or conventional stereotyped laboratory tests, the determination of NSPs' concentrations can be the basis for early diagnosis of HIV infection.

Basic myelin protein (BMP) is a basic component of the inner layer of myelin fiber, which makes up 30 % of myelin in the human nervous system. It is believed that it can provide structural support to the body's nerve cells. With any damage to the nervous system, the protein appears in the cerebrospinal fluid [30].

Neuronspecific enolase (NSE) – is a glycolytic neuronspecific isoenzyme of enolase. It is present in all cells of the body. This isoform is characteristic of neurons of the central and peripheral nervous system and cells of neuroendocrine origin. Their concentration can increase as a result of physical damage to nerve tissue, hypoxic phenomena and is directly proportional to the size of the area of tissue damage [29].

S-100 proteins are a group of calcium-binding proteins of astrocytic glia. Their concentration is able to increase with age, more in men than in women. The participation of this protein in the regulation of the processes of cognitive adaptation, learning, memory and possibly in the formation of neuroplasticity of the brain is known. S-100 proteins have two relevant specific monomers that form homo- and heterodimers. Proteins α and β are present in high concentrations in cells of the nervous system. Moreover, ββ is contained in glial and Schwann cells, and the αβ heterodimer is found only in glial cells. Proteins are expressed no more than 72 hours after tissue damage. Determination of S-100 protein is used to diagnose various post-ischemic neurological complications as a marker of various cancers, justifying it by the participation of protein in cell cycle regulation and apoptosis [29].

Neurotrophic factor of the brain (BDNF) – a specific protein of the human body. It belongs to neurotrophins, substances that support the growth and development of neuronal cells. It is expressed in astrocytes, neuronal cells, megakaryocytes and Schwann cells, probably in the area of damage. It affects the neurons of the central and peripheral nervous systems, helping to maintain the vital functions of young neurons in the early stages of maturation, increasing the number and differentiation of new cells and synapses [30].

BDNF stimulates active neuroprotection, protection of neurons from ischemia and death. High protein activity is found in the hippocampus, cerebral cortex and in front of the frontal lobe of the brain which are responsible for cognitive abilities. New research proves the role of protein in the formation of long-term memory and, probably, its participation in the activation of neurogenesis. Increased levels of neurotrophic factor occur in hypoxic, autoimmune, toxic or traumatic injuries of the nervous system [30].

Ciliary neurotrophic factor (CNTF) – plays an important role as a trophic factor for photoreceptors and retinal ganglion cells and promotes the survival of damaged nerve cells. CNTF is found in Schwann cells, type 1 astrocytes, glial cells and is studied as a dominant factor in the differentiation of neurons in the early stages of development. CNTF provides trophism and has a neuroprotective effect on damaged neurons. Along with the neurotrophic factor of the brain, it probably increases its activity when nerve cells of any etiology are damaged [31].

Glial fibrillar acidic protein (GFAP) is a specific protein produced by various cells of the central nervous system, including astrocytes and epindemic cells of the ventricles of the brain. The protein is actively connected with other substances of the intermediate filament type III, which are part of the structural and functional complex of the cell, supporting the structural basis of astrocyte cells, and the entire blood-brain barrier. Protein plays an important role in the regeneration of damaged neurons. In infectious diseases of the CNS or pathologies that cause neurodegeneration of tissues, an active decrease in some protein isoforms has been found. For example, the HIV glycoprotein gp120 inhibits protein production to low levels. Decreased GFAP levels have been shown in chickenpox, ischemic brain tissue, CNS injuries, Down's disease, schizophrenia, and other neurological disorders [30].

There are many neuroinfectious pathological conditions that require knowledge of the complex relationships of neuroimmunology and neurophysiology, without which the success of solving the above problems remains very low.

Remember that HIV probably begins its replicative activity in cells of the nervous system earlier than in cells of the immune system, so neurospecific marker proteins, in our opinion, can be the basis for a qualitative early diagnosis of HIV infection.

The main protein of myelin is a part of myelin fibers and is able to appear in the blood in many CNS pathologies. The S-100 has a direct link to glial and Schwann cells that can be damaged by HIV.

Brain neurotrophic factor and ciliary neurotrophic factor can serve as qualitative markers for predicting the degree of human cognitive disorders.

Glial fibrillar acidic protein plays an important role in the regeneration of nerve cells and can appear during the minimal damage to the cerebrospinal fluid and blood, with prospects for early diagnosis of neuroAIDS.

Expressive autoimmune processes in the CNS during HIV infection create prospects for the study of autoantibodies to the protein S-100, which is present in astrocytic cells that serve as a specific support carcass for neurons, having a high ability to damage during pathological disease processes.

Also, to achieve the most effective result in the future, there is a study of the relationship between neuron-specific enolase and S-100 protein. This will improve early diagnosis and make more accurate prediction of the disease by determining the focus of lesions of the nervous system and the degree of neurological disorders in humans.

Conclusions

There is an active spread and late detection of HIV in Ukraine, as a country trying to reach the level of highly developed countries. HIV infection in the early stages of the disease often has a latent course with the presence of periods of seronegative window, which makes laboratory diagnostic methods ineffective and threatens to worsen the epidemiological situation not only in Ukraine and around the world.

HIV quickly enters the CNS, begins its replication there and forms storage tanks, which threatens not only the formation of resistance to ART, but also difficulties in diagnosis. Thus, as long as HIV in the blood remains in a long latent period, it is likely that the virus at this time begins to actively function in brain cells.

Remain little studied: the links and features of the matrix HIV protein p-17 accumulation in the CNS, so we can assume that this protein appears long before the primary behavioral and cognitive disorders of neuroAIDS; links between cytochrome C, regulatory protein Vpr and the activity of cognitive and psychosomatic disorders. The activity of the transcriptional transactivator and its association with Claudin-1 and Claudin-5 in the endothelial cells of cerebral vessels may be a predictor of further prognosis of disease severity.

The question of the connection of neurospecific proteins as markers of a viral process in the human nervous system remains relevant. These biologically active molecules have a specific ability for each type of brain cells to separate the course of pathological processes in the tissues of the CNS.

Revision of the basics of early diagnosis of HIV infection will provide new opportunities to strengthen epidemiological control and prevent new cases of the disease, which will ultimately lead to a reduction in goverment funding for this problem not only in Ukraine but also in many countries.

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НЕЙРОІМУННІ ЗМІНИ В РАННІЙ ДІАГНОСТИЦІ ВІЛ-ІНФЕКЦІЇ

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РЕЗЮМЕ. ***Мета –*** *вивчення впливу нейроспецифічних білків на розвиток нейро-СНІДу, встановлення перспектив їх визначення з метою раннього діагностики ВІЛ-інфекції.*

У дослідженні використовували теоретичні методи, які включали аналіз та синтез вивчення сучасних світових наукових публікацій та клінічних спостережень, дедуктивно-індуктивні методи.

Висновки. *В Україні, як і у всьому світі, відбувається активне поширення та пізнє виявлення ВІЛ-інфекції. Стандартні методи лабораторної діагностики не можуть забезпечити якісну ранню діагностику хвороби.*

Швидке проникнення вірусу у центральну нервову систему (ЦНС) створює труднощі для диференційної діагностики з подальшим формуванням стійкості до антиретровірусних препаратів. Поки ВІЛ

у крові залишається протягом тривалого прихованого періоду, збудник активно реплікується у клітинах мозку і призводить до розвитку нейро-СНІДу.

Зв'язки та особливості накопичення матриксу ВІЛ-білка р-17 у ЦНС, активність транскрипційного трансактиватора, регуляторного білка Vpr залишаються недостатньо вивченими. Нейроспецифічні білки як маркери вірусного патологічного процесу у нервовій системі людини потребують особливої уваги та вивчення.

Перегляд основ ранньої діагностики ВІЛ-інфекції дасть можливості посилити епідеміологічний контроль та запобігати новим випадкам хвороби, що у підсумку приведе до зменшення фінансового навантаження щодо цієї проблеми не лише в Україні, а й у багатьох країнах світу.

Ключові слова: *діагностика, нейро-СНІД, нейроспецифічні білки.*

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