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CORRECTION OF COGNITIVE DISORDERS IN PATIENTS WITH HIV ENCEPHALOPATHY

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Annotation
Today, HIV infection is one of the most pressing medical and social problems worldwide. This article discusses one of the types of complication of HIV-infection as HIV-associated encephalopathy. The clinical features and diagnostic criteria of the disease are considered. Patients were examined using the Montreal Cognitive Assessment Scale and symptomatic treatment with the nootropic drug choline alfoscerate was carried out.

Keywords: HIV infection, human immunodeficiency virus, acquired immunodeficiency syndrome, cognitive status , encephalopathy, MoCA test, choline alfoscerate .

The AIDS virus was first described in 1983 at the same time in France at the Institute. L. Pasteur and in the USA in the laboratory of R. Gallo almost simultaneously. This virus belongs to the retrovirus family , a subfamily of lentiviruses . Today, the main routes of penetration of the AIDS virus into the brain and cerebrospinal fluid are perineural , hematogenous, and through the gaps between capillary endothelial cells [1,2]. The neurological features of neuroAIDS are divided into primary and secondary. The primary ones are associated with the direct damaging factor of the virus, the autoimmune processes of the body and the neurotoxic effect of antiretroviral therapy. Symptoms of the primary lesion of the nervous system in HIV infection are divided into lesions of the central nervous system and lesions of the peripheral nervous system [3,5,6]. Damage to the central nervous system is called HIV-associated cognitive-motor syndrome, which includes three forms or diseases:
1) HIV-associated dementia (HIV encephalopathy);
2) HIV-associated myelopathy ;
3) HIV-associated minimal cognitive-motor disorders. [four]
HIV encephalopathy is a common form of primary lesion of the central nervous system. It is found in 60% of AIDS patients. In recent years, thanks to highly active antiretroviral therapy, there has been a decrease in the frequency of this form of

neuroAIDS . In 25% of patients, it is observed as a primary manifestation of AIDS, that is, before the onset of other pathognomotic clinical syndromes. [4,5]

When studying and summarizing the literature, as well as including our own observations , the following clinical criteria for the diagnosis of HIV encephalopathy are distinguished. [6,7]. A triad of syndromes is characteristic: 1. intellectual- mnestic disorders; 2. altered behavioral responses, 3. movement disorders that develop gradually. The first signs of gradually developing dementia are usually a slight memory impairment, weakening of attention and concentration, difficulty in counting and reading, emotional and behavioral disorders, reactive depression, apathy, lethargy, asthenic syndrome, larval depression, in rare cases, acute psychosis may develop , which in the future are growing. [6,7] At the same time, organic disorders of the central nervous system increase, such as: pyramidal paresis, oculomotor disorders, parkinsonism, ataxia, and rarely epileptic seizures. [5]

In the cerebrospinal fluid, in more than 30% of cases, a small lymphocytic pleocytosis , (no more than 50 cells per 1 μl), a slight increase in protein concentration (5001000 mg / l), a high titer of antibodies to HIV, and more pronounced symptoms are especially important with a high content of antibody titer in the cerebrospinal fluid [7].

In the study of EEG in the early stages, changes are not characteristic. As the disease progresses , delta and theta slow waves are recorded. Changes in the state of the EEG also correlate with the severity and duration of the disease [8].

The possibility of treating HIV-infected patients with the use of antiretroviral drugs has reduced the death rate from AIDS by several times. In this regard, new challenges are being put forward for healthcare to improve the quality of life of HIV-infected people. An important task that requires special attention is the correction of disorders of the central nervous system in HIV-infected patients. The use of antiviral therapy has increased the life expectancy of patients with HIV infection, however, to date, such drugs that could completely eradicate the virus from the body. In this regard, it is necessary to deal with the pathological effect of the virus on body tissues, including nervous tissue, throughout the life of an HIV-infected patient.

This task is not only a medical, but also a social problem, since HIV is characterized by the defeat of young and working age, and lesions of the nervous system are often detected already in the early stages of the disease. Impairment of cognitive processes creates certain difficulties in study, work, daily activities and personal life of patients with HIV. About 1/3 of HIV-infected people are in the age range of 15-25 years. On average, this is about 3,000 new infections per day.

The CNS has two unique barriers that protect it from the effects of chemical and biological pathological factors. The cells of the blood-brain barrier are "sewn" together by tight bonds through which many cells cannot pass. From the side of the brain, the barrier is covered with a thin basement membrane. Pericytes are located on the membrane from the side of the nervous tissue. They are located along the capillaries and have a long process structure. The processes braid capillaries and form tight bonds with endotheliocytes .

There is evidence that pericytes can move, taking over the functions of macrophages. These cells are thought to be able to replicate and differentiate into osteoblasts, adipocytes , chondrocytes , smooth muscle cells, and others. The version that these cells may have the ability to differentiate into cells of the nervous tissue is not ruled out, which is currently being actively studied. In recent studies, data have been obtained indicating that a decrease in the number of pericytes in the CNS leads to impaired BBB permeability, and pathologies of neurocognitive processes associated with these disorders. The processes of astrocytes also have indirect protection functions , which tightly braid the vascular wall in the nervous tissue, creating a case for the capillaries of the brain.

The hematoliquor barrier is built from the cuboidal epithelium of the choroid sinus. It is also characterized by a close interweaving of cells with the formation of tight junctions, which prevents the transport of many pathogenic substances to the brain and spinal cord. However, this barrier is much weaker than the BBB, since the main function of this barrier is to maintain the required amount of cerebrospinal fluid.

The most popular theory is the penetration of the virus through the BBB with infected cells. Lymphocytes and monocytes become infected with the virus immediately before entering the CNS. After infection, they penetrate the BBB, where monocytes transform into perivascular macrophages, which have the ability to transmit the virus to other cells of the nervous tissue.

According to many scientific data, the endothelium of the vascular wall does not have CD4 receptors and co-receptors CCR5 and CXCR4. Most of the scientific evidence available to date indicates that there are no CD4 receptors in the cells of the walls of cerebral vessels, or they are present in a very small amount. At the same time, on the surface of nerve cells there are C-type lectins (MBL , a lectin that binds mannose), which has similar functions to DC-SIGN dendritic cells. Their only difference is that their affinity for gp120 of the virus is weaker. An important feature of the virus is its ability to enhance the expression of DC-SIGN, which contributes to the fact that the virus actively moves and multiplies in the nervous tissue.

An interesting fact is that in the urogenital tract, due to the absence of CD4 receptors in its epithelium, the virus uses the same mechanism for penetration and reproduction. The gp120 virus protein reacts with the C-type lectin of the epithelial wall. The result of this process is the destruction of tight intercellular junctions, due to which the virus gains access to CD4 receptors located in the mucous membrane. The dense epithelial barrier is only permeable to particles up to 30 nm in size , and the virus is known to be 80-100 nm in diameter. However, HIV passes through this barrier in 120 minutes.

The penetration of the virus into the CNS can also occur through the intercellular gaps of the endothelial wall. This mechanism is quite possible at later stages of HIV infection, when under the action of toxins and other pathogenic agents the endothelial wall is destroyed, intercellular contacts weaken and become easily accessible for the penetration of infectious particles. The virus can easily diffuse through such weakened contacts. The subsequent destruction of the nervous tissue occurs as a result of the direct effect of the virus on the brain cells. The addition of secondary diseases further worsens the state of the BBB, causing local inflammatory processes.

In the absence of adequate antiretroviral therapy, encephalopathy develops in 2/3 of HIV-infected patients. Signs of encephalopathy are detected in 25% of cases even at the stage of the absence of clinical manifestations of AIDS, and in 3-5% of cases they are the first manifestations of disease progression [8].

HIV encephalopathy is a special clinical syndrome of subcortical-frontal dementia that develops under the direct influence of the virus on the tissues of the nervous system and is characterized by motor, cognitive, and behavioral disorders [9]. The question of at what stage of HIV infection neurological disorders begin to develop is still open.

Damage to the nervous tissue occurs as a result of direct (with the participation of viral proteins) and indirect (inflammation) mechanisms [10]. Each model of damage implies infection of macrophages and microglia with viral particles at the initial stage . The direct mechanism of damage implies the death of neurons under the direct influence of viral proteins [12]. The second model explains neuronal damage through the inflammatory process of brain tissue in response to HIV integration. Both of these mechanisms can be present simultaneously at any stage of HIV infection [13]. The virus is not detected in the neurons themselves, however, various immunopathological mechanisms triggered by the presence of HIV in the nervous tissue cause functional and structural changes in neurons [14].

Virus-infected brain cells produce viral particles and inflammatory mediators. Due to their cytotoxic properties, densely packed endotheliocytes are destroyed , which leads

to a decrease in the total number of neurons and destruction of the myelin sheath of cells [15]. Viral replication also affects the functioning of oligodendrocytes and astrocytes . The neurotoxic effect of the gp120 viral protein has a detrimental effect on neurons, the effect of which is also due to the effect on neurotransmitter processes, which ultimately leads to the inevitable death of neurons [16].

Damage to astrocytes occurs due to the action of low molecular weight peptides produced by infected microglial cells [17]. This leads to an excess of glutamate , which has an excitatory effect on nerve cells. As a result of its excess, a number of biochemical processes are triggered, resulting in the destruction of the neuron membrane and cell death [18].

In addition to those described above, other processes mediated by an acute and subsequent chronic inflammatory process also have a damaging effect on the central nervous system. Cells are actively affected by inflammatory cytokines, chemokines and other substances that disrupt the electrolyte balance, integrity and biochemical processes of neurons. Nervous tissue cells are highly sensitive to any changes in the environment and are rapidly destroyed [19].

Viral particles multiply in the CNS with the formation of certain quasi -species , while their activity is very isolated from the lympho- and blood circulation [20]. In this regard, the selection of adequate ARVT has certain difficulties, since many drugs do not penetrate through the BBB. It is also important to note that the activity and metabolism of CD4 cells is relatively less pronounced in the brain; therefore, virions accumulating in the CNS have some autonomy in relation to the viral load of all other body systems. The viral load in the brain tissue in HIV encephalopathy is high, however, it does not correlate with the severity of the disease and is an indicator of virus activity [21].

CT and MRI neuroimaging revealed diffuse atrophy of the brain, expansion of the subarachnoid spaces and ventricles of the brain, subcortical multifocal focal changes in the frontal and parietal lobes and periventricular , hyperintense , without a mass effect and not accumulating a contrast agent, that is, with signs of secondary demyelination , which helps differentiate from multiple sclerosis. Changes in the frontal lobes are detected at early stages and remain pronounced at all stages of the course of the disease [22].

The tactics of treating neuroAIDS follows from the treatment of AIDS itself and the characteristics of the lesions of the National Assembly. At primary In neuroAIDS , the appointment of specific highly active antiretroviral therapy (HAART) can have a significant effect, slowing down the progression of the disease and temporarily stabilizing the patient's condition. And yet, at the first stage, symptomatic therapy is

decisive. In particular, in the treatment of manifestations of HIV encephalopathy , soft nootropics such as noofen , adaptol , phenotropil can be used . A good effect was obtained from the use of cerebrolysin , which has cerebroprotective properties, as well as citicoline , which improves synaptic transmission and plasticity of brain tissue by increasing the interaction of neurons and glial cells , preventing damage to dendrites (which is especially important in the treatment of subcortical type dementia) [23]

Among the drugs with a neurotrophic effect in vascular and metabolic dementia, the drug "Choline alfoscerate" is more often used today. This drug excites mainly the central cholinergic receptors , that is, it has a cholinomimetic effect. In the body, choline alfoscerate is broken down into choline and glycerophosphate, which is a precursor of the neurotransmitter acetylcholine and a component of phosphatidylcholine neuronal membranes. [10] Stimulating cholinergic activity improves neuronal membrane plasticity and receptor function, which in turn improves cerebral circulation and stimulates neuronal metabolism. The possibilities of choline alfoscerate in the treatment of HIV encephalopathy require further study and remain relevant today. [24,25]

Purpose of the study. The study of the cognitive status of HIV-infected patients, the study of the effect of nootropics on the cognitive status of patients with HIV-encephalopathy.

Materials and Methods: For the study, 23 patients were randomly selected who were treated at the Fergana branch of the Republican AIDS Center. Among them, 13 men (56.5%) and 10 women (43.5%), the average age of patients is 31.7 ± 1.1 years. For the study of cognitive function, a battery of tests was chosen - the Montreal Cognitive Function Assessment Scale or abbreviated MOCA - a test as the most sensitive and convenient for the study of patients with cognitive impairment. The collection of one-line tests consists of 30 items and is completed in an average of 12 minutes. [8] This scale assesses the seven most significant cognitive functions, which include: short-term memory (5 points), spatial-visual ability (4 points), aspects of executive function (3 points), attention and concentration (5 points), language functions (5 points), abstract thinking (2 points), orientation in time and space (6 points). The maximum score for this test is 30, of which 26 to 30 is normal, 22 to 25 means mild cognitive impairment, 17 to 21 moderate cognitive impairment, and 16 or below severe cognitive impairment. [8,9] To correct cognitive impairment in patients with HIV-encephalopathy, we decided to use choline alfoscerate at a dosage of 1000 mg intravenously for 10 days and then continue treatment with choline alfoscerate in tablet form 400 mg for 6 months.

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Research results. As a result of the study, it was found that the average score of the MoCA test among patients is 21.6 ± 0.85 points. Data on the severity of cognitive status disorders are displayed in Table No. 1 from which it follows that the main contingent of patients falls at the level of mild cognitive disorders

Table #1

Degree of cognitive deficit	Frequency of occurrence
No cognitive impairment	3 (13%)
With light KN	15.(65%)
With moderate KN	4(17.4%)
With heavy KN	1 (4.3%)

Patients were divided into groups depending on the duration of morbidity. The average indicators of the degree of cognitive impairment depending on the duration of the disease are shown in Table No. 2

Table number 2

Duration of HIV	MoCA test result
1 to 3 years	22.4±1.25
4-6 years old	22.1±0.84
7-10 years old	20.6±1.21
10 years or more	22.5±1.32

The patient, regardless of the antiretroviral drug taken, was prescribed choline alfoscerate at a dosage of 1000 mg intravenously for 10 days, after which treatment with a tablet form of choline alfoscerate at a dosage of 400 mg was continued for 6 months. Several repeated studies of cognitive status were conducted, the results of which are displayed in Table No. 3

Table No. 3

	Before treatment	After 10 days	After 1 month	In 3 months	In 6 months
MoCA test result	21.6±0.8	22.8±0.84	22.9±0.82	23.1±0.8	23.8±0.71

the drug for ten days, there was a slight improvement, after which the rate of improvement slowed down during the first three months of treatment. Based on the results, it can be determined that only after a long-term treatment of at least 6 months

can a statistically significant improvement in the patient's cognitive status be obtained (p <0.05).

Table No. 4

cognitive functions	Frequency of cognitive impairment before treatment	Frequency of cognitive impairment after treatment
1) orientation in time	14.6±4.2	13.2±6.1
2) orientation in place	7.4±3.1	7.1±3.9
3) self-orientation	0	0
4) involuntary memory	87.4±4.5	74.5±5.8
5) understanding of speech and complex logical and grammatical structures	28.0±6.5	26.5±7.8
6) expressive speech	16.8±4.2	15.0±5.8
7) dynamic praxis	46.2± 6.8	35.4± 7.6
8) constructive praxis	53.6±6.3	38.3±8.6
9) reading	28.2±6.5	24.5±7.0
10) letter	35.3±6.8	30.7±7.4
11) focus	80.3±5.3	64.6±9.3

When deploying the cognitive status during treatment, it can be seen that the main improvements affected involuntary memory, concentration, dynamic and constructive praxis to a greater extent than speech, reading and writing. There was practically no improvement in such cognitive functions as orientation in time, place and self.

Conclusions

1. The study of the cognitive status of patients with HIV encephalopathy shows the predominance of a mild degree of cognitive impairment, in contrast to earlier studies, which may be associated with the use of highly active antiretroviral therapy.
2. The duration of the course of HIV directly affects the state of cognitive status, the worst result of which shows the duration of the disease from 7 to 10 years.
3. The results of a dynamic neuropsychological examination using the drug choline alfoscerate revealed significantly positive dynamics in the form of an increase in the level of cognitive status by an average of 2.2 points on the Montreal Cognitive Function Assessment Scale .

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