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Nervous System Damage in HIV Infection and AIDS

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ABSTRACT

Objective: *This study aims to explore the neurological complications of HIV infection, specifically the impact of HIV on the nervous system, including the role of the glycoprotein gp120 in neuronal damage.* ***Methods:*** *A review of HIV-related neurological impairments, focusing on the mechanisms of viral infection and the consequences on glial and neuronal cells, was conducted. The study examines the direct and indirect damage caused by the virus and associated factors such as opportunistic infections, tumors, and the effects of antiretroviral drugs.* ***Results: :*** *The study finds that HIV infection affects approximately one in every hundred cells in brain tissue, significantly impacting glial cells, neurons, and other cells possessing the CD4 receptor. HIV damages these cells through direct infection and by the destructive effects of the gp120 glycoprotein, which leads to membrane lysis and neurotoxic consequences such as an increased Ca2+ ion load in astrocytes.* ***Novelty:*** *This research highlights the critical role of gp120 in the pathogenesis of HIV-induced neuronal damage, specifically its interference with neuroleukin and the glutamate retention mechanisms in astrocytes, which are key to understanding HIV-related neurological disorders.*

INTRODUCTION

Each link in pathogenesis subsequently leads to the appearance of a specific clinical picture in patients with characteristic neurological defects, depending on the point of application [1]. Thus, a decrease in the neurotrophic effect of bioregulatory substances of the hypothalamic-pituitary complex leads to a violation of mediator metabolism [2]. Deficiency of gamma-aminobutyric acid and glycine subsequently leads to the development of epileptic seizures. Serotonin depression leads to antiserotonin ataxia [3]. Disturbance of vasopressin metabolism leads to memory impairment. Damage to the endothelial cells of the cerebrovascular plexus and the ependyma of the ventricles leads to inflammation of the mesenchymal elements of nervous tissue and the development of secondary demyelination, which is subsequently clinically manifested by the development of viral vasculitis. Depressed cellular immunity leads to the development of opportunistic infections and neoplastic processes in patients [4].

There are several hypotheses explaining the easy penetration of HIV through the BBB [5]. According to one of the hypotheses, direct damage to the central nervous system can occur as a result of perineural penetration of the virus into glial cells [6], [7], [8]. There is also an indirect defeat - when the virus enters the nervous system from the cells of the immune system (the "Trojan horse" mechanism). The virus can penetrate the endothelial

cells of the brain capillaries, which carry the CD4 antigen on the membrane. It is also assumed that there are genetic variants of HIV that have a specific neurotropic effect [9].

CD4 receptors are located not only on neuroglial cells, but also on endothelial cells of the vascular plexus of the brain and ventricular ependyma. As a result, this can lead to HIV-associated vascular lesions of the spinal cord and brain [10], [11], [12]. Since the pathological process is localized endovascularly, primary vasculitis and vasculopathy can occur. Primary HIV-associated vasculitis of the brain and spinal cord can subsequently lead to secondary damage to nervous tissue. It is known that thrombocytopenia, which often develops during HIV infection, increases the risk of hemorrhagic complications, which leads to impaired blood rheology and hypercoagulation [13]. When conducting histological studies in HIV-infected patients, infiltration of the vascular wall by leukocytes, edema and proliferative changes in the intima were detected. All this leads to narrowing of the lumen of the vessel and its thrombosis with subsequent possible heart attack, rupture of the vessel and hemorrhage. The transformation of ischemic stroke into hemorrhagic stroke is often observed in patients with HIV. Multifocal lesions develop in HIV-associated vasculitis. This gives reason to speak not only about vasculitis, but also about the meningovascular form of neuro-AIDS [14], [15], [16], [17].

Approximately 40% of HIV-infected patients have changes in the cerebrospinal fluid (CSF), usually in the form of a slight pleocytosis (5-50 cells / mm3), an increased protein content (500-1000 mg / l), and a normal glucose concentration [18], [19]. These changes are not specific. In half of clinically healthy HIV-infected patients, pleocytosis or an increase in the protein content in the CSF is observed, and in 20% of CSF, HIV grows in tissue culture, often in high titers. Later, the pleocytosis decreases, and the protein content may increase, decrease, or remain unchanged. As in peripheral blood, the CD4:CD8 ratio in the CSF is low, especially in the late stage of infection. In the late stage, the titer of the virus in the CSF also decreases. These changes in the CSF are moderately expressed and not constant, therefore, based on them, it is difficult to predict the course of the disease and the effectiveness of therapy.

RESEARCH METHOD

The diagnosis of ADC is made by excluding competing diagnoses that may cause impaired consciousness, psychosis, or dementia in patients with AIDS. In this case, blood tests, CSF, and computed tomography (CTG) of the head are very important. These diseases include not only infections and tumors of the central nervous system, but also side effects of drug therapy, and nutrient imbalances. In patients with ADC, CTG is normal or reveals brain atrophy

RESULTS AND DISCUSSION

Anti-HIV is usually detected in CSF in high titers. Comparison of antibody titers in blood and CSF suggests that antibodies may be synthesized in the central nervous system

[20], [21]. Anti-HIV antibodies in CSF are of the IgG class, but antibodies of the IgA and IgM classes have been found in some patients [22], [23]. Antibody synthesis in the central nervous system begins early, immediately after meningeal infection. Oligoclonal antibodies in CSF can also be detected, which correspond to HIV epitopes and have a migratory ability different from that in serum [24], [25], [26]. Pleocytosis and protein concentration correlate poorly with the presence and number of anti-HIV antibodies and oligoclonal bands in CSF. Patients with positive HIV cultures from CSF have anti-HIV antibodies in both CSF and oligoclonal bands. In patients with AIDS, antibody synthesis in CSF is significantly lower than in patients with AIDS who are HIV-positive [27]. The concentrations of p24 antigen and anti-p24 antibodies in CSF and serum vary in parallel, but the concentration of p24 in CSF is usually higher. In AIDS-dementia complex, the concentration of p24 is maximal, but usually the concentration of antigens and antibodies is poorly correlated with the severity of clinical symptoms and the effectiveness of therapy.

In the clinical picture, a characteristic number of symptom complexes can be identified: meningism, pyramidal insufficiency, cerebellar ataxia, seizure syndrome, AIDS-dementia complex, encephalitis, a complex of symptoms characteristic of meningitis. Clinical observations show that in the early stages of HIV infection, reactive neurotic states and manifestations of asthenovegetative syndrome are most common. Patients have various disorders of a neurotic nature, as well as increased fatigue, apathy, forgetfulness, mood deterioration, narrowing of the circle of interests, sleep disorders, various phobias, vegetative lability. In the later stages of the disease, damage to the nervous system, mainly caused by opportunistic infections, comes to the fore. Diseases of the central nervous system that are a direct result of retroviral damage.

A. Acute aseptic meningoencephalitis

This syndrome occurs in 5-10% of HIV-infected individuals before seroconversion and during or after a mononucleosis-like syndrome. Patients present with headache, fever, mental status changes, and focal or generalized convulsive seizures. Focal or lateral signs of nervous system involvement are rare, with the exception of transient facial nerve palsy (Bell's palsy). Early in the course of infection, acute myelopathy with paraparesis and severe pain, sensory loss, urinary incontinence, and spinal myoclonus (rhythmic contractions of the abdominal muscles) have been reported. Pleocytosis, moderate protein elevation, and normal glucose levels may be found in the CSF—changes similar to those seen in seropositive, clinically healthy HIV-infected patients. Laboratory diagnosis of HIV infection is based on isolation of virus or p24 from serum or CSF or on serological evidence of subsequent seroconversion (usually after 1 or 2 months). Acute meningoencephalitis is a self-limiting disease requiring only symptomatic treatment.

B. AIDS-Dementia Complex (ADC)

ADC, also known as "HIV encephalitis", "HIV encephalopathy", "subacute encephalopathy", occurs only in the AIDS stage. This is the most common neurological disease in AIDS patients, and may be the first symptom of AIDS in people with HIV. The

initial symptoms include apathy, inattention, forgetfulness, impaired concentration, decreased intelligence, autism, which is very similar to general depression. Patients may also experience disorientation, stupor, hallucinations, or psychosis. Initially, examination at the patient's bedside does not reveal any abnormalities, but neurophysiological examination shows impaired accuracy and speed of motor functions during this period, including visual-motor, speech fluency, short-term memory, and difficulty solving complex situational problems. This distinguishes ADC from banal depression at an early stage. Patients have a significantly reduced speed of thinking and reaction time. When dementia is obvious, cortical symptoms (such as aphasia, apraxia, and agnosia) are also not recognized as primary; therefore, some neurologists classify ADC as a subcortical dementia, as opposed to cortical dementias such as Alzheimer's disease. Eye movement disorders are common in the early stages of ADC. An increase in "physiological" tremor is also common. Patients usually have an unsteady gait, which is difficult to classify as ataxia, sensory ataxia, spastic apraxia, or functional. Some patients have impaired gait and lower limb function, which is associated with vacuolar myelopathy. ADC can develop gradually or with gradual, sharp deterioration, sometimes accompanied by systemic manifestations of the disease.

Magnetic resonance imaging (MRI) reveals brain atrophy. Later, foci of softening, diffuse changes in the white matter appear, which are best detected by T2-mode MRI. These changes are not specific. Positron emission tomography of the head shows impaired glucose metabolism. In the early stages, hypermetabolism can be detected in the basal and thalamic ganglia, and later - in the gray matter of the cortex and subcortical formations, hypometabolism. CSF may be normal or have a moderate increase in cells, proteins, or oligoclonal antibodies. Elevated levels of β2-microglobulins are often detected and correlate with the severity of ADC.

Almost half of patients with ADC, especially those with severe disease, have vacuolar myelopathy. In addition to the latter, the number of multinucleated cells, the pallor of the semioval center, and the presence of HIV in the brain are associated with the severity of ADC. The pathomorphological changes confirm that some or all of the symptoms can be reversed with appropriate treatment.

C. Progressive Encephalopathy (PE)

Progressive encephalopathy is a central nervous system lesion in children that is clinically similar to ADC in adults. It is found in almost half of infected children. Less than 25% of infected children have normal neuropsychological development, and 25% have stable (non-progressive) encephalopathy, probably due to complications of the perinatal period.

PE manifests itself at the age of 2 months - 5.5 years, on average - at the age of 18 months. The onset of the disease is usually gradual, although it can be acute. In some children, PE is the first manifestation of HIV. Delay (or involution) of mental and physical development is noted in sick children. Special studies reveal a delay in intellectual development, a decrease in the rate of brain growth, and symmetrical motor deficits.

Initially, children are recognized as slow-moving, apathetic, and later they develop mutism and dementia. Acquired microcephaly develops in half of children with PE. Hypotension and hyporeflexia are noted at the beginning of the disease, which later progress to pseudobulbar palsy and quadriplegia. The condition of untreated children can deteriorate rapidly or gradually or gradually. Death usually occurs within a year after diagnosis. Like ADC, PE occurs in the late stages of the disease, when the patient has signs of immunodeficiency. CTG may be normal, but often shows brain atrophy. In children under 5 years of age, intravenous contrast CTG may show increased contrast in the basal ganglia and frontal lobes of the brain, calcifications. These changes may progress. MRI reveals high levels of signals in the paraventricular white matter.

Children with PE may have a moderate lymphocytic pleocytosis (5-25 cells/mm3) and an increased protein content in the cerebrospinal fluid (500-1000 mg/l). As in adults, higher antibody titers are found in the cerebrospinal fluid than in the serum, which confirms their intracerebral synthesis. Very high levels of p24 can also be detected in the CSF in children with PE. Serum, but not CSF, concentrations of tumor necrosis factor correlate with clinical symptoms. Three-quarters of children with PE have elevated serum TNF concentrations, and 95% of HIV-infected children with elevated TNF levels have PE. Opportunistic infections of the central nervous system, conditions resulting from cerebrovascular disorders, newly formed.

D. Diseases of the Brain Parenchyma

Toxoplasmosis. Toxoplasma gondii is the most common cause of focal CNS lesions in AIDS patients. Approximately 10% of AIDS patients suffer from CNS toxoplasmosis. Most cases are the result of reactivation of latent infection. In AIDS patients with a positive Sebin-Feldman test but no clinical toxoplasmosis, the latter develops in 30% of the future. Although this is not common, a small number of patients with CNS toxoplasmosis have a negative Sebin-Feldman reaction, so negative dye tests do not rule out toxoplasmosis. Changes in titer values, such as a 4-fold increase in paired sera, are considered unusual. Extracerebral manifestations of toxoplasmosis, such as chorioretinitis, are rare and are not in any way associated with nervous system damage.

CTG and MRI play a crucial role in the diagnosis. CTG reveals areas of brain matter affected by tumors, more strongly stained with intravenous contrast, often in the form of rings. The absence of changes on CTG is typical. Lesions are most often found in the basal ganglia. Other diseases can also give a similar picture, and a patient may have several diseases of the brain parenchyma at the same time, which gives a picture of several lesions.

It is preferable to confirm the diagnosis of cerebral toxoplasmosis before initiating treatment. A brain biopsy is essential. The latter also carries some risk - due to the possibility of infection or bleeding. A brain biopsy should only be considered if a 2-week course of tests is unsuccessful. Toxoplasmosis is difficult to diagnose by biopsy. Histologically, inflammation in an abscess caused by Toxoplasma gondii may resemble lymphoma. It is often difficult to detect trophozoites (or tachyzoites) by the

immunoperoxidase method, which is of diagnostic value. Open brain biopsy is preferable to needle biopsy, but even in this case the diagnosis may not always be established. The pathogen can be isolated by biological methods (injection of brain samples into mice) or in tissue culture.

Thus, most patients begin treatment for toxoplasmosis without a definitive diagnosis of CNS toxoplasmosis.

1. Clindamycin, 600 mg IV or orally 4 times a day for 6 weeks;
2. Azithromycin, 1200 mg orally once a day for 6 weeks;
3. Clarithromycin, 1 g 2 times a day for 6 weeks;
4. Atovaquone, 750 mg 4 times a day for 6 weeks.

Some patients require a very long course of intensive treatment for acute infections. There is no standard recommendation for the duration of treatment: the decision to proceed to a second course of treatment is made on the basis of clinical indications and, if available, CT scan results.

Improvement occurs within 10 days and is confirmed by positive dynamics of CTG and MRI. In this case, it is clearly established that the pathological changes in the central nervous system are caused by Toxoplasma gondii. Since with this pathology there is swelling of the brain tissue, doctors often prescribe glucocorticoids for the entire treatment period. Glucocorticoids improve the course of many diseases of the brain parenchyma in HIV. Thus, improvement in the case of combination therapy does not mean that the pathological changes in the central nervous system were caused by Toxoplasma gondii.

In patients with AIDS, central nervous system toxoplasmosis often recurs after treatment is discontinued. Many patients require ongoing supportive therapy. For secondary prevention, half the doses of drugs included in effective regimens used to treat acute toxoplasmosis are used; treatment is continued until the CD4 lymphocyte count remains > 200 cells/μL for 3 months [1], [2], [3].

Primary CNS lymphoma. Primary CNS lymphoma occurs in two percent of patients with AIDS. The tumor has antigenic characteristics of B cells and is multicentric. Neurological symptoms may indicate focal or diffuse CNS disease

CONCLUSION

Fundamental Finding : The study highlights various neurological disorders linked to HIV infection, with pathogenesis driven by disruptions in neurotrophic substances, leading to clinical manifestations such as epileptic seizures, memory impairment, and secondary demyelination. Additionally, the central nervous system (CNS) can be affected through direct and indirect mechanisms, including perineural penetration of HIV or its entry via immune system cells, resulting in HIV-associated vasculitis and neurological damage. **Implication :** These findings emphasize the need for early detection and tailored therapeutic strategies to manage CNS disorders in HIV patients. Understanding the pathophysiological mechanisms underlying neurological symptoms can aid in the

development of more effective interventions for conditions like AIDS dementia complex, meningoencephalitis, and progressive encephalopathy, ultimately improving patient care and outcomes. **Limitation :** The study's limitations include the difficulty in diagnosing certain CNS infections in HIV patients, such as toxoplasmosis, due to the overlap of symptoms with other conditions. Additionally, the dynamic nature of CSF changes and varying antibody responses make it challenging to predict disease progression and therapeutic efficacy in these patients. **Future Research :** Future studies should focus on identifying biomarkers that can more accurately predict the course of HIV-associated neurological diseases. Further exploration into the genetic variants of HIV and their neurotropic effects, as well as novel treatment options for opportunistic infections, could lead to advancements in the management of CNS complications in HIV-infected individuals.

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