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title

Neurocognitive disorders in HIV infected patients

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summary

HIV virus, early during the course of infection invades the central nervous system, and in spite of the effective antiretroviral therapy, neurocognitive disorders still cause a significant clinical problem. Because of that, better understanding of the mechanisms responsible for neurons injury, and an introduction of diagnostic methods, which allows rapid detection of patients, who are at special risk to develop such complications, as well as work up scores, which help to choose drugs with high therapeutic potential in the brain tissue seems to be very important.

key words

HIV, neurocognitive disorders, central nervous system, antiretroviral therapy

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The introduction of highly active antiretroviral therapy (HAART) significantly prolongs the life of HIV infected patients. The prevalence of different complications, including those coming from the central nervous system (CNS) have also decreased. It was established that the number of cases of HIV associated dementia (HAD) have decreased up to 50%. However, it should be remembered, that CNS belongs to such called sanctuary sites of HIV virus, and in spite of effective HAART, patients are still at risk to develop neurocognitive disorders, as an inhibition of the virus replication in the blood is not equivalent with the lost of replication in a brain tissue. It can be caused by a worse penetration of the antiretroviral (ARV) drugs through the blood-brain barrier (BBB), and their decreased activity in the sanctuary sites of the CNS such as perivascular macrophages, astrocytes, and microglia cells (1–3).

On the basis of conducted studies it was established that HIV virus in its early stage, which is during the first two weeks of infection invades the CNS. The most likely mechanism is due to a penetration of the virus through the BBB inside the infected macrophages. Then the infection spreads between the connected cells of the CNS, and this process is sometimes described as the Trojan horse mechanism (1). HIV virus has also been detected in endothelial cell of choroid plexus, which allows to suggest that HIV itself is also able to invade the CNS (3). It should be stressed that the fact of the invasion of HIV to the CNS and its presence in macrophages, microglia cells and astrocytes doesn't explain neurons injury which is observed during the course of the disease. This process can be explained by the toxic influence of released products on neurons by an infected cell. The nonstructural tat protein, proinflammatory cytokines (IFN-y, TNF-α, IL-1, IL-6, TGF-β), chemokines (MIP-1α, MIP-1β, RANTES) as well as glutaminases and nitric oxide (NO), neopterin, β_2 microglobulin play an important role here (1, 3, 5). It must be taken into consideration that the level of HIV replication in cerebrospinal fluid (CSF) doesn't express the dynamics of the process which takes place in the brain tissue. Neurocognitive disorders have been observed with HIV-RNA level in the CSF less than 400 copies/ml (6).

A lot of different factors such as nutrition status, the presence of metabolic disorders, vascular diseases, HCV coinfection, depression or other psychiatric disorders can have an impact on the development of neurocognitive disorders. The influence of different drugs on the CNS and psychoactive substances, especially alcohol and amphetamine which can be used by the patient cannot be forgotten. The important role in the development of neurocognitive disorders has been associated with aging of HIV-infected patients. Life prolongation among other conditions has been connected with the accumulation of β amyloid in the CNS. HIV tat protein is inhibiting neprylisin, enodpeptydase which is responsible for β amyloid degradation (1). There are also genetic predispositions for the development of neurocognitive disorders connected with the biologic reserves, which means the number of neurons, synapses, dendrites which determinate neuroplacticity (1, 7). A special role in the occurrence of neurocognitive disorders during the course of HIV play the individual features such as intelligence quotient, education, age, socioeconomic status, permanent stimulation (learning training), previous trauma and brain disorders.

As it was mentioned above HCV coinfection plays an important role in the development of neurocognitive disorders. 40% of HIV-infected patients are also infected with HCV, and among the intravenous drug abusers this percentage is as high as 80%. HCV is influencing the CNS function both indirectly as the result of liver dysfunction and development of encephalopathy, and directly as well, which has been confirmed by the detection of the virus in the CNS. Performed studies indicate the presence of HCV-RNA and its replication in the CSF of patients with neurocognitive disorders. HCV-RNA has been detected in astrocytes, macrophages, microglia cells, cortex and the white matter, and it can be connected with enhanced production of free radicals or activation of proinflammatory cascade (MCP-1, TNF-α, TNFRII) (4, 8, 9). Like during the course of HIV, also patients infected with HCV have changes in the imaging studies mainly in basal ganglia and white matter. These data indicate that HIV/HCV coinfection can have a significant impact on the development of changes in the CNS and an occurrence of neurocognitive disorders (10–12). In one of the studies HCV-RNA was detected in 60% of patients with coinfection, according to other investigators this percentage range from 24 to 100 (4, 13, 14). These differences can be connected with the stage of HIV infection, HCV genotype, as well as different diagnostic methods which were used. HIV can be responsible for the development of changes which allow HCV penetration into the CNS. It can be connected with increased permeability of the BBB and an enhanced migration of the infected leukocytes into the CNS. However interactions between viruses can be bilateral and the presence of HCV in the CNS can enhance expression of HIV in the brain tissue (9, 10).

Changes in the CNS observed during the course of HIV are mainly localized in the central part of the white matter, basal ganglia, cortex of the frontal lobes, thalamus and the brain stem. The most common abnormalities observed during the imaging studies are brain atrophy, enlargement of the ventricles and enhancement of the signal from white matter (15). Injury of subcortical structures (basal ganglia, thalamus, hipocamp), as well as cortical (frontal, temporal and parietal lobes) have been observed. Nerve tracts damage has also been commonly noticed (16).

Functional studies such as spectroscopy of magnetic resonance imaging (sMRI) reveal decrease of N-acetylaspartate metabolites (NAA), which are the marker of neurons mature. At the same time the c-holin and mioinositol concentration increased, what shows increased cells turnover and ongoing inflammation in the CNS (17).

From the clinical point of view changes which are observed in the CNS during the course of HIV can be responsible for the development of cognitive, behavioral, and motor disorders. At that moment the diagnostic criteria were revised and HIV-associated neurologic disorders (HAND) are divided into three categories:

1. Asymptomatic neurocognitive impairment (ANI) – neurocognitive disorders can be detected in neuropsychological tests, but with such small intensity, that they don't have a significant impact on everyday life.
2. Mild neurocognitive disorders (MND) – in neuropsychological test mild to moderate disorders are detected, which have the impact on everyday life and career, a cooperation with a doctor and an adherence to antiretroviral therapy. Some of these patients usually experience gradual deteriorations, which finally can lead to the development of dementia.