NEUROCOGNITIVE IMPLICATIONS IN HIV/AIDS INFECTION

Suferinţa neurocognitivă în infecţia HIV/SIDA

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ABSTRACT

Human immunodeficiency virus (HIV), a known lymphotropic and neurotropic germ, is able to impair the entire nervous system, during acute or chronic infection. Neurocognitive inflictions are common and culminate with the settlement of HIV associate dementia (HAD). Pathogeny of the ailment is not fully understood and there are no specific markers for the certitude of diagnosis. Practically antiretrovirals are the only remedy used against HAD. This article reviews the current knowledge on this matter and highlights further research trends.

Key words: HIV, HIV associate dementia, neurocognitive sufference

REZUMAT

Virusul imunodeficienței umane (HIV), un microorganism limfotrop şi neurotrop, poate interesa în cursul infecției întregul nevrax, imediat după infectare şi/sau pe parcursul suferinței cronice. Interesarea neurocognitivă este comună şi culminează cu instalarea demenței HIV-asociate (DHA). Patogenia suferinței nu este pe deplin elucidată şi nu există markeri specifici pentru un diagnostic de certitudine. Antiretroviralele constituie practic singura medicație utilizată pentru combaterea DHA. Articolul trece în revistă stadiul actual al cunoştiințelor în domeniu şi subliniază direcțiile de cercetare viitoare.

Cuvinte cheie: HIV, demență HIV asociată, suferință neurocognitivă

At the end of 2007, more over a quarter century of detecting the first cases of infection with human immunodeficiency virus (HIV), pandemic affects over 33 million people. Infectious and non-infectious inflictions may occur during this chronic infection – more numerous and more severe in the late stage of the disease (AIDS) – and may virtually affect all organs and systems. The whole nervous system may be impaired during ths lentiviral infection, even from the moment of primoinfection. Intensely debated and studied, neurocognitive impairment (NI) caused by HIV still remains a topical issue.

NI incidence is difficult to appreciate. In the United States, before the introduction of antiretroviral therapy (ART), is was recorded an incidence of 21 / 1000 patients / year; that amount was reduced to half by 1996. In advanced stages of HIV infection, dementia was found in 15-20% of patients, while minor cognitive-motor disorders (subclinical) is found in the other 10% of the remaining of cases (49). Other studies report a much higher incidence – 50% of patients in the initial period of the pandemic (2).

In Australia, although it decreased from 135 to 119 cases during 1993-1995, the prevalence of HIV-associated dementia (HAD) increased from 5.2% to 6.8% between 1996-2000, but the duration of life of these patients has also increased over seven times, i.e. from five months in the pre-

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HAART (highly active antiretroviral therapy) period to 38.5 months currently (46). According to Bartlett, HAD is met in 7% of seropositive individuals (7). In asymptomatic individuals, dementia occurs in <1% of cases, while HAD may be the first manifestation of HIV in 4-15% of U.S. clinical situations. Prevalence of the disease is increasing by three times if the CD_4 cell count is below 200/mm^3 and by 7 times if this count is below 100/mm^3 (45). Currently HAD seems to be the most common cause of dementia in patients under 40 years (35).

But these data presented above result from studies performed in the Western world, where subtype B of HIV predominates and where access to HAART is relatively facile. In contrast, few data are available regarding incidence of NI secondary of other subtypes of HIV (41) (e.g. subtype D, predominantly in Africa (10, 40, 43, 51), subtype C, prevalent in India - which seems to be less neurovirulent than subtype B (20, 34, 38) -, or F, dominant in Romania), requiring further study in this area.

As **risk factors** it is noted: low weight, presence of anemia or constitutional symptoms, low CD_4 lymphocytes count, high HIV viral load (45). It is considered that 5% of HIV-positive are at risk of developing HAD whether HIV RNA levels is below 3000 copii/mm^3, while the risk is tripling if the viral load exceeds 30 000 copii/mm^3 (33). People with high levels of HIV proviral DNA in peripheral blood mononuclear cells (PBMC) have an increased risk of developing HAD (50), but the time factor (time to occurrence of clinical changes) is less studied. Alcohol (100 nM in cell culture, but indeterminate amount in vivo) stimulates differentiation astrocytes and oligodendrocytes (52), cells that can accommodate HIV, being probably an additive risk factor. It is not recorded differences in terms of race or gender of HIV-infected individuals (46), but HAD incidence is increasing with age (46, 53).

An **anatomical study** recently conducted by U.S. researchers who analyzed samples from almost 600 brains stored in the last 10 years, revealed that only 22% of them were morphologically normal. Opportunistic infections have been found responsible for neuronal destructions in only 5% of cases. Parenchymal brain alterations was evident in 17.5% of the studied cases, but in the remaining of the situations it was identified other non-infectious conditions or even minimal disorders associated with neuroAIDS events. Clinical data revealed that 88% of subjects were detected, before death, with abnormalities consistent with the concept of HAD, 60% of them including a personal history of major depressive episode (17).

HAD **pathogenesis** is incompletely understood.

There are two key moments: penetrating of the blood-brain barrier (BBB) by HIV and producing functional alterations/destructions in the central nervous system. Primary blood-brain barrier penetration (BBB) by the HIV is realised through cellular and non-cellular mechanisms, even in the early stage of infection, most likely soon after seroconversion (2). Subsequently HIV repeatedly penetrate the nervous system (NS), depending on the level of viral replication in circulating sector, establishing a balance between it and the nervous compartment. A summary of the mechanisms of penetration of the BBB by HIV is presented in Table 1.

TABLE 1. *Mechanisms of HIV penetration through BBB*

Type of the mechanism	Penetration	Effects	Favoring factors
Cellular	Monocytes and macrophages (carring HIV)	Penetration of BBB	Beta-integrins: mediates the penetration of the endothelial layer of BBB **(1, 15)** Metalloproteinase MMP 2 / 9: favors the penetration of basal membrane and glial layer of BBB **(1, 15)**
Non-cellular	HIV	Penetration of BBB Disfunction of BBB	BBB molecules which bind HIV (sialic acid, proteoglycans acid, N-acetyl-beta-D glucosamine)
	gp 120	Penetration of BBB Disfunction of BBB Modulation of HIV endocytosis and transcytosis **(4, 5)**	
	α TNF	Induces the disfunction of BBB	
	MCP-1 / CCL2	Modulation of monocytes migration **(16, 35)**	
	γ IFN, β IL-1, β TGF	Stimulate *in vitro* transmigration through BBB f leucocytes **(55)**	
	RANTES / CCL5	Exacerbate the effects of MCP-1 / CCL2 **(13)**	

BBB tends to limit invasion of the NS both by its anatomical structure aa weel as by complex physiological mechanisms (efflux active pumps, passive efflux, enzyme systems) (5, 6, 37).

Astrocytes and oligodendrocytes (but not neurons) are susceptible to HIV, having CD_4 receptors, as well as CCR5, CCR3 and CXCR4 co-receptors on their surface, which is attaching HIV gp120 and gp 41 glycoproteins; after the penetration of these cells the replicative cycle of the virus is started.

Host response is based on mobilization of mononuclear cells and production of various cytokines (TNF-alpha, IL-1 beta, interferon gamma, etc.), which carries themselves negative effects on nervous tissue and, moreover, fail to curb the invasion of HIV of the NS.

The study of Evers et al (18) suggest that, regarding HAD, the protective effect of HAART is due to virostatic effect exercised in the circulating compartment, but not in the cerebrospinal fluid (CSF), which supports the hypothesis of NS negative effect of cytokines, produced in peripheral blood, in response to infection HIV.

Effects of the conflict between HIV and the host are complex,partly elucidated and summarized in Table 2.

Clinical, before detection of major cognitive and motor complex (HAD), encountered in the AIDS stage of the disease, it is described various neurological disorders defined as minor cognitive/motor disorder (MCMD). Diagnostic criteria of MCMD are presented in Table 3.

Onset is insidious, often subtle clinical, usually the patient is accusing the reductions of working capacity and concentration, low psychical activity, decreasing libido. Gradually apathy is installing, the individual is escaping from daily activities and of common motor disorders is emerging (disorders of maintaining corporal balance, muscle fatigue and slow movements, awkwardness) (46). The patient have a normal corporal temperature throughout the disease development (7, 8). Neurologically it is noted:

- Initially: normal neurological examination or signs defining the stage 0.5, according to Price and Brew classification of HAD
- Lately: motor signs suggesting frontal lobe impairment (tremor, clonus, hiperreflexie, spasticity, abnormal coordination movements) associated, in the terminal stages, with elements of dementia, psychomotor retardation, apraxia, paraparesis (46).

Diagnostic criteria of HAD are presented in Table 4.

Study of the cerebrospinal fluid (CSF) does not provide support for diagnostic; exploration may be normal in 30-50% of cases, or can demonstrate an increase of the monocytes number in 5-25% of

TABLE 2. *SN effects of HIV-host interactions*

Effects	Details
Neuronal distruction or injuries	Through the proteins encoded by the genes tat, nef, vpr and rev (direct distruction and / or activation of astrocytesmicroglial cells and macrophages IFN gamma: increases the production of PAF, derivates of quinolonic acid and tryptophan metabolites (35)
Apoptosis	HIV direct action
SN oxidative stress	Through proteins encoded by the tat gene
Impairing of neuronal excitability	By the emergence of channels / ion pumps (mainly calcium and potassium) (25) and by the appearance of receptors for some neurotransmitters (adenosine, dopamine, GABA)
Stimulation of astrocytosis	TNF alpha and beta IL-1
Synthesis of certain neurotoxic substances	L-cysteine, arachidonic acid, quinolonic acid, glutamate, nitric oxide, free radicals (41) TNF alpha Eicosanoids: increase the intraneuronal calcium concentration (35) IL-1 beta / IFN gamma: stimulates the nitric oxide synthesis (35)

TABLE 3. *Diagnosis criteria for the MCMD, according to the American Academy of Neurology Diagnostic*

Minor cognotive and motor HIV associated impairments	
Diagnosis criteria	At least two of the followings: – inability to maintain focus – decreased ability for mental concentration – reduced capacity of memorization – motor slowliness – personality disorder causing minor or moderate functional impairments Exclusion of other diagnosis

TABLE 4. *Diagnosis criteria for HIV associated dementia, according to the American Academy of Neurology Diagnostic*

HIV associated dementia (major motor and cognitive disorders)	
Diagnosis criteria	At least two of the followings: – inability to maintain focus – decreased ability for mental concentration – reduced capacity of memorization – motor slowliness – personality disorder causing major functional impairments acquired abnormalities of motor performance or behavior, gait Without loss of consciousness, CNS opportunistic infections, psychiatric disorders or drug consumption

cases, associated with increased albumin level in the CSF (60% cases); of all proteins, electrophoretically isolated from CSF, it is noted beta 2 microglobulin (> 3 mg/l) and neopterin (a marker of immune activation), or light chains of neurofilaments (marker of neuronal destructions) and IgG (2, 7, 23, 32 , 46). Detection of antibodies against neuronal structures and immune complex can serve as markers for HAD (62). *Tau* protein does not correlate with the evolution of HIV-associated neurological condition and, moreover, it is found in other disorders such as Altzheimer disease, Creutzfeld-Jakob encephalopathy or ischemic stroke (24, 32). Increased CSF levels of alpha-tocopherol, triglyceride C52 (produced by the oxidative stress), ceramides (degradation products of sfingomielinei) and 4-hidroxinonenal (HNE) is associated with the worsening of mental status (3, 25). Although the level of HIV RNA in the CSF may be quantified , its significance is unclear. Some authors consider that high levels (above median of 4.77 log copies/ml CSF (32)) is being correlated with the cognitive impairment (11). However neurological damage is not present in all patients who demonstrate a high replicative level (14). It should be taken into account that the blood-CSF barrier is more permeable than BBB (about 10 times, estimation based on its electrical resistance) (37), making the HIV RNA level in CSF not accurate for reflecting the viral replication in the brain

Electroencephalogram is not definitory for the diagnostic; in late stages it is recorded the overall reduction of the electrical waves (46).

Modern radiological exploration can support the diagnosis of HAD, excluding other neurological disorders.

Computed tomography and **magnetic resonance** shows cortical and subcortical atrophy and dilatation of lateral ventricles; over time these elements are progressing, the MRI can reveal hyperintense lesions of the white periventricular matter periventricular, initially focal, then diffuse located in the late stage. When contract is added no accentuation is observed. The lessions have no mass effect (7, 46). MRI can be used to dynamically monitor the loss of the white matter. A study presented at the 11th Conference on Retroviruses and Opportunistic Infections showed that annual white matter damages are double in people living with HIV (and even in heavy alcohol drinkers) compared with seronegative subjects (36). Positron emission tomography (PET) may reveal alterations of cortical metabolism and photon emission tomography (SPECT) shows abnormal blood flow in affected areas (46). Modern spectroscopic techniques – proton magnetic resonance spectroscopy, 1H-MRS – are used for research purposes to reveal metabolic abnormalities in various brain regions.

Animal models (macaque) have shown decreased N-acetilaspartatului level in the frontal lobe at the initial stage of infection, increased creatine in the white matter, increased choline and myoinositol all over the cortex (39). Glutathione and GABA levels are low (27). Expression changes seem to reflect neural injuries and practically gave birth to a new medical field – metabolomics.

Brain biopsy, though not recommended for routine practice, may confirm the diagnosis; it is noted cortical atrophy, mainly frontotemporal, vacuolation, neuronal destructions, reduced synaptic density and dendritic arborisation, apoptosis, pale white matter (30). It can be seen cellular infiltration, nodular or diffuse, moreover with perivascular localisation, in cortical white matter and subcortical gray substance, consisting of microglial cells, macrophages, lymphocytes and multinucleated giant cells (46). By immunohistochemical studies, the basal ganglia and frontal lobes are highlighting the gp41 protein, whose expression is correlated with severity of dementia (45). A number of markers of neuronal degeneration (amyloid beta or alpha

synuclein) are frequently identified, but appear to correlate with the duration of HIV infection and not with the frequency of neurocognitive disorders (26).

Evolution of HAD, according to Price and Brew staging (quoted by Bartlett (7)) is shown in Table 5). Prior to the introduction of HAART the average survival time was six months, while today it rose to almost 40 months (46).

THERAPEUTIC POSSIBILITIES

There is no specific treatment for HAD.

However, HAART regimens reduce the incidence of HAD and protect against this condition (46). As for the remission of this condition, the data are contradictory, some authors considering that there was insufficient evidence to support the role of antiretroviral therapy (ART) (7), while others sustain that HAART may slow down the progress of HAD (44, 46). Penetration of antiretrovirals into brain parenchyma is limited by the structure of the BBB, efflux pumps and the presence of enzymes that degrade these substances (54). Basically, it is recommended to choose a potent antiretroviral treatment (HAART). with at least two drugs with good penetration into the CSF (9), examples being AZT, d4T, ABC, NVP, EFV and IDV (8). However, Evers et al. demonstrate that, although HAART prevents cognitive deterioration associated with AIDS, this is not due to CSF concentrations of antiretroviral substances, but rathe to suppression of HIV found in the blood (18).

Psychotropic medication may be used with the adjuvant effect. It has been studied the effects of oral lithium (29), sodium valproate (47) or serotonin reuptake inhibitors (SRI). Regarding SRI, a study involving 600 subjects showed improvement of neurocognitive performance in the group thet has used this medication. However this results seems to be the effect of a better adherence to ART, secondary to the treatment of depression, with consequent decrease in HIV viral load (28).

Psychological support may be beneficial.

THERAPEUTIC PERSPECTIVES AND RESEARCH DIRECTIONS

In future, using nanotechnology, it may be obtained ART formulations with higher penetration of the BBB. *In vivo* studies using animal models have demonstrated superior penetrability of indinavir nano-formulated, transported by macrophages, particularly in the subcortical areas and also supported its release for 14 days after a single administration (long-release effect) (12, 37). Attempting to further increase the CNS concentration of nano-formulated drugs may be obtained by altering the BBB using chemical, biochemical or physical methods (e.g. osmotic – mannitol –, by ultrasound with MRI guidance to the area of interest, or by electromagnetic field), but these approacheas are limited by the fact that it also allows penetration of other undesirable components / toxic at this level (37).

Another modern approach for HAD treatment, currently in experimental stage, uses the transfer of genetic material from one cell (macrophages derived from circulating monocytes – MDM) to another via a defective lentivirus, thus introducing anti-HIV genes / or other neuroprotective genes in the CNS. Data obtained *in vitro* show a decrease of 4 to 5 times the capacity of HIV replication in MDM cultures (31, 56).

Ceftriaxone and minocycline showed experimentally the ability of influencing the developments of HAD. HIV, through its tat and gp120 proteins by, is setting the downregulation of the EAAT2 (excitatory amino acid transporter-2), responsible for inactivation of synaptic glutamate which is involved, in high concentrations, in neuronal

TABLE 5. *HAD staging according to Price and Brew (1988)*

Stage	Interpretation	Clinical features
0	Normal	Normal motor and cognitive functions
0,5	Subclinical	No symptoms or minimal – equivocal; no work impairment ; no influences over the daily activity. It could be noted a slowliness of ocular movement or proximal muscles
1	Minor impairment	Mild – minimal intellectual or motor impairment; without affecting the ability of daily care; the patient can walk alone; it is noted the decrease in intellectual performance and neuropsychological tests, with impaired ability to work under conditions of maximum demand
2	Moderate impairment	The patient is capable of self-care and daily minimal activities, but may require assistance; cannot perform tasks forcing the intellectual functions.
3	Severe impairment	Major intellectual disability (cannot watch news, cannot sustain complex conversation,"slow"gen eral mental functions). Cannot move without assistance, walking is difficult
4	End stage	Near vegetative stage ; paraplegia or quadriplegia

toxicity, while beta-lactams is inducing the up-regulation of EAAT2 (42). Minocycline reduces activation of macrophages and endothelial cells, reduces expression of certain markers of inflammation, in the brain and CSF, while *in vitro* it inhibits both HIV and simian immunodeficiency virus (19, 57). Besides its anti-inflammatory and anti-lentivirale (*in vitro*) effects, minocycline is showing additional antioxidant capacity, as well as and anti-apoptosis effects (57).

Antagonists of the NMDA receptor (e.g. nimodipine, memantine and nitroglycerin) are used for prevention of HAD (30).

In vitro experiments showed that antibodies against MCP-1 inhibits the chemokines production and transmigration of monocytes in the percentage of 85-90%. Antibodies against ICAM-1 and E-selectin molecules were used for the same purpose (55).

Other approaches is based on using the tetra-ethylammonium, a potassium channel blocker, thus braking the leukocyte passage (22). The above mentioned experimental results open new perspectives for future treatment

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